# UNIVERSITY OF SOUTHAMPTON

FACULTY OF MEDICINE, HEALTH & LIFE SCIENCES

School of Health Sciences

**The Investigation of Bursae in the Forefoot of Patients with Rheumatoid Arthritis Using Musculoskeletal Ultrasound Imaging Performed by a Podiatrist**

by

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UNIVERSITY OF SOUTHAMPTON
**ABSTRACT**

FACULTY OF MEDICINE, HEALTH AND LIFE SCIENCES
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INVESTIGATION OF BURSAE IN THE FOREFOOT OF PATIENTS WITH
RHEUMATOID ARTHRITIS USING MUSCULOSKELETAL ULTRASOUND
IMAGING PERFORMED BY A PODIATRIST

by Catherine Jane Bowen

Patients with rheumatoid arthritis (RA) frequently present with pain under their feet. Forefoot bursae can give rise to such symptoms, but are rarely investigated. The aim of this thesis was to use musculoskeletal ultrasound (MSUS) performed by a podiatrist to evaluate the prevalence and natural history of bursae in the forefoot in RA patients.

Once reliability of technique was established, a longitudinal study design was used in which a sample of RA patients (N=149) and a comparator group (N=50) of healthy individuals were assessed at baseline. A Diasus MSUS system was used to image the forefeet of all participants to determine prevalence of bursae. 120 patients (98 female, 22 male) with RA (24 seronegative, 93 seropositive, 3 unknown) completed the study at twelve months: mean age 60.7 (SD 12.1) years and disease duration 12.99 (10.4) years.

Results confirmed a high prevalence of forefoot bursae (92.6% of patients; mean per individual =3.54, range 0-9) and that these were often missed by clinical examination. Findings that there could be an association between patient reported foot impact scales of impairment/footwear ($LFIS_{IF}$) and activity participation restriction/limitation ($LFIS_{AP}$) and presence of bursae ($LFIS_{IF}$ $\beta$=0.377, p=0.033; $LFIS_{AP}$ $\beta$=0.762, p=0.013) independent of disease activity were unique. On examination of prospective data after one year, 25.8% of participants had increases in bursae and 23.3% decreases. There was a significant correlation between changes in bursae with changes in $LFIS_{IF}$ (PCC=0.216, p=0.018) and $LFIS_{AP}$ (PCC=0.193, p=0.036) and a significant negative correlation with changes in duration of RA (PCC=-0.269, p=0.003).

The findings imply that MSUS detectable bursae in the forefeet are highly prevalent, clinically under-reported and change over time.  The findings suggest that bursae within the foot in RA deserve increased clinical attention and that further work is required to confirm associations with patient reported foot impact outcome measures.

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# DECLARATION OF AUTHORSHIP

I Catherine Jane Bowen declare that the thesis entitled

The Investigation of Bursae in the Forefoot of Patients with Rheumatoid Arthritis Using Musculoskeletal Ultrasound Imaging Performed by a Podiatrist

and the work presented in the thesis are both my own, and have been generated by me as the result of my own original research. I confirm that:

- this work was done wholly or mainly while in candidature for a research degree at this University;

- where any part of this thesis has previously been submitted for a degree or any other qualification at this University or any other institution, this has been clearly stated;

- where I have consulted the published work of others, this is always clearly attributed;

- where I have quoted from the work of others, the source is always given. With the exception of such quotations, this thesis is entirely my own work;

- I have acknowledged all main sources of help;

- where the thesis is based on work done by myself jointly with others, I have made clear exactly what was done by others and what I have contributed myself;

- none of this work has been published before submission, **or** [delete as appropriate] parts of this work have been published as: [please list references]

**Signed:** ……………………………………………………………..

**Date:**……06.11.09……………………………………………….

# Author's Related Publications and Presentations

## Academic peer reviewed original papers

Bowen, C.J., Culliford, D., Dewbury, K., Sampson, M., Burridge, J.H., Hooper, L., Edwards, C.J., Arden, N.K. The clinical importance of ultrasound detectable forefoot bursae in rheumatoid arthritis. Rheumatology (*in press*).

Bowen, C.J., Dewbury, K., Sampson, M., Sawyer, S., Burridge, J.H., Edwards, C.J., Arden,.N.K. Musculoskeletal ultrasound imaging of the plantar forefoot in patients with rheumatoid arthritis: Inter-observer agreement between a podiatrist and a radiologist. Journal of Foot and Ankle Research 2008, 1:5 (28 Jul 2008).

## Academic peer reviewed review papers

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Bowen, C.J. Extending the Scope of Practice for Podiatrists: A consideration of the use of Diagnostic Ultrasound Imaging. Br J Podiatry, 2003, 6, (4): 92-95.

## Academic peer reviewed abstracts

Bowen, C.J., Culliford, D., Dewbury, K., Sampson, M., Burridge, J.H., Edwards, C.J., Arden, N.K. Investigation of the natural history of forefoot bursitis detected by musculoskeletal ultrasound and predictors of its changes after one year. Rheumatology, 2009, 48, (Supplement 1), i132.

Bowen, C.J., Burridge, J.H., Dewbury, K., Culliford, D., Arden, N.K. Bursitis of the foot is a clinically relevant factor in RA. Rheumatology, 2008, 47, (Supplement 2), ii24.

Bowen, C.J., Dewbury, K., Sampson, M., Sawyer, S., Bennet, S.P., Burridge, J.H., Edwards, C.J., Arden, N.K. Does bursitis of the forefoot improve in patients with rheumatoid arthritis on anti-TNFα therapy? Rheumatology, 2007, 46, (4): Abstracts Supplement: i30.

Bowen, C.J., Dewbury, K., Sampson, M., Sawyer, S., Bennet, S.P., Burridge, J.H., Edwards, C.J., Arden, N.K. Inter-observer reliability of a podiatrist and radiologist: results of ultrasound imaging of the plantar forefoot in patients with rheumatoid arthritis. Rheumatology, 2006, 45, (4): Abstracts Supplement: i184.

Bowen, C.J., Dewbury, K., Sampson, M., Sawyer, S., Bennet, S.P., Burridge, J.H., Edwards, C.J., Arden, N.K. Bursitis of the foot: a common and under diagnosed problem in patients with rheumatoid arthritis. Rheumatology, 2006, 45, (4): Abstracts supplement: i95.

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# List of Abbreviations

ACR: American College of Rheumatology

AIUM: The American Institute of Ultrasound in Medicine

ALARA: As Low As Reasonably Achievable

Arc: The Arthritis Research Campaign

BFS: The Bristol Foot Score

BMUS: British Medical Ultrasound Society

BSR: The British Society for Rheumatologists

COREC: Central Office for Research Ethics Committees

CRP: C-Reactive Protein

CT: Computed Tomography

DAS: Disease Activity Score

DOH: Department of Health

DMARD: Disease Modifying Anti Rheumatic Drug

EFSUMB: European federation of Societies for Ultrasound in Medicine and Biology

ESR: Erythrocyte Sedimentation Rate

EULAR: European League Against Rheumatism

FeeTURA: The Southampton study of the foot in rheumatoid arthritis using ultrasound imaging

FFI: The Foot Function Index

FHSQ: The Foot Health Status Questionnaire

GALS: Gait, Arms, Legs and Spine

GP: General Practitioner

HAQ: Health Assessment Questionnaire

HLA: Human Leucocyte Antigen

IPJ: Interphalangeal joint

IM: Inter-metatarsal

LFIS: The Leeds Foot Impact Score

$LFIS_{IF}$: The Leeds Foot Impact Score impairment and footwear subscale

$LFIS_{AP}$: The Leeds Foot Impact Score activity restriction and participation limitation subscale

$LFIS_{TOT}$: The Leeds Foot Impact Score total score of both subscales

MCP: Metacarpo-phalangeal

MHC: Major Histocompatability Complex

MFPDQ: Manchester Foot Pain and Disability Questionnaire

MRC: Medical Research Council

MSUS: Musculoskeletal ultrasound

MRI: Magnetic Resonance Imaging

MR: Magnetic Resonance

MTP: Metatarso-phalangeal

NHS: National Health Service

NOAR: The Norfolk Arthritis Register

OMERACT: The Outcome Measures in Rheumatology Clinical Trials

PA: Posteroanterior

PIP: Proximal interphalangeal joint

QAA: Quality Assurance Agency

RA: Rheumatoid arthritis

SD: Standard Deviation

Sle: Systemic Lupus erythematosus

SONAR: Sound, Navigation And Ranging

SPSS: Statistical package for Social Science

SUHT: Southampton University Hospital Trust

TNF: Tumour Necrosis Factor

UK: United Kingdom

USA: United States of America

VAS: Visual Analog Scale

WHO ICF: The World Health Organisation International Classification of Functioning, Disability and Health

# 1.0. Chapter One: Introduction to the Thesis

This thesis presents the work carried out to date as a post-graduate research student with the School of Health Sciences, University of Southampton. The thesis forms the requirement for Doctor of Philosophy.

In my clinical experience as a podiatrist, palpable and often painful swelling, attributed to bursae under the forefoot in patients with rheumatoid arthritis (RA) is a common complaint that is difficult to treat. Management of this problem is primarily aimed at deflecting pressure away from the affected areas. The treatment, however, is based on the notion that the aetiology of swollen bursae in the plantar forefoot area is mechanically derived, although there is very little research evidence to support this. In fact, patients' foot status and bursal swelling in many observed cases appear to become worse over time and do not respond to the intervention.

On questioning this further, it was clear that literature regarding bursae within the forefoot was confusing and, inevitably, that treatment was often mis-informed and less likely to be successful. At the beginning of the study, musculoskeletal ultrasound (MSUS) was emerging as a new diagnostic technique that was reported as superior to clinical examination in identifying soft tissue swelling. The technique was largely performed by non-radiologists, namely rheumatologists and no podiatrists had developed this within their practice. The stages of this doctoral thesis therefore follow a sequential programme of original work. A new scope of practice for podiatrists in the use of MSUS has been introduced and the prevalence and natural history of bursae within the forefoot in RA have subsequently been described using MSUS performed by a podiatrist.

## 1.1. Overview of the research problem

Foot health providers, such as podiatrists, have a prime role to play in the assessment and management of musculoskeletal foot and ankle pathology (ARMA 2008; NICE 2009). Rheumatoid Arthritis (RA) commonly affects the feet, causing swelling and pain that reduces a person's mobility (Costa, Rizack et al 2004). There is radiological evidence that the first signs of rheumatological disease may appear in the foot in about 20% of patients who have RA (Paimela 1992) and that rheumatoid involvement of the feet is as frequent as, or more

frequent than, that of the hands (Isomaki, Kaarela et al 1988).

Patients who have RA, however, rarely report foot problems (Williams and Bowden 2004) although what is not currently known is why this is the case. It might be possible that, due to the global nature of the disease process of RA, feet are not as important as other joints in this patient population.

Most evidence of the manifestations of RA disease within the foot is attributable to cross-sectional analytical data; longitudinal studies of manifestations of RA disease, within the foot and ankle, are rare. Accordingly, there remains a limited understanding of the full patho-physiology of this chronic disease within the foot and thus a relatively inadequate evidence base for currently used clinical interventions (Bowen, Burridge and Arden 2005; Farrow, Kingsley et al 2005; Clark, Rome et al 2006; van der Leeden, Steultjens et al 2008). Usually it is synovitis that is investigated and investigation of changes in disease state may include synovitis within the metatarso-phalangeal (MTP) joints, although do not necessarily form the main focus of studies (Ejbjerg, Vestergaard et al 2005; Naredo, Bonilla et al 2005; Joshua, Lassere et al 2007; van der Heijde, Landewe et al 2008). To our knowledge, no study has included forefoot bursae as potential confounding factors with MTP joint synovitis within the analyses.

Consequently the roles of inflamed soft tissues, such as bursae, in the process of RA and the resulting impact on foot disability and function are undetermined. Olivieri, Scarano et al (2004) highlighted that bursitis in the forefoot was poorly documented and emphasised the importance of rheumatologists being aware of the existence of numerous small, synovial bursae in the forefoot that may be difficult to detect clinically and be the cause of persistent pain. The findings from Brown, O'Connor et al (2006) in defining competency within musculoskeletal ultrasound (MSUS) concur, suggesting more specifically that the presence of bursitis between the metatarsal heads of the forefoot (intermetatarsal bursitis) was classified as 'must know' by rheumatologists.

Whilst bursae may be an important feature of the forefoot in RA, the terminology of forefoot bursitis within the literature is confusing. Some describe all bursae as fibrous sacs filled with synovial fluid (Saladin 2004) and others conversely describe the existence of two main types of bursa, anatomical bursae and adventitious bursae (Warwick, Williams et al 1973) or

convey bursae as being classified according to type (anatomical or adventitious), location, or nature (pathological or non pathological) (Hernandez, Hernandez and Hernandez 1991). It is possible that the lack of definition of forefoot bursae and consequent lack of identification of their aetiology could mean that treatment may be delayed or be inappropriate.

According to Warwick, Williams et al (1973), anatomical bursae are naturally occurring bursae that contain a capillary film of synovial fluid that acts as a lubricant and provides the cells of their synovial membrane with a wet environment on their free surfaces. Arguably, the synovium of anatomical bursae therefore may be susceptible to the pathological processes of RA (Palmer 1995; O'Brien, Hart et al 1997; Narvaez, Narvaez et al 2002). Within the plantar forefoot area four anatomical bursae are described as existing between the metatarsal heads in the intermetatarsal spaces (Theumann, Pfirrmann et al 2001). Adventitious bursae, on the other hand, are said to occur within the subcutaneous tissues or the plantar fat pad of the plantar forefoot and have no synovial lining (Hernandez, Hernandez and Hernandez 1991; Studler et al 2008). Differentiating adventitious bursae formation from anatomical bursae formation however is difficult unless confirmed by histology.

As technology has advanced for clinical diagnosis, MRI appears to give good detail on the differential diagnosis of swollen bursae from other inflammatory soft tissue pathologies that may occur within the forefoot (Bancroft, Peterson and Kransdorf 2008). MSUS is also promising in identifying forefoot bursitis (Koski et al 1998). Interestingly, Koski (1998) demonstrated a high prevalence of intermetatarsal bursitis within patients with early RA that were not clinically apparent (Koski et al 1998). Other work using MSUS has also highlighted a high presence of synovitis that was not clinically apparent in patients with RA (Brown, Quinn et al 2006) and within patients with oligoarthritis (Wakefield, Green et al 2004).

It has been suggested that results from MSUS investigations challenge current classifications of rheumatological disease (Bresnihan and Kane 2004). The new information revealed by MSUS can be attributed to the dramatic advancement in technology that has led to improved clinical expertise in performing MSUS (Gibbon 1996; O'Connor and Grainger 2002). MSUS imaging has advantages over conventional radiography, computed tomography, radioisotope scan and MRI (Magnetic Resonance Imaging) in that it is painless, does not use ionizing radiation, is less expensive, can be performed in real time and is clinically readily accessible

(Gibbon 1996).

MSUS imaging could be more clinically useful in determining foot status prior to podiatric treatment interventions than existing tools such as gait assessment and foot pressure measurement, which have emerged as useful outcome measures for interventions associated with foot and ankle pain (Budiman-Mak, Conrad et al 1995; Conrad, Budiman-Mak et al 1996; Fransen and Edmonds 1997; Hodge, Bach et al 1999; Macsween, Brysdon et al 1999; Chalmers, Busby et al 2000; Woodburn, Stableford et al 2000; Woodburn, Barker et al 2002; Turner, Helliwell et al 2008). Gait analysis and foot pressure measurement techniques are based on assessment of biomechanical influences that rely on the bony alignment of the foot joints and therapy is aimed at pain and pressure relief from customary clinical observations. Further knowledge of the status of soft tissues within the foot, especially within a chronic fluctuating disease such as RA, would allow better targeted therapeutic approaches, such as localised corticosteroid injection.

There have been a number of studies that have utilised MSUS to diagnose specific soft tissue foot pain in a range of different patient groups (Brown, Betts et al 1994; Bygrave, Betts et al 1998; Irwin, Konstantoulakis et al 2000) and soft tissue problems in RA (Coakley, Samanta et al 1994). More specifically for the forefoot, MSUS findings of MTP joint synovitis (Koski 1990; Szkudlarek, Narvestad et al 2004), plantar flexor tenosynovitis (Koski 1995) and plantar bursitis have been described (Koski 1998).

In the discipline of the podiatrist, foot health clinician or foot and ankle surgeon MSUS has, however, been deemed to be an under-utilised tool (Rockett 1999, Bowen 2003). Darzi (2008) recognises that delivery of modern health care will require crossing of traditional professional boundaries. It therefore follows that the ability of a suitably trained podiatrist to use and apply the techniques of real time diagnostic MSUS imaging within their consultations has great potential for enhancing the current assessment–referral pathways (ARMA 2008).

However, MSUS is affirmed as being highly operator dependent (Grassi and Cervini 1998). The procedure itself has no known specific side effects, although mis-diagnosis that may result from incorrect acquisition and interpretation of images has been highlighted as a potential risk (O'Connor and Grainger 2002). The reported challenges in training for this skill are primarily due to the quality and interpretation of the MSUS images, which are

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acknowledged as being greatly dependent on the expertise and experience of the operator (Balint and Sturrock 1997). Knowledge about the basic principles relevant to sound waves and a detailed anatomical knowledge of the structures under investigation are therefore mandatory (Backhaus, Burmester et al 2001).

Models for the use of MSUS by clinicians other than radiologists, have been demonstrated (Filippucci, Unlu et al 2003; Taggart, Filippucci et al 2006) and specific competencies for MSUS performed by non radiologists have been rigorously developed (Brown, O'Connor et al 2005; Brown, O'Connor et al 2006; Brown, Roberts et al 2007). The most recently proposed framework for development of competencies in MSUS scanning techniques recognises the challenges of training and recommends that learning is tailored to areas directly relevant to a clinician's discrete field of practice (Brown, Roberts et al 2007).

The use of MSUS assessment of the foot and ankle as a discrete field in podiatric clinical practice could thus be beneficial to patients with RA by facilitating more effective timely referral and management of foot problems. Additionally, there are perceived benefits to service providers, in lower costs. Robust diagnostic MSUS imaging studies of foot pathology will be an essential element in the development of such emerging clinical practices.

According to Bell and McNally (2002) the majority of musculoskeletal structures in the foot and ankle are relatively superficial, so they can be effectively imaged by MSUS. However, in recent reviews of podiatry interventions for the rheumatoid foot, none of the included studies utilised MSUS imaging techniques to assess severity and activity of inflammation within the foot joints (Bowen 2005; Farrow, Kingsley et al 2005; Clark, Rome et al 2006).

Using MSUS, Koski (1998) suggested that forefoot bursae in RA could be associated with forefoot symptoms but did not prove this within his small cross sectional study. In the absence of larger studies and longitudinal data, the relationship between forefoot bursae, poor clinical symptoms and foot disability therefore remains speculative. This becomes important in considering the clinical implications of forefoot bursae in causing metatarsalgia and consequent foot disability. Usually, in longitudinal studies, it is MTP joint synovitis or tenosynovitis that has been linked to metatarsalgia in patients with RA (Welsing, van Gestel et al 2001; Ødegard, Landewe et al 2006; van der Heijde, Landewe et al 2008; van der Leeden, Steultjens et al 2008). The lack of consideration of forefoot bursae

as a potential confounding variable in metatarsalgia within these studies may be a significant omission.

If non-invasive clinical palpation of the plantar metatarsal area is relatively insensitive for swollen forefoot bursae in RA disease, it is likely that diagnosis of foot symptoms may be delayed (Koski 1998). However, the evidence that suggests forefoot bursae are highly prevalent and clinically important in RA forefoot disease is currently limited. It therefore seems fundamental to clearly define the prevalence of forefoot bursae in a large population of patients with RA and to investigate the natural history of this over time. There is also a reasonable argument that the use of MSUS imaging performed by a podiatrist to achieve this has good potential.

## 1.2. Summary of thesis chapters

**Chapter one** has given an overview of the research problem and rationale for the studies. Forefoot bursae, as well as MTP joint synovitis and tenosynovitis are implicated as a cause of metatarsalgia within the forefoot in patients with RA. The chapter highlights that bursae within the forefoot in patients with RA are clinically mis-interpreted and under-investigated. MSUS imaging performed by a podiatrist is suggested as being a useful technique to investigate this further.

**Chapter two** of this thesis will seek to explore further the background and literature review and will bring together thoughts from the subject material read to date and the important issues regarding the confusion in terminology, classification and relevance of bursae in the forefoot in patients with rheumatoid arthritis. The potential use of MSUS imaging performed by a podiatrist to detect forefoot bursae is considered. The relevance to patient care and clinical practice of the use of MSUS performed by a podiatrist is also highlighted.

**Chapter three** explains the methodological approach for the programme of research study and the selection of study design for each phase of the work. The participant samples, MSUS protocols, observational outcomes, patient reported outcome measures, and statistical analyses are discussed and justified.

**Chapter four** details the first phase of the programme of research study in which the MSUS

technique of a podiatrist is tested for reliability. The prevalence of bursae within the forefoot is provisionally explored as well as the ability of MSUS to detect changes in the prevalence of forefoot over time following intervention. The results of the investigations are discussed in light of current evidence and the investigation of forefoot bursae by MSUS, performed by the podiatrist, is justified.

**Chapter five** presents the baseline cross sectional study of investigation of the prevalence of forefoot bursae in RA. The results of the study, detailing the prevalence of forefoot bursae detected by MSUS and by clinical examination are presented and their uniqueness discussed in light of current evidence. Further analyses of the associations of bursae within the forefoot detectable by MSUS but undetected clinically with patient reported foot symptoms are also presented and discussed in light of current evidence.

**Chapter six** presents the twelve month longitudinal prospective study that explores the natural history of bursae within the forefoot detectable by MSUS over time. Results from the longitudinal data are presented and the association of MSUS detectable forefoot bursae with patient reported foot symptoms at baseline and twelve months are compared. Predictors of change in MSUS detectable forefoot bursae status over time are also analysed and discussed in light of current evidence.

**Chapter seven** draws the discussions from chapters' four, five and six together and further critiques each of the studies' designs. Suggestions for improvement and plans for future research are proffered along with concluding remarks.

## 2.0 Chapter Two: Background and Literature Review

The aim of this chapter is to introduce the background to the research study, explore the rationale for the study and discuss the paradigm within which the piece of work is set. The literature review considers the various opinions regarding the pathological processes of RA and the assessment of musculoskeletal pathology by diagnostic imaging. The main ideas behind the need to define bursitis and increase the specificity of clinical diagnosis of forefoot pain are also discussed. Ultimately, this review considers the need for podiatrists to perform diagnostic MSUS imaging of the foot and ankle in the current climate of reduced service provision and low numbers of musculoskeletal radiologists.

### 2.1. Rheumatoid arthritis

This section explains the diagnosis and definition of rheumatoid arthritis and the current concepts in disease progression and variation.

#### 2.1.1. Epidemiology

Musculoskeletal diseases have been conveyed as the commonest cause of work-limiting health problems, long standing illness and sickness absence in the UK (Scott, Shipley et al 1998). Twenty million people in the United Kingdom are reported to experience a rheumatic disorder with eight million consulting their General Practitioners (GPs) in 1 year (Spector and MacGregor 2001). Musculoskeletal disease reportedly accounts for 23% of all GP consultations (Spector and MacGregor 2001) with high medical costs accounting for nearly 8% of Health Service related expenditure (Scott, Shipley et al 1998). Of the chronic inflammatory musculoskeletal diseases, RA is the most common, purportedly accounting for up to 50% of the workload of most rheumatologists (Spector and MacGregor 2001).

Epidemiological aspects of RA remain difficult to estimate as Symons & Silman (2003) suggested there is often a delay in presentation and problems concerning case definition of RA, due to the cumulative aspect of the ACR (American College of Rheumatology) classification criteria (Arnett, Edworthy et al 1988). Information generated by NOAR (The Norfolk Arthritis Register) suggests that in the United Kingdom the prevalence of RA is estimated at one percent and its incidence at 30.8/100 000 for women and 12.7/100 000 for men, if up to 12 months elapsed from symptom onset to notification (Wiles, Symmons et al 1999). When the ACR criteria is applied cumulatively over five years, annual incidence

estimates are higher, at 54.0/100 000 for women and 24.5/100 000 for men (Wiles, Symmons et al 1999).

Overall, the prevalence of RA is clearly higher in females (Kvien et al 2006) although the prevalence of RA in women may have fallen since the 1950s (Symmons, Turner et al 2002; Uhlig & Kvien 2005). RA affects all races and is evident throughout the world, with a lower prevalence in rural Sub-Saharan Africa and Caribbean blacks and a higher prevalence in the Prima Indians of the USA (MacGregor, Riste et al 1994; Sangha 2000). Trend analyses appear to be observing consistently improved health status for patients with RA through the new millennium (Uhlig, Heiberg et al 2008). The reported drop in the prevalence and incidence of RA has been attributed to better access to more aggressive treatments such as tumour necrosis factor alpha (TNF-α) agents (Uhlig, Heiberg et al 2008) and key trends in RA over a 40-year period, supporting the concept that the epidemiology of RA is a dynamic process (Doran, Crowson et al 2002).

The implications of RA to the patient and to society however remain staggering. The overall medical costs for this disease alone are high with mean annual direct and indirect costs, per person with RA, at the turn of the century being £3575 and £3638 respectively (Cooper 2000). In England, the total economic impact of RA was estimated to be £1.256 billion in 1992-3, over half of which was accounted for by loss of earnings caused by RA disability (McIntosh 1996). With the rising costs of inflation and medication these estimates would now be much higher.

Morbidity for people who have RA is substantial as, 6.4 years from disease onset, approximately 25% of patients are work disabled, rising to 50% at 20.9 years (Pincus, Wolfe et al 1994; Wolfe & Hawley 1998). Most studies agree that people with RA have a lower life expectancy compared with members of the general population of the same age and sex (Pincus, Wolfe et al 1994; Gabriel, Crowson et al 2003; Navarro-Cano, Del Rincon et al 2003). For the people with RA unable to work due to disability, family income is reduced by 35% with more abnormal scores for almost every demographic and clinical variable (joint counts, grip strength, sedimentation rate, pain, global severity, health assessment questionnaire, disability and anxiety and depression) (Pincus, Wolfe et al 1994; Wolfe & Hawley 1998).

### 2.1.2. Classification criteria

For classification purposes to allow comparisons between different populations and to serve as entry criteria for clinical trials, there is consensus that the diagnosis of RA is usually made according to specific criteria (van Gestel, Anderson et al 1999; Singh, Solomon et al 2006). Most studies report participants as being diagnosed with rheumatoid arthritis according to the 1987 revised criteria of The American College of Rheumatology (ACR - formerly the American Rheumatism Association, see **Table 1**, Arnett, Edworthy et al 1988).  The criteria, whilst providing a guide for classification of RA and an element of standardisation within clinical trials, have been criticised for exclusion of certain factors, especially lower limb detail such as foot erosions (Hulsmans, Jacobs et al 2000). Furthermore, the classification criteria are not designed to diagnose the individual patient in the clinic, where clinical judgment is deemed important (Harrison, Symmons et al 1998; Bukhari, Harrison et al 2001).

Classification of pathology in individuals with RA is further complicated due to the fluctuating nature of the disease. Investigators have attempted to set core endpoints in RA trials (Boers, van Riel et al 1995) and called for an update in response criteria (Singh, Solomon et al 2006) and reassessment of individuals' disease status on a regular basis (Hulsmans, Jacobs et al 2000). Fortin, Stucki and Katz (1995) challenged investigators to address the threats of relevance of change within their study designs, as most people with RA may not be in a steady state and disease variations may vary greatly from one individual to another.

Biochemical markers that have pathological relevance to RA may make classification and diagnosis more straightforward than reliance on specific criteria (Young-Min, Cawston et al 2008). Rheumatoid factor is the only serological parameter in the ACR criteria but has a low - moderate sensitivity of 60-80% and poor specificity, although has been prognostically useful as it has good correlation with functional and radiographic outcome (Quinn, Gough et al 2005).

The recent identification of citrullinated proteins and production of anti-CCP (anti-cyclic citrullinated peptide) antibodies in the immune response has led to the development of a test that has facilitated clinicians' ability to predict the development of RA in undifferentiated arthritis and even in healthy individuals many years prior to clinical onset (Zendman, van Venroij et al 2006; Avouac, Gossec and Dougados 2006). The anti CCP test has the potential

to revolutionise patient management as it can predict an aggressive disease course at diagnosis in undifferentiated arthritis and may be detected in healthy individuals many years prior to clinical onset of RA (Avouac, Gossec and Dougados 2006).

**Table 1.** The revised criteria for classification of Rheumatoid Arthritis (Arnett, Edworthy et al 1988).

| Criterion | Definition |
|---|---|
| Morning stiffness | Morning stiffness in and around the joints lasting at least one hour before maximal improvement. |
| Arthritis of 3 or more joints | At least 3 joints areas have simultaneously had soft tissue swelling or fluid (not bony overgrowth alone) observed by a physician. The fourteen possible joint areas are right or left PIP, MCP, wrist, elbow, knee, ankle and MTP joints. |
| Arthritis of the hand joints | At least one area swollen as above in the wrist, MCP or PIP. |
| Symmetric Arthritis | Simultaneous involvement of the same joint areas (as in 2) on both sides of the body (bilateral involvement of PIPs MCPs or MTPs is acceptable without absolute symmetry). |
| Rheumatoid nodules | Subcutaneous nodules over bony prominence, extensor surfaces, or in juxta-articular regions observed by the physician. |
| Serum Rheumatoid Factor | Demonstration of abnormal amounts of serum 'rheumatoid factor' by any method that has been positive in less than 5% of normal control subjects. |
| Radiological changes | Radiological changes typical of Rheumatoid Arthritis on PA hand and wrist roenterograms, which must include erosions or unequivocal bony decalcification localised to or most marked adjacent to the involved joints (osteoarthritis changes alone do not qualify) |

For classification purposes, a patient shall be said to have Rheumatoid Arthritis if he/she has satisfied at least four of the above seven criteria. Criteria 1 – 4 must have been present for at least six weeks. Patients with two clinical diagnoses are not excluded. Designations as 'classic', 'definite' or 'probable' rheumatoid arthritis are not to be made.

Key: PIPs = Proximal interphalangeal joints, MCPs = Metacarpophalangeal joints, MTP = Metatarsophalangeal joints, PA = Posterioanterior.

In considering early markers, such as rheumatoid factor and citrullinated proteins for better diagnosis, other ways of observing the ongoing process of RA include modern imaging methods such as MRI and MSUS imaging. Both technologies are sensitive to detecting inflammation and structural damage and it is possible that exploring the use of these technologies further may lead to changes in the way RA is classified and monitored (McGonagle and Conaghan 1999; Skudlarek, Narvestad 2004).

### 2.1.3. Aetiology and pathology

In order to develop an understanding of the foot manifestations of RA, it is first important to discuss current concepts in the aetiology and pathology of the disease process. Over the past twenty five years there has been tremendous change in the understanding of rheumatoid arthritis and although, as Brooks (1998) confirms, the aetiology of RA has remained elusive, its pathogenesis is becoming increasingly well characterized. It is this insight that has led to the development of new therapies and interventions that can alter the pathological course of RA and thus affect how foot manifestations may be managed.

Choy and Panayi (2001) present a paradigm shift in the approach to a patient with RA over the late 1980s and early 1990s that involved the transition of agreement from the traditional hypothesis that the pathogenesis of RA could be defined by a single cause external to the host. The paradigm shift brought new thinking that the pathogenesis of RA is multifactorial, including host genetic predispositions and internal dysregulations and may not require any external antigen or pathogen (Pincus and Wolfe 1994). It is suggested that the presentation of a relevant antigen to an immunogenetically susceptible host is believed to trigger RA (Harris 1990; Bukhari, Harrison et al 2001).

Emerging data indicates that several genetic risk determinants, each of which is non-pathologic if occurring alone, can add up to confer disease risk. One of these genetic elements in RA has been mapped to the human leucocyte antigen (HLA) region (Weyand and Goronzy 1997). RA has been found to be associated with several genes, mainly in the region encoding the major histocompatability complex (MHC) genes (MacGregor, Riste et al 1994). The presence of HLA-DR4 was significantly commoner among patients with RA who were caucasian (Sangha 2000). In populations of northern European descent, HLA-DR4 was associated with both an increased incidence of RA and more severe disease (O'Dell 2003).

However, only certain subtypes of HLA-DR4 (HLA-Dw4 and HLA-Dw14) have been associated with RA, with susceptibility being related to a shared epitope on the HLA molecule (Akil and Amos 1999). First degree relatives of those with RA are at an increased risk of developing RA, with siblings of severely affected patients at highest risk (MacGregor, Riste et al 1994). Monozygotic twins have a concordance rate of 12% to 15% whereas dizygotic twins have a rate one quarter of this (MacGregor, Riste et al 1994).

The realisation that RA is a genetic disease has been significant in the understanding of it's pathology with more detailed reviews now available (Wordsworth 1995; Lin, Cash et al 1998; Choy & Panayi 2001; Jawaheer and Gregersen 2002; Firestein 2003). The last two decades in RA research have also seen a major shift from premolecular to molecular techniques. A major effort has been to determine which cytokines and inflammatory mediators are produced at the site of disease (Weyand and Goronzy 1997). This in turn has led to the development of new medicines and more targeted therapeutic management approaches (Hau, Kneitz et al 2002; Taylor, Steuer et al 2006; Brown, Quinn et al 2006).

In brief, the major contributor to the pathogenesis of the synovitis and joint destruction in RA is thought to be cellular mechanisms initiated by the activation of T lymphocytes (Panayi 1994). The viewpoint that RA represents the sequelae of systemic proliferation is supported by the finding of autoreactive T cells with atypical growth and differentiation behaviour (Weyand and Goronzy 1997; Scutellari and Orzincolo 1998).

Panayi (1994) proposed a mechanism for RA as a pyramid that starts with the initiating event, the activation of the pathogenic T cells by the trimolecular complex consisting of the HLA-DR4/1 molecule, the unknown rheumatoid antigenic peptide and the α-β T-cell receptor.

Four stages have been classified (Panayi 1994) to aid in the thinking of possible targets for the development of new therapies. These are:

> **Stage 1**: Initiation
> **Stage 2**: Recruitment
> **Stage 3**: Amplification and joint destruction
> **Stage 4**: Repair

Patients are unlikely to have symptoms during the early events of immune recognition of

stage 1 of RA (Panayi 1994) and many patients do not develop erosions evident on radiograph until after two years from disease onset (Bukhari, Harrison et al 2001). The symptoms of RA are known to begin only when the production and release of cytokines by macrophages and activated T lymphocytes occur, angiogenesis begins in the synovial membrane, and neutrophils are attracted to the joint cavity in the recruitment phase (Panayi 1994; Weyand and Goronzy 1997).

These steps are mediated by the cytokines gamma-interferon (IFN-ɣ), interleukin-2 (IL-2), TNF-α (tumour necrosis factor) and IL-1 (interleukin-1) (Choy and Panayi 2001). Cytokines can amplify and perpetuate the inflammatory response and it is evident that the cytokines and their activities are complex (Choy and Panayi 2001). There is also little doubt that rheumatoid factor amplifies the inflammation in RA (Kalsi and Isenberg 1993; Panayi 1994).

As evidence builds, it is clear that knowledge of the sequence of pathological events will allow instigation of the most effective treatment for RA as soon as possible after diagnosis has been made. The effects of early therapeutic intervention and adjustment of pharmacological therapies at various stages of the pathological disease process of RA, will affect how the disease manifests itself within the foot (Helliwell, Woodburn et al 2007). The mechanical destruction of the foot joints and progression of structural foot joint deformity once the disease is established is evidently understood (Helliwell, Woodburn et al 2007). What is less clear is how the soft tissues within the feet react to the changing course of the pathological fluctuations of the disease and whether those changes can affect mobility or predict poor function.

### 2.1.4. Synovitis

Inflammation of synovial cellular lining is thus established as an important manifestation of the disease mechanism of RA. There are many areas within the foot that have synovium and therefore are susceptible to the pathological processes described above. It is therefore essential to outline the appearance of normal synovium and then synovitis associated with joint destruction in order to discuss how foot structures may become destroyed as RA disease progresses.

*2.1.4.1. Normal synovium*

Tarner, Harle et al (2005) give a detailed histological account of normal synovium and analysis of the different stages of synovitis. The following is a summary of the authors' explanation of normal synovium:

Normal synovial membrane can be identified macroscopically as a connective tissue layer of approximately 0.5 – 5mm thickness and covers the inner surface of joints, tendon sheaths and bursae. Synovial lining does not consist of a single specialized cell type with intercellular junctions and there is no continuous basement membrane. It is composed of two major types of synoviocytes; macrophage like (type A) and fibroblast-like (type-B). In normal synovium, the surface of the lining layer is formed by interdigitating synovial fibroblasts and synovial macrophages that are less abundant than the synovial fibroblasts (Tarner, Harle et al 2005).

The synovium has a two-layer architecture, synovial lining and sub-lining, equivalent to the architecture of epithelium and endothelium. The synovial fluid is a plasma dialysate formed by diffusion through the synovial sub-lining and lining. The synovial sub-lining consists of soft, loose connective tissue based on a network of elastic fibres and different collagens. Within joints it has a soft, folded architecture that fills space between the articular surfaces facilitating smooth movement of the joints. The synovial sub-lining contains blood and lymph vessels, nerve fibres and numerous interspersed cells including macrophages, fibroblasts and adipocytes. An important physiological function of normal synovium is the nutrition of articular cartilage by production of synovial fluid (Tarner, Harle et al 2005).

Tarner, Harle et al (2005) suggest that the innervation of the synovium has recently become a particular focus of rheumatology research because of its potential role in modulating synovial inflammation.

*2.1.4.2. Inflamed synovium of joints in rheumatoid arthritis*

According to Panayi (1994), once activated, the immune response becomes organised in the perivascular areas of the synovial membrane, as the increase in the number of T cells leads to the proliferation and differentiation of B cells and to the production of antibodies within an expanding scaffold of new blood vessels and synovial-cell proliferation.

The leukocytes, new blood vessels and synoviocytes form an inflammation activated synovium, often termed pannus (**Figure 1**), which is the pathological hallmark of the disease (Edwards 1988; Scott, Shipley et al 1998; Tarner, Harle et al 2005).

**Figure 1.** Typical synovial joint affected by rheumatoid arthritis
(*from Brill, Eckes et al 2004*).
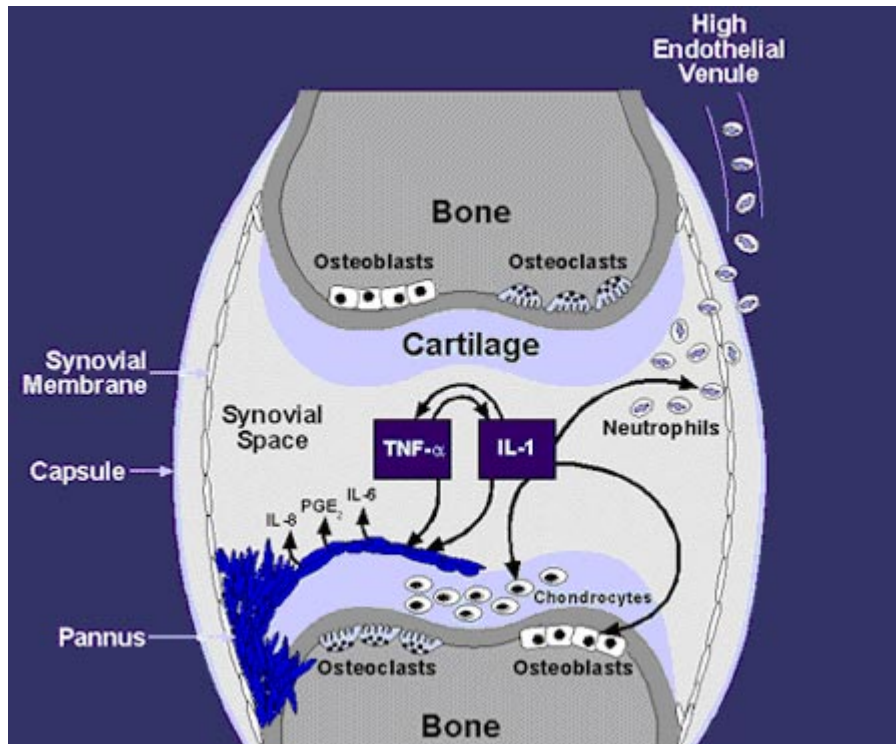


Panayi (1994) reports, on considerable evidence, that active attempts at healing are taking place within the rheumatoid synovium as new blood vessels are formed, leukocytes are recruited from the blood and there is proliferation of synoviocytes.

Tarner, Harle et al (2005) discuss the phenotype of synovium as being altered and developing into a thickened and invasively growing tissue that destroys the adjacent cartilage and bone. The resultant synovial thickening can be measured and may result in a depth of more than eight cells, although this may vary depending on the sampling method used (Youssef, Kraan et al 1998).

Although the pathogenesis of RA synovitis is described in stages (Panayi 1994), distinguishing the specific features of the different stages of RA has proven to be difficult (Tarner, Harle et al 2005). Examination of synovial tissue biopsies obtained by needle arthroscopy from patients with early (less than 1 year) and late (longer than 1 year) RA found significant histological differences (mean lining thickness of p= 0.040) between 'clinically active' (ie: swelling with joint effusion) and 'clinically inactive (ie: no joint effusion) synovitis, independent of disease duration (Baeten, Demetter et al 2000). These observations are consistent with other studies (Zvaifler, Boyle et al 1994; Tak et al 1997; Palosaari, Vuotila et al 2006).

Tarner, Harle et al (2005) conclude two reasons for this difficulty, the first being that inflammatory arthritis is a continuous process that develops at an individual pace, in individual structures, in individual patients. Secondly, that acute and early arthritis are terms defined by clinical observation of arthritis onset, while synovial cell activation and histologically defined synovitis may develop prior to clinical manifestation of disease and persist, despite remission of the clinical signs of inflammation. The question of when to classify this disease as being 'in remission' is interesting. In recent years, as technology has advanced, sub-clinical synovitis is consistently reported within imaging studies (Klarlund, Ostergaard et al 2000; Tan, Tanner et al 2003; Brown, Quinn et al 2006).

The differences observed, therefore, do not appear to depend primarily on disease duration but on disease activity at a given point in time during the course of the disease (Tarner, Harle et al 2005; Tak et al 1997; Palosaari, Vuotila et al 2006). RA synovium exhibits varying histology and, as Kirwan (2004) suggests, the different histological abnormalities may relate to the subsequent progression or non-progression of disease activity in different ways.

The relationship between synovitis and joint damage (conventionally described by radiographic erosions) remains controversial (Panayi 1994; Pullar 1997; Gordon, Jones et al 1997). Current opinion is split between authors who claim a direct link between synovitis and joint damage (Conaghan, O'Connor et al 2003; Tan, Tanner et al 2003) and those who suggest these are uncoupled processes (Kirwan 2004). The concept of two or more pathologies involved in RA stems from radiographic observations that erosions progress despite suppression of synovitis (Mulherin, Fitzgerald et al 1996; Kirwan 1997; Kirwan 2004) whilst studies utilising MRI suggest that bony changes in RA are secondary to

synovitis (McGonagle and Conaghan 1999; Conaghan, O'Connor et al 2003; Tan, Tanner et al 2003). Further evidence using MSUS supports the theory of joint synovitis remaining active as sub-clinical disease even after patients have been confirmed as being in 'clinical remission' (Brown, Quinn et al 2006; Tan, Tanner et al 2003).

Therefore, synovitis within the foot joints is potentially a dynamic and progressive process that may not be clinically measurable. In addition, usually, within the foot in longitudinal studies, it is MTP joint synovitis or tenosynovitis that has been linked to metatarsalgia in patients with RA (Welsing, van Gestel et al 2001; Ødegard, Landewe et al 2006; van der Heijde, Landewe et al 20087; van der Leeden, Steultjens et al 2008). However, anatomical bursae have synovium and synovial lining (Warwick, Williams et al 1973) that may also be susceptible to the pathological processes of RA described above. This becomes important in considering the clinical implications of forefoot bursae, as well as MTP joint synovitis and tenosynovitis in causing metatarsalgia and consequent foot disability in patients with RA.

## 2.2. The role of bursae within the RA foot

Bursae are documented within traditional anatomy texts as closed pouches of fluid that facilitate movement between adjacent structures that are under conditions of pressure (Warwick, Williams et al (1973). The synovial lining of some bursae types resembles that of joints and tendon sheaths and therefore may be susceptible to synovial inflammation as associated with RA (Palmer 1995; O'Brien, Hart et al 1997; Narvaez, Narvaez et al 2002). Bursae within the forefoot appear particularly apparent in RA (Koski 1998) however there is a lack of specific anatomical definition of these bursae. This section describes the anatomy and histology of bursae that occur within the forefoot and discusses this differing presentation within the literature. The potential role of bursae in the progression of forefoot deformity in RA is highlighted and the application to clinical management of metatarsalgia is discussed.

### 2.2.1. Classification of bursae
Bursae are often not sub-classified, however the terminology of all bursae as 'sacs' of fluid may be misleading as specification of the anatomy and histology of bursae appears to differ between texts. For example, Saladin (2004) describes all bursae as fibrous sacs filled with

synovial fluid. Warwick, Williams et al (1973) conversely describe the existence of two main types of bursa, anatomical bursae and adventitious bursae. In a review of the anatomy of bursae of the foot, Hernandez, Hernandez and Hernandez (1991) convey bursae as being classified according to type (anatomical or adventitious), location, or nature (pathological or non pathological). They suggest that differentiating bursae in this way allows more specific diagnosis of foot symptoms, thus facilitating better targeted treatment aiming to relieve pressure mechanically and / or managing inflammation locally or systemically (Hernandez, Hernandez and Hernandez 1991). Interestingly, the latter authors only report on surgical or cadaveric investigations and do not suggest how differentiation of forefoot bursae may be achieved clinically to facilitate better treatment outcomes (Hernandez, Hernandez and Hernandez 1991).

### 2.2.1.1. Anatomical bursae

According to Warwick, Williams et al (1973), anatomical bursae are also known as synovial bursae. Not all bursae are however filled with synovial fluid which appears to present opportunities for confusion of their classification within the forefoot which is discussed in more depth in the later section on adventitious bursae.

Warwick, Williams et al (1973), define anatomical bursae as naturally occurring bursae that develop during intrauterine life and contain a capillary film of synovial fluid that acts as a lubricant providing the cells of their synovial membrane with a wet environment on their free surfaces. This is described as a metabolic process that allows anatomical bursae to act as an intermediary between other anatomical structures and their surroundings (Warwick, Williams et al 1973). Arguably, the synovium of anatomical bursae therefore may be susceptible to the pathological processes of RA (Palmer 1995; O'Brien, Hart et al 1997; Narvaez, Narvaez et al 2002).

To compound the confusion over specifically diagnosing bursae pathology, anatomical bursae may occur in many sites throughout the human body and appear to vary widely in their presentation (McCance and Huether 2002). Anatomists have therefore attempted to address this by defining anatomical bursae via their location.

Warwick, Williams et al (1973) classify anatomical bursae as:

- Subtendinous: occuring between tendons and bone, tendons and ligaments, or between one tendon and another;
- Submuscular: occuring between muscle and bone, tendon or ligament;
- Subfascial: separating aponeurotic areas from bone;
- Interligamentous

However, Hernandez, Hernandez and Hernandez (1991) use slightly differing terminology and classify anatomical bursae via location as being subfascial, subcutaneous, intertendinous or interligamentous. They also classify subfascial anatomical bursae into two groups. Group I are said to be located between the origin or insertion of a tendon and bone. Group II are said to be located deep to tendon or muscle that crosses a bony prominence, between tendons and ligaments, or between tendons and muscles that glide over each other or run in close proximity to each other (Hernandez, Hernandez and Hernandez 1991).

Bursae located around the knee joint are a typical illustration of the variation in anatomical bursae presentation (Meenagh et al 2006). For example, the prepatellar bursa lies superficial to the patella and appears as a flattened sac of synovial membrane supported by dense irregular connective tissue and interposed between skin and bone in the superficial fascia. Whereas the suprapatellar bursa is located deep to the quadriceps tendon and is in direct communication with the knee joint (Warwick, Williams et al 1973; Meenagh et al 2006). Similarly, the largest para-articular anatomical bursa of the hip region, the iliopsoas bursa, exhibits a flattened collapsed appearance in its non-pathological state (Bianchi et al 2002).

Within the foot, the anatomical retro-calcaneal bursa, situated over the posterior-superior prominence of the calcaneus under the tendo-achilles contains a small amount of fluid rich in hyaluronate (Canoso et al 1988). Interestingly, Canoso et al (1988) also found that in healthy individuals the retrocaclcaneal bursa allows an extension of the fat pad to enter it during plantarflexion of the foot. In a cadaveric study, Theumann, Pfirrmann et al (2001) described the specifics of the anatomical intermetatarsal bursae in greater detail. Histopathologic analysis of the anatomical bursae between the metatarsal heads showed their appearance to be a space with an extremely attenuated cell lining on both sides and elongated, flattened nuclei that were subtended by a vascular connective tissue layer (see **Figure 2**) (Theumann, Pfirrmann et al (2001).

20

**Figure 2.** Histopathologic image of an anatomical bursa obtained between the metatarsal heads at the level of the phalangeal bases beyond the deep transverse metatarsal ligament. (From Theumann, Pfirrmann et al 2001).



The anatomical bursa is depicted by the straight black arrow and the attenuated cell lining is shown on both sides, with elongated flattened nuclei by the white arrow heads.

On magnetic resonance imaging, the anatomical intermetatarsal bursae appear oval or ellipsoid (see **Figure 3**) (Theumann, Pfirrmann et al 2001), although it appears that the sites and sizes of the intermetatarsal bursa may vary depending on the degree of metatarsal separation (Bossley and Cairney 1980; Claustre, Bonnel et al 1983; Chauveaux, Le Huec and Midy 1987; Theumann, Pfirrmann et al 2001).

**Figure 3.** Coronal fat-saturated T1-weighted spin-echo (500/12) magnetic resonance image of the anatomical intermetatarsal bursa obtained at the level of the phalangeal bases beyond the deep transverse metatarsal ligament (from Theumann, Pfirrmann et al 2001).
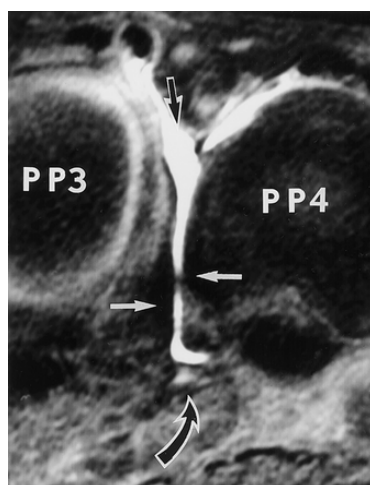


The anatomical intermetatarsal bursa (straight black arrow) lies between both interosseous tendons (white arrows) and the proximal phalanges of the third (PP3) and fourth (PP4) rays close to the neurovascular bundle (curved black arrow).

*2.2.1.2. Adventitious bursae*

Adventitious bursae receive less attention in the literature than anatomical bursae and are therefore less well understood. They are said to occur within the subcutaneous tissues and have no synovial lining (Hernandez, Hernandez and Hernandez 1991) suggesting that Saladin (2004) is therefore incorrect in his definition of bursae. Adventitious bursae are reported to be acquired as a result of friction related to abnormal movement, which leads to separation of collagen fibres resulting in a localized collection of fluid between them (Hernandez, Hernandez and Hernandez 1991).

The development of adventitious bursae is thus a consequence of mechanical trauma to provide the skin with more freedom of movement and they are not considered present before birth, being more common in adulthood (Warwick, Williams et al 1973). Warwick, Williams et al (1973) suggest that adventitious bursae are generally located in areas where the skin is subjected to repetitive shearing such as the forearm or elbow in writing or the buttock in certain sedentary occupations. Within the foot, the plantar forefoot fat pad area seems particularly susceptible to the development of adventitious bursae (Studler, Mengiardi, et al 2008).

Adventitious bursae have been described as multilocular, whilst anatomical bursae are unilocular (Hernandez, Hernandez and Hernandez 1991). However, the major differentiating factor between anatomical and adventitious bursae is in the histological appearance. Studler, Mengiardi et al (2008) compared magnetic resonance images of adventitious bursae within the forefoot in healthy subjects to histological appearance of cadaveric feet and symptomatic patients. They described the histological analysis of the adventitious bursae as always lacking an epithelial lining, but being 'slit-like' cavities within collagen sheets that contained areas of fibrosis tissue (see **Figure 4**) (Studler, Mengiardi et al 2008). On magnetic resonance imaging these bursae could be seen as alterations in the signal intensity of the plantar fat pad (**Figure 5**) (Studler, Mengiardi et al 2008).

**Figure 4.** Histopathologic image of an adventitious bursa in a cadaveric foot (from Studler, Mengiardi et al 2008).



The specimen reveals fibrosis (arrowheads) and a slitlike cavity within collagen sheets (arrow).
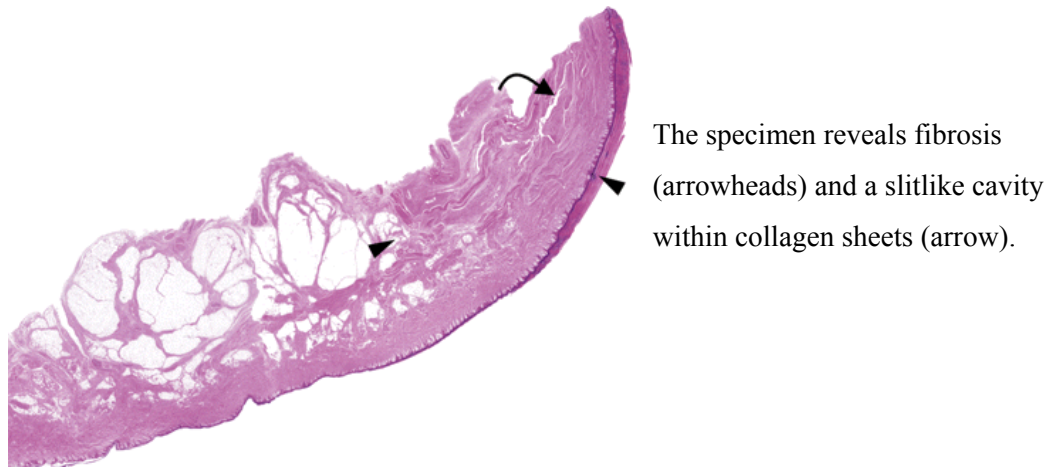
**Figure 5.** Coronal T1-weighted magnetic resonance image (470/20) of plantar fat pad signal intensity alterations in right cadaveric forefoot (from Studler, Mengiardi et al 2008).



The image shows fat pad signal intensity alterations (arrows) with blurred margins under first metatarsal head.
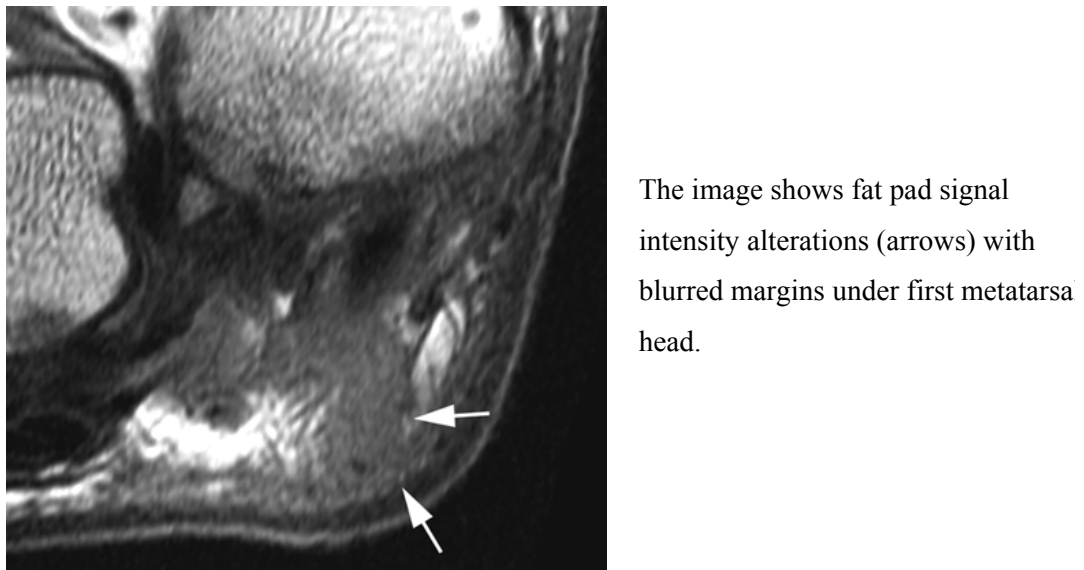
### 2.2.1.3. Pathological and non-pathological bursae

Rarely reported in anatomical texts, Hernandez, Hernandez and Hernandez (1991) cite a description of pathological bursae by Jahss (1982) as bursae that may be either anatomical or adventitious, which have become thick-walled and distended from chronic pressure,

inflammation or infection. They do not explain how to distinguish pathological anatomical or adventitious bursae but do state that all pathological bursae are smooth to palpate clinically, uniloculular, benign, distended, deeply fixed, and not usually tender (Hernandez, Hernandez and Hernandez 1991).

In their review of bursae within the foot, Hernandez, Hernandez and Hernandez (1991) also attempt to distinguish the variance in presentation of bursae within the foot by further classifying pathologic bursae as inflammatory, non inflammatory, suppurative and calcified or ossified. They then go on to further subdivide non-inflammatory bursae into pressure-induced, traumatic or spontaneous (Hernandez, Hernandez and Hernandez 1991).

The classification of bursae as pathological and non-pathological seems predominantly relevant to the forefoot however it also appears contradictary to the seminal 'Grays Anatomy' text definition presented by Warwick, Williams et al (1973) earlier in this section. This may explain why there appears to be confusion and a lack of detail in the literature over the description of the clinical appearance and clinical management of bursae within the forefoot. Discussion of the occurrence and presentation of bursae within the forefoot therefore warrants further attention.


### 2.2.3. Forefoot Bursae

The foot is a complex structure and there are many anatomical texts that describe the anatomy well (Warwick, Williams et al 1973; Sarrafian 1983; Romanes 1986). As discussed above, Hernandez, Hernandez and Hernandez (1991) report on cadaveric studies that have identified numerous small bursae throughout the foot that have differing presentation and histology. Within the forefoot, in healthy subjects, pathological pressure-induced bursae are reported to be the most common form (Hernandez, Hernandez and Hernandez 1991). These typically overlay bunion deformities, tailor's bunions, hammer toes, underlie plantarflexed metatarsals and overlay dorsal exostoses (Hernandez, Hernandez and Hernandez 1991). However, adventitious bursae within the plantar fat pad are commonly seen (Studler, Mengiardi et al 2008) particularly in RA (Helliwell et al 2007).

Hernandez, Hernandez and Hernandez (1991) describe the pathogenesis of adventitious bursae as an initial protective mechanism that causes increases in fibrosis and thickening of

the bursa walls via altered mechanical stress and friction forces within the tissues. A cycle of intermittent pain and inflammation that may lead to eventual chronic inflammation and constant pain can thus be created with further sequelae including localised necrosis with ulceration and possible sinus tract and fistula formation (Hernandez, Hernandez and Hernandez 1991). Helliwell et al (2007) similarly relate the development of adventitious bursae within the forefoot in RA to compressive and shearing forces acting on the skin sites of high pressure, for example, the MTP joints, although, in contrast to the study by Studler, Mengiardi et al (2008), they describe the bursae as forming in areas where the plantar fat pad has been displaced.

Whilst the focus has been towards the treatment and management of adventitious bursae within the forefoot, little has been directed towards the anatomical intermetatarsal bursae. It is possible that in patients with RA reported metatarsalgia could be related to enlarged bursae that are either adventitious or anatomical. Due to the similarities in the histology between anatomical intermetatarsal bursae and synovial tissue these may be a more probable cause of clinical symptoms of metatarsalgia in RA (Awerbuch, Shephard et al 1982; Koski 1998) than adventitious bursae.

Anatomical intermetatarsal bursae may also be more relevant in the cause of metatarsalgia due to their close anatomical association with the intermetatarsal neurovascular bundles. The intermetatarsal spaces are complex, being divided into inferior and superior levels that are separated by the deep transverse metatarsal ligament (Chauveaux, Le Huec and Midy 1987).

In the superior space, tendinous and ligamentous structures lay close together and in the inferior space, the lumbrical muscles lay adjacent to the neurovascular bundle (Theumann, Pfirrmann et al 2001). Anatomical intermetatarsal bursae are described as being located between two metatarsal heads, above the deep transverse metatarsal ligament (Bossley and Cairney 1980; Claustre, Bonnel et al 1983) and between the interosseous tendons in the superior level (Awerbuch, Shephard et al 1982). They are clearly depicted in cadaveric specimens as being intimately related with the neurovascular bundles (Theumann, Pfirrmann et al 2001, see **Figure 6**) and present in each of the four intermetatarsal spaces (Chauveaux, Le Huec and Midy 1987).

**Figure 6.** Line drawing of a coronal view of the forefoot at the level of the metatarsal heads (from Theumann, Pfirrmann et al 2001).
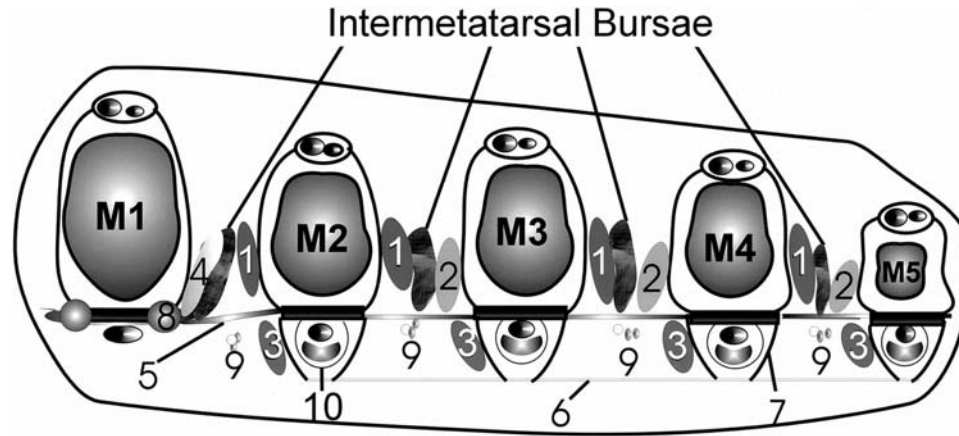


**Key:** 1 = dorsal interosseous tendons, 2 = plantar interosseous tendons, 3 = lumbrical muscles, 4 = adductor hallucis tendon, 5 = deep transverse metatarsal ligament, 6 = superficial transverse metatarsal ligament, 7 = perforating fibres, 8 = lateral sesamoid bone, 9 = neurovascular bundles, 10 = flexor digitorum longus tendons. Metatarsal heads 1-5 (M1-M5) are depicted.

In 25 cadaver dissections of healthy feet, Chauveaux, Le Huec and Midy (1987) demonstrated the presence of a bursa in the second and third spaces in every case, in the fourth space in 21 cases and 15 in the first space. They reported averages of the measurements of the bursae in the intermetatarsal spaces to be 2.3 to 3cm in anterior-posterior length for the second and third spaces and 2cm for the first and fourth spaces (Chauveaux, Le Huec and Midy 1987). In a later cadaveric study, the first intermetatarsal bursa is also described as having a unique anatomical shape as it was orientated along the adductor hallucis tendon like a tendon sheath (Theumann, Pfirrmann et al. 2001). In the second and third spaces, the bursa overlapped in front of the anterior aspect of the deep transverse metatarsal ligament, extending distally by about one centimetre to reach the lateral margin of the base of the proximal phalanx (see **Figure 7**) (Chauveaux, Le Huec and Midy 1987). The opposite was true in the fourth space where the bursa was clearly behind the posterior margin of the transverse ligament (Chauveaux, Le Huec and Midy 1987).

**Figure 7.** Anatomic section of the plantar forefoot depicting the intermetatarsal bursa of the 2$^{nd}$ and 3$^{rd}$ space. A schematic line drawing and B cadaveric plantar dissected approach (from Chaveaux et al 1987).
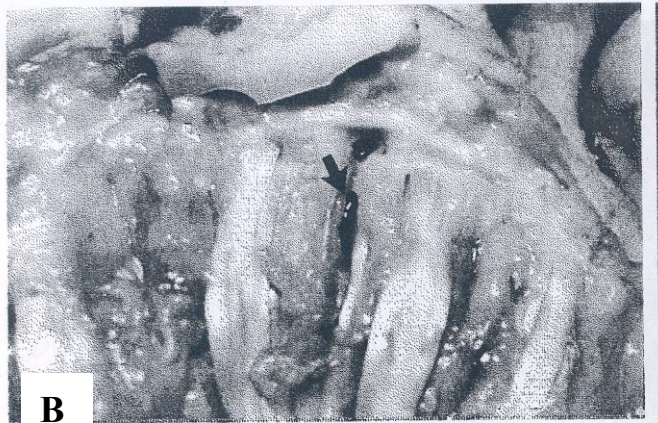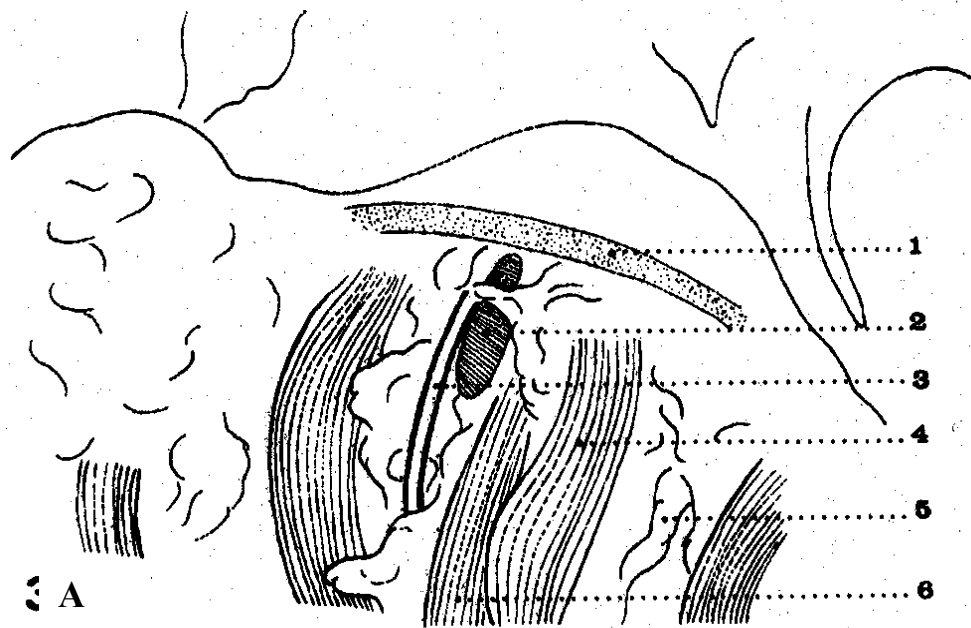


Key: 1=plantar interdigital ligament; 2 = supra-transverse intermetatarsacapital bursa; 3 = plantar digital nerve; 4 = tendon of flexor digitorum brevis; 5 = cellulo-adipose tissue; 6=tendon of flexor digitorum longus;

### 2.2.4. Forefoot bursitis

Bursitis, like synovitis, is particularly relevant in RA and often clinically dominant in early disease and with RA disease progression (O'Brien, Hart et al 1997; Grassi and Cervini 1998, Narvaez, Narvaez et al 2002; Scheel, Schmidt et al 2005). Patients with RA frequently present with a throbbing pain under the metatarsal head that usually persists at rest and is exacerbated when the area is first loaded (Woodburn and West 1999). Inferred links are made between the formation of adventitious bursae under the metatarsal head region in consequent areas of assumed torsional tissue stress and altered mechanical forces of foot function during gait in patients with RA (Woodburn and West 1999; Boutry, Larde et al 2003; Helliwell et al 2007).

Anatomical, intermetatarsal bursae, however, are less well discussed relative to the abnormal mechanical processes of RA. Mechanically, the anatomical intermetatarsal bursae have been suggested to be important in their role as shock absorbers as they facilitate the metatarsal heads to glide in a dorso-plantarly direction enabling the forefoot to adapt to irregularities of the ground surfaces, particularly during gait (Bossley and Cairney 1980; Awerbuch, Shephard et al 1982; Claustre, Bonnel et al 1983; Chauveaux, Le Huec and Midy 1987; Theumann, Pfirrmann et al 2001). Bursitis in the forefoot therefore may involve the anatomical intermetatarsal bursae or adventitious bursae within the fat pad beneath the metatarsal heads (Hernandez, Hernandez et al 1991; Ashman, Klecker et al 2001; Studlker et al 2008).

In healthy subjects, normal movement and stability of the forefoot at the level of the metatarsal heads are dependent upon stable metatarsals and good mobility of the MTP and interphalangeal (IP) joints (Donatelli and Wolf 1990). During gait the forefoot, via the metatarsal heads, tolerates up to 28% of the vertical forces of weightbearing (Bus, Maas et al 2004). Abnormal mechanical foot function related to pronation and supination within the joints of the foot and ankle, however, can cause hypermobility and hypomobility of the forefoot (Donatelli and Wolf 1990). Abnormal hindfoot pronation in particular may cause the metatarsals to rotate in a valgus direction, disrupting the architecture of the intermetatarsal spaces and triggering torsional stresses within the plantar fat pad of the forefoot (Donatelli and Wolf 1990). It is hypothesised that the torsional stresses within the fat pad may result in adventitious bursae formation (Studler, Mengiardi et al 2008). As the spaces become crushed between the metatarsal heads, the classic 'burning pain' of the forefoot may be linked linked to irritation and inflammation of the intermetatarsal bursae (Bossley and Cairney 1980;

Zanetti, Strehle et al 1997; Iagnocco, Coari et al 2001).

In contrast to adventitious bursitis (Studler, Mengiardi et al 2008), anatomical intermetatarsal bursitis reportedly has a low prevalence within healthy populations (Chauveaux, Le Huec and Midy 1987; Zanetti, Strehle et al 1997; Iagnocco, Coari et al 2001). The pathogenesis of anatomical intermetatarsal bursitis without underlying systemic disease remains unclear. Within RA, the process of intermetatarsal bursitis is complicated by the pathological invasion and destruction of synovial structures and the mechanical influences of forefoot loading during gait. The synovium of intermetatarsal bursae are susceptible to the pathological processes of RA in the same way as the synovium of joints and tendon sheaths (detailed in section 2.1.3, page 12). As RA disease progresses, the synovium of bursae become distended and thickened (O'Connor & Grainger 2002). Confirmed surgically, the intermetatarsal bursae reportedly hypertrophy in RA and gradually extend beyond their normal site towards the dorsal or plantar region of the foot (Claustre, Bonnel et al 1983). Consequently, when intermetatarsal bursae become hypertrophied and increased in size, they may compress the plantar digital nerves, resulting in the sensation of 'burning pain' similar to that of a Morton's neuroma (Bossley and Cairney 1980; Chauveaux, Le Huec and Midy 1987; Theumann, Pfirrmann et al 2001).

Loss of function of the anatomical intermetatarsal bursae within RA has received little attention in the conceptual thoughts of mechanical dysfunction of the foot. Explanations for the mechanical influences of synovitis in the foot joints and tenosynovitis in the forefoot tendons in RA are usually the focus of foot investigations. Foot deformities and anomalous concentrated foot pressures due to abnormal pronation are reported as being related to the combined effects of repeated episodes of synovitis, weakening of the joints and eventual destruction of the integrity of the feet in RA (Woodburn, Helliwell et al 2002; Turner, Helliwell et al 2006). It is possible that early inflammatory changes due to RA in the anatomical intermetatarsal bursae may contribute significantly to the mechanical disruption of the forefoot. Changes in soft tissue volume distribution through the forefoot during loading have been described (Weijers, Walenkamp et al 2003) and surgical studies have highlighted that as the anatomical intermetatarsal bursae become hypertrophic in RA they gradually extend beyond their normal site towards the dorsal or plantar region of the foot (Claustre, Bonnel et al 1983).

Most of the literature to date on forefoot bursae and bursitis has been presented via cadaveric and / or surgical investigation. What remains unclear is how the different presentations of bursitis within the forefoot may be clinically diagnosed, especially if the findings by Koski (1998) that intermetatarsal bursitis may be one of the first features of RA but is often missed by clinical examination are to be accepted. Furthermore, in cadaver or surgical studies, unless chronically inflamed (see **Figure 8**), both adventitious and anatomical intermetatarsal bursae are said to be easily ruptured, the latter due to a transparent membrane that is difficult to isolate from the adipose tissue (Chauveaux, Le Huec and Midy 1987). This may explain why forefoot bursitis in RA is under-reported in clinical studies.

**Figure 8.** Large chronic forefoot bursal swellings (white arrows) in a patient with severe rheumatoid arthritis undergoing extensive forefoot surgery
(reproduced with kind permission from Michael Backhouse 2006).
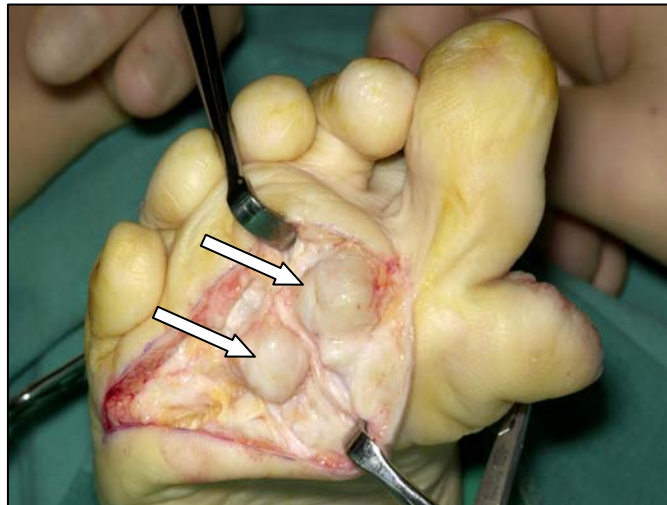


As technology has advanced, MSUS has been used to identify a high prevalence of intermetatarsal bursitis within patients with early RA that were not clinically apparent (Koski et al 1998). If non-invasive clinical palpation of the plantar metatarsal area is relatively insensitive for bursitis in early RA disease it is likely that diagnosis of foot symptoms may be delayed (Koski 1998). In late stage foot RA disease bursitis is usually described as a fluctuant palpable swelling (Helliwell, Woodburn et al 2007), (see **Figure 9**).

**Figure 9.** Photographs representing the foot in early stages of RA (A), established stages of RA (B) and advanced stages of RA (C) according to the classification by Helliwell, Woodburn et al (2007).



Palpable swelling indicative of bursitis can be seen in the region of the second and third MTP joints (C, white arrow heads).

Investigators have therefore proposed that intermetatarsal bursitis is often an undiagnosed cause of foot symptoms in these patients (Koski et al 1998; Olivieri, Scarano et al 2004). The evidence for this, however, remains limited. Both studies used small samples and the methodologies for specifying the identified structures as anatomical intermetatarsal bursitis, as opposed to adventitious bursitis, were not apparent.

It is possible that chronic adventitious bursae may appear the same on MSUS as anatomical bursae and that location becomes the only defining feature that characterises bursa in the clinical environment. MRI studies give better detail regarding the anatomical region of the

formation of chronically inflamed bursae within the forefoot, although without histological analysis confirmation of the bursal type remains speculative (Ashman, Klecker and Yu 2001; Helliwell et al 2007; Studler, Mengiardi et al 2008). Compare **Figure 10** and **Figure 11**.

**Figure 10.** Coronal T1-weighted magnetic resonance image of an adventitious bursa under the first metatarsal head in a symptomatic patient (from Studler, Mengiardi et al 2008).
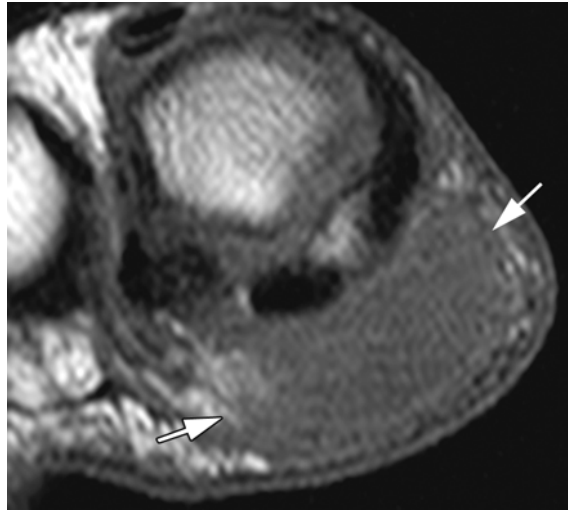


The image shows a signal intensity alteration (white arrows) with indistinct margins in plantar fat pad beneath first metatarsal head of right forefoot.

**Figure 11.** Transverse forefoot T1 weighted fat suppressed post iv gadolinium enhanced MR image of intermetatarsal bursitis in the third intermetatarsal space (from Helliwell et al 2007).
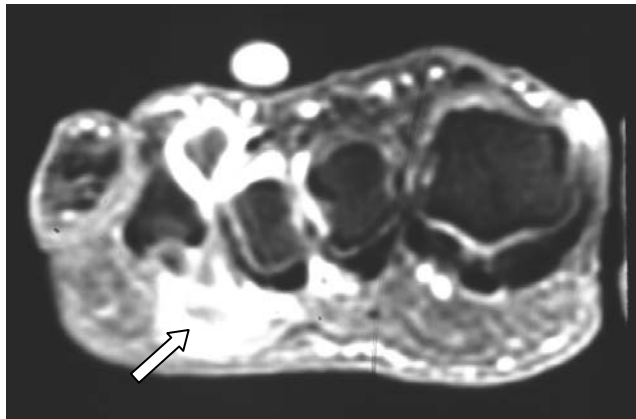


The image shows a pathological proven rheumatoid nodule formation within the intermetatarsal bursa (white arrow).

## *2.2.5. Relevance and differential diagnosis of forefoot bursitis*

Specific diagnosis of forefoot symptoms due to bursitis may thus be important in RA. Differentiating pain in the forefoot due to synovitis or tenosynovitis, from pain due to bursitis (either anatomical or adventitious), however, poses a problem clinically if the aim of treatment is more targeted, anatomically site-specific, therapeutic intervention. Diagnosing forefoot bursitis clinically is difficult, as many disorders may give rise to discomfort in the metatarsal region of the forefoot (Ashman, Klecker et al 2001; Bancroft, Peterson and Kransdorf 2008). Using MRI in a heterogenous population, Bancroft, Peterson and Kransdorf (2008) identify the following soft tissue pathologies that may occur:

- Cystic Tumor–Like Lesions
- Ganglia
- Synovial cysts
- Adventitious bursa
- Noncystic Tumor–Like Lesions
- Morton's neuroma
- Rheumatoid nodules
- Callus
- Synovial-Based Processes
- Synovial chondromatosis
- Pigmented villonodular synovitis
- Gout
- Plantar Fibromatosis
- Giant Cell Tumor of Tendon Sheath
- Lipoma
- Soft Tissue Chondroma
- Synovial Sarcoma
- Undifferentiated Pleomorphic Sarcoma
- Leiomyosarcoma

Notably within their list adventitious bursa is mentioned but not anatomical, intermetatarsal bursa (Bancroft, Peterson and Kransdorf 2008). In particular, reviews of foot pathology in RA often omit bursae and describe soft tissue complications such as MTP joint synovitis, synovial cysts (or herniation of the synovial membrane through the joint capsule), tenosynovitis or rheumatoid nodules as affecting the forefoot (Kerry, Holt et al 1994; Michelson, Easley et al 1994; Weiner-Ogilvie 1999).

Investigations of Morton's neuromas are often linked to anatomical intermetatarsal bursitis and both pathologies are considered to be related to abnormal mechanics or tight footwear in

otherwise healthy individuals (Awerbuch, Shephard et al 1982; Chauveaux, Le Huec and Midy 1987; Zanetti, Strehle et al 1997; Iagnocco, Coari et al 2001; Theumann, Pfirrmann et al 2001; Luukkainen 2009) as well as in patients with RA (Awerbuch, Shephard and Vernon-Roberts 1982). Interestingly, histopathological analysis of intermetatarsal spaces in ten patients from a sample of twenty who had been investigated surgically for Morton's neuroma revealed hypertrophy of synovium of the intermetatarsal bursae consistent with RA changes (Awerbuch, Shephard and Vernon-Roberts 1982). Of those ten patients, two already were known to have RA; three had no evidence at the time of surgery, but developed seropositive RA within four years following the surgery; one patient was seropositive but with no other evidence of RA and four patients had no serological or clinical features of RA at the time of the study (Awerbuch, Shephard and Vernon-Roberts 1982).

**Table 2.** The stages of foot disease in RA (Helliwell, Woodburn et al 2007).

| Disease stage | Clinical picture |
|---|---|
| Early Foot Disease | • Joint pain and stiffness in the foot and ankle<br>• Pain under the MTPJs<br>• Patients describe a sensation of 'walking on pebbles'<br>• Positive metatarsal squeeze test |
| Established Foot Disease | • Plastic changes<br>• Tibialis posterior tendon dysfunction<br>• Secondary features develop such as areas of raised plantar pressure or digital deformity<br>• Formation of secondary lesions such as corns or callus<br>• Complications may manifest: vasculitis, ulceration and neuropathy. |
| Advanced Foot Disease | • Mechanical instability exacerbates inflammatory processes<br>• Subtalar and midtarsal joint subluxation<br>• Planovalgus foot posture<br>• Marked forefoot deformity |

In their account of the epidemiology of foot disease, Helliwell, Woodburn et al (2007) specify a positive metatarsal squeeze test in early stage RA (refer to **Table 2**) although highlight that it is often difficult to distinguish between swelling due to joint effusion, synovitis or inflammation of periarticular structures. Forefoot bursitis, depending on the stage of the disease however, is a significant omission from the classification, further highlighting the lack of evidence on this feature.

In summary, the terminology of forefoot bursitis within the literature is confusing although bursae appear to be an important feature of the forefoot in RA. MRI appears to give good detail on the differential diagnosis of bursitis from other soft tissue pathologies that may occur within the forefoot. MRI may also give good detail on the location of bursitis. MSUS is promising in detecting location of bursae and appears to show a higher prevalence of forefoot bursitis in patients with RA than in healthy populations. Differentiating adventitious bursae formation from anatomical bursae formation however is difficult unless confirmed by histology. For these reasons it is possible that without appropriate investigative techniques, forefoot bursitis in RA is under-reported or mis-represented in clinical studies and therefore treatment may be delayed or be inappropriate. For example, if forefoot bursitis is related to the disease process of RA then treatment may be aimed at managing the disease, in contrast, if forefoot bursitis forms as a response to instability of the forefoot, treatment should be directed towards stabilising the forefoot.

In addition, in the absence of longitudinal data, the relationship between forefoot bursitis, poor clinical symptoms and foot disability remains speculative. This becomes important in considering the clinical implications of forefoot bursitis in causing metatarsalgia and consequent foot disability. Usually, in longitudinal studies, it is MTP joint synovitis or tenosynovitis that has been linked to metatarsalgia in patients with RA (Welsing, van Gestel et al 2001; Ødegard, Landewe et al 2006; van der Heijde, Landewe et al 20087; van der Leeden, Steultjens et al 2008). If, however, forefoot bursitis may be a manifestation of RA disease, it seems essential to clearly define the prevalence of this in a large population of patients with RA and to determine if it does change over time.

**2.3. Evaluation of the effects of rheumatoid arthritis on the foot**

To be effective in improving clinical outcomes, investigation and treatment of patients should be evidence based. Implicit in this is the need for an awareness of the presence, nature and extent of disease. Within this section, the literature is reviewed according to how the effects of disease in the foot and subsequent podiatric interventions are currently evaluated.

*2.3.1. Assessment of rheumatoid arthritis disease within the foot*

Study of the effects of disease in individuals with RA is complicated due to its fluctuating nature. Most people with RA may not be in a steady state and disease progress may vary greatly from one individual to another. The challenge for investigators is, therefore, in the measurement of predictive disease factors and interventional changes (Fortin, Stucki & Katz 1995) and many measures to assess disease process and effects of care in RA have been developed.

Benchmarks for longitudinal and observational studies in rheumatology include measures of impairment, disability and handicap (Helliwell, Woodburn et al 2007) (see **Table 3**). In order to facilitate the use of these in both clinical and research practices a core set of domains, that include measures of health status, disease process, damage, toxicity or adverse reactions, mortality, work disability and costs, has been suggested through the OMERACT (Outcome Measures in RA Clinical Trials) conferences (Molenaar, van der Heijde and Boers 2000). Unfortunately, within the field of podiatry no specific standard exists and the measurement of disease state of the foot due to RA remains limited (van der Leeden, Steultjens et al 2008).

When measuring RA disease activity in clinical studies, self-administered arthritis specific functional instruments such as the Health Assessment Questionnaire (Fries, Spitz et al 1980) and the Arthritis Impact Measurement Scale (Meenan, Mason et al 1984) are valid, reliable and have excellent correlation with long term outcomes. Unfortunately, these standard instruments have been criticised as they do not specifically or comprehensively measure symptoms directly attributable to RA foot disease (Saag, Saltzman et al 1996).

A review, detailing the instruments that have been used to specifically measure foot function, foot pain and foot-related disability in patients with RA, has recently been published (van der Leeden, Steultjens et al 2008). This review identified measurement instruments that have

been used within the published literature and investigated them for reliability, consistency and validity, however the authors concluded with concerns on the quality of many of these measures (van der Leeden, Steultjens et al 2008). Mostly the focus of outcome measures is on assessment of foot structure and gait mechanics and only recently has the assessment of foot related pain, disability and function been included in some studies (van der Leeden, Steultjens et al 2008).

**Table 3.** Examples of outcome measures for the foot
(adapted from Helliwell, Woodburn et al 2007).

| Outcome Measure | Instrument |
|---|---|
| Performance measure | Walking distances & times; grip strength |
| Measures of physical signs | DAS28; No of swollen joints; No of tender joints; Ritchie articular index, duration of morning stiffness, fatigue |
| Measures of symptoms | Pain – VAS, 5 point Likert scale; Mc Gill Questionaire |
| Functional status | The Stanford Health Assessment Questionnaire (HAQ); The Steinbrocker scale |
| Health status and Quality of Life (QoL) | SF-36; EuroQol; EQ-5D; Sickness Impact Profile |
| Disease Specific measures of health status and quality of life (QoL) | The Arthritis Impact Measurement Scale (AIMS); the Rheumatoid Arthrtitis-specific Quality of Life Instrument (RAQoL) |
| Laboratory measures | ESR, CRP, Rh Factor |
| Radiological assessments | Sharp index, Larsen index, Steinbroker, |

### 2.3.2. Assessment of foot structure and mechanics

Traditional podiatric assessment methods tend to focus on skeletal structure and biomechanical stresses on foot function.  These have been the cornerstone of practice for the past twenty years but have more recently been challenged as lacking in reliability (Weiner-Ogilvie & Rome 1998; Evans, Copper et al 2003) or not sufficiently validated (Wrobel 2000, Parker, Nester et al 2002). For assessment of the foot in RA, Helliwell, Woodburn et al

(2007) recommend the 'look, feel and move' principles based on the GALS (gait, arms, legs and spine) screening tool, although this has yet to be adopted within routine podiatry practice and remains a subjective exercise for research trials.

Weiner-Ogilvie (1999) concluded, in a review of foot involvement in RA, that no unified method was used to measure foot involvement in RA. Later, in a systematic review of podiatric interventions for the RA foot, the same conclusions were made (Bowen, Burridge and Arden 2005) although some main themes of outcome measures were collated as gait assessment, measurement of plantar foot pressures, pain measurement, assessment of physical function, and treatment tolerance (see **Table 4**).

Foot pressure measurement appeared to be the most common mode of outcome measure in determining the effectiveness of clinical interventions such as foot orthoses and callus debridement for patients with RA (Bowen, Burridge and Arden 2005). This may be because the equipment required for plantar foot pressure measurement is readily available, relatively easy to use and potentially clinically informative regarding foot orthotic interventions (Woodburn and Helliwell 1996; Otter, Bowen et al 2004; Tuna, Birtane et al 2005;  van der Leeden, Steultjens et al 2006; Turner, Helliwell et al 2006; Semple, Turner et al 2007).

More recently, evidence linking radiological erosion scores and joint damage on radiographs to increased plantar forefoot pressures has been found (Davys, Turner et al 2005; Tuna, Birtane et al 2005; van der Leeden, Steultjens et al 2006). However, joint damage is late stage disease and it would be useful to know if inflammation in early disease or during flares influences the biomechanics during gait. No interventional study has yet reported on assessment of soft tissue problems in RA, such as bursitis, relative to mechanical compensation and none have utilised MSUS imaging as a technique to assess and inform foot status in RA patients.

**Table 4.** Collated information under main theme headings of all outcome measures utilised within the review papers (adapted from Bowen, Burridge and Arden 2005).

| | |
|---|---|
| *Gait* | • 8m footswitch walkway<br>• Footswitch stride analyser<br>• Temporal distance values (Mean velocity, cadence, mean stride length, step width, step length, foot angle, walking distance/time, single limb stance) |
| *Pain* | • Visual analogue scales: 100mm / 0 -10 / 10cm<br>• Verbal report<br>• Foot pain & disability (Foot Function Index)<br>• Global arthritis pain |
| *Physical function* | • Functional capacity: Functional status: Steinbrocker classification & global scale of 0 – 10 (10 indicating total disability), Disease activity score (DAS), Health assessment questionnaire (HAQ), Larsen Index joint erosion scores in hands and feet, Disability (adapted Arthritic Impact Measurement Scales), Physiologic Cost Index (PCI), Patients' self assessment of performance of ADLs, Patient problems: National Centre for Medical Rehabilitation Research (NCMRR) template<br>• Grip strength (Vigormeter)<br>• Physical assessment of painful joints of feet, ankles, hands & wrists<br>• Lower extremity synovitis: joint count method of ACR<br>• Lower extremity function: ambulation section of the Robinson-Bashall functional assessment (standing, walking & stair climbing), & the walking & stair climbing components of the Toronto Activities of Daily Living Measure |
| *Foot pressure* | • Emed pedar in-shoe system (plantar pressures, stance phase duration, calculation of cadence)<br>• Emed Pedar (forefoot plantar pressures peak pressure, peak force, contact time)<br>• Emed Pedar (in-shoe peak pressures)<br>• Podoscope (weightbearing plantar pressure distribution)<br>• Prototype contact sensitive walkmat system<br>• Optical pedobarograph (highest pressure area under each foot) |
| *Treatment tolerance* | • Daily and weekly use patterns (semi-structured telephone interviews)<br>• Self reported adverse reactions, wearing time<br>• Subjects impression of treatment effectiveness: 10cm VAS<br>• Comfort assessment during walking – likert scale/ 5 options<br>• Patients asked their overall opinion regarding the hosiery.<br>• Perceived advantages and disadvantages of orthopaedic footwear<br>• Attitude to prescribing orthopaedic footwear<br>• Satisfaction with co-operation with pedorthists<br>• Satisfaction / Dissatisfaction (fit and comfort, style, colour, weight, other) |
| *Structural assessment* | • HAV angle measured with weightbearing radiographs<br>• Foot length and height measurement<br>• Range of motion (tibiotalar, subtalar, midtarsal, hip, knee joints) |
| *Physical examination* | • Strength of selected lower extremity muscles<br>• Range of motion & motor strength of the ankle and foot |
| *Visual observation* | • Complete lower extremity evaluation, stance and gait<br>• Unassisted gait and ability to perform heel rise test |
| *Material compression* | • Teclock® dial gauge (under 3$^{rd}$ met head) |
| *Sensation* | • Semmes-Weinstein monfilaments (1, 10 & 75g) |

### 2.3.3. Assessment of foot-related pain, disability and function

There are a growing number of examples of multi-domain questionnaires that seek to assess function, pain and disability relevant to the RA foot. These include the Foot Function Index (FFI) (Budiman-Mak, Conrad and Roach 1991); the Foot Health Status Questionnaire (FHSQ) (Bennett and Patterson 1998); the Manchester Foot Pain Disability Questionnaire (MFPDQ) (Garrow, Papageorgiou et al 2000), the Leeds Foot Impact Scale (LFIS) (Helliwell, Reay et al 2005) and the Bristol Foot Score (BFS) (Barnett, Campbell and Harvey 2005).

Interestingly the FHSQ, MFPDQ and BFS were developed for general populations (Bennett and Patterson 1998; Garrow, Papageorgiou et al 2000; Barnett, Campbell and Harvey 2005) yet the FFI and LFIS appear to be the most ultilised instruments with positive ratings (van der Leeden, Steultjens et al 2008). The FFI was developed to measure the impact of foot pathology on function, in terms of pain, disability and activity restriction, for assessment of surgical interventions (Budiman-Mak, Conrad and Roach 1991). The investigators did not intend it to be used specifically to RA as the source of the pathology although the test subjects all had a definitive diagnosis of RA (Budiman-Mak, Conrad and Roach 1991). The LFIS was developed specifically for RA patients to measure foot pain and disability at all stages, including early and late stage RA (Helliwell, Reay et al 2005).

Both the FHSQ and FFI are criticised as being developed by expert professionals (Barnett, Campbell and Harvey 2005) whereas MFPDQ, BFS and LFIS all were developed with qualitative methodological approaches that involved a series of patient questioning so that the more recently validated instruments are patient facing (Garrow, Papageorgiou et al 2000; Barnett, Campbell and Harvey 2005; Helliwell, Reay et al 2005).

It is clear that the emphasis is shifting from measurement of the biomechanical aspects of gait and foot function alone, towards developing patient-orientated measures based on the patient's own experience of their foot disease. Medical definitions of disease within the RA foot do, however, still tend to be omitted. Whether it is because access to diagnostic information (such as biopsy, serology and imaging results) has been difficult for podiatrists and foot health clinicians, or whether these facilities (in particular MSUS imaging) are seen as emerging practices, remains debatable.

## 2.4. The role of imaging modalities in the assessment of rheumatoid arthritis

The past three decades have seen extraordinary advances in medical imaging and innovations such as computed tomography, ultrasound and magnetic resonance imaging for evaluation of synovitis in RA (Tan, Tanner et al 2003). With the advent of improved imaging technology in the form of MRI and MSUS, specific diagnosis of symptoms within the forefoot is enhanced over clinical examination without the requirement for invasive surgical intervention (Weishaupt, Treiber et al 2003; Olivieri, Scarano et al 2004). This section discusses the main modalities utilised in musculoskeletal imaging and, in particular, discusses the recent developments of MSUS imaging as a clinical modality for assessment of foot status performed by podiatrists.

### 2.4.1. Radiography

Radiography was the first medical imaging modality used, when Wilhelm Conrad Roentgen discovered x-rays and their medical use, in 1895, whilst famously experimenting on his wife's hand (Bushberg, Seibert et al 2002). The radiation was unknown at the time and so Roentgen named the rays 'x' conceiving the term 'x-rays' (Bushberg, Seibert et al 2002).

The following is a summary of the physical properties of x-rays adapted from Bushberg, Seibert et al (2002):-

- x-rays are produced when highly energetic electrons interact with matter and convert their kinetic energy into electromagnetic radiation
- A large voltage is applied between two electrodes (cathode and anode) in an x-ray tube and, as electrons pass through, they attain the kinetic energy
- When x-rays have passed through body structures they are 'collected' onto specially-treated plates (similar to camera film) or digital media and a "negative" type picture is made (the radiograph)
- The more solid a structure is, the whiter it will appear on the film (bones therefore leave the film only slightly exposed and appear light or white on the x-ray film)

In RA, radiographic findings are classically described as periarticular osteopenia, marginal erosions, diffuse joint space narrowing, effusions and subluxations (Canoso 1997). Radiological damage is considered to be an outcome measure in clinical trials as well as

routine clinical examination that reflects the severity and progression of RA (Boers, Tugwell et al 1994) and is integral to the 1987 revised ACR classification of RA (Arnett, Edworthy et al 1988). Furthermore, within the feet in RA, evidence suggests that radiographic findings may be as frequent as, or more frequent than, those observed in the hands (Isomaki, Kaarela et al 1988).

Until recently, radiography has been the mainstay imaging technique for detection of RA disease. Latterly, however, the limitations of x-ray imaging have been highlighted due to it's insensitivity in the detection of early disease changes in RA (Conaghan, O'Connor et al 2003). Radiological diagnosis is insensitive to soft tissue changes, with poor association with pain and thus may take months or years for the plain film to detect cortical bone erosions which results in significant delay between presentation and treatment (Farrant, O'Connor and Grainger 2007).

A further limitation to x-rays is that they may be harmful due to the exposure of cells to ionising radiation. Exposure to radiation causes microscopic damage to living tissue, resulting in skin burns and radiation sickness at high doses and cancer, tumours and genetic damage at low doses. The biological effects of radiation may cause cell death and affect the function of an organ or genetically damaged cells that pass on the genetic transformations to their descendants, increasing the risk of cancer (Bushberg, Seibert et al 2002).

In addition x-rays are now criticised in that they produce a two-dimensional representation of a three-dimensional object and this limits the ability to measure structures and track progression of disease. In clinical trials the Sharp - van der Heijde and Larsen - Scott are the most widely used methods of scoring radiographs that provide objective measures and allow assessment of progression of disease (van der Heijde 1996; Ejbjerg, Vestergaard et al 2005). Both scoring systems are restricted by the ability of x-ray imaging to detect actual disease activity and magnetic resonance imaging (MRI) is emerging as more superior in the detection of temporal changes in structural joint damage in RA (Ejbjerg, Vestergaard et al 2005).

### 2.4.2. Magnetic resonance imaging

Magnetic Resonance Imaging is now established as a useful method for assessment of musculoskeletal status (Gaffney, Cookson et al 1995; Klarlund, Ostergaard et al 2000; Narvaez, Narvaez et al 2002; Tan, Tanner et al 2003). The principles of MRI are explained by

McGonagle and Conaghan (1999) relative to its use in rheumatology. MRI most frequently relies on the relaxation properties of excited hydrogen nuclei in water and lipids. Protons in human tissues are randomly oriented but when placed in a powerful, uniform magnetic field the protons with a resulting non-zero spin have to arrange either parallel (longitudinal magnetism) or antiparallel (transverse magenetism) to the applied magnetic field, according to quantum mechanics. The time taken for longitudinal magnetism to return to its original state is termed T1 and the time taken for transverse magnetism to disappear is termed T2. A magnetic resonance image is therefore formed by measurement of the resultant signal generated by movement of the protons in a magnetic field that has different strengths across a given area. Depending on which MRI sequences are used, the appearance of tissues will vary. The most commonly utilised MRI sequences are T1-weighted and T2-weighted spin echo (McGonagle and Conaghan 1999).

In clinical practice, one advantage of an MRI scan is that it is harmless to the patient (unless using gadolinium enhancement), as it uses strong magnetic fields and non-ionizing radiation. Compare this to Computed Tomography (CT) scans and traditional radiographs (x-rays) which involve doses of ionising radiation that may increase the risk of malignancy (McGonagle and Conaghan 1999; Bushberg, Seibert et al 2002). Furthermore, radiography is the most widely used imaging modality for rheumatoid arthritis, yet it is insensitive for showing bone damage in early RA disease and is insensitive to synovial inflammation, in contrast to MRI that is sensitive to synovitis (McGonagle and Conaghan 1999; McGonagle, Conaghan et al 2001; Evangelisto, Wakefield et al 2004).

MRI has an advantage over other imaging modalities in that it allows an effective assessment of both articular and soft tissue structures such as bursae (Narvaez, Narvaez et al 2002). Because of the synovial fluid that distends the bursa, bursitis typically appears with low signal intensity on T1-weighted images and high signal intensity on T2-weighted images (Narvaez, Narvaez et al 2002). A summary of the advantages and disadvantages of MRI formulated by Wakefield, Kong et al (2003) can be seen in **Table 5**.

There is no doubt that MRI contributes an additional tool, aimed at earlier and more accurate diagnosis, leading investigators to propose that MRI might allow an earlier decision to start appropriate medication in patients with early RA (McGonagle and Conaghan 1999; McGonagle, Conaghan et al 2001; Tan, Tanner et al 2003; Evangelisto, Wakefield et al 2004). MRI of the foot and ankle has formerly been considered to be advantageous in the assessment of musculoskeletal abnormalities as it enables clear depiction of tendons

ligaments, muscles, cartilage and bone (Heron 1993; Ostendorf, Scherer et al 2004). Analysis of MRI scans of the forefeet detected synovitis and bone oedema in patients with early RA in whom MRI of the finger joints was normal (Ostendorf, Scherer et al 2004). Heron (1993) believed that access to MRI would become more generally available to foot health providers and that it would replace many of the techniques employed in foot and ankle imaging. However, more than a decade later, the use of and referral for MRI remains relatively rare for musculoskeletal foot and ankle pathology.

**Table 5.** The Advantages and Disadvantages of MRI
(Adapted from Wakefield, Kong et al 2003).

| Advantages of MRI | Disadvantages of MRI |
|---|---|
| Multiplanar | Expensive (equipment, running and personnel costs) |
| No ionising radiation | Time consuming (eg. Hand and wrist takes approximately 50 mins.) |
| Considered a good imaging measure | |
| More sensitive than clinical, x-Ray and MSUS for the detection of synovitis and erosions | Not well tolerated by some patients who are anxious and claustrophobic (some may require sedation); problematic for elderly who find it difficult to lie flat or still; |
| Standardised inaging protocols and sequences | High level of expertise required |
| | Motion artefacts |
| | Too sensitive (ie. uncertainty about the clinical significance of findings) |
| | Unsuitable for patients with ferromagnetic devices/implants such as heart valve |
| | Possible harmful effects if gadolinium injections are required |

The reasons for this probably lay within the economics of MR imaging as a clinical tool. Costs of MRI have been questioned as a limitation (Wakefield, Balint et al 2005). High levels of expertise are required to operate the equipment and interpret the images and it can be time consuming, for example a hand and wrist may take approximately 50 minutes (Wakefield, Kong et al 2003). Further inconvenience may be experienced by the patient as, to undergo an MRI scan of their feet, they are required to attend the radiology department where the MRI scanner is housed for which there may be a delay of up-to six weeks from the time of their referral (Wakefield, Kong et al 2003). Wakefield, Kong et al (2003) further explain that the static image taken using high field MRI may be uncomfortable as patients have to maintain their foot in an exact position for lengths of time.

The development of dedicated extremity MR scanners for the peripheral joints has potential to be useful for diagnosis of musculoskeletal foot pathology (Naraghi, White et al 2009). Naraghi, White et al (2009) compared a 1.0-T extremity MR with a 1.5-T conventional high-field-strength MR. In that study the former machine was preferred by the majority RA participants in terms of system noise, and comfort (Naraghi, White et al 2009). Both machines were low resolution, which may affect accuracy of measurement, although the authors also reported good agreement for erosions and synovitis (Naraghi, White et al 2009). Whilst, extremity MR scanners may now be more feasible, further evidence is required that specifically addresses issues of low resolution and accuracy of measurement of foot pathology. The issue of extremity MR being a fixed, non-portable device also remains a limiting factor in its timely clinical use.

### 2.4.3. Musculoskeletal ultrasound imaging

Favourable comparisons of MRI to MSUS in the detection of inflammatory soft tissue lesions in rheumatological disease continue to be reported by authors (Gibbon and Wakefield 1999; Cantini, Salvarani et al 2001; Melchiorre, Calderazzi et al 2003; Terslev, Torp-Pedersen et al 2003; Szkudlarek, Narvestad et al 2004). In their review of the role of MRI and MSUS in early RA, Wakefield, Kong et al (2003) support the opinions that MSUS is painless, harmless (no ionising radiation), is readily accessible for use within the clinical environment and relatively inexpensive.

There are also important advantages for the patient with foot symptoms as the MSUS equipment can be made available within the clinical environment, any area of the foot can be

scanned rapidly at one time-point and treatment decisions, such as MSUS guided steroid injections can be made and implemented immediately. A summary of the advantages and disadvantages of MSUS formulated by Wakefield, Kong et al (2003) can be seen in **Table 6**.

**Table 6**. The Advantages and Disadvantages of MSUS
(Adapted from Wakefield, Kong et al 2003).

| Advantages of MSUS | Disadvantages of MSUS |
| --- | --- |
| Relatively inexpensive | Operator dependant and steep learning curve |
| Available in most radiology departments and increasingly available in many rheumatology departments | Limited transducer access, for example, for deep joints such as the hip or more superficial joints where adjacent joints are in close proximity such as carpal bones |
| Potential immediate availability in outpatient departments enabling rapid decision making | Limited data on sensitivity to change with treatment |
| Ability to scan several joints on one time point | Additional time required in clinical setting |
| Well tolerated | Lack of standardized methodology |
| No ionising radiation, allowing multiple assessments in time and place | |
| Relative short scanning time (all joints < 40 minutes, hands and feet 5 minutes) | |
| Allows real time, dynamic joint assessments | |
| Portable | |

Review of the medical literature reveals that MSUS imaging is becoming accepted in rheumatological clinical practice as an aid to musculoskeletal assessment and diagnosis (Wakefield, Gibbon et al 1999; Backhaus, Burmester et al 2001; Balint, Kane et al 2001).

However, MSUS is extremely operator dependant and the use of this technology involves not only the underpinning detailed anatomical knowledge and the ability to recognise structures on screen, but also the understanding of the physics of MSUS and the recognition of principles of safety and recognition of artefacts.

### 2.4.3.1. Basic principles of musculoskeletal ultrasound

A sound wave consists of a mechanical disturbance of a medium (gas, liquid or solid) caused by acoustic energy which passes through the medium at a fixed speed (Fish 1990). The vibrations are measured as cycles per second, or hertz (Hz). Audible sound is in the range of 60Hz to 20,000Hz and anything above 20,000Hz is considered ultrasound. In MSUS the vibrations are measured in 1 million hertz, or megahertz (MHz) so that frequencies used are high (1 - 20 MHz region) (Fish 1990).

Ultrasound scanners rely on the same principles as SONAR (<u>So</u>und, <u>N</u>avigation, <u>A</u>nd <u>R</u>anging) with pulse – echo (or pitch and catch) (Fish 1990). Sound waves are emitted from a probe housing an electro-mechanical transducer that contains piezo-electric crystals, which vibrate when an electrical voltage is applied (Fish 1990). Fish (1990) gives a useful text reference that gives a detailed account of the physics of ultrasound waves as the pass through the body tissues. A summary of this process is charted in **Figure 12**.

### 2.4.3.2. Musculoskeletal ultrasound artefacts

Understanding of the basic principles of sound and various artefacts is essential to optimise the diagnostic value of ultrasound images (**Table 7**). Anisotropy (**Figure 13**), acoustic shadowing, mirror images, comet tail effects, reverberation artefacts and slice thickness can lead to misdiagnoses (Fish 1990).

### 2.4.3.3. Musculoskeletal ultrasound safety

Techniques for medical imaging all utilize some form of energy that must be capable of penetrating tissues to produce an image (Bushberg, Seibert et al 2002). In diagnostic imaging, mechanical energy (in the form of high frequency sound waves) is used in ultrasound imaging and the electromagnetic spectrum outside the visible light region is used for x-ray imaging, MR imaging and nuclear medicine (Bushberg, Seibert et al 2002). The diagnostic advantage of a medical image relates to both the technical quality of the image and the conditions of its acquisition (Bushberg, Seibert et al 2002). Therefore, the higher the power levels of the ultrasound, the better the image.

**Figure 12.** Flow diagram of the passage of ultrasound waves through the body tissues (adapted from Fish 1990).

MSUS probe is placed on the skin surface.

↓

Sound waves pass through the tissues. → Speeds of propagation through different soft tissues varies slightly, but are approximately 1540m/s (transit time of 6.5μs/cm).

↓

At a boundary between two tissues, some ultrasound waves pass on and some are reflected, refracted, scattered, attenuated or absorbed as they pass through the body.

↓

Ultrasound is reflected at tissue interfaces where the beams angle of incidence is perpendicular to the interface. → The strength of the reflection depends on the angle that the beam is directed and the acoustic impedance of the tissue that the beam travels through.

↓ ↓

This is highly angle dependant and refraction can occur when the beam is bent by passing through an area of different acoustic impedance from the surrounding tissue.

At the boundary between two different types of soft tissue (eg: muscle-fat) the degree of reflection is small.

↓ ↓

Attenuation occurs throughout the image and occurs due to reflection, refraction, absorption and scatter.

Acoustic impedance is determined by the density and the stiffness of the tissue that the sound passes through.

↓ ↓

If the tissue boundary is small relative to the wavelength of ultrasound or the surface is rough, the ultrasound beam is diffused/scattered.

A large difference in acoustic impedance leads to a high degree of reflection eg. soft tissue-bone or soft tissue-air interfaces.

↓

Reflected sound waves pass back to the probe where mechanical vibrations are changed to electrical signals by the same transducer working in reverse.

**Table 7.** Common artefacts encountered with MSUS (adapted from Fish 1990).

| Artefact | Definition |
|---|---|
| Anisotropy or beam obliquity artefact | The most common and the result of the sound wave striking the anatomical structure at an angle of less than 90$^\circ$ so that the tissue does not appear to exhibit the same acoustic physical properties in all directions. Acoustic shadowing occurs after heavy attenuation of the signal compared to the surrounding tissue. Acoustic enhancement is the opposite. |
| Mirror images | Occasionally a very strong reflection can give rise to a mirror image of what is already seen. |
| Comet tail effects | When a long tail of bright echoes can sometimes be seen trailing from very strong reflectors. These can be caused by foreign bodies such as shot, metal-ware or gas bubbles. |
| Reverberation artefacts | Usually seen in the near field due to multiple reflection between the probe face and a deeper structure. |
| Slice thickness | The cross section of the slice thickness is greater than the structure being examined and instead of seeing a clear boundary it can sometimes fill in with echoes or appear a dark grey |

**Figure 13.** A posterior longitudinal MSUS scan to demonstrate anisotropy at the attachment of the Achilles tendon at the posterior aspect of the calcaneus in a healthy subject lying prone.
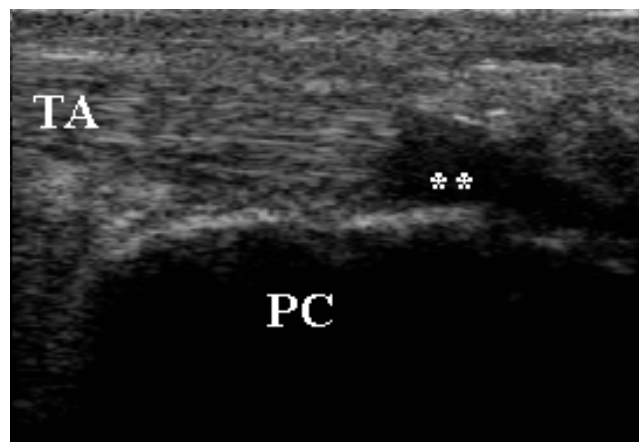


**Key:** ** = Anisotropy; PC = Posterior calcaneus; TA = Achilles tendon
**Equipment:** Diasus MSUS system (Dynamic Imaging Ltd. UK)

The American Institute of Ultrasound in Medicine Report on Medical Ultrasound Safety (AIUM 1994) reported on laboratory trials where some risk of ultrasound exposure damage to tissues has been documented at much higher intensities than is used in diagnostic ultrasound. As sound waves gradually travel through the body, they can be absorbed by the visco-elastic nature of the tissues they pass through, which can be likened to friction or damping and usually the energy is dispersed as heat (Fish 1990). This is supported by the 'Statement on the Safe Use, and Potential Hazards of Diagnostic Ultrasound' that was prepared by the Safety Group of the British Medical Ultrasound Society (BMUS) in June 2000 and reconfirmed by the BMUS Council in October 2007 (BMUS 2000).

All documented adverse biological effects induced by ultrasound have occurred at these higher intensities and include rise in tissue temperature and mechanical bioeffects such as cavitation (AIUM 1994). The risk associated with ultrasound is thus attributed to levels of exposure that are never used within clinical practice. An excellent safety record exists in that, after decades of clinical use, there is no known instance of human injury as a result of exposure to diagnostic ultrasound (AIUM 1994). The power levels used are thus a compromise and a balance between patient safety and image quality (Bushberg, Seibert et al 2002).

### 2.4.3.4. Musculoskeletal ultrasound equipment

According to the American Institute of Ultrasound in Medicine's official statement on clinical safety (AIUM 1994), current data indicate that the benefits to the patient of the prudent use of diagnostic ultrasound outweigh the risks, if any, that may be present. All modern MSUS systems should comply with the AIUM 1994 recommendations on the inclusion of thermal and mechanical indices within the output display. During clinical assessments with ultrasound equipment, the total ultrasound exposure is kept as low as reasonably achievable, known as the ALARA principle (As Low As Reasonably Achievable) (AIUM 1994; BMUS 2000).

The choice of equipment, in particular, the transducer is thus important yet may be confusing to the trainee user. The transducer is periodically driven by an electrical pulse and a pulse is then received back at the transducer after reflection or scatter of tissue interfaces (Kremkau

1998). The time of arrival of the echo from a given interface depends on the depth of that interface. The instrument can use the time of arrival of an echo after transmission as an indication of the depth of the interface.

Since the transducer is used to both transmit and receive the ultrasound beam, reviewers indicate that there is always a trade-off between depth of penetration and resolution (Wakefield, Gibbon et al 1999). That is, the higher the frequency, the greater the resolution, but the less depth of tissue penetrated (see **Figure 14**).

**Figure 14.** Longitudinal skin section demonstrating MSUS frequency (MHz) compared to depth of tissue penetrated in a large joint
(schematic by RH09 graphic design, Southampton, 2009).
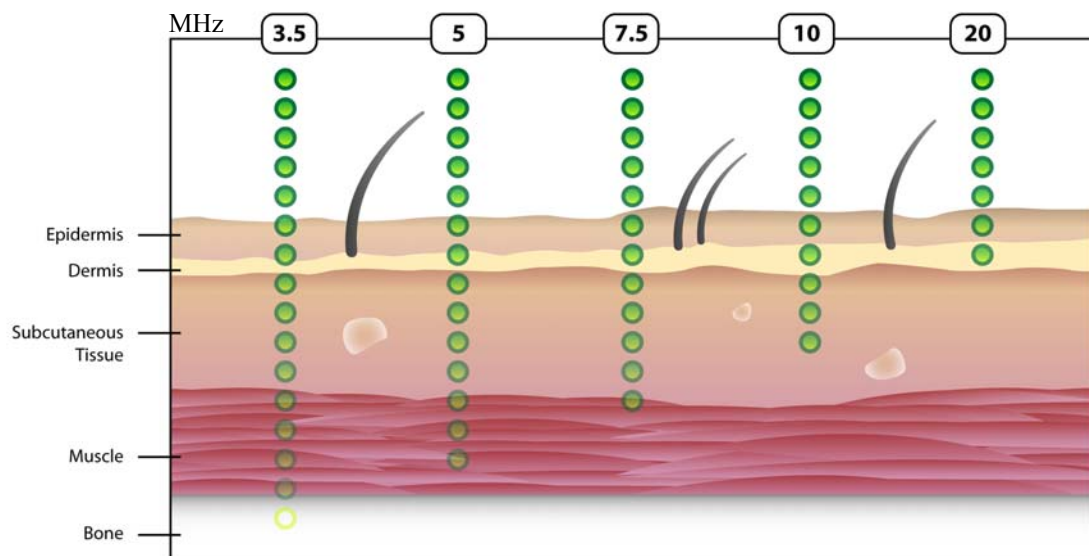


For MSUS, high frequency transducers of approximately 7.5 - 10MHz or higher are appropriate (O'Connor and Grainger 2002, see **Table 8**).

The size of the active length of the MSUS transducer (probe) is another important factor to consider (Backhaus, Burmester et al. 2001; Schmidt and Backhaus 2008). The active length of the MSUS transducer may vary from 6cm to 2cm depending on the machine into which they are built (Schmidt and Backhaus 2008). For example, longer probes are said to provide

good overviews for larger joints and tendons whereas small 'footprint' transducers, known as 'hockey sticks', allow better coupling to small joints and around bony surfaces (Schmidt and Backhaus 2008). In particular, these transducers are said to be excellent for visualization of small superficial structures such as hammer toes (Schmidt and Backhaus 2008). Most transducers used in MSUS practice are linear, however curved array probes are also available and are useful for visualize deeper anatomical structures and are mainly used for abdominal ultrasound (Schmidt and Backhaus 2008).

**Table 8.** Transducer frequency compared to depth of tissue penetrated (adapted from Rockett 1999; Backhaus, Burmester et al 2001).

| Transducer frequency | Structures readily identified |
|---|---|
| 3.5 – 7.5MHz | Large joints (eg: hip, shoulder) |
| 7.5 – 16MHz | Small joints, tendons, ligaments, neuroma, bursae, nodules |
| 10 – 20MHz | Very superficial structures (eg: extensor tendons of toes) |
| 16 – 28MHz | Discrete layers within the skin |

The use of 'stand off' pads and techniques for using a water bath to facilitate the ultrasound wave conduction over gross structural deformities are also available. These techniques reportedly increase the field of view in anatomical areas where the contour of the part is such that it only allows a small area of contact (Stokes, Hides and Nassiri 1997).

Cost of the equipment also requires consideration according to its proposed use. The cost of a high quality, high resolution system can range from £30,000 to over £130,000 and lower resolution units from £12,000 to £20,000. Wakefield, Gibbon et al (1999) argue that a misconception is often made that a low cost unit is ideal for use in the clinical setting but, unfortunately, this is often where the operator is the least experienced. In this situation, it is recommended that the highest possible imaging quality is essential and that a more experienced sonographer could probably manage with a lower resolution system.

### 2.4.3.5. Musculoskeletal ultrasound applications

Most MSUS investigations are performed using 'grey scale', which means images are produced in a black and white format; each white dot in the image represents a reflected sound wave (Kremkau 1998). Sound waves that return to the transducer (probe) are

interpreted as a signal on screen (white). When the sensor picks up no echoes, there will be no signal (black). When sound waves change speed, even minutely, the interface that exists between the tissues will appear as contrast (Fish 1990). For example, sound beams do not penetrate the bone cortex so it shows up as a bright echo and fluid is anechoic, with fluid in bursae depicted as being dark (Fish 1990; Kremkau 1998). Tendons are characteristically hyperechoic (bright) on ultrasound demonstrating a bright fibrous pattern. Muscle is relatively hypoechoic (dark) to tendon fibres and ligaments that are hyperechoic (bright) (**Figure 15**).

**Figure 15.** A longitudinal MSUS scan at the posterior aspect of the calcaneus in a healthy subject lying prone.
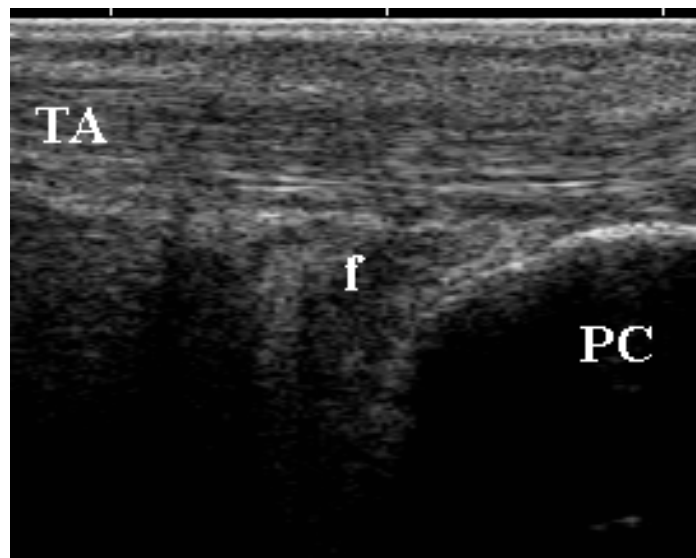


**Key:**.**TA** = Achilles tendon; **PC** = posterior aspect of calcaneal bone;
**f** = retrocalcaneal fat pad
**Equipment:** Diasus MSUS system (Dynamic Imaging LTd, UK)

Traditional grey scale MSUS imaging allows visualisation of synovitis, joint capsule rupture, bursitis, tenosynovitis, tendonitis and tendon rupture, joint surface irregularities and erosions, osteophytes, loose joint bodies and foreign bodies (Coakley, Samanta et al 1994; Koski 1998; Backhaus, Kamradt et al 1999; Schmidt, Volker et al 2000; Wakefield, Gibbon et al 2000; Grassi, Filippucci et al 2001).

Steroid injections, joint aspiration and synovial biopsy have also proven to be readily

performed under MSUS guidance (Kane, Greaney et al 1998; van Vugt, van Dalen et al 1998; Crawford et al 1999; Koski 2000; Wen-Chung 2000; Kane et al 2001; Qvistgaard et al 2001; Koski & Hermunen 2001; Balint, Kane et al 2002; Fredberg, Bolvig et al 2004; Grassi, Filipucci et al 2004; Genc, Saracoglu et al 2005).

Pathological changes of soft tissue structures within the foot are, reportedly, readily identified by MSUS which can be a useful aid in the diagnosis of foot symptoms (Riente, Sedie et al 2006) (**Table 9**).

**Table 9.** Reported applications for diagnostic ultrasound within the foot & ankle.

| | |
|---|---|
| Effusions and impingements of the ankle joints | Bell and McNally (2002) |
| Tenosynovitis of tibialis anterior, posterior and peroneus longus, brevis tendons | Koski (1995) |
| Achilles tendon imaged in its full length and calcification, ruptures and bursitis can be differentiated | Ridola and Palma (2001) |
| Lesions of plantar fascia and calcaneal spurs | Bygrave, Betts et al (1998); Kane, Greaney et al (2001); Balint, Kane et al (2002) |
| Diagnosis of morton's neuroma | Jones, Bygrave et al (1999); Irwin, Konstantoulakis et al (2000) |
| Diagnosis of persistent post operative pain | Brown, Betts et al (1994) |
| Screening of diabetic and rheumatoid patients for high metatarsal pressures | Young, Coffey et al (1995) |

More recently, the advances in colour Doppler and power Doppler MSUS have shifted the focus to assessing changes in joints and soft tissues as a result of inflammation such as effusions, proliferating synovium and active synovitis (Wakefield, Brown et al 2003). Balint, Mandl and Kane (2008) suggest that detection of changes in synovial perfusion by power Doppler could be advantageous in determining whether an erosion is active or burned out or

which parts of pannus are inflamed and which parts are fibrotic. Whilst this may provide more convincing evidence for targeted treatment, the authors also warn that interpretation of power Doppler MSUS is complicated by the frequent presence of artefacts (Balint, Mandl and Kane 2008).

### 2.4.3.6. The role of musculoskeletal ultrasound imaging in rheumatoid arthritis

Grey scale and power Doppler MSUS have become an established imaging technique for RA synovitis (Backhaus, Kamradt et al 1999; Wakefield, Gibbon et al 2000; Backhaus, Sandrock et al 2002; Hau, Kneitz et al 2002; Szkudlarek, Court-Payen et al 2003; Scheel, Schmidt et al 2005). Previously, criteria for diagnosis of early RA involved the assessment of bone erosion detected radiologically by x-ray (Arnett, Edworthy et al 1988). However, conventional radiography is insensitive in the detection of synovitis (Backhaus, Kamradt et al 1999; Wakefield, Gibbon et al 2000; Backhaus, Sandrock et al 2002). It is now also accepted that clinical examination may be relatively insensitive (Wakefield, Brown et al 2004; Brown, Quinn et al 2006; Brown, Conaghan et al 2008) and that imaging studies have confirmed a discrepancy between clinical examination and MRI-detected synovitis (Klarlund, Ostergaard et al 2000; Goupille, Roulot et al 2001; Brown, Quinn et al 2006). O'Connor and Grainger (2002) predicted that the demonstration of synovitis by MSUS would be most important in the measure of therapeutic response and outcome in patients with RA.

There appears to be agreement within the literature that MSUS is a sensitive measure for detection of synovitis and that MSUS is capable of detecting significantly more synovitis than clinical assessment alone (Bresnihan and Kane 2004; Wakefield, Green et al 2004). MSUS has been shown to detect extensive sub-clinical synovitis and that this led to altered management in 12% of cases (Karim, Wakefield et al 2001). Giving credence to this, patients with RA and apparent clinical remission have been demonstrated to have measurable synovitis by grey scale and power Doppler MSUS (Brown, Quinn et al 2006).

Despite this increasing evidence for the potential application of MSUS in the evaluation of RA synovitis and tenosynovitis, there remains a lack of standardisation between studies (Joshua, Lassere et al 2007). For example, synovitis may be detected by ultrasound when it is thickened, because it appears as hypoechoic intra-articular tissue (O'Connor and Grainger 2002) (**Figure 16**). The skill in interpretation of MSUS images is essential, as detection of

synovial hypertrophy by greyscale MSUS without power Doppler can be found in healthy subjects. Synovial hypertrophy has been observed by MSUS within healthy subjects with normal limits for MTP joint synovitis recorded as 2.9mm or less (Luukkainen, Ekman et al 2009).

Attempts have been made to produce semi-quantitative scoring methods for quantification of ultrasound detected synovitis (Szkudlarek, Court-Payen et al 2003; Scheel, Schmidt et al 2005) although in both studies mean disease duration of participants was indicative of late RA, suggesting that results may not be comparable for patients with early RA. The OMERACT Ultrasound Special Interest Group has gone some way to addressing these concerns, in continuing to focus its work on defining and standardizing approaches for MSUS assessment (Wakefield, Balint et al 2005; Wakefield, D'Agostino et al 2007; Joshua, Lassere et al 2007).

**Figure 16.** MSUS image of synovitis of the fifth metatarsal joint in a patient with rheumatoid arthritis (from: the EULAR Guidelines for Musculoskeletal Ultrasound in Rheumatology, Filippucci E and Farina A
http://www.doctor33.it/eular/ultrasound/Foot.htm Accessed February 2009).
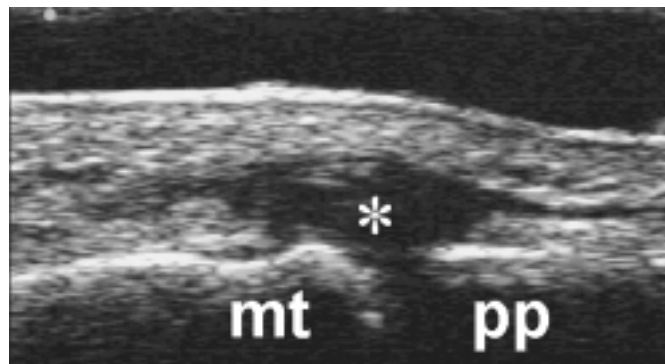


**Key:** Marked hypoanechoic joint cavity widening (*).
**mt** = metatarsal head; **pp** = proximal phalanx. AU4-Idea
**Equipment:** Esaote Biomedica

*2.4.3.7. Musculoskeletal ultrasound imaging of bursae in rheumatoid arthritis*

On MRI and MSUS the synovium of swollen bursae within the knee, hip and shoulder in patients with RA are reported as similar in appearance to the characteristics of joint synovitis (O'Connor and Grainger 2002; Hermann, Backhaus et al 2003; Meenagh, Iagnocco et al 2006; Finlay and Friedman 2006).

Swollen bursae are stated as more readily identifiable by MSUS than synovitis with thickened synovium of a bursa appearing as hypoechoic tissue and the fluid within appearing anechoic (O'Connor and Grainger 2002). Other authors however have reported poor reliability in the use of MSUS to detect swollen bursae within shoulders (Hermann, Backhaus et al 2003). Among 30 patients without demonstration of swollen bursae on ultrasound, MRI identified swollen bursae in 9 (30%). Of the 13 shoulders with swollen bursae demonstrated by ultrasound, 4 (31%) escaped detection by MR Imaging (P=0.2668) (Hermann, Backhaus et al 2003).

Identification of swollen forefoot bursae also appears challenging due to potential close associations with Morton's neuromas. Morton's neuromas are commonly mistaken for swollen intermetatarsal bursae (Bossley and Cairney 1980; Awerbuch, Shephard et al 1982; Zanetti, Strehle et al 1997; Iagnocco, Coari et al 2001) and therefore it is important to distinguish the appearance of these on MSUS.

Confusion may also exist in the use of MSUS to detect bursae in the plantar area of the forefoot as the appearance of other inflamed soft tissues may be similar. Other causes of soft tissue inflammation such as MTP joint synovitis, tenosynovitis, stress fracture, tendon sheath ganglion are readily distinguishable by MRI (Bancroft, Peterson and Kransdorf 2008). However, there appears to be very little evidence of studies using MSUS to distinguish pathology in the plantar forefoot area. Consequently, there is currently no standardized method for MSUS imaging of bursae in the plantar forefoot area.

In cadaver dissections, Chauveaux, Le Huec and Midy (1987) determined that the intermetatarsal bursae usually bulge spontaneously anteriorly beyond the transverse metatarsal ligament. Similarly, Claustre, Bonnel et al (1983) had previously described hypertrophied intermetatarsal bursae that had gradually extended beyond their normal site towards the dorsal or plantar region of the foot. In his investigation of intermetatarsal bursae

in patients with early RA, Koski (1998) used the latter information from cadaver studies to determine his MSUS protocol. On MSUS, he described intermetatarsal bursae as 'anechogenic' and bulging more than 1mm under the metatarsal head level (Koski 1998) (**Figure 17**). Morton's neuroma, on the other hand, are usually well defined by MSUS as an hypo-echoic mass, ovoid in shape, with its long axis aligning to the shaft of the metatarsals (Ellis, Teh et al 2002). van Holsbeeck (1999) suggested that compression with the transducer can aid diagnosis in this instance as bursae were compressible, whilst neuroma were not.

To complicate the picture further, adventitious bursae that may occur due to mechanical stress underneath the metatarsal heads within the plantar fat pad area are also readily identifiable by MSUS (Gregg, Schneider and Marks 2008). A major limitation of the study by Koski (1998) was that his technique for identifying the bursae on MSUS as anatomical intermetatarsal bursae was not validated against any other method, such as MRI or histological analysis through biopsy. His approach was justified through a detailed knowledge of the anatomical structures being imaged and the interpretation of the MSUS grey scale image of the bursae.

**Figure 17.** A) MSUS scan of bursitis (single white arrow) between the 2nd and 3rd metatarsal heads demonstrating an anechoic area whilst the area between the 3rd and 4th metatarsal heads is normal and echogenic. B) Photograph demonstrating the ultrasound scan taken in the transverse view of the right foot (from Koski 1998).



A                    B
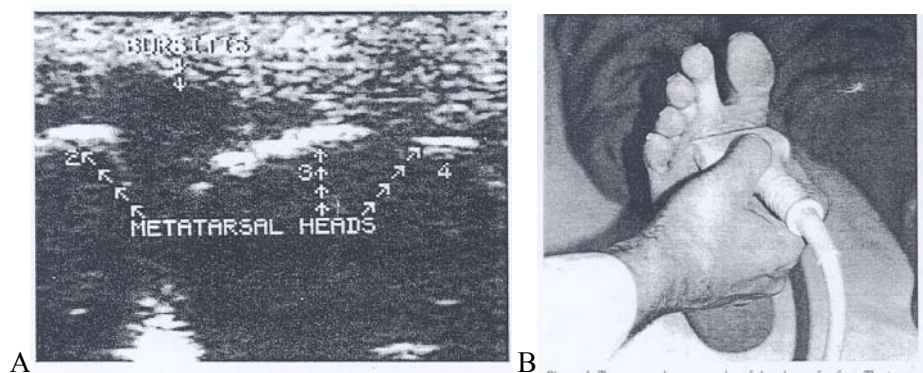
### 2.4.3.8. Documentation of musculoskeletal ultrasound images

For those clinicians trained in diagnostic MSUS techniques, further recommendations propose that all scans should be performed according to a standardised approach (Backhaus, Burmester et al 2001).

- All pathological findings should be documented in two perpendicular planes, longitudinal and transverse
- All scans should be performed moving from proximal to distal
- When examining the ankle and heel the patient should be in the supine position for ventral and lateral scans and the prone position for dorsal scans with the hip and knee joints in their neutral positions
- For the foot, the patient should be in the supine position for dorsal scans and the prone position for plantar scans.
- For the foot scans should be performed moving from proximal to distal

The OMERACT Ultrasound Special Interest Group have gone some way in defining and standardizing approaches for MSUS assessment (Wakefield, Balint et al 2005; Wakefield, D'Agostino et al 2007; Joshua, Lassere et al 2007) although there remains a reported lack of standardisation between published studies (Joshua, Lassere et al 2007). In particular, there appears to be little evidence for standardized MSUS imaging approaches for assessment of the foot and at the time of the studies that form this doctoral thesis there was no definition for MSUS assessment of plantar forefoot bursitis. It was anticipated that the development of tailored learning to areas directly relevant to the discrete field of foot and ankle pathology may be the answer to this (Brown, Roberts et al 2007).

### 2.4.3.9. Training issues and legislation for use of musculoskeletal ultrasound

Diagnostic ultrasound is stated as being the most operator dependent imaging technique (Grassi and Cervini 1998). Although the procedure itself has no specific side effects, harm may result from incorrect acquisition and interpretation of images (O'Connor and Grainger 2002). The reported lengthy learning curve for this skill is related primarily to the quality and interpretation of the ultrasound images that are greatly dependent on the expertise and experience of the operator (Balint and Sturrock 1997). Secondary to this is the use of older instrumentation where image quality may have been poorer and instruments were not so user

friendly (Balint and Sturrock 1997).

A critical issue is one of overall image resolution, which has to be analysed carefully. MSUS requires high frequency probes in order to achieve the necessary resolution for accurate diagnosis and artefacts are common with potential for variation in interpretation of image, particularly with respect to the positioning of the transducer array (O'Connor and Grainger 2002). For example, if structures that contain multiple parallel linear sound interfaces, such as tendons or muscles, are not visualised with the transducer array perpendicular to the long axis of the linear interfaces, there is reflection of the beam away from the transducer causing a reduction in echogenicity of the tissue (O'Connor and Grainger 2002). This mimics disease of these structures and represents a liability in the assessment of tendons and muscles (O'Connor and Grainger 2002). Knowledge about the basic principles relevant to sound waves and a detailed anatomical knowledge of the structures under investigation are therefore mandatory (Backhaus, Burmester et al 2001).

Recommendations by the professional body of the sonologists regarding the training for MSUS advise two supervised ultrasound lists per week over a six-month period (O'Connor and Grainger 2002). In an attempt to standardise the quality of MSUS education, national and international societies for example, BMUS (British Musculoskeletal Ultrasound Society), EULAR (European League Against Rheumatism) and EFSUMB (European Federation of Societies for Ultrasound in Medicine and Biology) have begun to establish training guidelines for MSUS (Backhaus, Burmester et al 2001; Valentin and Jager 2003). EULAR experts in MSUS have provided recommendations for the conduct and content of MSUS courses with hands on experience organized at different levels of basic, intermediate and advanced, specifically for non-radiologists (Naredo, Bijlsma et al 2008). Others have been developing specific competencies for MSUS (Brown, O'Connor et al 2005; Brown, O'Connor et al 2006) and e-learning packages that complement these training programmes are also available for the continued support in learning the techniques of MSUS (Filippucci,Meenagh et al 2007).

Repetition to the point of over-learning is needed to become really proficient (French, Neville et al 1994) and support from medical colleagues in the acquisition of these skills is a major factor. A good relationship with radiology colleagues is thus essential for the practice and development of the skills through the initial stages of the 'learning curve'.

### 2.4.3.10. The use of musculoskeletal ultrasound performed by a Podiatrist

As technology has improved, clinical expertise in performing musculoskeletal ultrasound has also advanced dramatically and some have made it clear that these techniques should be accessible to non-radiologists (Gibbon 1996; O'Connor and Grainger 2002). Podiatrists are required in their training to have a detailed thorough anatomical knowledge of the foot and ankle (QAA 2001) and could potentially be the most appropriate practitioners to include this skill as part of their role within foot and ankle assessment (Bowen 2003; Bowen, Dewbury et al 2008).

Models for the use of MSUS for health professionals other than radiologists have been demonstrated (Filipucci, Unlu et al 2003; Taggart, Filipucci et al 2006). There have been some attempts at defining the learning curve of rheumatologists. D'Agostino, Maillefert et al (2004) reported good achievement of agreement for two novices (kappa scores 0.63 and 0.62) but reduced accuracy for the third novice on diagnosis of 70 patients using MSUS. Agreement within this study was recorded as diagnosis with no attempt to blind each investigator to clinical signs (D'Agostino, Maillefert et al 2004). Other authors have investigated quality of image acquisition concluding that a novice could obtain acceptable images in 24 non-consecutive hours of active scanning after an intensive self teaching programme (Filipucci, Unlu et al 2003; Taggart, Filipucci et al 2006). Taggart, Filipucci et al (2006) suggest agreement of 80% of scans in interpretation of images during their competency assessment.

As explained earlier within this chapter (section 2.3, page 29) instrumentation for gait mechanics, foot pressure analysis and patient facing questionnaires have proven to be invaluable in aiding and augmenting investigations of the foot and ankle (Woodburn and Helliwell 1996; Hodge, Bach et al 1999; Garrow, Papageorgiou et al 2000; Barnett, Campbell and Harvey 2005; Helliwell, Reay et al 2005). The extensions to the scope of practice of diagnostic skills for the podiatric practitioner have enabled clinical access to information on body structures and systems with the outcome of more effective management of foot and ankle pain (Wall 1997; Puttemans and Nemery 1998; Hodge, Bach et al 1999). Similarities exist between these skills and the potential of diagnostic MSUS imaging for use by informed clinicians in aiding assessment and evaluation of the management of foot problems.

Real time MSUS imaging of foot and ankle structures could emerge as an adjunct to current

podiatric and rheumatologic practices or as an interim means of guiding clinical decisions towards other investigative routes. In achieving this, regulation of extended scope practices is essential for the safety of patients. The validation of education and skills training and subsequent professional indemnity insurance of Podiatrists are the responsibility of the Health Professions Council and The Society of Chiropodists and Podiatrists (London, UK) (DOH 2000). Effective communication with the OMERACT Ultrasound Special Interest Group and the professional bodies of rheumatologists and radiologists regarding the skills acquisition courses for diagnostic musculoskeletal ultrasound is therefore required to take the developments in training of podiatrists and other allied health professionals further.

## 2.5. Justification for the study

The justification brings together thoughts from the subject material presented in the literature review and the important issues regarding the relevance of bursae in the forefoot in patients with RA. In summary, the key issues identified are:

1. The effects on the foot are important in RA but under-investigated
2. Clinical examination alone is relatively insensitive to the detection of synovitis and bursitis within the foot in RA
3. Bursae appear to be important contributors to forefoot pathology in RA and may be readily identified with MSUS
4. MSUS imaging performed by a Podiatrist could enhance current clinical treatment decisions for pathology within the forefoot in RA

Many authors agree that RA commonly affects the feet causing swelling and pain within the foot joints that reduces a person's ability to walk (Platto, O'Connell et al 1991; Wiener-Ogilvie 1999; Costa, Rizack et al 2004; Redmond, Waxman et al 2006). However, most attention in the assessment of RA disease status is directed towards hands; for example the recommended standard for quantifying disease activity in RA, the Disease Activity Score (DAS28), does not include feet (Prevoo, van't Hof et al 1995) and classification criteria for RA have been criticised for exclusion of certain factors such as foot erosions (Hulsmans, Jacobs et al 2000).

The prevalence of foot pathology in RA is usually related to the duration of systemic illness (Spiegel and Spiegel 1982; Michelson, Easley et al. 1994; Shi, Tomita et al. 2000) yet little is

known about the appearance and progression of the patho-physiological effects of RA within the foot. Most studies that have reported on foot pathology and interventions for foot pathology in RA, utilize cross sectional designs but there is clearly a need for better quality information about progression and risk factors for progression of foot disease in RA to enable more fitting targeted therapies.

It is now accepted that clinical examination of RA synovitis within the foot is relatively insensitive (Woodburn, Udupa et al. 2002) and that imaging studies have confirmed a discrepancy between clinical examination and imaging detected synovitis (Klarlund, Ostergaard et al 2000; Goupille, Roulot et al 2001; Tan, Tanner et al 2003; Brown, Quinn et al 2006). As conventional radiography has also been confirmed as insensitive in the detection of synovitis (Backhaus, Kamradt et al 1999; Wakefield, Gibbon et al 2000; Backhaus, Sandrock et al 2002) assessment of the feet in patients with RA by MSUS could provide clinicians with further information regarding the patterns of soft tissue changes and progression of RA through the course of the disease. Notably, the presence of swollen anatomical bursae may be associated with the same disease process as synovitis of joints and tendons and is an important, but often may be an undiagnosed, cause of pain in the forefoot in RA (Koski 1998; Olivieri, Scarano et al 2004). Although the presence of swollen anatomical bursae have been linked with RA disease progression (O'Brien, Hart et al 1997; Narvaez, Narvaez et al 2002) and MSUS is more sensitive than clinical examination at detecting swollen anatomical intermetatarsal bursae (Koski 1998), the presence of anatomical bursae and adventitious bursae within the foot in patients with RA has largely received very little attention within the literature.

Following review of the literature (see **Appendix 1** for search strategy), no work has been identified that has sought to use MSUS to determine the prevalence and natural history of swollen bursae within the forefoot in patients with RA. It may be possible that the imaging of bursae within the forefoot by MSUS would add new information to the clinical assessment of the condition in RA. If this proves true, the information would provide immediate information to support more timely and effective targeted clinical management to address pain, disability and loss of mobility within the foot.

As training courses and competencies are designed for the use of MSUS by non-radiologists (Brown, O'Connor et al 2005; Brown, O'Connor et al 2006; Naredo, Bijlsma et al 2008) and

tailored learning to discrete areas of clinical practice are advocated (Brown, Roberts et al 2007) then the use of MSUS imaging performed by a podiatrist to identify swollen bursae within the forefoot could also be an important benefit to patient care.


## 2.6. Research questions

Using MSUS performed by a podiatrist, this doctoral study provided an opportunity to assess the prevalence and natural history of bursae occurring within the forefeet of patients in secondary care who were being managed for RA. A second aim was to determine if the presence of bursae occurring within the forefeet was associated with patient reported foot impact outcome measures in this patient population.


The outline research questions addressed within the thesis were therefore as follows:

### *Chapter 4: Reliability of the MSUS technique*

a)  *Is diagnostic ultrasound, performed by a podiatrist, a reliable technique to identify the prevalence of bursae in the RA plantar forefoot?*

b)  *Does the presence of MSUS detectable bursae in the plantar forefoot area of patients with RA change following a period of intervention (anti-TNF-α therapy)?*

c)  *Is MSUS responsive to change in prevalence of bursae in the plantar forefoot area of patients with RA following a period of intervention (anti-TNF-α therapy)?*

### *Chapter 5: Prevalence of MSUS detectable forefoot bursae in RA patients.*

a)  *What is the prevalence of bursae within the forefeet of healthy subjects and patients with RA detectable by MSUS and detectable clinically?*

b)  *Which are the most common sites in the RA plantar forefoot for MSUS detectable bursae?*

c)  *Is there a difference between the prevalence of MSUS detectable bursae within the forefeet of healthy subjects and RA participants?*

d)  *Is the prevalence of MSUS detectable bursae within the forefeet of RA participants associated with patient reported outcome measures such as LFIS?*

*Chapter 6: Changes in prevalence of MSUS detectable forefoot bursae in RA after one year.*

a) *Does the prevalence of MSUS detectable bursae in the plantar forefoot area of patients with RA change over time?*

b) *If the prevalence of MSUS detectable bursae does change after one year what predicts that change?*

## 2.7. Summary of chapter two

This chapter has laid the foundations for the thesis. It has introduced the research problem, background literature, justification and research questions. On these foundations, the report can proceed with a detailed description of the research.

The methodology and results are therefore discussed within the chapters three, four, five, six and seven of this doctoral thesis. Conclusions are also given, followed by implications for future research.

# 3.0 Chapter Three: Methodology

Following review of the literature, it is apparent that bursae appear to be an important contributor to forefoot pathology in RA and that MSUS performed by a podiatrist may be an effective method in evaluating this. However, there is currently no evidence to support this supposition.

## 3.1. Aim

The aim of this doctoral study was therefore to develop a reliable MSUS imaging technique to be performed by a podiatrist to assess the prevalence and natural history of bursae occurring within the forefeet of patients in secondary care who were being managed for RA. A second aim was to determine if the presence of bursae occurring within the forefeet was associated with patient reported foot impact outcome measures in this patient population.

## 3.2. Hypotheses

### 3.2.1. Null hypotheses ($H_o$)

1. A podiatrist performing MSUS is not reliable in the detection of forefoot bursae in patients with RA.

2. MSUS detectable bursae within the forefoot are not a prevalent factor in patients with RA.

3. MSUS detectable bursae within the forefoot are not associated with patient reported foot impact outcome measures in patients with RA.

### 3.2.2. Alternative hypotheses ($H_1$)

1. A podiatrist performing MSUS is reliable in the detection of forefoot bursae in patients with RA.

2. MSUS detectable bursae within the forefoot are a prevalent factor in patients with RA.

3. MSUS detectable bursae within the forefoot are associated with patient reported foot impact outcome measures in patients with RA.

### 3.3. Scope of the doctoral study

The three studies that form the scope of this thesis were conducted over a three and a half year period, from February 2005 to September 2008. All participants who had RA attended the Wellcome Trust Clinical Research Facility, Southampton Universities Hospital NHS Trust. All healthy control participants attended the Biomechanics Laboratory, School of Health Professions and Rehabilitation Sciences, University of Southampton.

### 3.4. Ethical approval

The Local Research Ethics Committee approved the protocol for the first phase of the study (assessment of the forefoot by MSUS in patients with rheumatoid arthritis on anti-TNFα therapy) in March 2004. Sponsorship and Professional Indemnity Insurance was received from the Southampton University Hospitals Trust (SUHT) in April 2004. This was followed by the period of recruitment (N=32), data collection and report for the first phase (reliability of the technique) of the study between February 2005 and June 2007.

The Local Research Ethics Committee approved the protocol for the second phase of the study (MSUS assessment of the forefeet of patients with rheumatoid arthritis, N=200, at baseline and twelve months) in June 2006 (see **Appendix 2**). Sponsorship and Professional Indemnity Insurance was also received from SUHT in June 2006. Recruitment and data collection of the second phase commenced in July 2006 and was completed in September 2007.

The School of Health Sciences Research Ethics Committee approved the protocol for the healthy control participants in the second phase of the study (MSUS assessment of the forefeet of participants who do not have systemic musculoskeletal pathology; N=20) in November 2006, subsequently approved for amendment to N=50 in November 2007 (see **Appendix 3**). Sponsorship and Professional Indemnity Insurance was received from the University of Southampton in December 2006 and for the amendment in November 2007. Recruitment and data collection of healthy control participants took place between February 2008 and April 2008.

### 3.5. Conflict of interest statement

No benefits in any form were received or will be received from a commercial party related directly or indirectly to the subject of this research. The reliability study, chapter 4, was financially supported by the Southampton Rheumatology Trust and Arthritis Research Campaign.

### 3.6. Study design

The overarching philosophy of the doctoral study is rooted in positivistic, epidemiological, observational (non-experimental) research. Bowling (2002) explains positivism as an approach that aims to discover laws using quantitative methods that emphasize positive facts, and epidemiology as being concerned with the distribution of, specific causes of, and risk factors for diseases in populations.

Most studies reporting on prevalence of foot manifestations in RA tend to use cross sectional methodological designs. For example, Shi, Tomita et al (2000) used a cross sectional design to investigate two groups of patient; those who had RA less than ten years and those who had RA for more than ten years. Michelson, Easley et al (1994) systematically examined the feet of an unselected group of ninety nine patients with RA, with average disease duration of thirteen years. The prevalence of the manifestations of RA within the foot in both studies was related to the duration of systemic illness (Michelson, Easley et al 1994; Shi, Tomita et al 2000).

However, cross sectional studies are limited to one time point and one population; so that exposure and outcome are measured at the same time (Byrne 1998) and little would therefore be known about the appearance and progression of pathology within the foot. Fortin, Stucki and Katz (1995) challenged researchers to address the "threats to relevance of change" in RA disease, within their study designs. In a cohort study, exposure is measured in the present and outcome is recorded at some point in the future (Byrne 1998). Therefore to confirm relationships and predictors of disease, longitudinal cohort studies with prospective measurements would be ideal (Byrne 1998) (**Table 10**).

To answer the research questions (Chapter two, section 2.6, page 64) and be able to accept or reject the null hypotheses, the optimal research design for studies two and three was selected

to be a longitudinal cohort study. Embedded within the design of study two was a case reference study, to enable comparisons of baseline demographic and clinical characteristics of the RA study sample.

**Table 10.** Summary of the ideal study design (from Byrne 1998).

| *A measure of outcome should be:* |
| --- |
| ▪ Well defined |
| ▪ Specific |
| ▪ Objective |
| ▪ Widely accepted as a measure of success |
| ▪ Directly observed by an independent observer |
| ▪ Based on long-term, quality-of-life variables (ideally from questionnaires answered by patients) |
| ▪ Measured prospectively |
| ▪ Recorded as part of a comprehensive database, along with all potentially confounding factors, and quantified or coded properly |

The aim of the comparison was to identify factors that reduced or increased the presence MSUS detectable bursae related to RA patients that were not present in healthy individuals. For the preliminary phase of the research, the reliability of the MSUS technique (chapter four, page 96), a short, interventional, prospective study was deemed an appropriate method of provisionally exploring the research hypotheses for studies two and three and at the same time enabling reliability of MSUS technique to be determined.

## 3.7. Sample

For medical clinical research Byrne (1998) describes an ideal sample as one which is:

- Large enough to answer the research question
- Homogenous for the topic or research question
- Representative of a broad population and
- Drawn from several different hospitals (multicentre)

This was used to guide this research sample.

### 3.7.1. Sample size and power calculations: RA participants

No data exists that compares forefoot bursae with patient-related foot disability and function,

therefore power calculations were performed from correlation sample size tables (Machin, Campbell et al 1997) using initial data analyses from 20 participants in the preliminary validation study (Chapter 4, page 96). A small sample of twenty from the preliminary study gives an idea of what correlation coefficient could be anticipated for significance in results, although the power calculations may still be interpretable as the data would be highly variable (Machin, Campbell et al 1997). Since the main outcome variable for this study was to be patient-related foot disability and function, with MSUS detectable bursae as the predictor variable, data for the association between foot pain and disability (measured by the MFPDQ) and presence of MSUS detectable bursae from the preliminary study (chapter four, page 96) formed the primary power calculation.

Associations between foot pain and disability (measured by the MFPDQ) and presence of MSUS detectable bursae resulted in a Pearson's Correlation coefficient of 0.211 (p=0.371). From the preliminary study data, power calculations indicated that to establish levels of association between 'foot pain and disability' and 'presence of bursae' at the 5% two sided significance level with 80% power, 179 cases would be appropriate and with 90% power, 239 would be appropriate using Pearson's Correlation Coefficient. Furthermore, it was agreed that:

- this figure should be raised to allow for 20% drop out and in case the data was found to be non-normally distributed and
- Spearman's Correlation Coefficient should be used instead.

Secondly, within the pilot study, associations between patients' global impression of their well being and presence of MSUS detectable bursae were of borderline significance and therefore formed the next power calculation. From the study one data, associations between patients' global impression of their well being and presence of MSUS detectable bursae resulted in Pearson's Correlation coefficient of 0.444 (p=0.057). Power calculations indicated that to establish levels of association between 'well being' and presence of MSUS detectable bursae at the 5% two sided significance level with 80% power, 36 cases would be appropriate and with 90% power, 47 would be appropriate using Pearson's Correlation Coefficient. Again, it was agreed that:

- this figure should be raised to allow for 20% drop out and in case the data was found to be non-normally distributed and
- Spearman's Correlation Coefficient should be used instead.

Finally, initial data analysis for associations between DAS-28 scores and presence of MSUS detectable bursae resulted in Pearson's Correlation coefficient of 0.076 (p=0.749) indicating little or no association. Therefore, this data was the focus of the final power calculations and suggested that to establish levels of no association between DAS-28 and presence of bursae at the 5% two sided significance level with 80% or 90% power, the number of cases should be as high as feasible using Pearson's Correlation Coefficient (or Spearman's Correlation Coefficient if the data was found to be non-normally distributed).

There are currently 1400 RA patients registered with Southampton General Hospital Rheumatology department and on average 70 are seen each week. Within the time and resource limits of this pragmatic clinical study, the proposed recruitment target was a sample of 200 patients with RA.

### 3.7.2. Sample Size: Control Participants

As the study was not a case matched controlled interventional study, the control sample size was selected as one third of the RA participant sample to act as a comparator sample for descriptive purposes that was analogous with other studies in this field (Szkudlarek, Court-Payen et al 2001; Ejbjerg, Vestergaard et al 2005; Brown, Conaghan et al 2008).

### 3.7.3. Sample selection: RA participants

During the preliminary determination of the reliability of the MSUS technique study (Chapter four, page 96) a consecutive sample of participants with RA who were starting anti-TNF-α therapy and who were attending the Rheumatology Department, Southampton General Hospital were recruited. For studies two and three (Chapter five, section 5.4, page 127 and Chapter six, section 6.4,  page 165) a consecutive sample of participants with RA, who were attending the Rheumatology Department, Southampton General Hospital as part of their normal care, were investigated.

In all studies the population investigated was homogenous for RA which was required to be diagnosed according to the ACR criteria (Arnett, Edworthy et al 1988) and the clear eligibility criteria (section 4.4.2. page 97, section 5.4.2.1, page128, section 6.4.2.1 page 166) ensured that members of both samples were representative of the wide spectrum of adults

who have RA.

Byrne (1998) describes a homogenous sample as being part of the criteria for an ideal sample. The participants in all three studies were homogenous for RA, although within the samples for studies two and three there was a wide variation in disease state and manifestations of disease on the foot. According to Byrne (1998), including different disease states in the same study may reduce validity of results and careful consideration of conclusions that can subsequently be drawn is deemed essential.

Using MSUS, one small study had previously suggested that MSUS detectable forefoot bursae were highly prevalent and of clinical importance in a sample of patients with early RA (Koski 1998). To our knowledge, there was no other existing longitudinal data that had investigated the prevalence of forefoot bursae in RA and it had received little attention in the literature (see Section 2.2, Chapter 2, page 18). The participant sample for the preliminary study was homogenous in that all participants were starting anti-TNF-$\alpha$ therapy. However, for studies two and three, to determine the true prevalence of MSUS detectable forefoot bursae in secondary care, it was important to include a wide variety of disease states. Interpretation of results, therefore, have to be noted with caution as, it is possible that, splitting the participants into groups for the analyses of associations of MSUS detectable forefoot bursae may have reduced the statistical power. Further investigation in other groups, for example early RA, would be interesting follow up studies.

The approach of the overall study was a pragmatic, clinical one; thus the samples were both drawn from one population of those who were registered under the care of the Rheumatology Department, Southampton University Hospitals' Trust. Therefore, although this ensured good internal validity, findings from this study can only apply to the population of RA patients registered under the care of the Rheumatology Department, Southampton University Hospitals' Trust. Multi-centre collaborative studies are recommended to reduce threats to reliability and validity of an investigation (Bowling 2002) although this was not a feasible option within the scope of this research.

For ease of recruitment within each study a consecutive sampling method was utilised. Advantages of consecutive samples are that they enable easier monitoring and follow-up with good response rates and retention of sample members (Bowling 2002). Random sampling is

considered the 'gold standard' method for recruitment of participants as it allows each member of the target population group a 'non-zero' chance of inclusion within the sample, but is more difficult to achieve (Bowling 2002). To minimize selection bias within the studies, the recruitment of participants was targeted at the whole population attending within a clearly defined time frame of six months. The response bias, or extent to which the RA population within the main study deviated from the whole population of patients who attended within that time frame, could then be determined via non-responder analyses conducted at both baseline (section 5.8.1, page 135) and twelve month assessments (section 6.7.1.1, page 170) .

### 3.7.4. Sample selection: control participants

A convenience sample of staff and students within the School of Health Sciences, University of Southampton, were recruited onto the study to act as comparator healthy controls to the RA participants. Like consecutive sampling, convenience sampling has advantages in analytic research in that subjects are easy to recruit, near at hand and likely to respond (Bowling 2002) making it the most appropriate method to recruit the control participants.

## 3.8. Observational outcomes

### 3.8.1 Preliminary study (reliability of technique)

In order for a technique to be accurate in detecting alterations in observed disease state, it must first be proven reliable (Bowling 2002). Usually a new technique is tested against a 'reference test' or 'gold standard' (Bowling 2002). To determine the ability of MSUS performed by a podiatrist (CB) to detect forefoot bursae within RA, inter-rater reliability was assessed against two consultant radiologists (KD or MS). Both consultant radiologists (KD and MS) were expert in musculoskeletal ultrasound and one (KD) had acted as mentor to the podiatrist (CB) in learning the techniques of MSUS assessment of the forefoot.

#### 3.8.1.1. Musculoskeletal ultrasound imaging equipment

A Diasus diagnostic ultrasound scanner (Dynamic Imaging, Livingston, Scotland UK) was used by the podiatrist (CB) (see **Appendix 4** for technical specifications). The Diasus scanner is a musculoskeletal application specific ultrasound system dedicated to detailed high resolution imaging including: mains-lead, footswitch, operator manual (**Figure 18**). It

operates as a system with dual probe, but for the study, a 5-10MHz 26mm ultra wideband linear array probe was used.

A Philips HDI 5000 System (Royal Philips Electronics, Netherlands) was used by the radiologist (KD or MS). The Philips system includes MicroFine™ Imaging, Broadband Flow® Imaging, Power Contrast Harmonic Imaging, Tissue Harmonic Imaging, Tissue Doppler Imaging, Pulse Inversion Harmonics, Power Motion Imaging, Advanced 3D imaging, Panoramic imaging, adaptive system intelligence and leading-edge connectivity (http://www.heartstream.com/main/products/ultrasound/general/philips_5000/index.html). This system operates with broadband linear probes and in order for direct comparisons to be made within the study a 5 - 12 MHz probe was also used.

**Figure 18.** Photographs of the Diasus MSUS machine used by the Podiatrist within all three studies.



### 3.8.1.2. Musculoskeletal ultrasound scanning protocol

On the same day, both MSUS foot scans were performed (see **Table 11** for overview of scanning protocol) in real time. Scanning was in B-Mode using the 5 – 10 MHz probe. Images were recorded in two perpendicular planes, longitudinal and transverse and performed moving from proximal to distal as suggested by the EULAR (European League

against Rheumatism) "working group for musculoskeletal ultrasound in rheumatology" guidelines (Backhaus, Burmester et al 2001). The EULAR guidelines recommend a dorsal approach to detect MTP joint synovitis with the patient in a supine position however at the time of this study there was no definition for detecting clinically apparent plantar forefoot bursae. Lack of standardization and variation in scanning technique amongst sonographers has been deliberated as contributing to disagreement between experts (Scheel, Schmidt et al 2005).We therefore decided to use a plantar approach to determine the prevalence of MSUS detectable bursae within the forefoot.

**Table 11.** Overview of MSUS technique scanning protocol.

| 1. | The nature of the test was explained |
|----|--------------------------------------|
| 2. | The participant was asked to sit in a supine position on the bed |
| 3. | The participant's hosiery was removed and the ultrasound probe placed on the plantar aspect of each foot |
| 4. | The forefeet of all participants were scanned by the investigators using 5 – 10 MHz probes. |
| 5. | Scans for bursitis were taken both longitudinally and transversely from a plantar approach of the forefoot |
| 6. | The second and fifth MTP joints and inter-metatarsal spaces for both feet were scanned longitudinally and transversely from the plantar view |
| 7. | Images of the plantar aspects of the forefoot in both feet were recorded in transverse and longitudinal aspects and saved on the Diasus ultrasound machine hard drive |
| 8. | Observations of synovial thickening / synovitis (grey scale and power Doppler) and erosions of the second and fifth metatarsophalangeal joints were noted |

Koski (1998) also utilised a plantar approach to detect intermetatarsal bursae sonographically and clinically by palpation, however the reason for this and the limitations were not discussed in his paper. Our justification for using a plantar approach was based on the work by Koski (1998) and on previous clinical observations of pain and palpable bursae occurring within the plantar forefoot area. In addition, from review of the literature (see section 2.2, page 18) the classification of forefoot bursae was confusing and it was apparent that the plantar swellings that had been observed clinically by palpation could be attributed

to either anatomical intermetatarsal bursae or adventitious bursae within the plantar fat pad. Our technique for scanning the plantar forefoot area was also later described by the AIUM (2007) for investigation of the presence of neuroma or intermetatarsal bursitis. A further justification for the plantar MSUS scan approach was that previous cadaver studies investigating forefoot bursae had been conducted via a plantar approach (Chauveaux, Le Huec and Midy 1987; Studler et al 2008) as had MSUS and surgical studies of Morton's neuroma (Irwin, Konstantoulakis et al 2000; Jones, Bygrave et al 1999).

For each scan in our preliminary study the participant was therefore seated, with legs extended on a flatbed plinth so that the soles of the feet were facing the operator, with ankles dorsiflexed. The transducer was placed longitudinally on the plantar aspect of the first intermetatarsal space, and digital pressure was applied by the examiner on the dorsal surface of the foot. The transducer was moved laterally with its centre at the level of the metatarsal heads. The process was repeated for the remaining inter metatarsal spaces and then repeated transversely (see **Figure 19**).

**Figure 19.** Photographs demonstrating the transverse (A) and longitudinal (B) positions of the MSUS transducer to assess the plantar forefoot area.
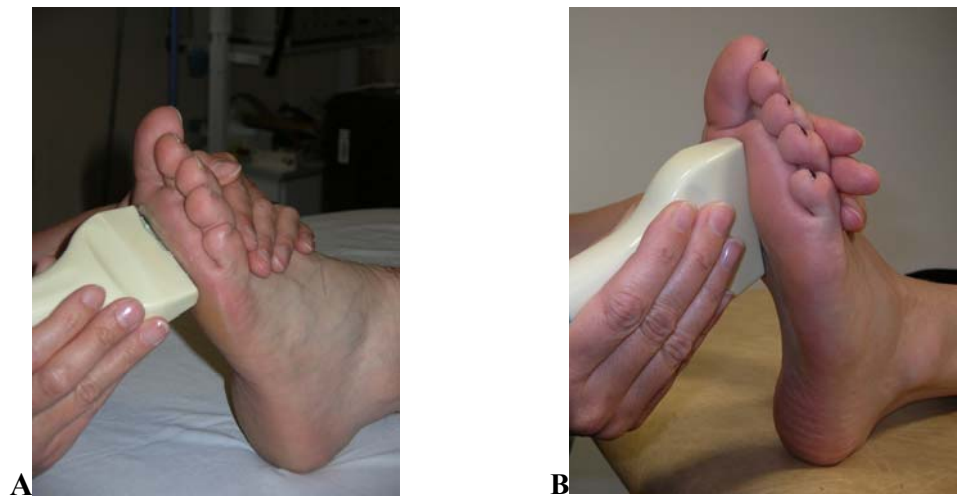


To judge the extent of forefoot bursae against the extent of effect of RA on the forefoot joints, the second and fifth MTP joints were also scanned longitudinally and transversely from the plantar view. Due to timing and availability of the radiologists within the preliminary study only thirty minutes was allowed for each foot assessment. Therefore observations of synovitis and erosions by MSUS were conducted within just two joints in

each foot (second and fifth MTP joints) also from the plantar approach rather than the more conventional dorsal approach.

The second MTPJ was selected for investigation because it is in line with the centre of load through the forefoot during gait (Jacob 2001), it is easily accessible for the MSUS transducers, and was considered representative of the MTPJs. The fifth MTPJ was also selected for its ease of accessibility with the MSUS probes (Szkudlarek , Narvestad et al 2004) and as it has been reported as being the most common site of radiographic and sonographic erosion (Grassi et al 2001). The first MTPJ was excluded due to the sesamoid bones underlying its plantar aspect.

The presence and location of any bursal swelling across the plantar forefoot region and any synovial thickening/synovitis and erosion within the second and fifth MTPJs identified by MSUS was recorded on a data sheet (see MSUS data sheet in **Appendix 5**). Transverse and longitudinal ultrasound images of each plantar forefoot and longitudinal images of each fifth and second MTP joint were saved by the podiatrist on the Diasus ultrasound machine.

To reduce recall bias, all investigators (CB, KD and MS) were blinded to each other's results. Participants were primarily assessed by the podiatrist (CB) within the Wellcome Trust Clinical Research Facility, Southampton General Hospital. Participants were then escorted by a research nurse to the Radiology department where the second MSUS scan was performed by the radiologist (KD or MS).

During the data collection for this preliminary study, it became clear that the plantar approach to detect MTP joint synovial thickening / synovitis was a major limitation. The ability to assess synovitis in some participants, using the linear MSUS 5 – 10 MHz transducer (active length 40mm; see **Figure 20**) to achieve 7.5 MHz frequency with the Diasus machine, was hampered by structural lesser toe deformities and MTP joint subluxation, even with use of liberal amounts of coupling gel.

| **Figure 20.** Photograph of the Diasus MSUS system 8 – 16MHz (active length 26mm) and 5 – 10 MHz (active length 40mm) transducers. |
| --- |



Therefore a dorsal approach to assess MTP joint synovial thickening / synovitis, as recommended by the EULAR "working group for musculoskeletal ultrasound in rheumatology" guidelines was considered for the main study (Backhaus, Burmester et al 2001). However some expected difficulty in assessing MTP joint synovial thickening / synovitis from the dorsal approach still existed, as severe retraction of the lesser toes and subluxation of the MTP joints did not allow good transducer contact from this direction either.

In retrospect, the use of 'stand off' pads and techniques for using a water bath to facilitate the ultrasound wave conduction over gross structural deformities of the foot may have produced better results. These techniques reportedly increase the field of view in anatomical areas where the contour of the part is such that it only allows a small area of contact (Stokes, Hides and Nassiri 1997). At the time of this study these techniques were not readily available within either the podiatric or radiology clinical department. Similarly, small transducer footprints such as 'hockey stick' probes, may have also been easier to use over the deranged MTP joints (Backhaus, Burmester et al 2001), but this was not an available feature of the Diasus machine used within the study either.

Additionally, in the preliminary study, due to forefoot structural deformity in some participants, it was clear from the conceptual stage that tenosynovitis was too difficult to assess using the proposed Diasus ultrasound machine. As well as MTP joint synovitis, the appearance of flexor tenosynovitis on MSUS is a key differential diagnosis for plantar forefoot tenderness (Koski 1995). This inability to measure tenosynovitis using the Diasus MSUS machine also has to be acknowledged as a significant omission and therefore a major limitation in the second and third studies regarding the assessment of the associations of MSUS detectable forefoot bursae with patient reported foot impact outcome measures.

### 3.8.1.3. Reliability of MSUS technique performed by a podiatrist

An important issue within the preliminary study one was measurement error between clinicians and between machines. For the preliminary study, the podiatrist's (CB) technique was tested for reliability against expert radiologists (KD and MS). Although this is a common way of determining reliability, validity can be questioned, especially with the use of two different machines and two different radiologists. In the design of the reliability study, two assumptions were made, firstly that the radiologists were experts in the field of MSUS imaging and secondly that their inter-tester reliability in technique in detecting forefoot bursae was of an acceptable standard.

The OMERACT (Outcome Measures in Rheumatology) framework incorporates a filter to aid decisions as to the applicability of measures (Boers, Brooks et al 1998). The filter incorporates truth, discrimination and feasibility as words that represent questions to be answered of the measure (Boers, Brooks et al 1998). Truth represents issues of face, content and construct and criterion validity; discrimination represents issues of reliability and sensitivity to change; feasibility represents selection of measures (Boers, Brooks et al 1998).

From **Table 12** it can be seen that using the OMERACT filter, that, although the podiatrist's technique was confirmed as being reliable, there are limitations that affect the overall validity of the technique in the detection of forefoot bursae. In terms of 'truth' the result is relevant against an expert in imaging techniques but the podiatrist's (CB) technique may be biased towards over detection of forefoot bursae.

| Table 12. Evaluation of the podiatrist's MSUS technique reliability against the OMERACT filter (Boers, Brooks et al 1998). | |
|---|---|
| Truth<br><br>Is the measure truthful?<br><br>Does it measure what is intended?<br><br>Is the result unbiased and relevant? | The Podiatrist's technique in detecting forefoot bursae with MSUS was reliable with very good agreement with radiologists.<br><br>The Podiatrist's ability to acquire and interpret images from the Diasus MSUS machine was comparable to the radiologists using the higher definition and more costly Philips HDI 5000 system.<br><br>Detection of bursae by any investigator or either MSUS machine was not validated by any other imaging method such as MRI.<br><br>Detection of bursae by any investigator or either MSUS machine was not validated by histological biopsy analysis.<br><br>Detection of bursae by the podiatrist was not validated by cadaveric investigations. |
| Discrimination<br><br>Does the measure discriminate between situations of interest?<br><br>States at one time (for classification or prognosis)<br><br>States at different times (to measure change) | Using an intervention that enabled observation of a quick change in RA disease state, changes in the presence of forefoot bursae were detected by the radiologists over a twelve week period.<br><br>The technique was not sensitive enough to measure actual change of individual bursae that may have altered in size.<br><br>The technique for the ability of MSUS to detect change in forefoot bursae only refers to the radiologists and the Philips HDI 5000 system. |
| Feasibility<br><br>Can the measure be applied easily, given the constraints of time, money, and interpretability? | The MSUS machine was relatively low cost, readily available and portable for use in the clinical setting. The consensus meeting indicated low error in the podiatrist's (CB) technique for interpretation and acquisition of images of the machine indicated good reliability within against a high specification machine utilised in radiology. |

The presence of MSUS detectable bursae within the forefoot was not validated by any other 'gold standard' imaging technique, such as MRI or by histological analysis through biopsy. As well as intermetatarsal bursae and adventitious bursae, soft tissue swelling at the level of the MTP joints can be related to MTP joint synovitis or tenosynovitis that could be better differentiated using MRI (Ashman, Klacker and Yu 2001; Helliwell, Woodburn et al 2007; Studler et al 2008). At the time of the preliminary reliability study, the OMERACT MSUS special interest group had highlighted limited data in terms of comparisons of MRI with MSUS (Wakefield, Balint et al 2005). Due to its restricted availability MRI was not feasible for our study.

Whilst MRI may give better detail regarding anatomical location of a bursa within the forefoot than MSUS, without histological analysis, confirmation of the tissue type remains speculative (Ashman, Klacker and Yu 2001; Studler et al 2008). Similarly, reliability of technique may have been better confirmed by cross referencing MSUS assessment of fresh cadaver forefeet from patients with RA with findings following immediate dissection. Access to fresh cadaver feet was not feasible within the remit of this study.

In terms of discrimination, MSUS was able to detect change in presence of forefoot bursae, although was not sensitive enough to measure actual change of individual bursae that may have altered in size. Of note is that the technique for the ability of MSUS to detect change in forefoot bursae only refers to the radiologists and the Philips HDI 5000 system. Assumptions were made that these results could be conferred to the podiatrist and the Diasus MSUS machine, following good agreements from the baseline data. This could, however, have reduced the reliability of the findings from the longitudinal data in study three and further analysis of agreements for the change data in the preliminary, reliability study would have been beneficial.

In terms of feasibility, the implications for this part of the study did include the potential for utilizing the more affordable, MSUS machine in the clinical environment for more timely. We confirmed that the technique could be applied easily, within the constraints of time, money, and interpretability and demonstrated that MSUS has the potential to be employed to further investigate and undertake assessment of forefoot bursae. However, further work is necessary to validate the technique and gain accurate results.

Given unlimited resources, to validate the MSUS technique for detection of forefoot bursae would ideally involve:-

- A study that allowed MSUS imaging of fresh cadaver feet from individuals who had RA with confirmation of detected bursae by immediate dissection

- The use of MRI as an external validator for location of forefoot bursae in patients with RA

- The use of MSUS guided biopsy of forefoot bursae in patients with RA to confirm tissue type through histological analysis.

### 3.8.2. Prevalence and natural history of musculoskeletal ultrasound detectable forefoot bursae

Once reliability of technique had been established, the main variables of interest investigated within studies two and three were the prevalence of MSUS detectable forefoot bursae (explanatory variable) and patient reported foot disability and impairment (dependent variable).

### 3.8.2.1. Musculoskeletal ultrasound scanning protocol

For the second and third studies (Chapter five, page 125 and chapter six, page 164) the podiatrist (CB) used the Diasus diagnostic ultrasound scanner (Dynamic Imaging, Livingston, Scotland UK) in the same mode as for the first phase reliability study (Chapter four, page 96). Following analysis of the reliability study data, whilst agreements for techniques in identifying forefoot bursae and MTP joint erosions were very good, agreements between the investigators for MTP joint synovitis were poor. The scanning protocol from study one (**Table 11**) was modified for studies two and three to include the observation of all MTP joints via a dorsal approach, although for identification of plantar forefoot bursae a plantar scan approach was maintained, as discussed above. The reliability of the data for MTP joint synovitis and erosion from the second and third studies was, however, not retested and therefore not known, so had to be excluded from the final analyses.

Within the analyses for studies two and three there is thus a possibility that MSUS detectable bursae and MTP joint synovitis may be correlated and collinear but with the lack of data on

MTP joint synovitis we cannot be sure. We did adjust for disease activity which does suggest that MSUS detectable bursae may be independent of MTP joint synovitis, however clarification of this is recommended for future investigations.

Failure to use the measures of MTP joint synovitis and erosion and failure to measure tenosynovitis within the second and third studies using the Diasus MSUS machine has to be acknowledged as a significant limitation regarding the assessment of the associations of MSUS detectable bursae with patient reported foot impact outcome measures. This is, however, a feature that is endemic in all studies on MTP joint synovitis in the foot in RA that haven't taken account of forefoot bursae. Furthermore, it does not invalidate MSUS as a tool for predicting foot symptoms in RA.

Scans were completed after the foot assessments but during the same visit within the Wellcome Trust Clinical Research Facility, Southampton General Hospital. Within the reliability study, clinical foot status was determined by the podiatrist (CB) so that the radiologists (KD and MS) were blinded to the results of the foot assessment. However, this meant that the MSUS measurements performed by the podiatrist (CB) were not performed independently to the clinical foot assessments. The same approach was used within the second and third studies (Chapter five, page 125 and Chapter six, page 164), that is the clinical activity and clinical foot assessments were performed by the same individual (CB) and not determined by an independent assessor. Thus there was no attempt at blinding of the results of the clinical foot assessments from results of the MSUS assessments.

For the second and third studies it was not feasible to have numerous independent investigators and as such investigator bias and recall bias therefore need to be taken account when interpreting the data. Investigator bias is common in social research on human beings (Bowling 2002) and we attempted to reduce the effect of this bias by maintaining a systematic order to the data collection (see study protocol flow charts, Chapter five, page 134, Chapter six, page 169) and using experienced independent data handlers to double enter and clean all the information onto the SPSS data sheet.

### 3.8.2.2. Assessment of patient reported foot impact in RA

For foot and ankle investigations it is recommended that as a minimum for data collection,

researchers capture the variables of local pain, global pain, foot function and general function (activities of daily living) (Bowen, Burridge and Arden 2005).

Within the preliminary reliability study (Chapter four, page 96), foot pain and disability were determined by the use of a validated patient administered questionnaire, the Manchester Foot Pain and Disability Questionnaire (MFPDQ) (Garrow, Papageorgiou et al 2000) (see **Appendix 6**). A second instrument, the foot function index (Budiman-Mak, Conrad and Roach 1991) was also trialled within the preliminary reliability study with a view to undertaking a cross-reference study to determine which instrument would be most beneficial for use within the second and third studies.

The MFPDQ asked participants to rate a series of questions that took approximately five minutes to complete at the same visit as the MSUS scans. The MFPDQ index consists of 19 items divided into four sub scales; functional problems, pain intensity, personal appearance and difficulties in performing work or leisure related tasks (Garrow, Papageorgiou et al 2000). Responders are asked to grade the severity of their disability by marking whether the disability is present 'none of the time' (scored 0), 'on some days' (scored 1) or 'on most or every day' (scored 2). Total scores for each of the subscales are then calculated and expressed as a percentage (Garrow, Papageorgiou et al 2000). However, validation of the instrument did not apply to the separate domains, creating concerns for internal validity if the different domains are analysed separately. The MFPDQ was therefore analysed as a total score within the preliminary reliability study, however the results were limited as this tool had not been validated for sensitivity to change in RA related foot status.

The FFI asked patients to score, on a series of 100mm visual analog scales, their foot pathology in terms of three sub scales for foot pain, foot disability and activity restriction. It also took approximately five minutes to complete at the same visit as the MSUS scans. A criticism of the FFI is that it was designed by groups of professionals and then validated using RA patients to sensitively measure foot pathology in terms of the three sub scales (Barnett, Campbell and Harvey 2005). Further issues arose within the preliminary reliability study in the complex way that the final score is derived. For each item a score is derived, by dividing the attached 100mm horizontal line into ten equal segments and assigning a number ranging from 0 to 9 to each segment. To obtain a sub scale score, the item scores for a sub-scale are totaled and then divided by the maximum total possible for all the sub-scale items

which the patient indicated were applicable. The score is multiplied by 100 and a total FFI score is derived by calculating the average of the three sub-scales (Budiman-Mak, Conrad and Roach 1991).

The most common problem encountered by the investigator within the preliminary reliability study with this instrument was in the calculation of a score from a point that was exactly on a whole number; for example, where a patient had annotated exactly over 8mm, a decision had to be made as to whether the score should be 7, or 8. Patients also encountered difficulty in completing the FFI scales and many did not complete all sections. Furthermore, some patients may have had ankle joint pain but did not report it as the questions within the FFI are focused on the foot. Therefore, in light of the experienced limitations, the FFI was discounted from the study and the MFPDQ was considered for use as the measure for foot pain and disability within studies two and three without undertaking a cross-reference study of the two outcome measures.

During the preliminary reliability study it was evident that MFPDQ was a more suitable instrument than FFI, however, limitations of concern for the MFPDQ also existed. The MFPDQ had been developed and validated for use with general populations and therefore was not specific to RA (Garrow, Papageorgiou et al 2000). The questions within the MFPDQ had the rider "because of pain in my feet" and therefore some aspects of the impact of RA on the feet may have been under-reported. This may be why the MFPDQ reportedly has a demonstrated floor and ceiling effect for patients with severe RA foot deformity (Helliwell 2003). Furthermore, some participants within the preliminary reliability study had hindfoot symptoms (when assessed by the podiatrist) but did not report them as they stated that "the questions were focused on pain in their feet and not their ankles".

The decision to use the MFPDQ in studies two and three was ultimately changed and a different, new measure, the Leeds Foot Impact Scale (LFIS) was used instead within the second and third studies (see **Appendix 7**). The rationale for the change in approach was that during the course of the preliminary reliability study, results from the validation of the LFIS were published, with high reliability for measurement of patient related foot symptoms in RA and sensitive to change in foot status (Helliwell, Reay et al 2005).

The advantage of LFIS over MFPDQ was that it was developed specifically for RA patients

to measure foot symptoms related to impairment, footwear and activity participation limitation and restriction at all stages of their disease (to include early and late stage RA) (Helliwell, Reay et al 2005).

In the development of LFIS, 131 items were selected, from patient interviews and a series of statements broken into three subgroups classified according to the WHO ICD (The World Health Organization International Classification of Diseases) classification of 'activity' (37 items), 'impairments' (56 items) and 'participation' (24 items), with 'impairment' and a further subgroup classified as 'footwear related' (14 items) (Helliwell, Reay et al 2005). Following further analysis, the final version of LFIS now has:

- two dimensions with fifty one items
- good test, retest reliability
- no systematic differences
- been tested for responsiveness to change (Helliwell, Reay et al 2005).

LFIS is presented as a self-completed questionnaire that takes about five minutes for patients to complete, with the two subscales for impairment and footwear (LFIS$_{IF}$), and activity limitation and participation restriction (LFIS$_{AP}$) that are used for analyses. LFIS$_{IF}$ contains twenty one items related to foot pain and joint stiffness, as well as footwear related impairments. LFIS$_{AP}$ contains thirty items related to activity limitation and participation restriction (Helliwell, Reay et al 2005). Responses to each question are dichotomized as yes or no and scoring is a simple tally and therefore advocated as clinically simple to use (Helliwell, Reay et al 2005).

Having decided to use LFIS instead of MFPDQ in studies two and three, at that stage, a cross reference study between MFPDQ and LFIS would have been interesting; however in the development of LFIS the authors had reported that it did demonstrate good concurrent validity to the MFPDQ (Helliwell, Reay et al 2005). In addition, in 2008, van der Leeden, Steultjens et al rated LFIS as one of the most utilized instruments for measurement of the impact of RA disease on the foot. As studies two and three were not directly compared to study one, this would not introduce any bias.

Therefore, LFIS was justified as being selected over MFPDQ, as the better measure of assessment of the impact of RA disease on the foot over time for use within studies two and

three. Permission was granted from the authors for LFIS to be used within this doctoral study.

### 3.8.2.3. Assessment of confounding factors

The confidence that a change in MSUS detectable bursae is followed by changes in LFIS subscale scores is subject to interpretation bias due to extraneous variables that could confound the results. Bowling (2002) describes a confounding variable as an extraneous factor (a factor other than the variables under study), not controlled for, which distorts the results. Confounding thus arises when an association between an explanatory variable and dependent variable is being investigated, but the outcome and exposure are both strongly associated with a third variable (Petrie and Sabin 2005).

Age and gender are common confounding variables (Bowling 2002) and so these variables were controlled for separately by observation of the comparator healthy subjects at the baseline assessments. A second key method for addressing confounding variables is to fit a regression model (Bowling 2002) so that the relationship between the variable of interest (MSUS detectable bursae) and the outcome ($LFIS_{IF}$ and $LFIS_{AP}$) can be examined while holding the other variables constant.

Confounding variables should be considered on the basis of biological or clinical view and be related to the outcome. Confounding variables therefore identified from the preliminary study (Chapter four, page 96) were:

- Age
- Gender
- Disease duration (years)
- Presence of rheumatoid factor (sero-positive or sero-negative)
- Weight  (kg)
- Height (cm)
- Limb dominance (left or right)
- Current medication and previous use of Disease Modifying Anti-Rheumatic Drugs (DMARDs)
- C-reactive protein (CRP) (mg/litre)
- Erythrocyte Sedimentation Rate (ESR) (mm/hour)
- Participants' global impression of well being measured via a visual analog scale

(VAS 100mm where 0 was 'Best Imaginable Health State' and 100 equal to 'Worst Imaginable Health State')

- DAS-28 (ie. assessment of the patient's global impression of health and disease activity and the number of painful, tender and swollen joints calculated as part of the 28 joint Disease Activity Score; DAS-28 remission scores < 2.6; low disease activity scores ≥ 2.6 but < 3.2; moderate disease activity scores ≥ 3.2 but < 5.1; high disease activity scores ≥ 5.1; van der Heijde, van't Hof, et al 1993)

- Foot joint mobility (observation of the range of movement within the ankle joints, sub-talar joints, mid-tarsal joints and first MTP joints were recorded by CB and documented as full range, limited range or absent range)

- Foot structure (observation of MTP joint subluxation and pes-planus)

Copies of the demographic and clinical data collection forms are attached in **Appendix 8**, **Appendix 9** and **Appendix 10**.

Of note is that within the preliminary (reliability) study clinical activity was measured via the DAS-28 score that was performed independently by a trained joint assessor. For the second study, DAS-28 scores were obtained from clinical medical notes and the rheumatology department database. During the second study, DAS-28 scores were however not available for all participants. Therefore for the final study, the investigator (CB) was trained in DAS-28 technique and also performed these assessments.

In study three, the fact that there was a change in personnel performing the DAS-28 obviously had no impact between studies one and two as the data between those studies was not used interchangeably. During study three, the DAS-28 assessment was always performed before the MSUS foot assessments and it is possible that at a purely subconscious level that this may have affected the interpretation of the MSUS images leading to a greater reporting of MSUS detectable forefoot bursae. Whilst we cannot fully rule this out, the prevalence of MSUS detectable forefoot bursae and the association between MSUS detectable forefoot bursae and DAS-28 did not differ significantly between studies two and three. This would argue against a major bias.

**3.9. Data storage**

The chief investigator has overall control of and acts as custodian for the data generated by studies.

*3.9.1. Preliminary study (reliability of technique)*

This study was embedded within a larger study that was investigating RA participants' responses to anti-TNF-α therapy. The custodian of the data was therefore the chief investigator for that study and all data was held at the Rheumatology Research Department, Southampton Hospital NHS Trust, in a locked filing cabinet. Access to the data was restricted to the researcher and the research team as identified at ethical approval.

All information recorded was stored on a password locked computer database and coded such that all participants' names were replaced with two letters to ensure anonymity and that at no time any personal details were revealed. Data stored on the Diasus ultrasound system, also at that stage was coded and not directly identifiable to any participants. The Diasus ultrasound system is owned by the School of Health Sciences, University of Southampton and housed within a gait laboratory that is managed by a laboratory technician and locked when not in use.

Participants were also encouraged to review their individual records, however no requests were forthcoming.

*3.9.2. Prevalence and natural history of musculoskeletal ultrasound detectable forefoot bursae*

The chief investigator for this study was the main investigator and custodian of the data. All personal information therefore is held within a locked filing cabinet within the secure office of the Chief Investigator in the School of Health Sciences and will be stored for 15 years in line with the University of Southampton data protection policy and ethical approval.

All information recorded was stored on a password locked computer database and coded such that all participants' names were replaced with a number to ensure anonymity and that at no time any personal details were revealed. As above in the preliminary study data stored on the Diasus ultrasound system was also at that stage coded and not directly identifiable to any participants.

## 3.10. Statistical analysis

All statistical analyses were performed by the investigator (CB) and checked for accuracy by an expert medical statistician.

Throughout the statistical analyses, statistical significance is stated as $p<0.05$ as well as whether one or two tailed tests were used to avoid Type 1 and Type II errors. The error of rejecting a true null hypothesis is a type 1 error (or alpha error) and the failure to reject a null hypothesis when it is actually false is a type II error (beta error) (Byrne 1998) (**Table 13**). This section outlines the statistical methods and data analysis techniques used to minimize risk of type I and type II errors.

**Table 13.** Features of Type I and Type II errors (Adapted from Byrne 1998).

| Features of a Type I Error | Features of a Type II Error |
|---|---|
| ◆ Rejection of a true null hypothesis | ◆ An acceptance of a false null hypothesis |
| | ◆ The chance of missing a real effect |
| ◆ False claim of a difference | ◆ False claim of no difference when a difference actually exists, but the sample size is too small to prove it |
| ◆ Common when a researcher is too ready to reject the null hypothesis (alpha error) | ◆ Common when a researcher is too ready to accept the null hypothesis (beta error) |
| ◆ Occurs approximately 5% of the time with a P value threshold of <0.05 | ◆ Occurs approximately 20% of the time with a power of 80% (power = $1 – ß$) |
| ◆ Analogous to convicting an innocent person | ◆ Analogous to acquitting a guilty person |

### 3.10.1. Data evaluation software

Data evaluation and statistical analysis were performed using the Statistical Package for Social Sciences (SPSS) version 14.0 software (SPSS, Chicago IL).

### 3.10.2. Data entry

Bias can occur within studies due to incorrect data entry (Byrne 1998). To minimize data entry error, all data was entered onto the SPSS data sheet by the investigator (CB) for the preliminary, validation study (Chapter four, page 96) and checked by a second investigator (SS) for errors. Prior to analysis of data in the main study (Chapters five, page 125 and six, page 164), all data was double entered and cleaned by independent MRC (Medical Research Council) data managers for both baseline and twelve month assessments.

### 3.10.3. Checking assumptions

Each data set was initially examined by the investigator (CB) using histograms and scatter plots to determine normalcy and any 'outliers' that may have occurred due to data entry bias or normal biological outliers.

For investigation of associations, before the relationship between MSUS detectable forefoot bursae and foot impact scores could be entered into a multivariate regression model with the predictor, confounding variables, diagnostic tests for assumptions were performed. Diagnostic tests for colinearity, constant variance and normal probability of standardized residuals were executed to determine suitability for multiple linear regression modeling.

### 3.10.4. Descriptive statistics

The demographic and clinical characteristics of the study participants are presented as the mean, standard deviations (SD) and range and presented graphically as histograms and bar charts.

### 3.10.5. Study one: inter-observer agreements

Levels of agreement may be calculated using Bland and Altman plots, intra class correlation coefficients or by Cohen's kappa statistic (Petrie and Sabin 2005). The former are used to measure continuous data and the latter measure categorical data (Petrie and Sabin 2005).

Sensitivity and specificity diagnostic tests provide further information about the levels of agreement (Petrie and Sabin 2005).

Inter-observer agreements between the podiatrist (CB) and radiologists (KD or MS) produced categorical data and therefore were calculated by overall agreement (percentage of observed exact agreement), sensitivity and specificity values and kappa statistics.

### 3.10.5.1. Study one: sensitivity and specificity

Sensitivity is the proportion of individuals with the disease who are correctly identified by the test (true positives). Specificity is the proportion of individuals without the disease who are correctly identified by the test (true negatives) (Petrie and Sabin 2005). Both should, ideally, be close to 1 (or 100%), however in clinical practice this is not always achievable and it may be that sensitivity may be excellent at the expense of specificity and vice versa (Petrie and Sabin 2005). Generally, in clinical studies, it appears that if both values are over 80% the results are very good and if both are over 70% the test results could be reasonably accepted (Bowling 2002).

### 3.10.5.2. Study one: kappa agreement

The kappa statistic allows assessment of the extent of the reproducibility of a measurement (reliability) and is useful to measure agreement between different observers (inter-rater agreement) using the same measurement techniques and agreement between replicate measurements taken at different points in time. Therefore kappa is useful as it informs how much of the possible agreement between two observers has occurred over and above chance (McGinn, Wyer et al 2004). The use of kappa to test agreement can sometimes be difficult to interpret, as it may reflect actual change rather than poor reliability of the measure (Bowling 2005).

Kappa can be thought of as the chance-corrected proportional agreement, and possible values range from +1 (perfect agreement) via 0 (no agreement above that expected by chance) to -1 (complete disagreement) (**Table 14**). The unweighted kappa statistic (unweighted for dichotomous scoring, that is, presence or absence of MSUS detectable bursae) was the most appropriate test for this reliability study.

**Table 14.** Qualitative classification of kappa values as degree of agreement beyond chance (McGinn, Wyer et al 2004).

| Kappa Value | Degree of agreement beyond chance |
|---|---|
| 0 | None |
| 0-0.2 | Slight |
| 0.2-0.4 | Fair |
| 0.4-0.6 | Moderate |
| 0.6-0.8 | Substantial |
| 0.8-1.0 | Almost perfect |

### 3.10.6. Studies two and three: Prevalence and natural history of musculoskeletal ultrasound detectable forefoot bursae

The prevalence of bursae per foot and per anatomical site within the forefoot is described via the mean, standard deviations and frequencies and presented graphically as histograms, bar charts and box plots. Differences in the prevalence of MSUS detectable bursae and clinically detectable bursae were determined by non parametric Chi squared analyses for independent samples. Chi squared analysis allows the numbers with, and without, the characteristic in each of the response groups to be tested for discrepancies. A large discrepancy between observed and corresponding expected frequencies is an indication that the two groups differ (Petrie and Sabin 2005).

To explore whether there were differences between those individuals with MSUS detectable bursae only and those with MSUS detectable bursae that were also clinically palpable, the data was split into groups that were analysed for differences using analysis of variance. This test allows a single global statistical assessment to determine whether the means differ in any group and is more appropriate than performing tests to compare means in each of the pairs of groups that is linked to high Type I errors (Petrie and Sabin 2005).

Due to the small number of patients in the preliminary reliability study, normal distribution of the data was not assumed and Spearman's Correlation Coefficient was used to determine interrelationships between the MSUS imaging data and the clinical observations and

demographical variables. Within the studies two and three, Gaussian distribution was observed for each of the variables and so Pearson's correlation coefficient was used to determine interrelationships between the MSUS detectable bursae, $LFIS_{IF}$ and $LFIS_{AP}$ and other explanatory variables.

Correlation analysis is concerned with measuring the degree of association between two variables. The measurement demonstrates how close the observations are to a straight line drawn through the midst of the points between two variables (Petrie and Sabin 2005). The range is from -1 to +1, where perfect correlation is either +1 or -1 and no correlation is 0 (Petrie and Sabin 2005). To investigate the extent to which two variables are associated linear regression techniques are used, whilst multiple linear regression techniques are used to investigate the extent of relationships that include more than one explanatory variable (Petrie and Sabin 2005).

### 3.10.7. Studies two and three: Regression models

Once assumptions had been checked and suitability established, linear and logistic regression analyses were used to determine associations between the individual data for total numbers of MSUS detectable bursae, disease impact on the foot ($LFIS_{IF}$ and $LFIS_{AP}$) and other explanatory variables. Multiple linear regression techniques were also used to assess the impact of disease impact on the foot ($LFIS_{IF}$ and $LFIS_{AP}$) and other explanatory variables that were significantly associated with both disease impact on the foot ($LFIS_{IF}$ and $LFIS_{AP}$) and the total numbers of MSUS detectable bursae.

### 3.10.8. Study three: Natural history of MSUS detectable bursae

Differences between baseline and one year measures for returnees were analysed using paired t-tests for parametric related numerical data for explanatory and outcome variables of weight, height, global well-being VAS, ESR, CRP, DAS-28, MSUS detectable bursae, $LFIS_{IF}$ and $LFIS_{AP}$. Chi squared tests were used to analyse differences for non-parametric data related to clinical foot care, use of DMARDs and anti-TNF-α therapy and foot structure.

### 3.10.9. Studies two and three: Non responder analyses

To ensure that the responder populations for studies two and three were representative of the RA population after checking assumptions of normality, an unpaired t-test for numerical parametric data was performed to compare the means in the responders and non responders for age. Simple chi squared analyses were performed on the categorical data of gender, seropositivity, and number of DMARDs and anti TNFα therapy between responders and non-responders.

The same approach was used to determine if there were any differences between the returnees and non returnees at the twelve month assessments.

## 3.11. Timescale for completion of the studies

The time frame for the main data collection was dependent on the recruitment of suitable participants and, as such, the end of the study data collection occurred when the last patient had attended.

All pilot work and validation of the technique within the preliminary study took place between July 2004 and June 2007. Ethical approval was granted from the Local Research Ethics Committee in March 2004. Data collection for the RA participants recruited to the studies two and three (Chapter five, page 125 and Chapter six, page 164) were performed between July 2006 and September 2008. Ethical approval for the latter study was granted from the Local Research Ethics Committee in June 2006.

Data collection for the healthy participants recruited to the main study took place during a two week period in February 2008. Ethical approval was granted from the School of Health Sciences Research Ethics Committee in November 2006 and subsequent amendments to the study protocol were approved in December 2007 (See Gantt Chart **Appendix 11**).

## 4.0 Chapter Four: Reliability of musculoskeletal ultrasound technique and pilot study to test the methodology for subsequent study

### 4.1. Introduction

Due to the wide use of MSUS and the depth and breadth of training required, new proposals advocate tailored learning of the technique to discrete fields of practice (Brown, Roberts et al 2007). This doctoral work was novel, in that it was the first study to evaluate tailored learning by consensus of image interpretation and also by reproducibility of technique of MSUS to the discrete field of foot and ankle practice. In other words, evaluation of the inter-observer agreement in the use of MSUS, between an allied health professional (podiatrist) and a radiologist, expert on MSUS imaging of the foot.

### 4.2. Aims

This study provided an opportunity to evaluate the inter-observer agreement between a radiologist and podiatrist, in the MSUS assessment of the forefoot of patients with RA. The study also allowed investigators to determine whether MSUS is a key modality for assessing the prevalence of plantar forefoot bursae in RA and the responsiveness of MSUS to demonstrate change in bursae.

Data from this study was therefore used to answer the following research questions:

d) *Is diagnostic ultrasound, performed by a podiatrist, a reliable technique to identify the prevalence of bursae in the RA plantar forefoot?*

e) *Does the prevalence of MSUS detectable bursae in the plantar forefoot area of patients with RA change following a period of intervention (anti-TNF-α therapy)?*

f) *Is MSUS responsive to change in prevalence of bursae in the plantar forefoot area of patients with RA following a period of intervention (anti-TNF-α therapy)?*

### 4.3. Study design

A blinded inter rater reliability study design was utilized, in which the forefeet of a consecutive cohort of patients with RA were examined with MSUS, by two investigators.

## 4.4. Subjects

A consecutive cohort of patients with RA diagnosed according to the ACR criteria (Arnett, Edworthy et al 1988) starting anti-TNF-α therapy (infliximab, etanercept or adalimumab) was examined at baseline and twelve weeks following therapy.

### 4.4.1. Participant recruitment

The initial approach for recruitment was based upon potential participants with RA attending the Rheumatology Department, Southampton General Hospital NHS Trust who were starting anti-TNF-α therapy.  Those responding to the request for assistance were entered onto the test programme following a detailed patient interview and explanation of the study.  During this initial phase of contact, the individual was actively given the opportunity to ask any questions.  Finally, informed consent was successfully obtained and documented for each recruit.  An example of the patient information sheet is included in **Appendix 12**.

### 4.4.2. Selection criteria

All individuals with RA who were undergoing active treatment and starting anti-TNF-α therapy were considered appropriate for this study.  However, those with learning difficulties or unable to comprehend the patient information sheet were not selected, as the nature of consent would have been inappropriate.

#### Inclusion criteria

- Individuals with RA diagnosed according to the ACR criteria (Arnett, Edworthy et al 1988; table 1, page 11).
- Individuals with RA who were undergoing active treatment at the Rheumatology Department, Southampton General Hospital.

#### Exclusion criteria

- Individuals who had previous surgery to the forefoot.
- Individuals who had received a corticosteroid injection to the forefoot within the 3 months prior to commencement of the study.
- Individuals who had concomitant musculoskeletal disease, such as primary

osteoarthritis, gout, Pagets, systemic lupus erythematosus (sle).

- Individuals who had a serious medical (other than RA) or psychological disorder that may affect the study protocol.

- Individuals who were unable to give informed consent.

### 4.4.3. Rheumatology screening

Prior to data collection, the diagnosis of RA was confirmed by the supervising consultant. Moreover, the same consultant was available throughout the study to avoid any potential investigator bias. Following acceptance into the study all participants were assessed by a trained specialist rheumatology nurse and Disease Activity Scores (DAS-28) were calculated (Prevoo, van't Hof et al 1995).

## 4.5. Data collected

All investigators were blinded to the other's results in order to minimise the risk of selection bias (Bowling 2005).

### 4.5.1. Location

All data collection during this phase that was undertaken by the Podiatrist (CB), took place in the 'Wellcome Trust' Clinical Research Facility. All data collection during this phase that was undertaken by the Radiologist (KD or MS), took place in the Department of Radiology, Southampton General Hospital. On each occasion, the same treatment bays and ultrasound facilities were utilised in an attempt to standardise environmental factors, such as room temperature and scanning positions. Furthermore, whilst the preliminary examination was conducted, at each site, curtains surrounding the beds were drawn. This action was undertaken to preserve the patient's dignity at all times, in line with ethical guidelines.

### 4.5.2. Assessment of demographic and clinical characteristics

General demographic data of age, sex, disease duration, presence of rheumatoid factor, weight, limb dominance, current medication, current and previous use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) were obtained from the Rheumatology Department database and clinical notes.

Clinical characteristics included visual analog scale (VAS 100mm) assessment for the patient's global impression of health and assessment of disease activity by the number of painful, tender and swollen joints calculated as Disease Activity Scores (DAS-28). Foot symptoms were determined by the use of a validated patient administered questionnaire, the Manchester Foot Pain and Disability Questionnaire (MFPDQ) (Garrow, Papageorgiou et al 2000). The MFPDQ asked participants to rate a series of questions and took approximately five minutes for participants to complete at the same time as the MSUS scans. A copy of the MFPDQ form can be seen in **Appendix 6**.

### 4.5.3. Other clinical data

Laboratory assessments included blood tests for C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) on the same day as the MSUS scans.

The patients' hospital notes were examined for any reference to forefoot bursitis, synovitis or erosion. The forefeet of all patients were assessed by an experienced podiatrist (CB) and the presence of swelling and tenderness of the MTP joints and the location and numbers of clinically apparent plantar bursae were recorded.

### 4.5.4. Imaging data

On the same day, the MSUS foot scans were performed by both the podiatrist (CB) and a radiologist (KD or MS) in real time but both investigators were blinded to each other's results. A research assistant ensured that participants were escorted between the two MSUS assessment areas and also ensured that neither investigators could view the others findings. A Diasus MSUS scanner (Dynamic Imaging, Livingston, Scotland UK) was used by the podiatrist (CB) and a Philips HDI 5000 System (Royal Philips Electronics, Netherlands) was used by the radiologist (KD or MS) (see Chapter three, section 3.8.1.1, page 73).

To judge the extent of forefoot bursae against the extent of effect of RA on the forefoot joints, the second and fifth MTP joints were also scanned longitudinally and transversely from the plantar view (for rationale see Chapter three, section 3.8.1.1, page 73). See **Appendix 5** for MSUS data collection sheet).

### 4.5.5. Musculoskeletal ultrasound imaging protocol
See Chapter 3, section 3.8.1.2, page 74.

## 4.6. Consensus of image interpretation protocol

At the end of the data collection period, a consensus meeting took place between the radiologist (KD) and the podiatrist (CB). During this meeting, all images as recorded by the Diasus (Dynamic Imaging Ltd, Livingston, Scotland, UK) MSUS unit where there was no agreement of presence of forefoot bursae, MTP joint synovitis and erosion from the results of the study were discussed. The radiologist (KD) explained to the podiatrist (CB) how to improve on MSUS image interpretation.

Following the consensus meeting, 36 ultrasound real time images were randomly selected from the data collected using the Diasus (Dynamic Imaging Ltd, Livingston, Scotland, UK) MSUS unit, by an independent research assistant (OS). All images from which the 36 were selected had previously been confirmed by the radiologist as being MSUS detectable forefoot bursae, MTP joint synovitis, erosion or normal. All 36 images were numbered and logged by the research assistant (OS). All 36 images were randomised in an unrestricted random method of allocation by the research assistant (OS) and the sequence for image viewing was selected by the research assistant (OS) drawing the numbers from a hat. Both the primary investigator (CB) and consultant radiologist (KD) were blinded to the image selection procedure.

The two investigators independently scored all 36 images for the presence of forefoot bursae, MTP joint synovitis, MTP joint erosions or healthy. The Investigator (CB) identified images as forefoot bursae, MTP joint synovitis, MTP joint erosions or healthy and recorded as such against the image number. The radiologist (KD) also identified the images at the same time as forefoot bursae, MTP joint synovitis, MTP joint erosions or healthy and recorded as such against the image number. The investigator (CB) and radiologist (KD) were blinded to each others findings.

## 4.7. Summary of study one protocol

For a summary of study one protocol see **Figure 21**.

**Figure 21.** Flow diagram of a summary of the protocol for study one.

| | |
|---|---|
| **1**. All patients with RA about to begin treatment with anti-TNF-α therapies were rescreened by rheumatology nurse specialist | **1i.** Interested and suitable participants invited to discuss the study further with rheumatology consultant. |
| **2.** Informed consent taken and copy given to patient. | **1ii.** patient information sheet and consent form to be given to prospective participants by rheumatology consultant |
| | **1iii.** GP information letters to be sent |
| **3.** Willing participants complete commence anti-TNF-α therapy regimen in Wellcome Trust Clinical Research Facility | **3i** Blood tests carried out for CRP and ESR |
| **4.** Assessment of demographic and clinical characteristics carried out in Wellcome Trust Clinical Research Facility on the same day as anti-TNF-α therapy regimen commences. | **4i.** Podiatrist assessed both feet clinically |
| | **4ii.** Participants completed the MFPDQ questionnaire |
| **5.** All MSUS scans performed on the same day as anti-TNF-α therapy regimen commences. | **5i.** MSUS scans of both feet performed by Podiatrist in Wellcome Trust Clinical Research Facility |
| **6.** Medical notes consulted for background clinical demographic information | **5ii.** MSUS scans of both feet performed by Radiologist in Department of Radiology |
| **7.** Participants return for reassessment at twelve weeks following commencement of anti-TNF-α therapy regimen | **7i.** Results analysed at end of study period. |
| | **7ii.** Consensus meeting on agreement of image interpretation between radiologist and podiatrist |

## 4.8. Results

The analysis focuses on:

1. Clinical and demographical description of the participants
2. Inter-observer reliability of MSUS technique
3. Prevalence of plantar forefoot bursae detected by MSUS by the radiologist
4. Change in prevalence of plantar forefoot bursae following anti-TNFα therapy intervention

### 4.8.1. Participant demographics at baseline visit

A consecutive sample of thirty two patients with RA and starting anti-TNF-α therapy were recruited. All patients fulfilled the classification criteria of the American College of Rheumatology for RA (Arnett, Edworthy et al 1988, table 1, page 11). One patient withdrew due to time issues during the visit. Thirty one patients completed the study at baseline. There were 24 female and 7 male patients, 12 rheumatoid factor negative and 19 rheumatoid factor positive. The mean age was 59.58 (SD 10.14) years, mean weight 70.66 (SD 15.35) kg, mean reported well-being was 60.92 (SD 21.12) mm and all patients had active disease with mean DAS-28 scores of 5.8 (SD 0.9), mean ESR 37.86 (24.48) mm/hr and mean CRP of 31.92 (27.15) mg/l. The mean number of MSUS detectable forefoot bursae per individual was 3.8 (SD 2.5) and mean number of clinically detectable forefoot bursae was 1.5 (SD 1.9) (**Table 15** and **Table 16**).

**Table 15.** Demographic characteristics of the validation study participants at baseline.

| Variable | No | Mean (SD) | Range |
|---|---|---|---|
| Age (years) | 31 | 58.97 (10.56) | 37-76 |
| Time since RA diagnosis (years) | 31 | 11.13 (10.52) | 1-39 |
| Weight (kg) | 31 | 70.8 (15.35) | 47.7-107.5 |
| MFPDQ (max /38) | 29 | 23.17 (9.23) | 0-35 |
| Overall well being (100mm VAS) | 28 | 60.29 (21.12) | 20-100 |
| MSUS detectable forefoot bursae | 30 | 3.8 (2.5) | 0 - 9 |
| Clinically detectable forefoot bursae | 30 | 1.5 (1.9) | 0 - 6 |

**Table 16.** Clinical characteristics of the validation study participants at baseline.

| Variable | No | Mean (SD) | Range |
| --- | --- | --- | --- |
| ESR (mm/hour) | 29 | 37.86 (24.48) | 4.0-106.0 |
| CRP (mg/litre) | 29 | 31.92 (27.15) | 2.0-117.0 |
| DAS-28 | 29 | 5.76 (0.93) | 3.91-7.52 |

### *4.8.2. Participant demographics at twelve week follow up visit*

All thirty one participants returned for reassessment at twelve weeks. There was a trend towards reduction in all outcome variables with mean ESR of 26.5 (16.4) mm/hr, mean CRP of 13.98 (15.38) mg/l, mean DAS-28 scores of 4.54 (1.5), mean reported well being of 45.31 (23.25) mm, mean MFPDQ of 17.13 (9.73), mean number of MSUS detectable forefoot bursae 3.6 (2.8) and mean number of clinically detectable forefoot bursae 1.1 (2.0) (**Table 17** and **Table 18**).

**Table 17.** Demographic characteristics of the study participants at twelve weeks.

| Variable | No | Mean (SD) | Range |
| --- | --- | --- | --- |
| Age (years) | 31 | 58.97 (10.56) | 37-76 |
| Time since RA diagnosis (years) | 31 | 11.13 (10.52) | 1-39 |
| Weight (Kg) | 27 | 73.25 (15.25) | 50-108.18 |
| MFPDQ (max /38) | 24 | 17.13 (9.73) | 0-34 |
| Overall well being (100mm VAS) | 26 | 45.31 (23.25) | 0-100 |
| MSUS detectable forefoot bursae* | 26 | 3.6 (2.8) | 0 - 9 |
| Clinically detectable forefoot bursae** | 26 | 1.1 (2.0) | 0 - 7 |

**Key:** *Total numbers of MSUS detectable bursae per individual; ** Total numbers of clinically palpable bursae per individual

**Table 18.** Clinical characteristics of the study participants at twelve weeks.

| Variable | No | Mean (SD) | Range |
|---|---|---|---|
| ESR (mm/hour) | 26 | 26.5 (16.4) | 2-67 |
| CRP (mg/litre) | 26 | 13.98 (15.38) | 2-55.5 |
| DAS-28 | 26 | 4.54 (1.5) | 2.04-7.03 |

### *4.8.3. Inter-observer agreement in detection of forefoot bursae using ultrasound*

To determine the ability of the podiatrist (CB) to reliably detect bursae within the forefoot, the results of MSUS scan interpretations were compared against expert MSUS radiologists (KD or MS) who acted as the 'gold standard' assessors.

#### *4.8.3.1. Exact agreements*

Overall agreement was 83.3% for presence or absence of MSUS detectable forefoot bursae (**Table 19**), 81.8% for presence or absence of MTP joint erosion (**Table 20**) and 68.4% for presence or absence of MTP joint synovitis (**Table 21**).

**Table 19.** Relation between the podiatrist's and radiologist's results of MSUS scans for the detection of the presence or absence of plantar forefoot bursae (N=60 feet, two feet data missing), in the RA study participants

| | Pod presence | Pod absence | Total |
|---|---|---|---|
| **Rad Bursae Presence,** N(%) | 42 (70%) | 9 (15%) | 51 |
| **Rad Bursae Absence,** N(%) | 1 (1.7%) | 8 (13.3%) | 9 |

**Key:** Pod = Podiatrist; Rad = Radiologist

**Table 20.** Relation between the podiatrist's and radiologist's results of MSUS scans for the detection of the presence or absence of MTP joint erosion (N=110 joints, 14 joint data missing) in the RA study participants.

| | Pod presence | Pod absence | Total |
|---|---|---|---|
| **Rad Erosion Presence,** N(%) | 44 (40%) | 9 (8.2%) | 53 |
| **Rad Erosion Absence,** N(%) | 11 (10%) | 46 (41.8%) | 57 |

**Key:** Pod = Podiatrist; Rad = Radiologist

.

**Table 21.** Relation between the podiatrist's and radiologist's results of MSUS scans for the detection of MTP joint synovitis (N=120 joints, 4 joint data missing) in the RA study participants.

|  | **Pod presence** | **Pod absence** | **Total** |
|---|---|---|---|
| **Rad Synovitis Presence,** N(%) | 68 (56.7%) | 13 (10.8%) | 81 |
| **Rad Synovitis Absence,** N(%) | 25 (20.8%) | 14 (11.7%) | 39 |

**Key:** Pod = Podiatrist; Rad = Radiologist

### 4.8.3.2. Sensitivity and specificity

Results from analysis in this study of both feet for forefoot bursae as individual data, show that the sensitivity of clinical examination by palpation by the podiatrist was 50% and specificity was 75% for detection of bursae, when compared to MSUS detection by the radiologist (**Table 22**). Therefore there was low (50%) agreement between the proportion of individuals identified with forefoot bursae by clinical palpation when compared to detection of forefoot bursae by MSUS performed by the radiologist. Agreement was higher (75%) for the proportion of individuals without bursae identified by clinical palpation when compared to detection of forefoot bursae by MSUS performed by the radiologist.

**Table 22.** A two by two table showing the raw data of agreement scores for clinical examination by a podiatrist compared to a radiologist performing MSUS imaging to detect bursae in the forefeet of patients with RA.

| **N=60 feet** | | **Presence of MSUS bursae baseline visit, radiologist** | |
|---|---|---|---|
| | | **presence** | **absence** |
| **Presence of clinically palpable bursae, baseline visit, podiatrist** | **presence** | 13 (a) | 1 (b) |
| | **absence** | 13 (c) | 3 (d) |

**Sensitivity = a/(a+c) = 13/(13+13) = 50%;  Specificity = d/(b+d) = 3/(1+3) = 75%**

Results from analysis in this study of both feet (for bursae, MTP joint erosion and synovitis) and each MTP joint (for erosion and synovitis) as individual data show that the

sensitivity of the podiatrist using MSUS was 82.4% for detection of forefoot bursae, 83.0% for detection of MTP joint erosion and 83.4% for detection of MTP joint synovitis. Specificity of the podiatrist using MSUS was 88.9% for detection of forefoot bursae, 80.7% for detection of MTP joint erosion and 35.9% for detection of MTP joint synovitis (**Table 23**, **Table 24**, and **Table 25**).

In other words, there was high (82.4%) agreement between the proportions of individuals identified with forefoot bursae by MSUS performed by the podiatrist when compared to detection of forefoot bursae by MSUS performed by the radiologist. Agreement was higher (88.9%) for the proportion of individuals without bursae identified by MSUS performed by the podiatrist when compared to detection of forefoot bursae by MSUS performed by the radiologist.

**Table 23.** A two by two table showing the raw data of agreement scores for a podiatrist compared to a radiologist performing MSUS imaging to detect bursae in the forefeet of patients with RA.

| N=60 feet | | Radiologist | |
|---|---|---|---|
| | | **Bursae Positive** | **Bursae Negative** |
| **Podiatrist** | **Bursae positive** | 42 (a) | 1 (b) |
| | **Bursae negative** | 9 (c) | 8 (d) |

**Sensitivity = a/(a+c) = 42/(42+9) = 82.4%;  Specificity = d/(b+d) = 8/(1+8) = 88.9%**

**Table 24.** A two by two table showing the raw data of agreement scores for a podiatrist compared to a radiologist performing MSUS imaging to detect erosion in the second and fifth MTPJs of the forefeet of patients with RA.

| N=110 joints | | Radiologist | |
|---|---|---|---|
| | | **Erosion Positive** | **Erosion Negative** |
| **Podiatrist** | **Erosion positive** | 44 (a) | 11 (b) |
| | **Erosion negative** | 9 (c) | 46 (d) |

**Sensitivity = a/(a+c) = 44/(44+9) = 83.0%;  Specificity = d/(b+d) = 46/(11+46)= 80.7%**

**Table 25.** A two by two table showing the raw data of agreement scores for a podiatrist compared to a radiologist performing MSUS imaging to detect synovitis in the in the second and fifth MTPJs of the forefeet of patients with RA.

| N=120 joints | | Radiologist | |
|---|---|---|---|
| | | **Synovitis Positive** | **Synovitis Negative** |
| **Podiatrist** | **Synovitis positive** | 68 (a) | 25 (b) |
| | **Synovitis negative** | 13 (c) | 14 (d) |

**Sensitivity = a/(a+c) = 68/(68+13) = 83.4%;  Specificity = d/(b+d) = 14/(25+14) = 35.9%**

There was high (83.0%) agreement between the proportions of individuals identified with MTP joint erosion by MSUS performed by the podiatrist when compared to detection of MTP joint erosion by MSUS performed by the radiologist. Agreement was also high (80.7%) for the proportion of individuals without MTP joint erosion identified by MSUS performed by the podiatrist when compared to detection of MTP joint erosion by MSUS performed by the radiologist.

There was high (83.4%) agreement between the proportions of individuals identified with MTP joint synovitis by MSUS performed by the podiatrist when compared to detection of MTP joint synovitis by MSUS performed by the radiologist. Agreement was however low (35.9%) for the proportion of individuals without MTP joint synovitis identified by MSUS performed by the podiatrist when compared to detection of MTP joint synovitis by MSUS performed by the radiologist.

Results demonstrate that sensitivity and specificity values for the podiatrist in detecting bursae and MTP joint erosions within the forefeet of participants with RA are both over 80% and therefore very acceptable. However, results for the detection of MTP joint synovitis by the podiatrist were less acceptable. Whilst sensitivity for MTP joint synovitis was over 80% and thus very good, specificity was poor at 35.9% indicating that the podiatrist was over-reporting false positives (**Table 26**).

**Table 26.** Summary of sensitivity and specificity values for inter-tester reliability of a podiatrist compared to a radiologist performing MSUS imaging to detect bursae, erosion and synovitis in the forefeet of patients with RA.

|  | **Sensitivity** | **Specificity** |
|---|---|---|
| **Bursae** | 82.4% | 88.9% |
| **Erosion** | 83.0% | 80.7% |
| **Synovitis** | 84.0% | 35.9% |

During the data collection for this preliminary study, it became clear that the plantar approach used to detect MTP joint synovial thickening / synovitis was a major limitation. The ability to assess synovitis in some participants, using the linear MSUS 5 – 10 MHz transducer (active length 26mm; see **Figure 20**, page 78) to achieve 7.5 MHz frequency with the Diasus machine, was hampered by structural lesser toe deformities and MTP joint subluxation, even with use of liberal amounts of coupling gel. This may account for the poor agreements in the MSUS detection of MTP joint synovitis between the investigators.

Clinically, it is important to decide whether a test requires high sensitivity or high specificity and what the implications of false positives and false negative test results are (Petrie and Sabin 2005).

**Figure 22.** Schematic diagram depicting sensitivity and specificity relative to false positive and false negative results (adapted from Petrie and Sabin 2005).
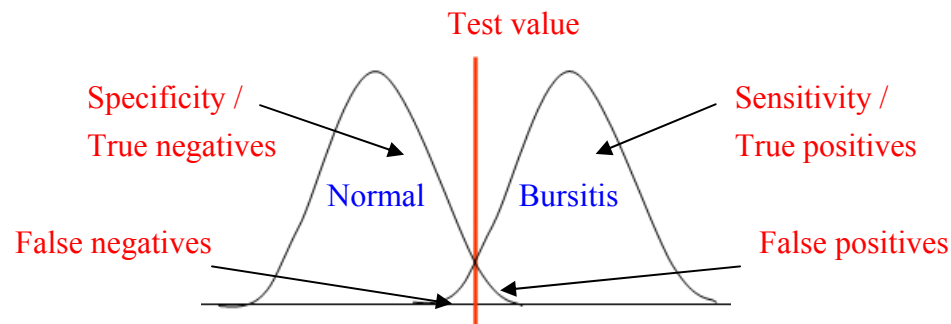
In this study, synovitis, for example, is readily treatable and therefore the high sensitivity of 84% in detecting it is preferred. If synovitis was a serious and untreatable pathology, high specificity would be preferred to avoid making a false positive diagnosis (**Figure 22**) and the low specificity of 35.9% would be unacceptable.

### 4.8.3.3. Kappa

Kappa scores for from the primary data revealed moderate agreement for MSUS detectable bursae (N=60, kappa 0.522; p<0.001) and MTP joint erosions (N=110, kappa 0.636; p<0.001) and fair agreement for MTP joint synovitis (N=120, kappa 0.216; p=0.015) (see **Table 27**).

**Table 27.** Kappa values for inter-tester reliability of a podiatrist compared to a radiologist performing MSUS imaging to detect bursae, erosion and synovitis in the forefeet of patients with RA.

|  | Kappa statistic | P value |
|---|---|---|
| Bursitis | 0.522 | p<0.001 |
| Erosion | 0.636 | p<0.001 |
| Synovitis | 0.216 | p=0.015 |
| Consensus | 0.702 | p<0.001 |

Data from this analysis therefore indicates that acceptable sonographic images were obtained from the primary investigation, particularly for bursae, by the podiatrist with significant and moderate agreement with the radiologist.

### 4.8.4. Image interpretation consensus meeting

During the consensus meeting, images recorded by the Diasus MSUS unit were discussed and agreed as MSUS detectable bursae (**Figure 23**), MTP joint synovitis (**Figure 24**) and MTP joint erosion (**Figure 24**).

**Figure 23.** MSUS image of the left foot plantar metatarsal area of a study participant with RA demonstrating a bursa as a demarcated complex mass protruding beyond the 3rd and 4th metatarsal heads with hypertrophied synovium and anechoic spaces containing synovial fluid (arrow). The image is seen from the plantar aspect and in the transverse plane.
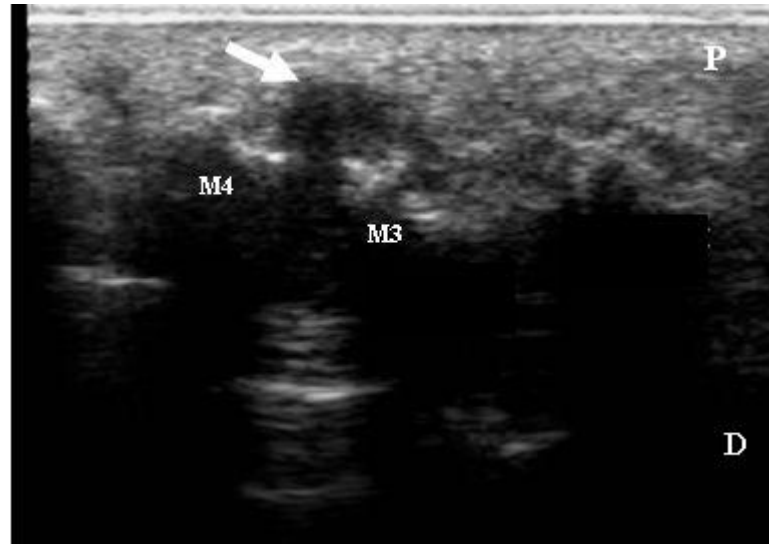


**Key:** M4 = 4$^{th}$ metatarsal head; M3 = 3$^{rd}$ metatarsal head; P = plantar surface; D = dorsal surface
**Equipment:** Diasus MSUS system (Dynamic Imaging LTd, UK)

**Figure 24.** A MSUS image of synovial thickening (S), joint effusion (E) and bone changes (B) within the right fifth plantar MTPJ of a study participant with RA. The image is seen from the plantar aspect and in the longitudinal plane.
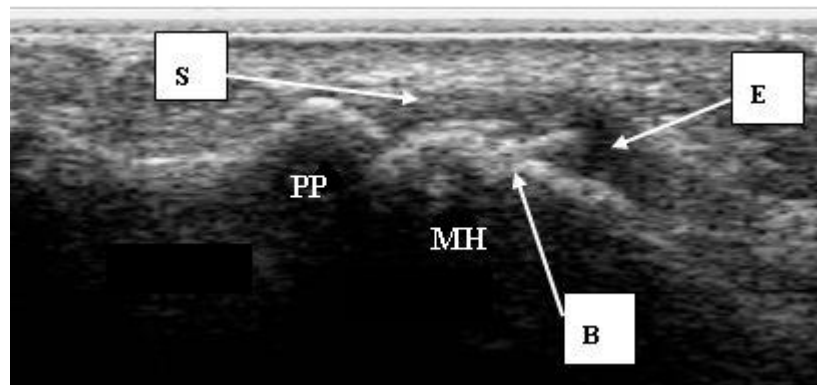


**Key:** PP = proximal phalanx; MH = metatarsal head.
**Equipment:** Diasus MSUS system (Dynamic Imaging LTd, UK)

Following the consensus meeting, and tests on a randomised selection of 36 images from the Diasus machine, substantial levels of agreement were achieved between the podiatrist and radiologist for 8/9 forefoot bursae, 4/10 MTP joint synovitis, 6/9 MTP joint erosions and 8/8 healthy images (**Table 28**) with kappa 0.702; p<0.001 (**Table 31**).

**Table 28.** Contingency table showing a comparison of results between the radiologist and podiatrist for image interpretation following the consensus meeting.

| | | Radiologist | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | synovitis | erosion | bursae | healthy | poor image | |
| Podiatrist | synovitis | 4 | 0 | 0 | 4 | 0 | 8 |
| | erosion | 1 | 5 | 0 | 1 | 0 | 7 |
| | bursae | 0 | 1 | 8 | 0 | 0 | 9 |
| | healthy | 1 | 0 | 0 | 10 | 0 | 11 |
| | poor image | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | | 6 | 6 | 8 | 15 | 1 | 36 |

**Table 29.** Contingency table showing a comparison of results between the podiatrist and actual images for image interpretation following the consensus meeting.

| | | Original images | | | | | Total |
|---|---|---|---|---|---|---|---|
| | | synovitis | erosion | bursae | healthy | poor image | |
| Podiatrist | synovitis | 8 | 0 | 0 | 0 | 0 | 8 |
| | erosion | 1 | 6 | 0 | 0 | 0 | 7 |
| | bursae | 0 | 0 | 9 | 0 | 0 | 9 |
| | healthy | 2 | 1 | 0 | 8 | 0 | 11 |
| | poor image | 0 | 0 | 0 | 0 | 1 | 1 |
| Total | | 11 | 7 | 9 | 8 | 1 | 36 |

**Table 30.** Contingency table showing a comparison of results between the radiologist and actual images for image interpretation following the consensus meeting.

|  |  | Original images | | | | | |
|---|---|---|---|---|---|---|---|
|  |  | synovitis | erosion | bursae | healthy | poor image | Total |
| Radiologist | synovitis | 5 | 0 | 0 | 1 | 0 | 6 |
|  | erosion | 0 | 5 | 1 | 0 | 0 | 6 |
|  | bursae | 0 | 0 | 8 | 0 | 0 | 8 |
|  | healthy | 6 | 2 | 0 | 7 | 0 | 15 |
|  | poor image | 0 | 0 | 0 | 0 | 1 | 1 |
| Total |  | 11 | 7 | 9 | 8 | 1 | 36 |

Agreement between the podiatrist and original images was 9/9 forefoot bursae, 8/10 MTP joint synovitis, 6/9 MTP joint erosion and 8/8 healthy images (**Table 29)** with kappa 0.854 (p<0.001) (**Table 31**). Agreement between the radiologist and original images was 8/9 forefoot bursae, 5/10 MTP joint synovitis, 6/9 MTP joint erosions and 7/8 healthy images (**Table 30**) with kappa 0.638, p<0.001 (**Table 31**).

Following further training, levels of agreement increased to a 'very good standard' that was also 'statistically significant' (p<0.001). Interestingly, following further training, the levels of agreement between the podiatrist and the original images increased to the category of 'almost perfect' (p<0.001) whilst agreement scores for the radiologist were lower, but still significant (p<0.001) (**Table 30**).

**Table 31.** Summary of kappa values for inter-tester reliability of a podiatrist, radiologist and actual images for image interpretation following the consensus meeting.

|  | **Kappa statistic** | **P value** |
|---|---|---|
| **Podiatrist v Radiologist** | 0.702 | p<0.001 |
| **Podiatrist v Original images** | 0.854 | p<0.001 |
| **Radiologist v Original images** | 0.638 | p<0.001 |

### 4.8.5. Prevalence of forefoot bursae in patients with RA detected by MSUS performed by an experienced radiologist at baseline

Bursae were detectable in 82.4% (51/62) of feet, synovitis in 65.3% (81/124) of MTP joints and erosions in 42.7% (53/124) of MTP joints detected by MSUS and scanned by the radiologist. The mean number of bursae per patient detected by MSUS was 3.8 (SD 2.5) and by clinical examination was 1.5 (SD 1.9). On clinical examination by palpation of the plantar forefoot area 41.4% (N=24/58 feet, 4 missing data) of feet had clinically detectable bursae. On retrospective analysis of participants' clinical notes, no documentation of foot related bursitis was found in the medical records of any of the participants (**Figure 25**).

**Figure 25.** A stacked bar chart representing the comparison between the numbers of plantar forefoot bursae detected by clinical palpation, MSUS by radiologist and reported within medical records for individual data.
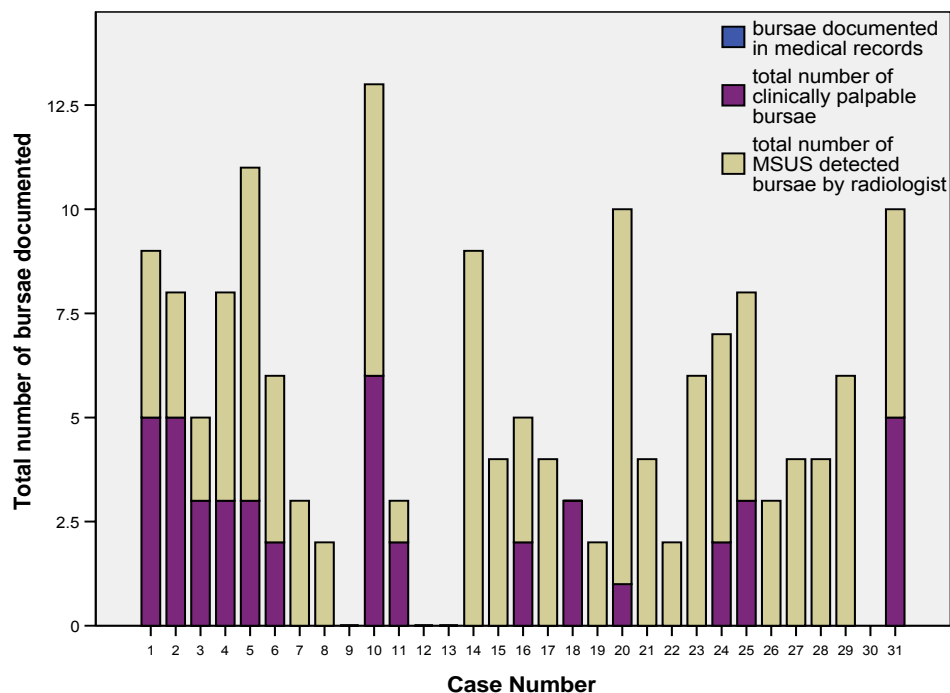
Of those with MSUS detectable bursae 96.6% had bursae in both feet. Of those with clinically detectable bursae, 64.3% had bursae in both feet. In comparison, on clinical examination 46.6% (N= 27/58 feet, 4 missing data) had detectable MTP joint synovitis (**Figure 30**). The mean number of synovitis affected MTP joints per patient was 2.39 (SD 2.9) by clinical examination. Of those with clinically detectable MTP joint synovitis (N=17/31), 76.4% (N=13/17) demonstrated MTP joint synovitis in both feet.

**Figure 26.** A bar chart representing the comparison between the percentage of forefoot bursae, MTP joint synovitis, and erosion detected by clinical palpation, MSUS by radiologist and reported within medical records for individual data.
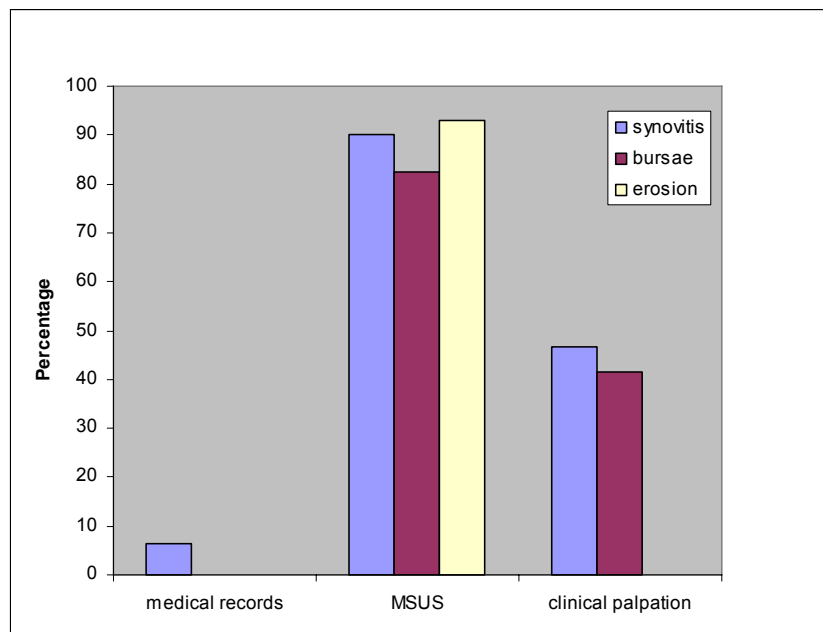


On retrospective analysis of participants' clinical notes documentation of synovitis within the MTP joints was found in the medical records of 6.5% (N=2) of the patients and in a further 19.4% (N=6) foot pain or foot problems were documented, although not attributed to any cause. On MSUS for individual cases 90% (N=27/30 feet) displayed MTP joint synovitis and from those, 59.3% (N=16/27) displayed symmetry within the second MTPJs and 74.1% (N=20/27) displayed symmetry within the fifth MTP joints.

On MSUS for individual cases in 93.1% (N=27/29 feet, 2 missing data) of patients erosion of at least one MTP joint was noted (**Figure 26**). From those 14.8% (N=4/27) displayed symmetry within the second MTP joints and 59.3% (N=16/27) displayed symmetry within

the fifth MTP joints.


### 4.8.6. Prevalence of forefoot bursae detectable by MSUS in patients with RA performed by an experienced radiologist after twelve weeks of anti-TNF-α therapy

Tumour Necrosis Factor (TNF) inhibition is known to be an effective way of reducing synovitis (Hau, Kneitz et al 2002; Taylor,Steuer et al 2006) and a high prevalence of forefoot bursae have been linked with RA disease progression. Therefore reassessment following twelve weeks of therapy was an ideal opportunity to determine whether MSUS could be responsive to change in prevalence of forefoot bursae within the foot in RA participants.

All thirty one participants returned for reassessment at twelve weeks. There was a trend towards reduction in all outcome variables (**Tables 15, 16, 17, 18**, pages 102 and 103; **Figure 27**) and using paired samples t-tests all differences between baseline and twelve weeks for clinical disease measures were significant: DAS-28 (t = 3.712, p = 0.001), CRP (t = 3.889, p = 0.001), ESR (t = 4.014, p < 0.001), foot pain and disability (t = 3.712, p = 0.001) and global wellbeing VAS (t = 2.7351, p =0.011).


**Figure 27.** A simple bar chart representing changes in clinical and disease variables following twelve weeks of anti-TNF-α therapy.
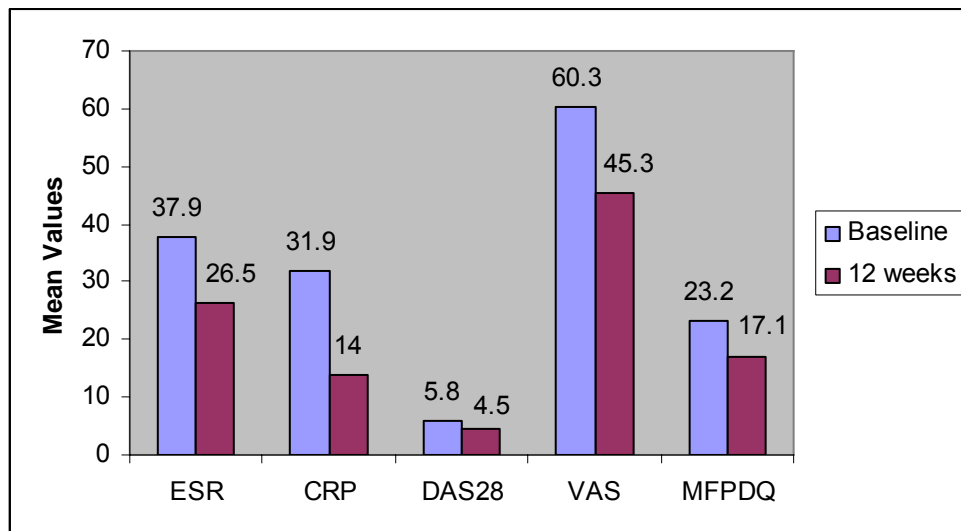
**Figure 28.** A simple bar chart representing the percentages of cases of MSUS detectable forefoot bursae and MTP joint synovitis at baseline and following twelve weeks of anti-TNF-α therapy.
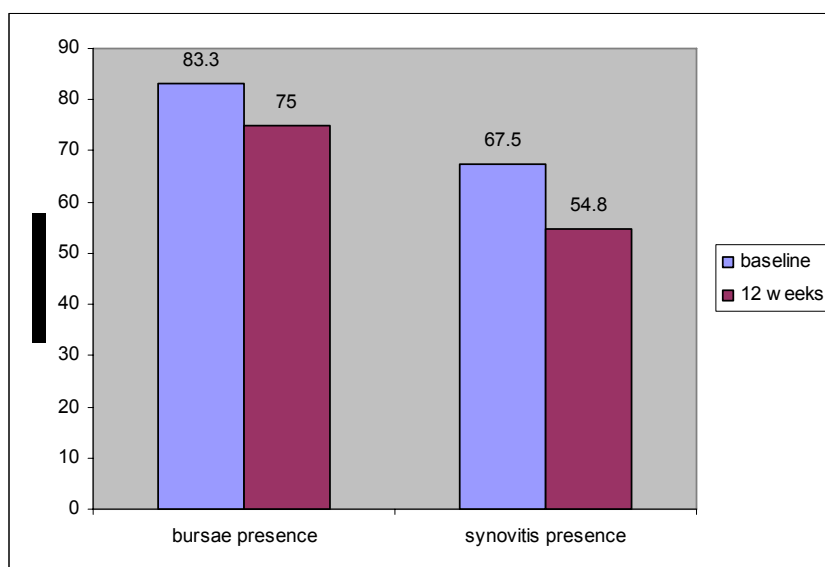
Observed presence of MSUS detectable forefoot bursae was noted in 83.3% (50/60) of feet at baseline and 75% (39/52) of feet at twelve weeks (Figure 20). At twelve weeks 19.2% (10/52) of feet had changed from MSUS detectable forefoot bursae being present to absent and 9.6% (5/52) changed from MSUS detectable forefoot bursae being absent to present. No change was observed in presence of MSUS detectable forefoot bursae in 63.5% (33/52) of feet and absence in 5.8% (3/52) of feet.

Observed presence of MTP joint synovitis by MSUS from 60 feet (120 joints) indicates presence in 67.5% (81/120 joints) at baseline and 54.8% (57/104 joints) at twelve weeks (**Figure 28**). At twelve weeks 25.9% (27/104 joints) had changed from MTP joint synovitis being present to absent, and 13.5% (14/104 joints) changed from MTP joint synovitis being absent to present. No change was observed in presence of MTP joint synovitis in 41.3% (43/104 joints) and absence in 19.2% (20/104 joints).

There was a trend towards reduction in presence of MSUS detectable forefoot bursae and MTP joint synovitis that was observed by MSUS performed by the radiologist (**Figure 28**) however using a McNemar test for categorical data of related groups, no significance was found.

## 4.9 Summary of findings

### 1. Inter-observer reliability between the podiatrist and radiologist performing MSUS imaging of the forefoot

The first part of the investigation set out to test the reliability of a podiatrist using a MSUS to assess forefoot pathology in patients with RA. Acceptable sonographic images were obtained from the primary investigation by the podiatrist with moderate agreements with the expert radiologist for MSUS detectable forefoot bursae and MTP joint erosion. Following further training, levels of agreement increased to a very good standard for MSUS detectable forefoot bursae, MTP joint erosion and MTP joint synovitis.

### 2. MSUS detection of forefoot bursae

The second part of this preliminary study attempted to investigate the presence of bursae within the forefeet of patients with RA using two different methods, clinical examination and MSUS. The data suggests that forefoot bursae are a common and under-reported cause of foot problems, that MSUS detected a higher prevalence of forefoot bursae than clinical examination and that this was an area in which MSUS could provide further important, clinically relevant, information.  These findings provided information regarding the prevalence of MSUS detectable bursae as observed by an experienced radiologist using a high resolution Philips HDI 5000 MSUS system.

### 3. MSUS detection of change in prevalence of plantar forefoot bursae following a period of intervention

Findings from this study indicate that there is a trend towards change in MSUS detectable bursae within the forefoot, towards a reduction in number after twelve weeks of anti-TNF-α therapy, although the reduction was not statistically significant. The same trend was also observed for reduction in synovitis within the second and fifth MTP joints, which also was not statistically significant. Findings also indicate that MSUS is an acceptable technique to detect changes in the prevalence of forefoot bursae.

## 4.10. Discussion

### 4.10.1. Reliability of technique

This was the first study to investigate tailored learning of MSUS to the discrete field of foot and ankle practice, in evaluating the inter-observer agreement in the use of MSUS between an allied health professional (podiatrist) and an expert radiologist on imaging of the foot. We demonstrated good agreement for MSUS detectable forefoot bursae and MTP joint erosions, but only fair agreement for the presence of MTP joint synovitis.

Competency assessment in MSUS is an important issue (Brown, O'Connor et al 2005). Usually, reliability in technique is reported by rheumatologists who have trained, or are being trained, in MSUS that are tested against experienced MSUS sonographers or radiologists (Szkudlarek, Court-Payen et al 2003; D'Agostino, Maillefert et al 2004; Scheel, Schmidt et al 2005; Naredo, Moller et al 2006). The podiatrist in this study had followed recommended BSR (British Society for Rheumatologists) training in MSUS techniques, followed by further training and mentorship from expert radiologists. Podiatrists are regularly involved in the assessment and management of musculoskeletal foot and ankle pathology. With extended scope practice in the use of MSUS by podiatrists, there are the potentially valuable benefits to patients, as well as lower costs in service provision.

In our study overall exact agreement between the radiologist and podiatrist was recorded as 83.3% for MSUS detectable forefoot bursae, 68.3% for MTP joint synovitis and 81.8% for MTP joint erosions. Acceptable sonographic images were obtained by the podiatrist with moderate agreements for MSUS detectable forefoot bursae (kappa 0.522, $p < 0.001$) and MTP joint erosions (kappa 0.636, $p < 0.001$). Low agreements for MTP joint synovitis (kappa 0.216, $p = 0.015$) were obtained initially, however following further training, levels of agreement for all three variables increased to a good standard (kappa 0.702, $p < 0.001$).

Within the MSUS literature, the foot is under-investigated and those who have reported on assessments of the foot joints have observed similar low agreement scores for synovitis (Szkudlarek, Court-Payen et al 2003; D'Agostino, Maillefert et al 2004; Scheel, Schmidt et al 2005; Naredo, Moller et al 2006). Inter-observer reliability among 14 experts in MSUS produced overall good agreements for all examined joints (kappa 0.76) although low agreement for ankle and toe joints (kappa 0.28) was reported (Scheel, Schmidt et al 2005).

In evaluating scanning technique and diagnostic criteria, a group of 23 experts in MSUS who scanned shoulder, wrist and hand, ankle and foot, and knee joints, reported 'exact' overall agreement of 91% for synovitis, 87% for cortical abnormalities and 83.5% for bursitis but only 'fair' agreements for the ankle and foot region (kappa 0.54) (Naredo, Moller et al 2006). In MSUS examination of synovitis of the metacarpophalangeal joints and MTP joints, the learning curve of three rheumatologists in MSUS techniques was investigated (D'Agostino, Maillefert et al 2004). The agreements at the final evaluations were good for two of the trainees, (kappa 0.63 and 0.62), consistent with our findings, however for the third trainees was poor (kappa 0.18). This highlights the variability of learning requirements for the technique (D'Agostino, Maillefert et al 2004).

The use of MSUS by the podiatrist within this study did reveal good sensitivity and specificity for detecting forefoot bursae (82.4% and 88.9%) and MTP joint erosion (83.0% and 80.7%), although in detection of MTP synovitis sensitivity was good, specificity was low (83.4% and 35.9%) with over-reporting of false positives.

Disagreement between experts in clinical MSUS imaging techniques is not uncommon, with sonographers differing (sometimes substantially) in their interpretation of images (Scheel, Schmidt et al 2005). A lack of standardisation and variation in scanning technique amongst sonographers has been deliberated as contributing to the disagreements (Scheel, Schmidt et al 2005). Results following the consensus meeting in this study, indicated that there was a small amount of disagreement observed between the podiatrist and the radiologist; it is unclear whether the disagreement was due to the podiatrist's technique, image resolution or differing specifications of the MSUS machines.

In common with other researchers (Scheel, Schmidt et al 2005) this research team did encounter difficulties in our technique for using MSUS to detect synovitis in the MTP joints from the plantar aspect of the foot, especially if deformities or subluxation of those joints were present. Difficulty in assessing MTP joint synovial thickening / synovitis existed where severe retraction of the lesser toes and subluxation of the MTP joints did not allow good transducer contact. Interestingly, others have scanned each joint in the dorsal aspect of the hands and feet, reporting that this technique was preferred to a palmer or plantar scan because of its reliability for detecting synovitis (D'Agostino, Maillefert et al 2004) although they did not mention technique where deformity and subluxation existed in the MTP joints. Therefore

a dorsal approach to assess MTP joint synovial thickening / synovitis, as recommended by the EULAR "working group for musculoskeletal ultrasound in rheumatology" guidelines was considered more appropriate for the next phase of the research (Backhaus, Burmester et al 2001).

In retrospect, the use of 'stand off' pads and techniques for using a water bath to facilitate the ultrasound wave conduction over gross structural deformities of the foot may have produced better results. These techniques reportedly increase the field of view in anatomical areas where the contour of the part is such that it only allows a small area of contact (Stokes, Hides and Nassiri 1997). At the time of this study these techniques were not readily available within either the podiatric or radiology clinical department. Similarly, small transducer footprints such as 'hockey stick' probes, may have also been easier to use over the deranged MTP joints (Backhaus, Burmester et al 2001), but this was not an available feature of the Diasus machine used within the study.

From our experiences within this study, the technique for image acquisition and interpretation of forefoot bursae was acceptable, although we recommend that further work on establishing reliability of protocols for MSUS assessment of the foot and ankle joints be undertaken.

Inter-machine and intra-operator reliability would have added credence to the validity of the technique we have developed within this study, for using MSUS imaging to detect forefoot bursae in patients with RA. However, the feasibility of testing intra-operator reliability to detect forefoot bursae for this study was questioned and debated. If the technique is tested too soon, the operator may remember, and recall bias will affect the results but if the test is undertaken too late, the prevalence of forefoot bursae may have changed. Therefore at this stage, a pragmatic clinical approach was adopted and no further reliability testing was undertaken.

### 4.10.2. Prevalence of forefoot bursae

Using MSUS we confirmed a high prevalence of plantar forefoot bursae in patients with RA within this study and have demonstrated that these bursae are usually bilateral and symmetrical. The use of MSUS within this study did reveal a higher sensitivity for

detecting forefoot bursae than clinical palpation. Based on the study participants, of those with MSUS detected bursae only 50% would be detected by clinical examination alone. Clinical examination of the plantar forefoot missed many cases of forefoot bursae, suggesting that bursae within the forefoot may be a common but under-reported cause of problems in RA.

There are other reports of similar findings, of bursae in the forefoot being poorly documented, that have emphasised the importance of rheumatologists being aware of the existence of numerous small, synovial bursae in the forefoot (Olivieri, Scarano et al 2004). In a previous similar study investigating early RA (mean disease duration of 1.1 years), intermetatarsal bursae were reported as clinically palpable in 5 patients from a cohort of 25 (20%); yet 14 of 25 (56%) patients were deemed to have MSUS detectable plantar forefoot bursae (Koski 1998). Our own study findings in patients with more established severe disease, reveal a higher prevalence of MSUS detectable plantar forefoot bursae with 26 of 30 (83.9%) patients recorded as having presence MSUS detectable plantar forefoot bursae and 14 of 30 (48.4%) detected by clinical palpation. Differences in the participant sample (mean disease duration 11.13 years in our study) and MSUS machine specifications, however, make true comparisons between the studies difficult.

### 4.10.3. Changes in presence of MSUS detectable forefoot bursae following intervention therapy

The second part of this study involved the investigation of plantar forefoot bursae detectable by MSUS, performed by a radiologist, following a period of intervention. Using the small sample of subjects from the preliminary study, this question formed an important foundation in the development of the next phase of the study that aimed to investigate the prevalence and natural history of plantar forefoot bursae in a larger sample.

Whilst no statistical significance, in changes in the presence of MSUS detectable plantar forefoot bursae or MTP joint synovitis, was found there was an observable trend towards their reduction after twelve weeks of anti-TNF-α therapy. The trend was also noted in the clinical and laboratory assessments of RA disease status (ESR, CRP, DAS-28 and MFPDQ) and these reductions were statistically significant demonstrating that TNF inhibition did dampen down the disease process in the RA participants within this study.

It may be that treatment switches off the disease process of RA, but twelve weeks was not enough time for synovial hypertrophy to regress, or that disease that is not clinically evident remains longer than thought, as recently reported by Brown et al (2006). Therefore, acknowledging that the changes that occurred in MSUS detectable plantar forefoot bursae and MTP joint synovitis followed the same pattern as the trend to reduction in clinical and laboratory measures, pragmatically it was accepted that MSUS was responsive to those changes.

Of further note, in the minority of patients where the prevalence of MSUS detectable plantar forefoot did increase, some patients' MFPDQ scores (perceived foot pain) improved. This anomalous increase could be attributable to adventitious bursae, due to increased mechanical stress as mobility improved for those patients, rather than an increase in anatomical bursae due to the disease process of RA.

## 4.11. Potential limitations

A number of potential limitations within this preliminary study should be acknowledged. The prevalence of MSUS detectable bursae within the forefoot was not validated by any other 'gold standard' imaging technique, such as MRI or by histological analysis through biopsy. As well as intermetatarsal bursae and adventitious bursae, soft tissue swelling at the level of the MTP joints can be related to MTP joint synovitis or tenosynovitis that could be better differentiated using MRI (Ashman, Klacker and Yu 2001; Helliwell, Woodburn et al 2007; Studler et al 2008). At the time of the preliminary reliability study, the OMERACT MSUS special interest group had highlighted limited data in terms of comparisons of MRI with MSUS (Wakefield, Balint et al 2005). Due to its restricted availability MRI was not feasible for our study. Others have attempted to validate imaging findings using fresh cadavers (Theumann, Pfirmann et al 2001; Studler et al 2008) however this technique was also not a feasible option during the initial phases of our study.

Furthermore, in the preliminary study, due to forefoot structural deformity in some participants, it was clear from the conceptual stage that tenosynovitis was too difficult to assess using the proposed Diasus ultrasound machine. As well as MTP joint synovitis, the appearance of flexor tenosynovitis on MSUS is a key differential diagnosis for plantar forefoot tenderness (Koski 1995). This inability to measure tenosynovitis using the Diasus

MSUS machine also has to be acknowledged as a significant omission and therefore a major limitation in the second and third studies regarding the assessment of the associations of MSUS detectable forefoot bursae with patient reported foot impact outcome measures.

Previously in the literature, MSUS detectable bursae in the forefoot have been referred to as 'bursitis' (Koski 1998) yet more recently power Doppler mode is advocated to determine whether synovium is actively inflamed, allowing a more precise definition of 'active synovitis' (Brown, Quinn et al 2006; Balint, Mandl and Kane 2008). The technique for the use of power Doppler in assessment of changes in synovial perfusion has been a development subsequent to the commencement of this doctoral thesis (Balint, Mandl and Kane 2008). Whilst the MSUS machine utilised by the radiologists had power Doppler mode, the MSUS machine utilised by the podiatrist (CB) did not. To avoid complication in the use of terminology, at this stage of the study a decision was made to refrain from using the term 'bursitis', preferring the term 'MSUS detectable bursae' instead. For future studies, a MSUS machine with Power Doppler will be a prerequisite.

An important issue within this preliminary study one was measurement error between clinicians and between machines. For the preliminary study, the podiatrist's (CB) technique was tested for reliability against expert radiologists (KD and MS). Although this is a common way of determining reliability, validity can be questioned, especially with the use of two different machines and two different radiologists. In the design of the reliability study, two assumptions were made, firstly that the radiologists were experts in the field of MSUS imaging and secondly that their inter-tester reliability in technique in detecting forefoot bursitis was of an acceptable standard. Using the OMERACT filter (Boers, Brooks et al 1998) (see **Table 12**, page 80) it can be seen that, although the podiatrist's technique was confirmed as being reliable, there are limitations that affect the overall validity of the technique in the detection of forefoot bursae.

Limitations relating to the sample are also highlighted. The sample was relatively small and comprised patients with severe disease; therefore generalizibility to the whole population of patients with RA needs to be confirmed.  Finally, whilst the consensus meeting did take place once data collection was complete, it is possible that there may have been an element of recall bias that should be acknowledged.  Image interpretation may have been enhanced during the post-consensus test as the images selected were taken from part of the cohort

that the podiatrist and radiologist used for the initial reliability analyses.

## 4.12. Conclusion

This study was the first to attempt to investigate inter-observer agreement in the use of MSUS, between an allied health professional (podiatrist) and an expert radiologist. Performance of MSUS in image acquisition and interpretation by the podiatrist was of an acceptable standard during the primary investigation and, following further training, levels of agreement increased to a very good standard. We observed a high prevalence of MSUS detectable plantar forefoot bursae in patients with RA. Furthermore, there was a trend for MSUS detectable bursae within the forefoot to decrease after twelve weeks of anti-TNFα therapy, although this was not significant. Clinical examination of the plantar forefoot missed many cases of MSUS detectable bursae indicating that MSUS may be a valuable tool for providing clinically relevant information as part of the ongoing clinical assessment of the foot in RA.

This preliminary study therefore laid the foundations for the next phase of the research. The MSUS imaging technique for the proposed primary investigator (CB) within study two was proven to a very good standard. MSUS was accepted as a key modality for assessing the prevalence and natural history of plantar forefoot bursae in RA.

# 5.0 Chapter Five: Prevalence of MSUS Detectable Forefoot Bursae in RA Participants

## 5.1. Introduction

During the reliability study in chapter four we noticed that both investigators (Radiologist and Podiatrist) identified a high prevalence of MSUS detectable forefoot bursae. As the sample was small and there were no control subjects we were unable to determine if this was a relevant finding. Chapter five details the second study which forms the doctoral thesis and, in view of the findings, provides a frame of reference for the prevalence of MSUS detectable bursae in a larger cohort.

From the literature review (Chapter 2, page 8) it was evident that the role of soft tissues such as bursae in the process of rheumatoid foot disability is less well explored than MTP joint synovitis (Costa, Rizack and Zimmermann 2004; van der Leeden, Steultjens et al 2008).

The anatomy and physiology of bursae within the foot and the confusion over terminology of those detectable within the plantar forefoot area are outlined in detail in Chapter two (section 2.2, page 18). Specific features of bursae within the plantar forefoot area have previously been identified using MRI and histological analyses (Theumann, Pfirrmann et al 2001; Studler, Mengiardi et al 2008). Whilst MRI has become the gold standard imaging modality in the detection of soft tissue lesions in RA, it remains a less economical clinical tool than musculoskeletal ultrasound (MSUS). MSUS continues to be reported as comparable and more readily accessible in assessing soft tissues in RA (Melchiorre, Calderazzi et al 2003; Terslev, Torp-Pedersen et al 2003; Szkudlarek, Narvestad et al 2004). In healthy subjects, bursae are reportedly not detectable by MSUS (Meenagh, Iagnocco et al 2006), but the presence of hypertrophied bursae within the anatomical areas of the hip, shoulder and knee have been readily identified by MSUS (Hermann, Backhaus et al 2003; Finlay and Friedman 2006; Meenagh, Iagnocco et al 2006). Bursae detectable by MSUS are described as having similar echo characteristics to joint synovitis (O'Connor and Grainger 2002).

In a small cross sectional study of patients with early RA, a higher prevalence of bursae within the forefoot detectable by MSUS imaging was reported than were detectable in

normal control participants (Koski 1998). Further findings within that study suggested that bursae could promote symptoms within the forefoot in RA patients and that their detection clinically appears to be less sensitive than by MSUS imaging (Koski 1998).

Other authors have suggested that bursae within the foot in RA may cause clinical symptoms when they enlarge or become inflamed (Hernandez, Hernandez and Hernandez 1991; Beggs 2002). In the absence of large cohort, prospective data, however, the prevalence of bursae detectable by MSUS that are not clinically apparent within the fore foot in RA patients remains speculative.

## 5.2. Aims

The aim of this study was to investigate bursae (both adventitious and anatomical), occurring within the forefoot using MSUS, in a large cross-sectional cohort of patients with RA and a comparator cohort of healthy participants. A further aim was to test the hypothesis that the presence of MSUS detectable bursae is a clinically relevant factor in patient reported foot disability in RA.

Data from this study was used to address the following research questions:

e) *What is the prevalence of bursae within the forefeet of healthy subjects and patients with RA detectable by MSUS and detectable clinically?*
f) *Which are the most common sites in the RA plantar forefoot for MSUS detectable bursae?*
g) *Is there a difference between the prevalence of bursae within the forefeet of healthy subjects and RA participants detected by MSUS?*
h) *Is the prevalence of MSUS detectable bursae within the forefeet of RA participants associated with patient reported outcome measures such as LFIS?*

## 5.3. Study design

A controlled cross sectional study design was used, in which a large sample of RA patients and a matched sample of healthy participants were investigated for presence of bursae within their forefeet. The study design was based upon the preliminary study data results (Chapter 4, section 4.8, page 102).

### 5.4. Subjects: RA Participants

A cross section of patients with RA diagnosed according to the ACR criteria, (Arnett, Edworthy et al 1988) who were attending secondary care rheumatology clinics as part of their normal care was investigated.

#### 5.4.1. Sample size: RA participants

For explanation of how the sample size was calculated to ensure adequate power for statistical analyses, see Chapter 3, section 3.7.1, page 69.

#### 5.4.2. Participant recruitment: RA participants

Consecutive patients attending outpatient clinics over a period of six months with a diagnosis of RA fulfilling the ACR criteria (Arnett, Edworthy et al 1988, Table 1, page 11) were identified from the Rheumatology Outpatient database, Southampton General Hospital (Southampton University Hospitals NHS Trust). Potential participants were sent a letter of invitation and a participant information sheet (**Appendix 13**) by post prior to their normal rheumatology appointment. These described the study protocol and their proposed involvement and were received at least two days prior to their clinical appointment.

Posters (**Appendix 14**) were also available within the Rheumatology Outpatients department for any patients to view, prior to commencement of the study. Suitable patients who, after reading the posters, wished to be considered for the study were given the appropriate letter of invitation and information sheet to contemplate participation at their next clinical visit.

Patients who were willing to be considered for the study at that stage were asked, within the letter of invitation, to complete a reply slip which they were to return to the Rheumatology Research Department. Potential participants at that stage were given the opportunity to discuss the details of the study with the Principal Investigator for the site, or the Chief Investigator. If required, potential participants could postpone their decision until their next clinical appointment, providing the clinical appointment fell within the study timeframe.

Those patients who were willing to take part in the study met with the Chief Investigator at

the end of their regular clinical appointment and the study protocol was explained in detail. Participants were encouraged to ask further questions before deciding to sign the form of consent. All willing participants were given a copy of the participant information sheet to keep and a copy of their signed consent form (**Appendix 15**).

Once informed consent was obtained, patients were screened for acceptance onto the study.

### 5.4.2.1. Selection criteria: RA participants

All patients with RA attending the Rheumatology Outpatients' clinic at Southampton General Hospital as part of their normal care within a six month period (July 2006 –January 2007) were considered appropriate for this study.

### Inclusion Criteria

- Individuals with a diagnosis of RA according to the ACR criteria (Arnett, Edworthy et al 1988; Table 1, page 11)
- Individuals aged 18 years or over
- Individuals with RA undergoing routine care at the Rheumatology Department, Southampton General Hospital

### Exclusion Criteria

- Individuals who had received a corticosteroid injection to the forefoot within the previous three months prior to the foot assessments within the study
- Individuals who could not walk five metres
- Individuals who had concomitant musculoskeletal disease (for example, primary osteoarthritis, gout, Paget's disease, systemic lupus erythematosus)
- Individuals who had a serious medical (other than RA) or psychological disorder that could affect the study protocol
- Individuals who were unable to give informed consent

## 5.5. Subjects: control participants

Staff and students within the University of Southampton were invited to participate within the study.

### 5.5.1. Sample size: control participants

For explanation of how the sample size was calculated to ensure adequate power for statistical analyses, see Chapter 3, section 3.7.2, page 71.

### 5.5.2. Participant recruitment: control participants

Posters (**Appendix 16**) were available within the School of Health Professions and Rehabilitation Sciences for any staff or students to view, prior to commencement of the study. Staff and students, who after reading the posters, wished to be considered for the study were given the appropriate letter of invitation and information sheet (**Appendix 17**). These described the study protocol and their proposed involvement, and were sent out at least two days prior to their participation in the study.

Those staff and students who were willing to take part in the study met with the chief investigator prior to their participation and the study protocol was explained in detail. Staff and students were allowed to ask further questions before deciding to sign the form of consent. All willing participants were given a copy of the participant information sheet to keep and a copy of their signed consent form.

Once informed consent had been obtained, participants were screened for acceptance onto the study.

#### 5.5.2.1. Selection criteria: control participants

Staff and students from the University of Southampton were considered appropriate to participate within this study.

*Inclusion criteria*
- Staff or student at the University of Southampton
- Individuals who were aged 18 years or over

*Exclusion criteria*
- Individuals who had received a corticosteroid injection to the forefoot within the 3 months prior to commencement of the study

- Individuals who could not walk five metres
- Individuals who had a diagnosed musculoskeletal disease (for example, rheumatoid arthritis, primary osteoarthritis, gout, Paget's, systemic lupus erythematosus)
- Individuals who had a serious medical or psychological disorder that could affect the study protocol
- Individuals who were unable to give informed consent.

## 5.6. Data collected

Data collection for the RA participants took place between August 2006 and September 2007. Data collection for the control participants took place in February 2008 during a two week period.

### 5.6.1. Location

All data collection for the RA participants was undertaken in the Wellcome Trust Clinical Research Facility, Southampton General Hospital.  On each occasion, the same consultation rooms and ultrasound facilities were utilised in an attempt to standardize environmental factors, such as room temperature and scanning positions.  Furthermore, whilst the preliminary examination was conducted, at each site, action was taken to preserve the patient's dignity at all times, in line with ethical guidelines.

All data collection for the control participants was undertaken in the biomechanics laboratory, School of Health Professions and Rehabilitation Sciences (now School of Health Sciences), University of Southampton.

### 5.6.2. Assessment of demographic and clinical characteristics

For the RA participants, general demographic data including age, gender, disease duration, presence of rheumatoid factor, weight and limb dominance were noted. Current medication and previous use of Disease Modifying Anti-Rheumatic Drugs (DMARDs) were obtained from the clinical notes and Rheumatology Department database. Laboratory assessments included C-reactive protein (CRP) and Erythrocyte Sedimentation Rate (ESR) and were obtained from the clinical notes and Rheumatology Department database.

Clinical characteristics collected included the participants' global impression of well-being measured via a visual analog scale (VAS 100mm, where 0 was 'Best Imaginable Health State' and 100 was equal to 'Worst Imaginable Health State'). Assessment of the patient's global impression of health and disease activity and the number of painful, tender and swollen joints was by the 28 joint Disease Activity Score (DAS-28) (van der Heijde, van't Hof, et al 1993). DAS-28 remission scores < 2.6; low disease activity scores $\geq$ 2.6 but < 3.2; moderate disease activity scores $\geq$ 3.2 but < 5.1; high disease activity scores $\geq$ 5.1 (van der Heijde, van't Hof, et al 1993). DAS-28 scores were obtained from the clinical notes and Rheumatology Department database.

For the control participants, general demographic data including age, gender, weight and limb dominance were noted. Clinical characteristics collected included participants' global impression of wellbeing measured via a visual analog scale (VAS 100mm), the same as for the RA participants.

### 5.6.3. Assessment of foot status

All participants, both RA and controls, underwent the same foot assessments conducted prior to the MSUS assessments. The feet were examined clinically for the presence of bursae by an experienced podiatrist (CB) using palpation of the plantar forefoot areas for the presence of fluctuant swellings separate from synovitis and tenosynovitis. The range of movement at the ankle, subtalar and first MTP joints were noted as being 'full', 'limited' or 'rigid' and the presence of MTP joint subluxation and pes-planus foot type (determined by observed flattening of the medial longitudinal arch on weightbearing) were also noted by the podiatrist (CB) (see **Appendix 18**).

Assessment of the impact of RA disease on the feet was measured using a validated patient administered questionnaire, the Leeds Foot Impact Scale (LFIS) (Helliwell, Reay et al 2005) (**Appendix 7**). Although presented as one self completed questionnaire there are two subscales for impairment/footwear (LFIS$_{IF}$) and activity limitation/participation restriction (LFIS$_{AP}$). LFIS$_{IF}$ contains twenty one items related to foot pain and joint stiffness as well as footwear related impairments and LFIS$_{AP}$ contains thirty items related to activity limitation and participation restriction (Helliwell, Reay et al 2005).

### 5.6.4. MSUS imaging data

All participants, both RA and controls underwent the same MSUS foot scans by the same investigator (CB). The MSUS foot scans were performed, on the same day following the clinical foot examinations, using a Diasus ultrasound system with a broadband linear 5 – 12 MHz probe (Dynamic Imaging Ltd. Scotland UK). The scanning protocol from the preliminary validation study (Chapter three, section 3.8.1.2, page 75) was modified slightly. Scanning was in B-Mode using the 5 – 10 MHz probe. Images were recorded in two perpendicular planes, longitudinal and transverse and performed moving from proximal to distal as suggested by the EULAR (European League against Rheumatism) "working group for musculoskeletal ultrasound in rheumatology" guidelines (Backhaus, Burmester et al 2001). The EULAR guidelines recommend a dorsal approach to detect MTP joint synovitis with the patient in a supine position however at the time of this study there was no definition for detecting clinically apparent swollen plantar forefoot bursae. We therefore decided to use a plantar approach to determine the prevalence of bursitis within the forefoot which we tested for reliability during study one (Chapter four, page 96).

The presence and location of bursae across the plantar forefoot region for each participant identified by MSUS, previously defined as anechoic demarcated complex masses (both anatomical intermetatarsal and adventitious) and bulging more than 1mm under the metatarsal heads (anatomical intermetatarsal bursae) (Koski 1998, Bowen, Dewbury et al 2008), were annotated on a foot chart adapted from study one (see MSUS data collection sheet, **Appendix 19** for an example of a completed data sheet).

### 5.6.5. MSUS training

Prior to starting this second phase of the research, the reliability of the investigator's (CB) scanning technique for the detection of bursae had been proven to a good standard of agreement against an expert MSUS radiologist (KD) (kappa 0.702; p<0.01) (Chapter four, page 96). That study has recently been published (Bowen, Dewbury et al 2008).

## 5.7. Summary of study protocols

For a summary of study protocols see **Figure 29** and **Figure 30**.

**Figure 29.** Summary of the protocol for RA participants for the baseline study of the clinical relevance of MSUS detectable bursae.

| | |
|---|---|
| **1**. Suitable patients to be identified from SGH rheumatology database. | **1i.** Letters of invitation to be sent. |
| | **1ii.** Patients to be sent the participant information sheet with letters of invitation. |
| **2.** Willing patients complete reply slip and return to rheumatology research department. | **2i.** Research administrator to add to Investigator's Folder (held in rheumatology research department). |
| **3.** Appointments sent to willing patients to coincide with their clinical visit. | **2ii.** Potential participants also to be offered the opportunity to discuss the study with Dr Nigel Arden or Mrs. Catherine Bowen. |
| **4.** Willing patients to meet the chief investigator, Mrs Catherine Bowen and discuss study after their clinical appointment time. | |
| **5.** Informed consent taken and copy given to patient. | **5i.** Patients screened for inclusion into the study. |
| **6.** Medical notes consulted for background clinical demographic information. | **5ii**. Patients accepted onto study and sticker with study details placed in medical records. Patient details coded. |
| **7.** Foot assessments carried out. | **7i.** Participant to complete the LFIS questionnaire. |
| | **7ii.** Investigator to assess both feet clinically. |
| **8.** Participants to be informed of results of foot assessments and details for 12 month return visit. | **7iii.** Investigator to scan both forefoot areas and complete ultrasound data collection sheet. |
| **9**. Make provisional arrangements for 12 month return appointment. | |
| **10.** GP information letters to be sent. | |

**Figure 30.** Summary of the protocol for control participants for the baseline study of the clinical relevance of MSUS detectable bursae.



1. Posters to be placed within the School of Health professions and Rehabilitation Sciences.

2. Potential staff/student participants to notify the chief investigator, Mrs Catherine Bowen.

2i. Potential staff/student participants to be given the participant information sheet with letters of invitation.

2ii. Potential participants also to be offered the opportunity to discuss the study with Mrs Catherine Bowen or Dr Nigel Arden.

3. Willing staff/student participants to meet the chief investigator, Mrs Catherine Bowen and discuss study.

4. Informed consent taken and copy given to staff/student.

4i. Staff/Students screened for inclusion into the study.

4ii. Staff/ Students accepted onto study and student details coded.

5. Foot assessments carried out.

5i. Participant to complete the LFIS questionnaire.

5ii. Investigator to assess both feet clinically.

7. Participants to be informed of results of foot assessments.

5.iii. Investigator to scan both forefoot areas and complete ultrasound data collection sheet.

## 5.8. Results

The analyses focused on:

1. Description of the prevalence of MSUS detectable forefoot bursae in RA.
2. Associations of clinical outcome variables with the presence of MSUS detectable bursae and patient reported foot disability.
3. Analysis of the relationship between MSUS detectable forefoot bursae and patient reported foot disability.

### 5.8.1. Participant demographic

Of the 275 patients approached, 166 patients with RA agreed to participate in the study. Seventeen were subsequently excluded, following the assessment for suitability, as they did not meet all the inclusion criteria (**Figure 31**). After checking assumptions of normality, an unpaired t-test for numerical parametric data was performed to compare the means in the responders and non responders for age. Levene's test for equality of variances was significant (p=0.038), suggesting one group was more variable in age distribution than the other, therefore 'equal variances not assumed t statistic' was used and there were no significant differences in the mean ages between responders and non-responders (t=0.765, p=0.445).

Using Chi squared analyses for non parametric categorical data, there were no significant differences in terms of gender, seropositivity or number of DMARDs between responders and non-responders (**Table 32**).

**Table 32.** Demographic comparison of responders and non responders for the baseline study of the clinical relevance of MSUS detectable bursae.

| | Responders (N=149) | Non Responders (N= 126) | Statistical values |
|---|---|---|---|
| **Age** | 59.43 (12.3) (range: 25-87) | 58.18 (14.4) (range: 19-90) | t = 0.765; p = 0.445 |
| **Gender** | 119 (79.9%) female 30 (20.1%) male | 96 (76.2%) female 30 (23.8%) male | $\chi^2$ = 0.541; p = 0.462; df=1 |
| **Seropositivity** | 114 (76.5%) sero +ve 32 (21.5%) sero -ve 3 (2.0%) missing | 96 (76.2%) sero +ve 24 (19.0%) sero -ve 6 (4.8%) missing | $\chi^2$ = 0.146; p = 0.703; df=1 |
| **DMARDs** | 120 (80.5%) yes 29 (19.5%) none | 107 (84.9%) yes 19 (15.1%) none | $\chi^2$ = 2.980; p = 0.395; df=3 |

**Key**: +ve= positive; -ve=negative; t = test statistic; $\chi^2$ = Pearson Chi- Square; df=degrees of freedom

**Figure 31.** RA participant recruitment flow chart of responders and non responders for the baseline study of the clinical relevance of MSUS detectable bursae.



275 letters sent
July 2006 – March 2007

166 responders to participate

8 replied with definite no, did not want to take part

101 no response

154 participants recruited: FeeTURA 1

12 responded yes but then withdrew/ withdrawn before assessment for suitability

1 excluded due to being too ill to attend

1 excluded due to being in another study

1 excluded due to recent leg fracture

1 excluded due to open foot wounds

1 excluded due to having Psoriatic Arthritis

9 responded to participate but then did not respond to telephone messages to arrange study appointments

1 withdrew due to being called in hospital to have surgery

2 responded, but subsequently deceased

149 participants completed the study/baseline assessments

One hundred and forty nine patients (119 female and 30 male, 25 seronegative and 114 seropositive) completed the study. Clinical and demographic variables are seen in **Table 33.** The participants' regular treatment of RA included 63.1% (N=94) taking methotrexate and 43.6% (N=65) taking anti-TNFα (Humira, Infliximab, Etanercept) therapy. Although 59.1% had recorded foot symptoms in their clinical notes, only 32.9% were currently receiving clinical foot care on a regular basis (**Table 34**).

**Table 33.** Demographic and clinical characteristics of the RA study participants for the baseline study of the clinical relevance of MSUS detectable bursae.

| Variable | N | Mean (SD) | Range |
|---|---|---|---|
| Age (years) | 149 | 59.3 (12.5) | 25 - 87 |
| Duration of Arthritis (years) | 148 | 12.3 (10.3) | 0.5 - 43 |
| Weight (Kg) | 148 | 73.3 (14.9) | 43.8 - 118.9 |
| Height (cm) | 115 | 164.2 (7.9) | 147.0 - 187.5 |
| Global wellbeing (100mmVAS) | 148 | 40.2 (24.2) | 0 - 98 |
| ESR (mm/hour) | 145 | 23.3 (19.2) | 2.0 - 108.0 |
| CRP (mg/litre) | 149 | 12.5 (18.1) | 1.0 - 129.0 |
| DAS-28 | 111 | 3.9 (1.3) | 1.11 - 6.9 |

**Key:** SD=standard deviation; RA = Rheumatoid arthritis; VAS = visual analog score; DAS-28 = 28 joint disease activity score.

Foot characteristics of the participants are reported in **Table 35**. The majority of participants experienced moderate foot impairment and footwear impact (mean LFIS$_{IF}$ score of 11.09, SD 4.9) and moderate levels of activity participation limitation (mean LFIS$_{AP}$ score of 17.58, SD 9.2). The majority of participants also had bursae that were detectable by MSUS (mean number per individual 3.54, SD 2.2) and intermetatarsal bursae were the dominant bursae type (mean number per individual 2.81, SD 1.8). Observations of foot structure noted a high presence of a pes-planus foot type amongst the participants that was the same in both feet (94.8%; N=128/135). MTP joint subluxation was present within 75.7% (N=112/148) in the right foot and 76.4% (113/148) within the left foot (**Table 36**).

**Table 34.** Clinical foot care of the RA study participants for the baseline study.

| Variable | Yes | No |
|---|---|---|
| Foot symptoms in clinical notes | 88 (59.1%) | 59 (39.6%) |
| Had seen a Chiropodist/ Podiatrist in the past | 91 (61.1%) | 58 (38.9%) |
| Seeing a Chiropodist/Podiatrist on a regular basis | 49 (32.9%) | 100 (67.1%) |

**Table 35.** Foot characteristics of the RA study participants for the baseline study.

| Variable | N | Mean (SD) | Range |
|---|---|---|---|
| MSUS detectable bursae* | 149 | 3.54 (2.2) | 0 - 9 |
| Clinically detectable bursae** | 149 | 0.48 (1.1) | 0 - 6 |
| $LFIS_{TOT}$ (x/51) | 149 | 28.8 (13.1) | 0 - 50 |
| $LFIS_{IF}$ (x/21) | 149 | 11.09 (4.9) | 0-21 |
| $LFIS_{AP}$ (x/30) | 149 | 17.58 (9.2) | 0-30 |

**Key:** SD=standard deviation; *Total numbers of MSUS detectable bursae per individual; ** Total numbers of clinically palpable bursae per individual; $LFIS_{TOT}$= Leeds Foot Impact Score, Total; $LFIS_{IF}$ = Leeds Foot Impact Score, Impairment/Footwear subscale; $LFIS_{AP}$ = Leeds Foot Impact Score, Activity Participation Limitation subscale.

**Table 36.** Prevalence of foot structure deformity of the RA study participants for the baseline study.

| Variable | Deformity present | Deformity absent |
|---|---|---|
| R MTP joint subluxation (N=148) | 112 (75.2%) | 36 (24.2%) |
| L MTP joint subluxation (N=148) | 113 (75.8%) | 35 (23.5%) |
| R Pes planus (N = 135) | 128 (85.9%) | 7 (4.7%) |
| L Pes planus (N = 135) | 128 (85.9%) | 7 (4.7%) |

### 5.8.2. Prevalence of forefoot bursae in the RA study group

Using MSUS, 92.6% (N= 138) of patients had detectable bursae (mean numbers of bursae per individual = 3.54, range 0-9) within the plantar forefoot and of these 89.9% (N=124/138) had bursae in both feet. On clinical examination by palpation 23.5% (N=35) of patients had detectable bursae within the plantar forefoot. Of those that could be detected by MSUS, only 24.6% (N=34) had been picked up by clinical examination. Using a related samples t-test, the difference between bursae detected clinically and bursae detected by MSUS was significant (t=18.671; p<0.001).

To explore whether there were differences between those individuals with MSUS detectable bursae only and those with MSUS detectable bursae that were also clinically palpable, the data was split into groups (no detectable bursae: group 1; bursae detectable by both MSUS and clinical palpation: group 2; bursae detectable by MSUS only: group 3; bursae detectable by clinical palpation only: group 4). The characteristics of each group can be seen in **Table 37** and **Table 38**.

**Table 37.** A two by two table showing the number and percentage of RA participants within each of the groups according to whether bursae are detectable clinically, by MSUS, by both MSUS and clinically or are not detectable.

| | | Clinically palpable bursae | |
|---|---|---|---|
| | | **No** | **Yes** |
| **MSUS detectable bursae** | **No** | Group 1 <br> 10 (6.7%) | Group 4 <br> 1 (0.7%) |
| | **Yes** | Group 3 <br> 104 (69.8%) | Group 2 <br> 34 (22.8%) |

The data was then tested for 'between group effects' in clinical and disease variables using analysis of variance. As variables are constant when bursae group is group 4 as there is only one participant it was omitted from the statistical analyses and graphs.

**Table 38.** Demographic and clinical characteristics of the RA study participants divided by whether bursae are not detected, detectable by MSUS, detectable by both MSUS and clinical palpation or detectable by clinical palpation alone.

| | Group 1 N=10 | Group 2 N=34 | Group 3 N=104 | *Group 4* *N=1* | ANOVA p-values |
|---|---|---|---|---|---|
| **Age (years)** | 53.7 (17.1) 25-87 | 59.0 (11.3) 33-81 | 60.0 (12.1) 26-85 | *76* | 0.241 |
| **Duration of Arthritis (years)** | 6.5 (4.6) 2-16 | 18.5 (11.5) 1-43 | 10.83 (9.5) 0-43 | *16* | 0.000 |
| **Global wellbeing (VAS 100mm)** | 52.3 (25.1) 0-79 | 38.9 (23.3) 0-81 | 39.1 (23.8) 0-98 | *88* | 0.079 |
| **ESR (mm/hour)** | 19.1 (20.2) 2-61 | 23.0 (17.9) 5-100 | 24.0 (19.6) 2-108 | *6.0* | 0.698 |
| **CRP (mg/litre)** | 14.7 (21.5) 1-69 | 11.8 (12.1) 1-46.9 | 12.6 (19.5) 1-129 | *2.0* | 0.911 |
| **DAS-28** | 4.2 (1.2) 2.6-5.4 | 3.9 (1.2) 1.8-6.2 | 3.9 (1.4) 1.1-7.0 | *-* | 0.934 |
| **LFIS Total (n/51)** | 25.5 (16.7) 2-47 | 31.2 (12.7) 4-48 | 28.1 (12.8) 0-50 | *31* | 0.549 |
| **LFIS$_{IF}$ (n/21)** | 10.7 (7.0) 0-18 | 12.3 (4.3) 3-19 | 10.7 (4.9) 0-21 | *14* | 0.404 |
| **LFIS$_{AP}$ (n/30)** | 14.7 (10.9) 0-29 | 18.9 (9.3) 1-30 | 17.3 (9.0) 0-30 | *17* | 0.615 |

**Key:** no detectable bursae: group 1; bursae detectable by both MSUS and clinical palpation: group 2; bursae detectable by MSUS only: group 3; bursae detectable by clinical palpation only: group 4

Although some trends could be observed between groups (**Table 38** and **Figure 32**) for each of the predictor variables, no significant differences between groups were found for age, weight, wellbeing (VAS), ESR, CRP, DAS-28, LFIS$_{IF}$ and LFIS$_{AP}$. There was however a significant difference for duration of RA (p<0.001) with group 2 (both clinical and MSUS detectable bursae) having the greatest disease duration (**Figure 33**).

**Figure 32.** A bar chart representing the mean values of predictor variables within each of the groups according to whether bursae are detectable clinically, by MSUS, by both MSUS and clinically or are not detectable.
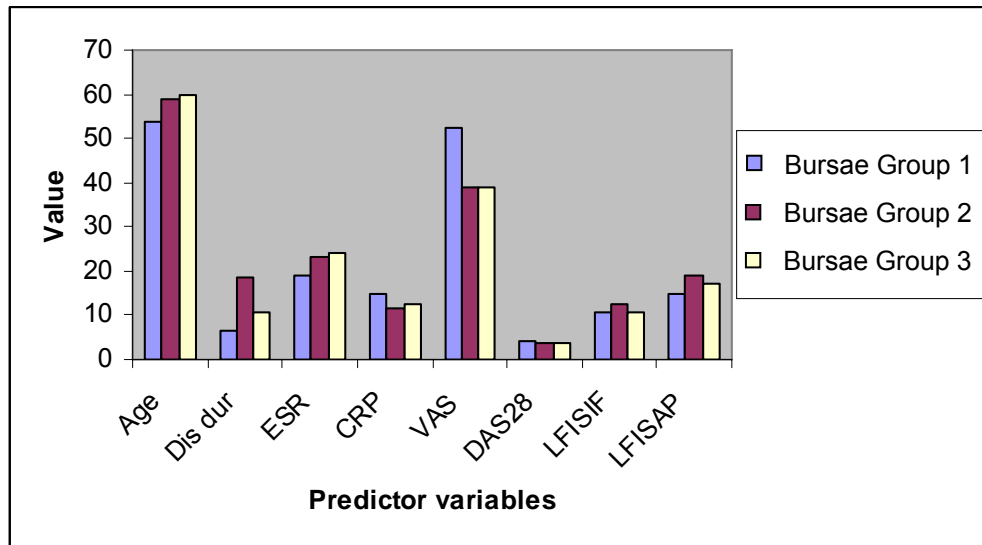


**Figure 33.** Stem and Leaf plots for duration of RA within each of the groups according to whether bursae are detectable clinically, by MSUS, by both MSUS and clinically or are not detectable.
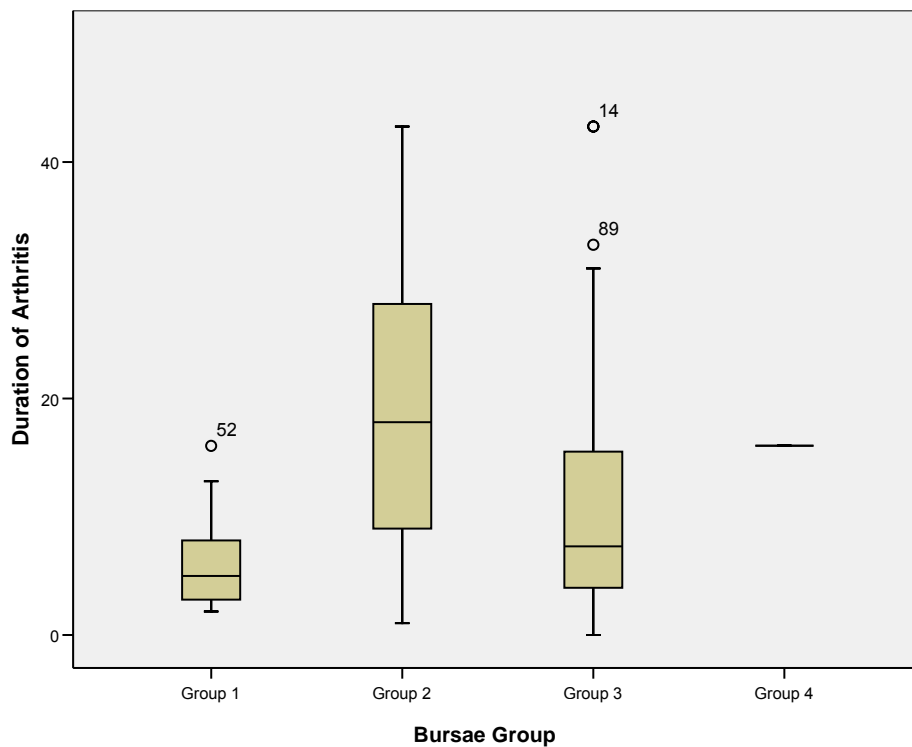
After adjusting the p values for the number of tests performed, using Bonferroni correction for duration of RA, the significant differences were indicated between group 1 and group 2 (p=0.003) and between group 2 and group 3 (p<0.001). These findings suggest that individuals with no detectable bursae by either MSUS or clinical palpation are more likely to have lower disease duration than those with both MSUS and clinically detectable bursae. Further, those individuals with MSUS detectable bursae only (no clinical detection) are also more likely to have lower disease duration than those with both MSUS and clinically detectable bursae.

### 5.8.3. Further categorical analysis of RA participants between MSUS detectable bursae, disease duration and disease severity

MSUS detectable bursae were recoded into two categories, those individuals with one or no bursa and those with the presence of two or more bursae. The rationale for the cut- off point was that, on analysis of the healthy participant control data, only one or no bursae were identified in any individual. Disease activity was categorized by DAS-28 into remission (0-2.59), low activity (2.6-3.19), moderate disease activity (3.2-5.09), high disease activity (5.1 and above). Disease severity was categorized as rheumatoid factor positive or rheumatoid factor negative.

On cross tabulation of data the majority of participants that had two or more bursae also had sero-positive disease (82.5%) (**Table 39**) and moderate levels of disease activity (37.8%) (**Table 40**).

**Table 39.** A two by two table showing the cross tabulation results for dichotomized MSUS detectable bursae and disease severity (defined by presence of rheumatoid factor) of the RA study participants for the baseline study.

| | MSUS detectable bursae | |
| --- | --- | --- |
| | **Little/no bursae** | **Presence of 2 or more bursae** |
| **Sero-positive** | 20 (17.5%) | 94 (82.5%) |
| **Sero-negative** | 10 (30%) | 22 (69.7%) |

$\chi2$= 2.875; p= 0.090

**Table 40.** A two by two table showing cross tabulation results for dichotomized MSUS detectable bursae and disease activity (defined by categorized DAS-28 scores) of the RA study participants for the baseline study.

| | | MSUS detectable bursae | |
| --- | --- | --- | --- |
| | | Little/ no bursae | Presence of 2 or more bursae |
| **DAS-28 category** | **Remission** | 0 (0%) | 20 (18%) |
| | **Low activity** | 3 (2.7%) | 10 (9%) |
| | **Moderate activity** | 13 (11.7%) | 42 (37.8%) |
| | **High activity** | 4 (3.6%) | 19 (17.1%) |

$\chi2$= 5.802; p= 0.122

The categorical data was explored further for significant associations using logistic regression analyses. No significant associations were found between dichotomized MSUS detectable bursae and either disease severity or disease activity**.**

### 5.8.4. Location of forefoot bursae in the RA study group

The most common location for MSUS detectable bursae was the intermetatarsal (IM) 4/5 space for both feet followed in order by IM 3/4, IM 1/2, IM 2/3, sub-metatarsal head (submet) 5, submet 2, submet 1, submet 3, submet 4 (**Figure 34**). Of note is that MSUS detectable intermetatarsal bursae were observed in 90.6% (N=135) of the RA participants (mean 2.81, range 0–8).

**Figure 34.** Line drawings of a cross section of the left and right forefeet, at the level of the metatarsal heads. The drawing represents the presence and location of MSUS detectable bursae within the forefeet of patients with rheumatoid arthritis detectable by MSUS. Presence and location of MSUS detectable bursae in healthy control participants are also included as italicised data.
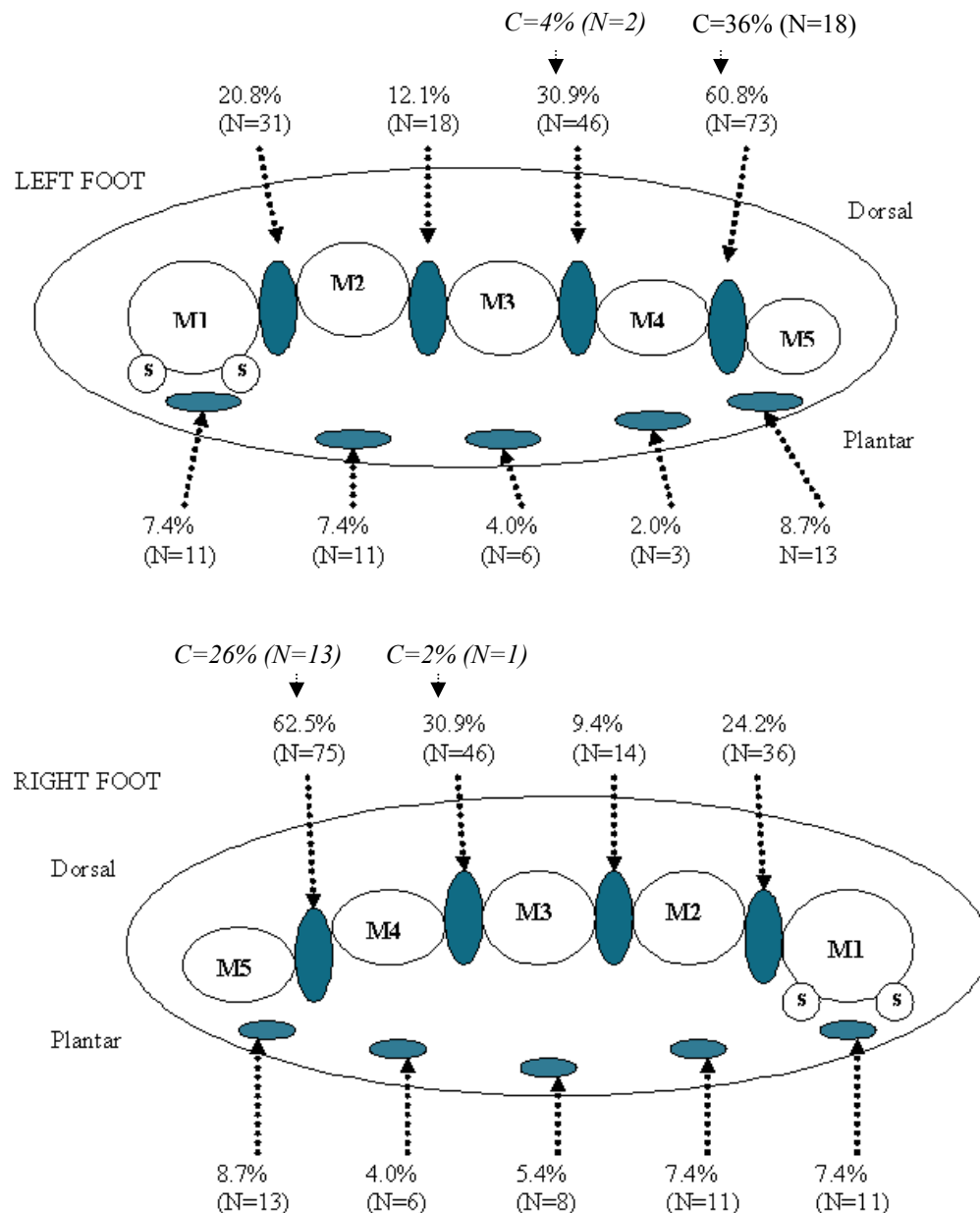


**Key:** M1=first metatarsal head, M2=second metatarsal head, M3=third metatarsal head, M4=fourth metatarsal head, M5=fifth metatarsal head, MS=medial sesamoid, LS=lateral sesamoid.

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### 5.8.5. Analysis of associations for MSUS detectable bursae with patient reported foot impact outcome measures in RA participants

To investigate whether MSUS detectable bursae were associated with patient reported foot impact outcome measures, the data was primarily explored using scatter plots and correlation plots to determine which clinical variables, decided on the basis of biological and clinical relevance, were related to MSUS bursae.

#### 5.8.5.1. Correlations

Findings showed that total numbers of MSUS detectable bursae were significantly correlated with duration of RA (r=0.283, p<0.001), anti-TNF-α therapy (R=0.174, 0.034) and ESR (r=0.166, p=0.045) but no associations were seen with age, weight, wellbeing, CRP, DAS-28, methotrexate or foot structure variables (MTP joint subluxation and pes-planus foot type) (**Table 41** and **Table 42**). There was a significant weak correlation between total numbers of MSUS detectable bursae and impact of RA disease on the foot for both subscales of LFIS (LFIS$_{IF}$ r=0.182, p=0.026; LFIS$_{AP}$ r=0.215, p=0.009). In contrast, a zero correlation between MSUS detectable bursae and global wellbeing was noted (**Table 41**).

**Table 41.** The continuous data correlations between MSUS detectable bursae and relevant clinical variables for RA participants for the baseline study

|  | Pearson Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **Age (N=149)** | -0.023 | 0.780 |
| **Duration of RA (N=148) \*\*** | 0.283 | 0.000 |
| **Weight(kgs) (N=148)** | 0.048 | 0.562 |
| **Height(cms) (N=115)** | 0.027 | 0.778 |
| **Global wellbeing VAS (N=148)** | 0.000 | 0.996 |
| **ESR (N=145) \*** | 0.166 | 0.045 |
| **CRP (N=141)** | 0.082 | 0.333 |
| **DAS-28 (N=111)** | -0.076 | 0.426 |
| **LFIS$_{IF}$ (N=149) \*** | 0.182 | 0.026 |
| **LFIS$_{AP}$ (N=149) \*\*** | 0.215 | 0.009 |

**Key:** \*\*Correlation is significant at the 0.01 level (2-tailed); \*Correlation is significant at the 0.05 level (2-tailed).

**Table 42.** The categorical data correlations between MSUS detectable bursae and relevant clinical variables for RA participants for the baseline study.

| | Spearman's Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **Disease severity (N=146) \*\*** | 0.243 | 0.003 |
| **Current TNF (N=149) \*** | 0.174 | 0.034 |
| **Current MTX (N=149)** | -0.034 | 0.684 |

**Key:** \*\*Correlation is significant at the 0.01 level (2-tailed); \*Correlation is significant at the 0.05 level (2-tailed); TNF=anti-TNFα therapy; MTX = methotrexate.

From the significantly correlated variables, foot impact scores ($LFIS_{IF}$ and $LFIS_{AP}$) are the most clinically important within this study. To determine other explanatory variables for the variance in foot impact scores, correlations were also analysed between $LFIS_{IF}$ and $LFIS_{AP}$ and age, duration of RA, weight, height, global well being (VAS), ESR, CRP and DAS-28 (**Table 43** and **Table 44**).

**Table 43.** Continuous data correlations between $LFIS_{IF}$ and explanatory variables for RA participants for the baseline study.

| | Pearson Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **MSUS bursae (N=149)\*** | 0.182 | 0.026 |
| **Age (N=149)** | 0.005 | 0.956 |
| **Duration of RA (N=148)** | 0.125 | 0.130 |
| **Weight (N=148)** | -0.030 | 0.717 |
| **Global well being VAS (N= 148)\*\*** | 0.370 | <0.001 |
| **ESR (N=145)** | 0.193 | 0.020 |
| **CRP (N= 141)** | 0.074 | 0.383 |
| **DAS-28 (N= 97)\*\*** | 0.237 | 0.012 |

**Key:** \*\* Correlation is significant at the 0.01 level (2-tailed); \*Correlation is significant at the 0.05 level (2-tailed)

**Table 43** shows the findings that $LFIS_{IF}$ was also significantly correlated with wellbeing VAS and ESR and **Table 44** shows the findings that $LFIS_{AP}$ was also significantly correlated with age, duration of RA, wellbeing VAS, ESR and CRP.

**Table 44.** Continuous data correlations between LFIS$_{AP}$ and explanatory variables for RA participants for the baseline study.

| | Pearson Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **MSUS bursae (N=149)\*\*** | 0.215 | 0.009 |
| **Age (N=149)\*\*** | 0.295 | <0.001 |
| **Duration of RA (N=148)\*\*** | 0.174 | 0.034 |
| **Weight (N=148)** | -0.065 | 0.436 |
| **Global well being VAS (N=148)\*\*** | 0.327 | <0.001 |
| **ESR (N=145)\*\*** | 0.319 | <0.001 |
| **CRP (N=141)\*** | 0.182 | 0.031 |
| **DAS-28 (N=111)\*\*** | 0.315 | 0.001 |

In the determination of other explanatory variables for the variance in foot impact scores, correlations between LFIS$_{IF}$ and LFIS$_{AP}$ and non-parametric data of current medication (methotrexate and anti-TNF-α therapy) and disease severity were also analysed (**Table 45** and **Table 46**).

**Table 45**. Categorical data correlations between LFIS$_{IF}$ and explanatory variables for RA participants for the baseline study.

| | Spearman's Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **Disease severity (N=146)** | -0.057 | 0.491 |
| **Currently on anti-TNF-α therapy (N=149)** | 0.071 | 0.388 |
| **Currently on methotrexate (N=149)** | 0.098 | 0.234 |

**Table 46**. Categorical data correlations between LFIS$_{AP}$ and explanatory variables for RA participants for the baseline study.

| | Spearman's Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **Currently on methotrexate (N=149)** | -0.081 | 0.328 |
| **Currently on anti-TNFα therapy (N=149)\*** | 0.164 | 0.046 |
| **Disease severity (N=146)** | 0.021 | 0.797 |

**Key:** \* Correlation is significant at the 0.05 level (2-tailed)

**Table 46** shows that only a weak significant correlation was found between $LFIS_{AP}$ and participants who were taking anti-TNF-α therapy.

### 5.8.5.2. Univariate linear regression analyses

The relationship between foot impact scores and MSUS detectable bursae was then investigated further using and univariate and multivariate regression modelling with the identified confounding variables from results of the correlation analyses (**Table 47** and **Table 48**).

**Table 47.** Univariate linear regression results for associations between $LFIS_{IF}$ and predictor confounding variables for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae* | $LFIS_{IF}$ | 0.406 | 0.180 | P=0.026 | 0.049-0.763 |
| Age | $LFIS_{IF}$ | 0.002 | 0.033 | P=0.956 | -0.063-0.067 |
| Duration of RA | $LFIS_{IF}$ | 0.060 | 0.039 | P=0.130 | -0.018-0.138 |
| Wellbeing VAS* | $LFIS_{IF}$ | 0.076 | 0.016 | P<0.001 | 0.045-0.107 |
| Weight | $LFIS_{IF}$ | -0.010 | 0.027 | P=0.717 | -0.064-0.044 |
| ESR* | $LFIS_{IF}$ | 0.050 | 0,021 | P=0.020 | 0.008-0.092 |
| CRP | $LFIS_{IF}$ | 0.020 | 0.023 | P=0.383 | -0.025-0.065 |
| DAS-28* | $LFIS_{IF}$ | 0.853 | 0.334 | P=0.012 | 0.190-1.515 |

**Key:** *denotes significant values

Within **Table 47** and **Table 48**, results using univariate linear regression show the regression coefficients extent and statistical significance that each of the predictor variables change for unit changes in $LFIS_{IF}$ and $LFIS_{AP}$. There were significant associations for MSUS detectable bursae ($LFIS_{IF}$ β=0.406, p=0.026; $LFIS_{AP}$ β=0.891, p=0.009). This indicates that $LFIS_{IF}$ score increases by 0.406 and $LFIS_{AP}$ score increases by 0.891 for a unit increase in MSUS detectable bursae.

The $r^2$ (R square) was 0.033 for the linear model of MSUS detectable bursae with $LFIS_{IF}$ which indicates that the significant associations explain 3.3% of the variance in $LFIS_{IF}$. The $r^2$ (R square) was 0.047 for the linear model of MSUS detectable bursae with $LFIS_{AP}$ which indicates that the significant associations explain 4.7% of the variance in $LFIS_{AP}$.

**Table 48.** Univariate linear regression results for associations between LFIS$_{AP}$ and predictor confounding variables for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae* | LFIS$_{AP}$ | 0.889 | 0.333 | P=0.009 | 0.230-1.547 |
| Age* | LFIS$_{AP}$ | 0.217 | 0.059 | p<0.001 | 0.104-0.336 |
| Duration of RA* | LFIS$_{AP}$ | 0.159 | 0.073 | P=0.030 | 0.012-0.299 |
| Wellbeing VAS* | LFIS$_{AP}$ | 0.124 | 0.030 | P<0.001 | 0.066-0.183 |
| Weight | LFIS$_{AP}$ | -0.044 | 0.051 | P=0.384 | -0.145-0.056 |
| ESR* | LFIS$_{AP}$ | 0.154 | 0.038 | P<0.001 | 0.079-0.230 |
| CRP* | LFIS$_{AP}$ | 0.092 | 0.042 | P=0.031 | 0.009-0.174 |
| DAS28* | LFIS$_{AP}$ | 1.980 | 0.571 | P=0.001 | 0.849-3.111 |

**Key:** * denotes significant values

There were also significant associations for wellbeing (β=0.076; p<0.001), ESR (β=0.05; p=0.020) and DAS-28 (β=0.853; p=0.012) with LFIS$_{IF.}$ For LFIS$_{AP}$ there were significant associations for wellbeing (β=0.124; p<0.001), ESR (β=0.154; p<0.001), CRP (β=0.092; p=0.031) and DAS-28 (β=1.98; p=0.001) (**Table 47** and **Table 48**).

In addition, when the correlation coefficient values are compared, LFIS$_{AP}$ associations appeared to be stronger than LFIS$_{IF}$ associations with both the primary and secondary outcome variables. Caution applies in interpretation of this as the scales for LFIS$_{IF}$ and LFIS$_{AP}$ are not equal, with LFIS$_{IF}$ being nine points less. However, in an additional analysis, global well-being scores (due to its clinical relevance with mobility and disability) were computed with LFIS$_{IF}$ and LFIS$_{AP}$ scores transformed into percentages. Scatter plots and the estimate of the effect of well-being on LFIS$_{IF}$ was 0.363 (CIs 0.214 – 0.512) and on LFIS$_{AP}$ was 0.434 (CIs 0.237 – 0.631). Therefore well being appears to be a better association with activity participation limitation.

*5.8.5.3. Multivariate regression model analyses*
Potential confounding factors, with the relationship between patient reported impact of RA disease on the foot and total numbers of MSUS detectable bursae from predictor variables, were therefore identified as wellbeing VAS, ESR, DAS-28 and left foot MTP joint subluxation for LFIS$_{IF}$ and age, duration of RA, wellbeing VAS, ESR, CRP, DAS-28 and left foot MTP joint subluxation for LFIS$_{AP}$.

Before the relationship between MSUS detectable bursae and foot impact scores could be entered into a multivariate regression model with the predictor confounding variables diagnostic tests for assumptions were performed. All histograms and normal probability plots of standardised residuals showed that the distribution of the residuals was normal. All constant variance scatter plots showed no particular tendency for residuals to increase or decrease systematically, with the fitted values indicating that the constant variance assumption is almost met. In all scatter plots of residuals versus explanatory variable (MSUS bursae) there was no particular pattern, indicating a linear relationship between $LFIS_{IF}$ and MSUS detectable bursae and $LFIS_{AP}$ and MSUS detectable bursae. There were no colinearity indications for any of the models. The diagnostic tests for assumptions showed that the use of multiple linear regressions was an appropriate method of investigating further the extent to which MSUS bursae was linearly related to the outcome variable (LFIS) after adjusting for the other predictor variables.

Having satisfied the assumptions, firstly, the potential confounding variables of age and disease duration were entered into a multivariate linear regression analysis model with $LFIS_{AP}$ as the outcome variable and tested for interaction with MSUS detectable bursae. A significant relationship between $LFIS_{AP}$ and total MSUS detectable bursae ($\beta= 0.803$, $p<0.02$) remained even after controlling for age and disease duration (**Table 49**). Disease duration was no longer significant, probably due to its colinearity with age.

Thus controlling for age and disease duration, there is a significant linear relationship between $LFIS_{AP}$ and MSUS detectable bursae ($\beta=0.803$, $p=0.019$). This indicates that $LFIS_{AP}$ score increases by 0.803 for every unit increase in MSUS bursae while age and duration of RA remain constant. The $r^2$ (R square) was 0.136 for the model, which indicates that the significant associations explain 13.6% of the variance in $LFIS_{AP}$.

**Table 49.** Multivariate linear regression models for LFIS activity participation subscale scores ($LFIS_{AP}$) and predictor confounding variables for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{AP}$ | 0.803 | 0.338 | 0.019 | 0.135–1.471 |
| Age | $LFIS_{AP}$ | 0.209 | 0.059 | 0.001 | 0.093-0.326 |
| Duration of RA | $LFIS_{AP}$ | 0.072 | 0.073 | 0.329 | -0.073-0.217 |

Secondly, to assess the influence of disease activity on the association between the occurrences of MSUS detectable bursae and foot impact scores, confounding measures of disease activity, ESR and global wellbeing (VAS) were also tested for interaction with both LFIS sub scales. The variables of CRP and DAS-28 were omitted from the model with $LFIS_{IF}$ as they were not significant in the linear regression relationship and were omitted from the model with $LFIS_{AP}$ due to their colinearity with ESR and wellbeing VAS.

After adjusting for confounding variables of disease activity (ESR and wellbeing VAS), a significant linear relationship remained between MSUS detectable bursae and $LFIS_{IF}$ (ß=0.377, p=0.033). The $r^2$ (R square) for this model was 0.177 which indicates that the significant associations for MSUS detectable bursae, age, global wellbeing (VAS) and ESR explain 17.7% of the variance in $LFIS_{IF}$ (**Table 50**).

Similarly, after adjusting for confounding variables of disease activity (ESR and wellbeing VAS), a significant linear relationship remained between MSUS detectable bursae and $LFIS_{AP}$ (ß = 0.762, p=0.013). The $r^2$ (R square) for this model was 0.285 which indicates that the significant associations for MSUS detectable bursae, age, global wellbeing (VAS) and ESR explain 28.5% of the variance in $LFIS_{IF}$ (**Table 51**).

These findings indicate that $LFIS_{IF}$ score increases by 0.379 for every unit increase in MSUS bursae and that $LFIS_{AP}$ score increases by 0.703 for every unit increase in MSUS bursae while wellbeing VAS and ESR remain constant.

**Table 50.** Multiple linear regression models for LFIS impairment subscale scores, MSUS detectable bursae and disease activity for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | LFIS $_{IF}$ | 0.377 | 0.175 | 0.033 | 0.031 - 0.722 |
| Age | LFIS $_{IF}$ | -0.010 | 0.032 | 0.758 | -0.073 - 0.053 |
| Global VAS | LFIS $_{IF}$ | 0.072 | 0.016 | <0.001 | 0.039 - 0.104 |
| ESR | LFIS $_{IF}$ | 0.026 | 0.021 | 0.212 | -0.015 - 0.068 |

**Table 51.** Multiple linear regression models for LFIS activity limitation subscale scores, MSUS detectable bursae and disease activity for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | SE | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{AP}$ | 0.762 | 0.302 | 0.013 | 0.164 - 1.359 |
| Age | $LFIS_{AP}$ | 0.212 | 0.055 | <0.001 | 0.103 - 0.320 |
| Global VAS | $LFIS_{AP}$ | 0.106 | 0.028 | <0.001 | 0.050 - 0.162 |
| ESR | $LFIS_{AP}$ | 0.094 | 0.036 | 0.010 | 0.023 - 0.166 |

*5.8.6. Analysis of the relationship of MSUS detectable bursae in RA participants and foot structure deformity*

Having produced a stable multivariate model, measures of the presence of forefoot deformity (MTP joint subluxation) were further investigated, in order to assess whether the association between the numbers of MSUS detectable bursae and $LFIS_{IF}$ and $LFIS_{AP}$ was independent of these confounding variables too.

Results from the categorical correlations had showed a significant association between both LFIS subscale scores for the presence of MTP joint subluxation in left feet but none with right foot MTP joint subluxation, right foot pes-planus or left foot pes-planus. Higher mean scores for patient related foot symptoms ($LFIS_{IF}$ and $LFIS_{AP}$) are seen with foot structure deformity in **Table 52**.

Using univariate linear regression there were significant associations for left foot MTP joint subluxation for both $LFIS_{IF}$.(β=1.898; p=0.046) and $LFIS_{AP}$ (β=3.599; p=0.042) (**Table 53**). The $r^2$ (R square) was 0.026 for the $LFIS_{IF}$ model and 0.028 for the $LFIS_{AP}$ model, which indicates that the significant associations explain 2.7% of the variance in $LFIS_{IF}$ and 2.8% of $LFIS_{AP}$.

**Table 52.** A table showing the mean, standard deviation (SD) and range for LFIS$_{IF}$ and LFIS$_{AP}$ scores according to presence or absence of foot deformity for RA participants for the baseline study.

| | LFIS$_{IF}$ (x/21) | | LFIS$_{AP}$ (x/30) | |
|---|---|---|---|---|
| | **Deformity present** | **Deformity absent** | **Deformity present** | **Deformity absent** |
| **Right MTP joint subluxation** | 11.6 (4.7) <br> 0-20 | 9.75 (5.2) <br> 0-21 | 18.5 (8.9) <br> 0-30 | 15.19 (9.5) <br> 0-29 |
| **Left MTP joint subluxation** | 11.6 (4.7) <br> 0-20 | 9.7 (5.3) <br> 0-21 | 18.51 (8.9) <br> 0-30 | 14.9 (9.5) <br> 0-29 |
| **Right Pes-planus** | 11.27 (4.8) <br> 0-21 | 10.14 (6.0) <br> 4-19 | 18.33 (8.9) <br> 0-30 | 14.14 (10.1) <br> 3-29 |
| **Left Pes-planus** | 11.27 (4.8) <br> 0-21 | 10.14 (6.0) <br> 4-19 | 18.33 (8.9) <br> 0-30 | 14.14 (10.1) <br> 3-29 |

**Table 53.** Univariate linear regression results for associations between LFIS$_{IF}$, LFIS$_{AP}$ and predictor foot structure confounding variables for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Right MTP joint subluxation | LFIS$_{IF}$ | 1.830 | 0.934 | 0.052 | -0.015 – 3.676 |
| Left MTP joint subluxation* | LFIS$_{IF}$ | 1.898 | 0.942 | 0.046 | 0.036 – 3.760 |
| Right pes-planus | LFIS$_{IF}$ | 1.123 | 1.903 | 0.556 | -2.641 – 4.886 |
| Left pes-planus | LFIS$_{IF}$ | 1.123 | 1.903 | 0.556 | -2.641 – 4.886 |
| Right MTP joint subluxation | LFIS$_{AP}$ | 3.261 | 1.739 | 0.063 | -0.176 – 6.698 |
| Left MTP joint subluxation* | LFIS$_{AP}$ | 3.599 | 1.752 | 0.042 | 0.137 – 7.061 |
| Right pes-planus | LFIS$_{AP}$ | 4.185 | 3.479 | 0.231 | -2.696 – 11.066 |
| Left pes-planus | LFIS$_{AP}$ | 4.185 | 3.479 | 0.231 | -2.696 – 11.066 |

**Key:** * denotes significant values

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To assess the relevance of foot structure deformity on the association between the occurrences of MSUS detectable bursae and foot impact scores, the confounding variable of left foot MTP joint subluxation was tested for interaction with both LFIS sub scales. When the left foot MTP joint variable was entered into the multivariate model, the association between MSUS detectable bursae and LFIS remained statistically significant (LFIS$_{IF}$ ß=0.380, p=0.035; LFIS$_{AP}$ ß=0.890, p=0.006) (**Table 54** and **Table 55**).

**Table 54.** Multiple linear regression models for LFIS impairment subscale scores and foot structure of participants for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | LFIS $_{IF}$ | 0.380 | 0.179 | 0.035 | 0.026 – 0.734 |
| Age | LFIS $_{IF}$ | -0.020 | 0.033 | 0.561 | -.0086 – 0.047 |
| Left MTP joint Subluxation | LFIS $_{IF}$ | 1.993 | 0.964 | 0.040 | 0.089 – 3.898 |

**Table 55.** Multiple linear regression models for LFIS activity participation limitation subscale scores and foot structure of participants for RA participants for the baseline study.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | LFIS $_{AP}$ | 0.890 | 0.319 | 0.006 | 0.259 – 1.520 |
| Age | LFIS $_{AP}$ | 0.199 | 0.060 | 0.001 | 0.082 – 0.317 |
| Left MTP joint Subluxation | LFIS $_{AP}$ | 2.064 | 1.716 | 0.231 | -1.329 – 5.457 |

The $r^2$ (R square) was 0.059 for the LFIS$_{IF}$ model and 0.138 for the LFIS$_{AP}$ model which indicates that the significant associations explain 5.9% of the variance in LFIS$_{IF}$ and 13.8% of LFIS$_{AP}$.

The result that one foot (left) MTP joint subluxation should have a significant correlation whilst the other (right) had none, was investigated further to determine if the results were

due to measurement error. Three further models were therefore analysed. The regression model was firstly recalculated using right foot MTP joint subluxation (model a). Secondly both left and right feet MTP joint subluxation were entered into the model (model b). Finally a new variable was calculated as presence of MTP joint subluxation for both feet and this too was then entered into the model (model c).

In each model with both LFIS$_{IF}$ and LFIS$_{AP}$, MSUS detectable bursae remained significant:

- Model a. LFIS$_{IF}$ $\beta$ = 0.384, p=0.033; LFIS$_{AP}$ $\beta$ = 0.895, p= 0.006
- Model b. LFIS$_{IF}$ $\beta$ = 0.381, p=0.036; LFIS$_{AP}$ $\beta$ = 0.878, p=0.007
- Model c. LFIS$_{IF}$ $\beta$ = 0.380, p=0.035; LFIS$_{AP}$ $\beta$ = 0.890, p=0.006

### 5.8.7. Analysis of the relationship of MSUS detectable bursae in RA participants when grouped according to whether clinically detectable or MSUS detectable

The group data for bursae (section 5.8.2, page 138) that is, those individuals who had MSUS detectable bursae and clinically detectable bursae (group 2) and those individuals who had MSUS only detectable bursae (group 3) were investigated to see if there was a linear relationship between both LFIS$_{IF}$ and LFIS$_{AP}$ scores and MSUS detectable bursae within the groups.

There were no significant linear associations between either LFIS$_{IF}$ or LFIS$_{AP}$ scores or MSUS detectable bursae (**Table 56**) and the confidence intervals for each of the groups do not appear much different from each other, indicating reduced association. A trend can however be seen in the reduction in $\beta$ values from those individuals who had MSUS detectable bursae and clinically detectable bursae (group 2) and those individuals who had MSUS only detectable bursae (group 3) for both LFIS$_{IF}$ and LFIS$_{AP}$.

Comparing $\beta$ values does give more information on whether the lack of significance is that the association is different or is due to lack of statistical power (Petrie and Sabin 2005). In Chapter three (section 3.7.1, page 69) power calculations indicated that the sample was just adequately powered for reasonable statistical analyses. However when the data was split into groups for trend analyses, the power for each sample was not recalculated and it is very likely that the groups are underpowered and therefore statistical analyses on the group data should be interpreted with caution. This is a common problem in studies where the study is

well powered but becomes underpowered for grouping of data analyses (Petrie and Sabin 2005).

Nevertheless, the β values have not decreased to zero, therefore there is possibly an effect or association but not enough statistical power to determine this.

**Table 56.** Univariate linear regression results for associations between LFIS$_{IF}$, LFIS$_{AP}$ and MSUS detectable bursae within bursae groups for RA participants for the baseline study.

|  | Explanatory Variable | Outcome variable | Regression coefficient β | SE | P Value | 95% CI |
|---|---|---|---|---|---|---|
| Group 2 | Total bursae | LFIS $_{IF}$ | 0.592 | 0.351 | 0.101 | -0.123 – 1.307 |
| Group 2 | Total bursae | LFIS $_{AP}$ | 1.117 | 0.763 | 0.153 | -0.436 – 2.67 |
| Group 3 | Total bursae | LFIS $_{IF}$ | 0.382 | 0.264 | 0.152 | -0.142 – 0.906 |
| Group 3 | Total bursae | LFIS $_{AP}$ | 0.876 | 0.483 | 0.073 | -0.082 – 1.834 |

*5.8.8. Characteristics and prevalence of forefoot bursae in the control group participants*

Demographic and clinical variables are presented in **Table 57**. Of the 50 control participants, pes-planus foot type was present in 59.2% (N=29/49) within the right foot and 67.3% (N=29/49) within the left foot. No control participants were reported as having MTP joint subluxation in either foot. No bursae was observed clinically in any of the control participants however on MSUS, 38% (N=19) of participants had detectable bursae, although the mean numbers per individual were small (μ 0.68, range 0-3).

**Table 57.** Demographic and clinical characteristics of the healthy control study participants for the baseline study.

| Variable | N | Mean (SD) | Range |
|---|---|---|---|
| Age (years) | 50 | 33.2 (10.7) | 19-61 |
| Weight (Kg) | 50 | 73.99 (13.4) | 54.5-120 |
| Height (cm) | 50 | 170.5 (8.5) | 150-191 |
| MSUS detectable bursae* | 50 | 0.68 (0.9) | 0 - 3 |
| Clinically detectable bursae** | 50 | 0.00 (0.0) | 0 |
| LFIS$_{TOT}$ | 50 | 1.1 (2.5) | 0-13 |
| LFIS$_{IF}$ | 50 | 1.02 (2.2) | 0-10 |
| LFIS$_{AP}$ | 50 | 0.1 (0.5) | 0-3 |
| Global wellbeing (100mm VAS) | 50 | 11.6 (9.2) | 0-58 |

**Key:** SD=standard deviation; *Total numbers of MSUS detectable bursae per individual; ** Total numbers of clinically palpable bursae per individual; LFIS$_{TOT}$=Leeds Foot Impact Score, Total; LFIS$_{IF}$=Leeds Foot Impact Score, Impairment/Footwear subscale; LFIS$_{AP}$=Leeds Foot Impact Score, Activity Participation Limitation subscale; VAS=visual analogue scale.

The location of the MSUS detectable bursae were IM 4/5 (L 36%, N=18; R 26%, N=13) followed by IM 3/4 (L 4%, N=2; R 2%, N=1). No associations of these bursae were seen with age, weight, height, foot structure variables and LFIS$_{IF}$ or LFIS$_{AP}$.

Differences between MSUS detectable bursae of the control participants and study RA participants were statistically significant (p<0.001). To ensure that this was not due to differences in age between the RA patients and controls we performed two additional analyses. Firstly we restricted both patients and controls to those below the age of 55 and secondly we performed analysis of variance on the whole cohort with age as a confounding variable. In both cases the p value remained statistically significant (p<0.001).

### 5.9. Summary of results

**1. Description of the prevalence of bursae within the forefoot in RA.**

In a large cross section of patients with RA in a hospital setting, bursae within the plantar forefoot detectable by MSUS are highly prevalent but under detected clinically. The prevalence of bursae within the plantar forefoot detectable by MSUS is significantly higher than in normal control subjects. The most common locations for MSUS detectable bursae in both RA and healthy participants were between the 4th and 5th metatarsal heads.

**2. Associations of the presence of MSUS detectable forefoot bursae with patient reported foot impact and clinical outcome variables.**

In a large cross section of patients with RA the presence of MSUS detectable bursae was associated with the patient reported foot impact as assessed by the Leeds Foot Impact Score. The strength of the association was higher between MSUS detectable bursae and activity participation limitation which also had a stronger association with global well-being, indicating that this may be important to patients.

**3. Analysis of the relationship between MSUS detectable bursae and patient reported foot impact**.

In a large cross section of patients with RA, the association of MSUS detectable bursae and patient reported foot impact remained significant even when confounding factors associated with age and disease activity are adjusted for.

## 5.10. Discussion

This study further demonstrates the use of MSUS in the detection of bursae in plantar forefoot in RA participants and also provides additional evidence for the prevalence of bursae within the forefoot in a large cross sectional cohort of patients with RA. We found that, of the plantar forefoot bursae that were detectable by MSUS in patients with RA, only a quarter were detected clinically. MSUS detectable forefoot bursae in RA participants were also significantly higher than in healthy control participants. Furthermore, the MSUS detectable bursae in the study patients with RA were significantly associated with patient reported foot impact outcome measures, which was independent of overall disease activity and foot structure deformity.

Prior to the use of MSUS and MR imaging techniques, studies of bursae in RA feet have been based on cadaveric or surgical investigations (Bossley and Cairney 1980; Claustre, Bonnel et al 1983; Shi, Tomita et al 2000). They suggested that swelling of forefoot bursae was more common with longer disease duration, which we have confirmed in this large clinical study. When the data was split into groups however, longer disease duration was associated with clinically palpable bursae and those with MSUS detectable bursae only were more likely to have the shortest disease durations. It highlights that in this cohort of RA participants, clinical examination alone would have missed considerable bursae in those with early disease.

The high prevalence of MSUS detectable bursae in our study is confirmed by previous MRI findings in which bursitis was observed in 63% of patients with early RA also located between or beneath the metatarsal heads (Boutry, Larde et al 2003). Manifestations of RA have also been observed within the forefeet when hands have shown no abnormalities (Ostendorf , Scherer et al 2004) or less pathological changes than the feet (Boutry, Larde et al 2003; Ostendorf , Scherer et al 2004). Others using MRI have clearly indicated that bursitis in RA should not be overlooked and that imaging of the foot provides more information about the effects of RA (Ashman, Klecker and Yu 2001; Narvaez, Narvaez et al 2002).

The use of MSUS to detect pathology in RA that is not clinically apparent and to guide treatment decisions is gaining recognition (Wakefield, Green et al 2004, Brown, Quinn et al 2006; Wakefield, Freeston et al 2008). Difficulty in diagnosing specific soft tissue

pathology, such as synovitis or pathological changes in bursae within the foot clinically, has previously been reported (Beggs 2002; Ashman, Klecker, and Yu 2001; Luukkainen, Saltyshev et al 2003; Davys, Turner et al 2005).

We did observe a substantial discrepancy between MSUS detectable bursae and clinically detectable bursae in our RA population, however there was also a moderate prevalence (38%) of MSUS detectable bursae between the fourth and fifth metatarsal heads in asymptomatic healthy controls. The latter were not clinically palpable and had no associations to foot structure or LFIS subscales and were probably physiological as described by Zanetti, Strehle et al (1997). Bossley and Cairney (1980) suggested that forefoot bursae vary depending on the degree of metatarsal separation and it may be that in some individuals the fourth intermetatarsal space is the largest and thus the bursa in that space more obvious. Luukkainen, Ekman et al (2009) also found moderate MTP joint synovitis detectable by MSUS in healthy participants, questioning the ability for MSUS techniques to differentiate between physiological and pathological tissue states. Nonetheless this does not explain the discrepancy between MSUS detectable bursae and clinically detectable bursae, as the MSUS detectable bursae within the control group of this study accounted for only half the MSUS detectable only bursae in the RA participants and the difference was real and statistically significant.

A key and unique finding was the clear association between MSUS detectable bursae within the foot and patient reported foot impact assessed by both the impairment (LFIS$_{IF}$) and activity limitation (LFIS$_{AP}$) subscales of LFIS. To ascertain whether the association of MSUS detectable bursae with LFIS was due to disease activity, we initially explored the association of MSUS detectable bursae with markers of disease activity. Secondly we explored the association of MSUS detectable bursae with foot structure variables. Potential confounding factors within this relationship were age, disease duration ESR, CRP, DAS-28, wellbeing and MTP joint subluxation. When the association of MSUS detectable bursae and LFIS was adjusted for the confounding factors there was still a significant association, suggesting that bursae may lead to foot related disability and poor function independent of overall disease activity and foot structure deformity. Other investigators have also found foot related symptoms in RA participants that were independent of disease activity (Turner, Helliwell et al 2008). In that study foot status was measured by both LFIS subscales and mechanical function and no imaging techniques were used to identify pathology.

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These findings are also concurrent with others who have reported radiographic damage and disease activity independently contributing to changes in physical function in RA, regardless of disease activity (Kuper, van Leeuwen et al 1997; Welsing, van Gestel et al 2001; van der Heijde, Landewé et al 2008).

Whilst our findings indicate that there is an association of MSUS detectable forefoot bursae with patient reported foot impact scores, this does not necessarily constitute proof. As well as forefoot bursae, MTP joint synovitis, and flexor tenosynovitis on MSUS is a key differential diagnosis for plantar forefoot tenderness (Koski 1995). This inability to measure MTP joint synovitis and tenosynovitis using the Diasus MSUS machine has to be acknowledged as a significant omission (see Chapter three, section 3.8.1.2. page 75). Within the analyses there is thus a possibility that MSUS detectable bursae and MTP joint synovitis may be correlated and collinear but with the lack of data on MTP joint synovitis or tenosynovitis we cannot be sure. We did adjust for disease activity which does suggest that MSUS detectable bursae may be independent of MTP joint synovitis, however clarification of this is recommended for future investigations.

It is not surprising that in the cross sectional sample with varied levels of RA disease duration and activity that structural deformities within the forefoot were highly prevalent. However, the lack of association of MTP joint subluxation with MSUS detectable bursae was surprising because it was associated with patient reported foot impact and was present in three quarters of the RA participants, but absent within healthy control participants. MTP joint subluxation is an important finding in the RA forefoot in later stage disease as concomitant displacement of the fatty pad can produce symptoms of foot pain and callosities (Costa, Rizack and Zimmermann 2004; van der Leeden,  Steultjens et al 2008). As bursae, detectable by MSUS but not apparent clinically, were more likely to seen in early RA disease, it is probable that MSUS detectable bursae are present in the forefoot prior to the onset of clinical deformity. This argument however lacks strength, as the examination of foot structure in this study was based on expert clinical judgement of the non weight-bearing foot. Dynamic plantar pressure measurements and gait data (to define foot status and determine foot loading to explore whether plantar forefoot bursae in the RA participants was related to a progress of rheumatic deformity of the foot) was not feasible within the confines of this study and will form the subject of a future study.

Interestingly there was an association of increased numbers of MSUS detectable bursae with anti-TNF-α therapy (but not methotrexate). The length of time that participants had been taking anti-TNF-α therapy was not recorded within this study; however those individuals taking anti-TNF-α therapy are also likely to have the most aggressive RA and therefore would be expected to have the worse joint and soft tissue involvement.

Finally, we noticed that MSUS detectable bursae were more strongly associated with $LFIS_{AP}$ than $LFIS_{IF}$ and that $LFIS_{AP}$ was also more strongly associated with global wellbeing than $LFIS_{IF}$. Patients with RA have reported greater physical functional deterioration in lower limbs compared to upper limbs (Ringen, Dagfinrud et al 2008). This implies that bursae within the forefoot may have a crucial contributing impact on activity participation limitation which also significantly affects the patient's global wellbeing. Of note, this was true for all the MSUS detectable bursae, even those not clinically detectable, therefore further highlighting the potential importance of identifying pathological bursae.

### 5.11. Strengths and potential limitations

This study has several strengths and a number of potential limitations. Strengths include:
- the large sample size
- a pragmatic clinical study representative of secondary care in the UK
- the use of patient reported clinical outcomes including disease activity and foot specific measures

Potential limitations include the fact the presence of MSUS detectable bursae within the forefoot was not validated by any other 'gold standard' imaging technique, such as MRI or by histological analysis through biopsy.

As well as intermetatarsal bursae and adventitious bursae, soft tissue swelling between the MTP joints can be related to MTP joint synovitis or tenosynovitis that could be better differentiated using MR imaging (Ashman, Klacker and Yu 2001; Helliwell, Woodburn et al 2007; Studler et al 2008. Gadolinium enhanced MRI would also provide clearer information relating to both synovial thickness, increased blood flow and inflammatory activity (Gaffney, Cookson et al 1995). Most previous studies have not used MRI due to its limited availability (Szkudlarek, Court-Payen et al 2003; D'Agostino, Maillefert et al 2004;

Naredo, Moller et al 2006). At the time of the preliminary reliability study, the OMERACT MSUS special interest group highlighted limited data in terms of comparisons of MRI with MSUS (Wakefield, Balint et al 2005), however due to its restricted availability MRI was not feasible for our study.

The lack of availability of Power Doppler within this study to determine bursitis over bursae has already been highlighted in Chapter four (section 4.11, Page 121).

Failure to use the measures of MTP joint synovitis and erosion and failure to measure tenosynovitis has to be acknowledged as a significant limitation regarding the assessment of the associations of MSUS detectable bursae with patient reported foot impact outcome measures. This is, however, a feature that is endemic in all studies on MTP joint synovitis in the foot in RA that haven't taken account of forefoot bursae. It also does not invalidate MSUS as a tool for predicting foot symptoms in RA.

Finally, patients treated in primary care only who may have less severe RA disease are not included and controls were not age matched, although limited analysis showed that this did not appear to significantly alter the findings (see section 5.8.9, page 157).

## 5.12. Conclusion

In a cross sectional study of patients with RA in a hospital setting, bursae within the forefoot were a common finding on MSUS, but less common in healthy controls. These findings also indicate that MSUS detectable bursae, within the foot in RA patients, may be associated with measures of foot impairment and disability that is important to the patient, independent of forefoot structural deformity, independent of RA disease activity and under-detected clinically. Further work, however, is required to confirm this.

This study has provided the baseline data for RA participants, with respect to the prevalence of MSUS detectable bursae. The data from this study therefore formed the base on which the final phase of the study progressed to evaluate the natural history of bursae within the feet.

## 6.0 Chapter 6: The natural history of MSUS detectable forefoot bursae in RA participants after one year

Within chapter five we confirmed that MSUS detectable bursae within the forefoot are highly prevalent and under-diagnosed clinically. The study was conducted in accordance with routine clinical practice and also demonstrated that MSUS detectable bursae may be associated with patients' foot symptoms, mobility and quality of life. In order to optimize the management of foot symptoms associated with RA it would seem essential to describe the natural history and progression of bursae, detectable by MSUS, over time. Chapter six forms the final phase of the doctoral study in which changes in the presence of MSUS detectable forefoot bursae and factors that may predict those changes over time are investigated.

### 6.1. Introduction

There is a growing body of evidence that modern imaging modalities such as MRI and MSUS appear to be more superior than radiography in detection of temporal changes in structural joint damage in RA (Backhaus, Burmester et al 2002; Hau, Kneitz et al 2002; Ejbjerg, Vestergaard et al 2005; Naredo, Collado et al 2007; Iagnocco, Naredo and Tripodo 2008; Brown, Conaghan et al 2008). MSUS has demonstrated that synovitis can progress, despite the improvement in traditional laboratory and clinical findings (Brown, Quinn et al 2006; Brown, Conaghan et al 2008).

The ability of MSUS to detect changes in RA disease before the onset of structural damage has become important with the advent of biologic therapies that can switch off the disease processes and thus arrest disease progression (Iagnocco, Naredo and Tripodo 2008). Usually it is synovitis that is investigated and investigation of changes in disease state may include synovitis within the MTP joints, although do not form the main focus of study (Ejbjerg, Vestergaard et al 2005; Naredo, Bonilla et al 20065; Joshua, Lassere et al 2007; van der Heijde, Landewe et al 2008).

Longitudinal studies of manifestations of RA disease within the foot and ankle are lacking and most evidence is attributable to cross-sectional analytical data. Very little regarding the effect of RA disease on bursae within the forefoot is known, although it is typically accepted that some adventitious bursae are acquired as a result of biomechanical stress

through shearing forces related to abnormal movement (Hernandez, Hernandez, and Hernandez 1991).

In our baseline study (Chapter five, page 125) we demonstrated that 92.6% of the RA participants had MSUS detectable bursae within their forefeet and that there was an independent association between MSUS detectable bursae and patient reported foot impact. To our knowledge, no studies have addressed the question of whether investigation of the natural history of forefoot bursae by MSUS would provide further insight into the manifestations of RA disease within the foot and whether this might be associated with patient reported foot impact outcome measures over time.

## 6.2. Aims

The aim of the final part of the investigation of RA patients was to determine if there was any change in the presence of MSUS detectable bursae over time and if there was what predicted that change?

Data from this study was used to answer the following research questions:
a) *Does the presence of MSUS detectable bursae in the plantar forefoot area of patients with RA change over time?*
b) *If the presence of MSUS detectable bursae does change after one year what predicts that change?*

## 6.3. Study design

A one year cohort study design was used in which a sample of RA patients who had already been assessed (Chapter five, page 125) were reassessed one year following their initial visit.

## 6.4. Subjects

From the initial 149 patients who participated in the baseline study (chapter five, page 125) 120 agreed to return at one year for reassessment.

### 6.4.1. Sample size

For explanation of how the sample size was calculated to ensure adequate power for statistical analyses see Chapter 3, section 3.7.1, page 69.

### 6.4.2. Participant recruitment

All participants who took part in the baseline assessments (Chapter five, page 104) were contacted, via a letter of invitation and a participant information sheet, to return for reassessment at twelve months. Patients who were willing to be considered for the follow up study at this stage were asked, within the letter of invitation, to complete an enclosed reply slip. Potential participants at this stage were given the opportunity to discuss the details of the follow up study with the Principal Investigator for the site, or the Chief Investigator if they wished.

#### 6.4.2.1. Selection criteria

All individuals with RA who had taken part in the baseline assessments were considered appropriate for this study according to the following criteria:

##### Inclusion criteria
- Individuals who had taken part in the baseline assessments
- Individuals who had a diagnosis of RA according to the ACR criteria (Arnett, Edworthy et al 1988; Table 1, page 11
- Individuals who were attending the rheumatology outpatients' clinic at Southampton General Hospital
- Individuals who were aged 18 years and over

##### Exclusion criteria
- Individuals who had not taken part in the baseline assessments
- Individuals who had corticosteroid injection to the forefoot within the previous 3 months prior to commencement of the study
- Individuals who could not walk five metres
- Individuals who had concomitant musculoskeletal disease (for example, primary osteoarthritis, gout, Paget's disease, systemic lupus erythematosus)
- Individuals who had a serious medical (other than RA) or psychological disorder that could affect the study protocol
- Individuals who were unable to give informed consent

## 6.5. Data Collected

Data collection took place between August 2007 and September 2008.

### 6.5.1. Location

For standardization all data collection during this study was undertaken in the same environment as the baseline assessments for the RA participants (chapter five, page 125), the 'Wellcome Trust Clinical Research Facility, Southampton General Hospital. On each occasion, the same consultation rooms and ultrasound facilities were utilised.

### 6.5.2. Assessment of demographic and clinical characteristics

For standardization, exactly the same demographic and clinical information was collected and noted in the same way as the baseline assessments for the RA participants (Chapter five, page 125). General demographic data including age, gender, disease duration, presence of rheumatoid factor, weight and limb dominance were noted.

Current medication and use of DMARDs during the previous year were obtained from the clinical notes and rheumatology department database. Laboratory assessments included CRP and ESR and were obtained from the clinical notes and Rheumatology Department database.

Clinical characteristics collected included participants' impression of global well being measured via a visual analog scale (VAS 100mm, where 0 was 'Best Imaginable Health State' and 100 equal to 'Worst Imaginable Health State'), assessment of the participants' global impression of health and disease activity and the number of painful, tender and swollen joints calculated as part of the 28 joint Disease Activity Score (DAS-28) (van der Heijde, van't Hof, et al 1993). For DAS-28 scores are, remission < 2.6; low disease activity $\geq 2.6$ but < 3.2; moderate disease activity $\geq 3.2$ but < 5.1; high disease activity $\geq 5.1$ (van der Heijde, van't Hof, et al 1993).

For the baseline study, DAS-28 scores were obtained from clinical medical notes and the rheumatology department database. During that study, however, DAS-28 scores were not available for all participants. Therefore for this twelve month study, the investigator (CB) was trained in DAS-28 technique and also performed these assessments.

### 6.5.3. Assessment of foot status

For standardization, all returning participants underwent the same foot assessments performed and noted in the same way as in the baseline assessments (Chapter five, page 125). The feet were examined clinically for the presence of bursae by an experienced podiatrist (CB) using palpation of the plantar forefoot areas, for the presence of fluctuant swellings separate from synovitis and tenosynovitis. The range of movement at the ankle, subtalar and first MTP joints were noted as being full, limited or rigid and the presence of MTP joint subluxation and pes-planus foot type (determined by observed flattening of the medial longitudinal arch on weightbearing) were also noted by the podiatrist (CB).

Assessment of the impact of foot disease was measured using the validated patient administered questionnaire, the Leeds Foot Impact Scale (LFIS) (Helliwell, Reay et al 2005). Both subscales for impairment/footwear (LFIS$_{IF}$) and activity limitation or participation restriction (LFIS$_{AP}$) were used for analyses (Helliwell, Reay et al 2005).

### 6.5.4. MSUS imaging data

For standardization, exactly the same MSUS assessments were performed and noted by the same investigator (CB) in the same way as in the baseline assessments (Chapter five, page 125). The MSUS foot scans were performed on the same day immediately after the clinical foot examinations using a Diasus ultrasound system with a broadband linear 5 – 12 MHz probe (Dynamic Imaging Ltd. Scotland UK). The same MSUS imaging scanning protocol that was developed during the validation study (chapter three, section 3.8.1.2, page 75) and used in the baseline study was performed. The presence and location of bursae across the plantar forefoot region for each participant identified by MSUS, previously defined as an anechoic demarcated complex mass (both intermetatarsal and adventitious) and bulging more than 1mm under the metatarsal heads (intermetatarsal bursae) (Koski 1998, Bowen, Dewbury et al 2008), were annotated on a foot chart adapted from the validation study (Chapter four, page 96; see MSUS data collection sheet, **Appendix 19**).

## 6.6. Summary of study three protocol

For a summary of study three (twelve month returns) protocol see **Figure 35**.

**Figure 35.** Summary of protocol for RA participants for the return assessments at twelve months.

**1**. Participants from study two to be identified six weeks prior to their proposed one year follow up visit.

**1i.** Letters of invitation to return to be sent.

**1ii.** Patients to be resent the participant information sheet with letters of invitation.

**2.** Willing participants complete reply slip and return to rheumatology research department.

**2i.** Research administrator to add to Investigator's Folder (held in rheumatology research department).

**3.** Appointments sent to willing returning participants to coincide with their clinical visit.

**2ii.** All returning potential participants also to be offered the opportunity to discuss the study with Dr Nigel Arden or Mrs. Catherine Bowen.

**4.** Willing returning particpants to meet the chief investigator, Mrs Catherine Bowen and discuss study after their clinical appointment time.

**4i.** Patients screened for re-inclusion into the study.

**5.** Medical notes consulted for updates on background clinical demographic information.

**6.** Foot assessments carried out.

**6i.** Participant to complete the LFIS questionnaire.

**6ii.** Investigator to assess both feet clinically.

**7.** Participants to be informed of results of follow up foot assessments.

**6iii.** Investigator to scan both forefoot areas and complete ultrasound data collection sheet.

**8.** Medical notes signed for completion of study.

## 6.7. Results

The analyses focused on:

1. Descriptive changes in the prevalence and distribution of MSUS detectable forefoot bursae after a period of twelve months
2. Associations of MSUS detectable bursae with patient reported foot impact measures and clinical outcome variables after a period of twelve months
3. Predictors of change in presence of MSUS detectable bursae

### 6.7.1. Participant demographic

Of the 149 RA patients who were assessed at baseline 120 agreed to return at one year in the study giving a response rate of 80.5% (**Figure 36**). Of the 29 participants who did not wish to return to the study:

- nineteen participants chose to withdraw from the study for various reasons
- three agreed to return, but were withdrawn from the study due to issues with appointment times
- seven gave no response from the letters of invitation to return

### 6.7.1.1. Non-returnee analyses

After checking assumptions of normality, an unpaired t-test for numerical parametric data was performed to compare the means in the responders and non responders for age, duration of RA, global well being VAS, ESR, CRP, DAS-28, $LFIS_{TOT}$, $LFIS_{IF}$, $LFIS_{AP}$, MSUS detectable bursae and MSUS detectable intermetatarsal bursae. Levene's test for equality of variances was significant for $LFIS_{TOT}$ (p=0.010) and $LFIS_{IF}$ (p=0.018), suggesting one group was more variable in $LFIS_{TOT}$ and $LFIS_{IF}$ distribution than the other, therefore 'equal variances not assumed t statistic' was used.

There were no significant differences between returnees and non-returnees for any of the tested variables (**Table 58** and **Table 59**).

Using Chi squared analyses for non parametric categorical data, there were also no significant differences between responders and non-responders in terms of gender, seropositivity, number of DMARDs, foot structure or clinical foot care (**Tables 60, 61** and **62**). For the number of DMARDs and number of DMARDs plus anti-TNFα therapy some cells had expected count data of less than 5. Some have proscribed the use of chi squared when expected frequency is <5 (Kinnear and Gray 2006) therefore the Fishers exact test was also performed and in both cases the p value remained not significant.

**Figure 36.** RA participant recruitment flow chart of returnees and non returnees for the twelve month follow up study.



FeeTURA
149 participants

120 participants completed FeeTURA phase 2

29 non responders

19 withdrawn

3 agreed to return but then did not attend the study appointment

7 No response from phone/letter still being chased up

1 not thought relevant

1 in wheelchair and too difficult to attend

4 too ill

1 deceased

1 moved out of area

2 very sorry but were not able to take part at that moment in time

9 gave no reason

1 cancelled appointment then no response at chase up phone calls

2 did not attend appointment then no response at chase up phone calls

**Table 58.** Demographic and clinical variable comparisons of returnees and non returnees for the twelve month follow up study showing the mean (standard deviation) and range for each.

| | Returnees: Baseline (N=120) | Non returnees: Baseline (N=29) | Statistical values |
|---|---|---|---|
| **Age (years)** | 59.7 (12.1) <br> 25 - 87 | 58.3 (13.3) <br> 26 - 82 | t=-0.543, p=0.588 |
| **Duration of RA (years)** | 12.0 (10.4) <br> 0.6 - 43 | 13.4 (10.0) <br> 1 – 33 | t=0.616, p=0.539 |
| **Global well being (100mm VAS)** | 39.9 (23.9) <br> 0 - 98 | 41.9 (25.3) <br> 0 - 97 | t=0.379, p=0.705 |
| **ESR (mm/hour)** | 22.9 (18.3) <br> 2 - 100 | 25.1 (22.7) <br> 2 - 108 | t=0.555, p=0.580 |
| **CRP (mg/litre)** | 12.5 (19.3) <br> 1 - 129 | 12.1 (11.8) <br> 1 – 48.4 | t=-0.126, p=0.900 |
| **DAS-28** | 3.9 (1.3) <br> 1.1 – 6.8 | 4.4 (1.5) <br> 1.8 – 7.0 | t=1.565, p=0.121 |

**Table 59.** Foot assessment variable comparisons of returnees and non returnees for the twelve month follow up study showing the mean (standard deviation) and range for each.

| | Returnees: Baseline (N=120) | Non returnees: Baseline (N=29) | Statistical values |
|---|---|---|---|
| **LFIS$_{TOT}$** | 27.9 (13.5) <br> 0 – 50 | 31.8 (10.3) <br> 2 – 48 | t=1.717, p=0.092 |
| **LFIS$_{IF}$** | 10.9 (4.9) <br> 0 - 21 | 11.8 (4.9) <br> 2 - 19 | t=1.798, p=0.078 |
| **LFIS$_{AP}$** | 16.9 (9.5) <br> 0 – 30 | 19.9 (7.4) <br> 0 -29 | t=-0.269, p=0.789 |
| MSUS detectable bursae* | 3.6 (2.2) <br> 0 - 9 | 3.28 (2.1) <br> 0 - 9 | t=-0.705, p=0.482 |
| Clinically detectable bursae** | 0.52 (1.1) <br> 0 - 6 | 0.31 (0.9) <br> 0 - 3 | t=-0.944, p=0.347 |

**Key:** * = Total numbers of MSUS detectable bursae; ** = Total numbers of clinically palpable bursae per individual; LFIS$_{TOT}$= Leeds Foot Impact Score, Total; LFIS$_{IF}$ = Leeds Foot Impact Score, Impairment/Footwear subscale; LFIS$_{AP}$ = Leeds Foot Impact Score, Activity limitation/Participation restriction subscale.

**Table 60.** Categorical demographic comparisons of returnees and non returnees for the twelve month follow up study.

| | Returnees: Baseline (N=120) | Non returnees: Baseline (N=29) | Statistical values |
|---|---|---|---|
| **Gender** | 98 (81.7%) female<br>22 (18.3%) male | 21 (72.4%) female<br>8 (27.6%) male | $\chi^2$= 1.244, p=0.265<br>df=1 |
| **Seropositivity** | 93 (77.5%) sero +ve<br>24 (20.0%) sero -ve | 21 (72.4%) sero +ve<br>8 (27.6%) sero -ve | $\chi^2$= 0.679, p=0.410<br>df=1 |
| **DMARDs** | 88 (73.3%) ≥1<br>32 (26.7%) none | 20 (69.0%) ≥1<br>9 (31.0%) none | $\chi^2$=4.659*,p=0.199<br>f=3.928, p=0.304<br>df=3 |
| **DMARDs and TNFα therapy** | 99 (82.5%) yes<br>21 (17.5%) none | 21 (72.4%) yes<br>8 (27.6%) none | $\chi^2$=2.849**,p=0.415<br>f=2.866, p=0.401<br>df=3 |

Key: +ve= positive; -ve=negative; t = test statistic; $\chi^2$ = Pearson Chi- Square; f=Fishers exact test; df=degrees of freedom; *3 cells (37.5%) have expected count less than 5. The minimum expected count is 19; ** 1 cell (12.5%) has expected count less than 5. The minimum expected count is 1.36.

**Table 61.** Foot structure comparisons of returnees and non returnees for the twelve month follow up study.

| | Returnees: Baseline (N=120) | Non returnees: Baseline(N=29) | Statistical values |
|---|---|---|---|
| **Right MTP joint subluxation** Missing 1 (0.8%) | Yes 91 (76.5%)<br>No 28 (23.5%) | Yes 21 (72.4%),<br>no 8 (27.6%) | $\chi^2$=0.208, p=0.648<br>df=1 |
| **Left MTP joint subluxation** B:Missing 1 (0.8%) | Yes 92 (77.3%)<br>No 27 (22.5%) | Yes 21 (72.4%),<br>no 8 (27.6%) | $\chi^2$=0.310, p=0.578<br>df=1 |
| **Right Pes-planus** B:Missing 10 (8.3%) R: missing 4 (13.8%) | Yes 106 (96.4%)<br>No 4 (3.6%) | Yes 22 (75.9%),<br>No 3 (10.3%) | $\chi^2$=2.898, p=0.089<br>df=1 |
| **Left Pes-planus** B:Missing 10 (8.3%) R: missing 4 (13.8%) | Yes 106 (96.4%)<br>No 4 (3.3%) | Yes 22 (75.9%),<br>No 3 (10.3%) | $\chi^2$=2.898, p=0.089<br>df=1 |

**Key:** B=baseline visit; R=return visit; df=degrees of freedom

**Table 62.** Clinical foot care comparisons of returnees and non returnees for the twelve month follow up study.

| | Returnees Baseline (N=120) | Non returnees Baseline (N=29) | Statistical values |
|---|---|---|---|
| **Foot symptoms in notes** | Yes 68 (56.7%) No 52 (43.3%) | Yes 17 (58.6%), No 12 (41.4%) | $\chi^2$=0.036, p=0.849 df=1 |
| **Seen podiatrist in past** | Yes 74 (61.7%) No 46 (38.3%) | Yes 17 (58.6%), No 12 (41.4%) | $\chi^2$=0.091, p=0.763 df=1 |
| **Currently seeing a podiatrist** | Yes 38 (31.7%) No 82 (68.3%) | Yes 11 (37.9%), No 18 (62.1%) | $\chi^2$=0.415, p=0.519 df=1 |

*6.7.1.2. Returnee demographic*

120 patients (98 female and 22 male) with RA (24 seronegative and 93 seropositive, 3 data missing) completed the study: mean age 60.7 (SD 12.1) years, disease duration 12.99 (10.4) years. Treatment at twelve months included 78 (65%) taking methotrexate and 55 (45.7%) taking anti-TNF-α therapy. Baseline and one year follow up data for weight, height, global wellbeing VAS, ESR, CRP, DAS-28, total numbers of MSUS detectable bursae, total numbers of MSUS detectable intermetatarsal bursae, $LFIS_{IF}$, $LFIS_{AP}$ and foot structure are shown in **Table 63** and **Table 64**.

After twelve months, the mean change in the number of MSUS detectable forefoot bursae observed showed an average increase with a magnitude of 0.1 for both, whilst mean changes in LFIS total ($LFIS_{TOT}$) and subscale scores ($LFIS_{IF}$ and $LFIS_{AP}$) showed an average decrease with a magnitude of -0.7, -0.5 and -0.1 respectively. The mean change in global well being (VAS) decreased (equivalent to improvement in well being) and weight and height decreased by magnitude of -4.1, -0.1 and -0.25, respectively, whilst mean change in ESR, CRP and DAS-28 scores showed an increase by a magnitude of 1.7, 2.5 and 0.2 respectively.

After checking assumptions of normality, a paired t-test for related numerical parametric data was performed to compare the means at baseline and at twelve months for weight, height, global wellbeing VAS, ESR, CRP, DAS-28, total numbers of MSUS detectable forefoot bursae $LFIS_{TOT}$, $LFIS_{IF}$ and $LFIS_{AP}$. Missing values were omitted from the analyses so that actual paired values are represented and there were no statistical differences for any of the variables.

**Table 63.** Comparison of demographic and clinical characteristics of the RA study participants at baseline and after twelve months.

|  | Baseline (N=120) Mean (SD) | 12 months (N=120) Mean (SD) | Raw Change Mean (SD) |
|---|---|---|---|
| **Weight (kgs)** | 72.7 (15.3) | 72.6 (15.3) | -0.1 (4.3) |
| **Height (cm)** | 164.3 (7.5) | 164.3 (7.9) | -0.3 (2.0) |
| **Wellbeing (VAS)** | 39.9 (23.9) | 35.8 (22.6) | -4.1 (25.7) |
| **ESR (mm/hour)** | 22.9 (18.3) | 24.4 (20.0) | 1.7 (16.5) |
| **CRP (mg/litre)** | 12.6 (19.3) | 14.6 (25.0) | 2.5 (28.6) |
| **DAS-28** | 3.9 (1.3) | 4.1 (1.5) | 0.2 (1.7) |

**Table 64.** Comparison of foot characteristics of the returning RA study participants at baseline and after twelve months.

|  | Baseline (N=120) Mean (SD) | 12 months (N=120) Mean (SD) | Raw change Mean (SD) |
|---|---|---|---|
| MSUS detectable bursae* | 3.6 (2.2) | 3.7 (2.2) | 0.1 (2.8) |
| Clinically detectable bursae** | 0.52 (1.1) | 0.47 (1.0) | -0.5 (1.2) |
| **LFIS$_{TOTAL}$ (x/51)** | 27.9 (13.5) | 27.2 (13.4) | -0.7 (7.8) |
| **LFIS$_{IF}$ (x/21)** | 10.9 (4.9) | 10.4 (4.8) | -0.5 (3.2) |
| **LFIS$_{AP}$ (x/30)** | 16.9 (9.5) | 16.8 (9.7) | -0.1 (5.7) |

**Key:** * = Total numbers of MSUS detectable bursae; ** = Total numbers of clinically palpable bursae per individual;; LFIS$_{TOT}$= Leeds Foot Impact Score, Total; LFIS$_{IF}$ = Leeds Foot Impact Score, Impairment/Footwear subscale; LFIS$_{AP}$ = Leeds Foot Impact Score, Activity Participation Limitation subscale.

Using Chi squared analysis for categorical data of clinical foot care, use of DMARDs, use of anti-TNF-α therapy and foot structure, statistically significant differences were noted for "currently seeing a chiropodist/podiatrist" ($\chi^2$=36.015, p<0.001), number of DMARDs including methotrexate ($\chi^2$=58.155, p<0.001), number of DMARDs including methotrexate and anti-TNF-α therapy ($\chi^2$=59.860, p<0.001), right MTPJ subluxation ($\chi^2$=22.978, p<0.001) and left MTPJ subluxation ($\chi^2$=22.327, p<0.001) (**Table 65** and **Table 66**).

**Table 65.** Comparison of clinical foot care of the returning RA study participants at baseline and after twelve months.

| | Baseline (N=120) | 12 months (N=120) | Raw Change |
|---|---|---|---|
| **Currently seeing a chiropodist/podiatrist** | 38 (31.7%) | 54 (45.0%) | 16 (13.33%) |

**Table 66.** Comparison of prevalence of foot structure deformity of the returning RA study participants at baseline and after twelve months.

| | Baseline (N=120) | 12 months (N=120) | Raw Change |
|---|---|---|---|
| **Right MTP joint subluxation** | 91 (75.8%) | 65 (54.0%) | - 26 (21.8%) |
| **Left MTP joint subluxation** | 92 (76.7%) | 66 (55.0%) | - 26 (21.7%) |
| **Right pes planus** | 106 (88.3%) | 115 (95.8%) | 9 (7.5%) |
| **Left pes planus** | 106 (88.3%) | 116 (96.7%) | 10 (8.4%) |

No significant differences were found for pes-planus foot types. Of note, however, in **Table 66** are the raw changes in MTP joint subluxation between baseline and twelve months, in which foot structure deformity appears to have significantly reduced in participants over time.  Caution should be heeded in interpreting these results as the measurements undertaken for MTP joint subluxation were by subjective observation and it is possible that the results are due to measurement bias rather than true differences.

**6.7.2. Presence of MSUS detectable bursae at twelve months**

At twelve months following baseline assessments, using MSUS 93.5 % (N = 112) of patients had detectable bursae (mean numbers of bursae per individual = 3.7, SD = 2.2, range 0 - 11) within the plantar forefoot and of these, 85.7 % (N = 96) had bursae in both feet.

After twelve months, the most common location for MSUS detectable bursae remained the intermetatarsal (IM) 4/5 space for both feet followed, in order by IM 1/2, IM 3/4, IM 2/3, sub-metatarsal head (submet) 5, submet 2, submet 1, submet 3, submet 4 (**Figure 37** and **Figure 38**). MSUS detectable intermetatarsal bursae were found in 90.8% (N=109) of the RA participants (mean number per individual = 2.93, SD = 1.8, range 0 to 7).

**Figure 37.** Bar chart showing the locations and frequencies of MSUS detectable plantar forefoot bursae within the left feet of RA participants at both baseline and twelve month assessments.
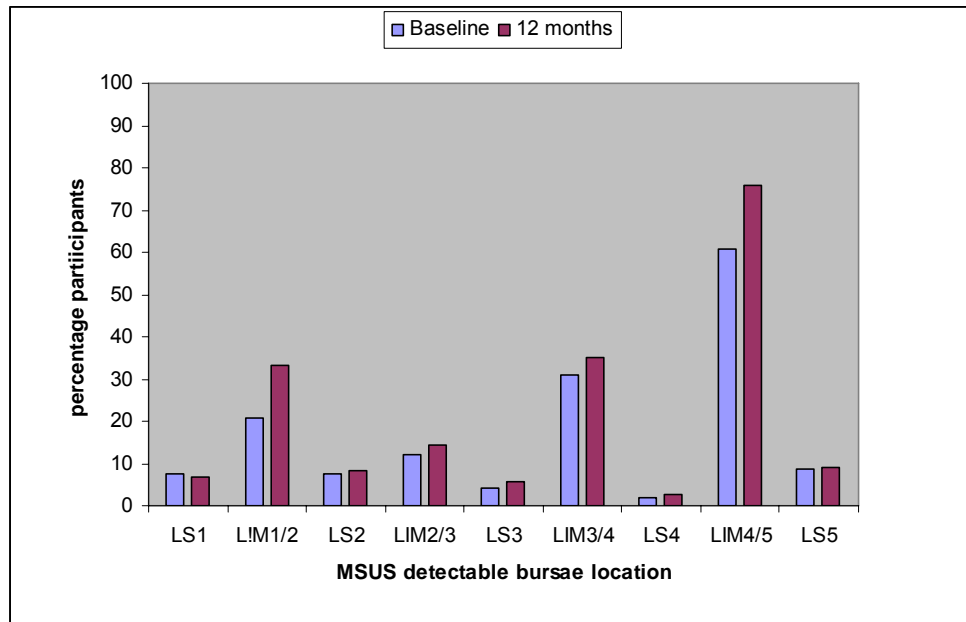


**Key:** L= left; IM= intermetatarsal; s=sub-metatarsal

**Figure 38**. Bar chart showing the locations and frequencies of MSUS detectable plantar forefoot bursae within the right feet of RA participants at both baseline and twelve month assessments.
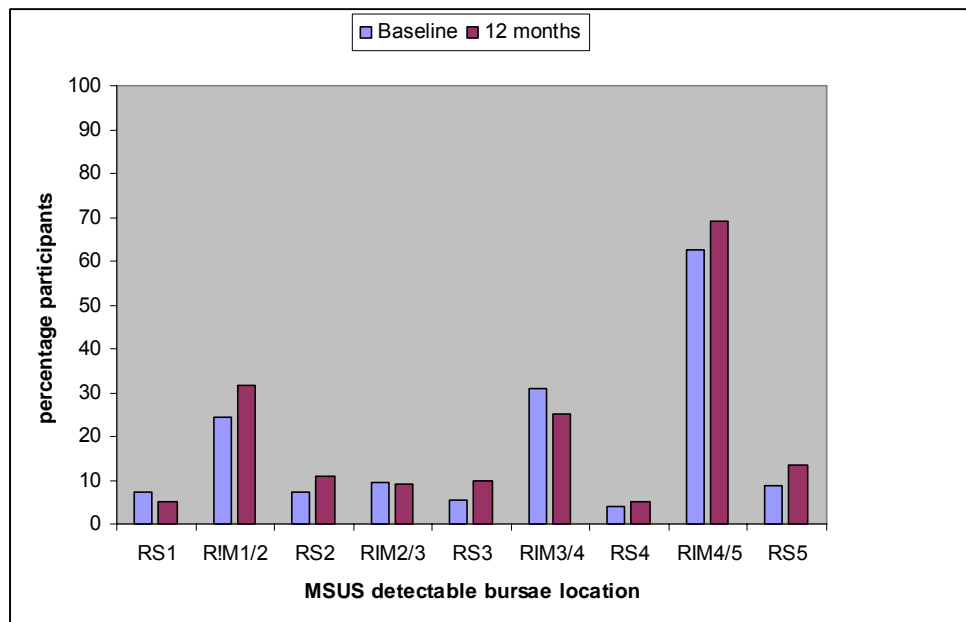


**Key:** R= right; IM= intermetatarsal; s=sub-metatarsal

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### 6.7.3. Associations of MSUS detectable bursae at twelve months

To investigate whether MSUS detectable bursae remained independently associated with patient reported foot impact outcome measures after twelve months, the data was primarily explored, as for the baseline visit, using scatter plots and correlation plots.

*6.7.3.1. Cross sectional correlations at twelve months*

Cross sectional findings showed that total numbers of MSUS detectable forefoot bursae were significantly correlated with impact of RA disease on the foot for the primary outcome of foot impact scores ($LFIS_{IF}$ r=0.236, p=0.009; $LFIS_{AP}$ r=0.235, p=0.010) at twelve months, but there were no significant associations with any of the other clinical variables (**Table 67** and **Table 68**).

**Table 67.** Continuous data correlations between MSUS detectable bursae and relevant clinical variables for RA participants at twelve months.

|  | Pearson Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **Age (N=120)** | 0.106 | 0.248 |
| **Duration of Arthritis (N=119)** | 0.063 | 0.496 |
| **Weight (kgs) (N=120)** | -0.069 | 0.451 |
| **Height (cms) (N=119)** | -0.030 | 0.748 |
| **Global wellbeing 100mm VAS (N=120)** | 0.114 | 0.217 |
| **ESR mm/hr ( (N=115)** | 0.043 | 0.644 |
| **CRP mg/l (N=113)** | -0.120 | 0.204 |
| **DAS-28 (N=97)** | 0.041 | 0.693 |
| **$LFIS_{IF}$ (N=120) \*\*** | 0.236 | 0.009 |
| **$LFIS_{AP}$ (N=120) \*\*** | 0.235 | 0.010 |

**Key:** \*\*Correlation is significant at the 0.01 level (2-tailed)/

Interestingly, within the baseline study (N=149), significant correlations had also been noted between MSUS detectable bursae and duration of RA and ESR (**Table 41**, Chapter five, page 145). Non returnee analyses demonstrated no significant differences within the returnee group, suggesting that the associations of MSUS detectable bursae with duration of RA and ESR at baseline may have been anomalous. Associations of MSUS detectable bursae with foot impact scores, on the other hand, have been justified as significant at two different time points (**Table 67**).

**Table 68.** Categorical data correlations between MSUS detectable bursae and relevant clinical variables for RA participants at twelve months.

| | Spearman's Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **Right MTP joint subluxation (N=120)** | -0.038 | 0.678 |
| **Left MTP joint subluxation (N=120)** | -0.160 | 0.863 |
| **Right pes planus (N=117)** | 0.095 | 0.310 |
| **Left pes planus (N=118)** | 0.095 | 0.304 |
| **Disease severity (N=117)** | -0.106 | 0.255 |
| **Currently taking TNF (N=117)** | -0.014 | 0.880 |
| **Currently taking MTX (N=149)** | -0.010 | 0.917 |

**Key:** TNF=antiTNFα therapy; MTX=methotrexate.

The same methodology was used as for the baseline visit to assess clinical correlations at twelve months with foot impact scores (LFIS$_{IF}$ and LFIS$_{AP}$) (chapter five, section 5.8.5.1, page 145). Significant associations at twelve months were observed between LFIS$_{IF}$ and MSUS detectable bursae, global well being and DAS-28 (**Table 69**). Significant associations at twelve months were observed between LFIS$_{AP}$ and MSUS detectable bursae, age, global well being, disease duration, ESR, CRP and DAS-28 were observed (**Table 70**).

**Table 69.** Continuous data correlations between LFIS$_{IF}$ and explanatory variables for RA participants at the twelve month return visit.

| | Pearson Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **MSUS bursae (N=120)**\*\* | 0.236 | 0.009 |
| **Age (N=120)** | -0.009 | 0.923 |
| **Duration of RA (N=119)** | 0.131 | 0.155 |
| **Weight (N=120)** | -0.015 | 0.870 |
| **Global well being VAS (N= 120)**\*\* | 0.449 | <0.001 |
| **ESR (N=115)** | 0.172 | 0.066 |
| **CRP (N= 113)** | 0.170 | 0.073 |
| **DAS-28 (N= 97)**\*\* | 0.415 | <0.001 |

Key: \*\* Correlation is significant at the 0.01 level (2-tailed).

**Table 70.** Continuous data correlations between LFIS$_{AP}$ and explanatory variables for RA participants at the twelve month return visit.

| | Pearson Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| **MSUS bursae (N=120)\*\*** | 0.235 | 0.010 |
| **Age (N=120)\*\*** | 0.315 | <0.001 |
| **Duration of RA (N=119)\*\*** | 0.251 | 0.006 |
| **Weight (N=120)** | 0.015 | 0.874 |
| **Global well being VAS (N=120)\*\*** | 0.502 | <0.001 |
| **ESR (N=115)\*\*** | 0.353 | <0.001 |
| **CRP (N=113)\*** | 0.218 | 0.020 |
| **DAS-28 (N=97)\*\*** | 0.457 | <0.001 |

**Key:** \*\* Correlation is significant at the 0.01 level (2-tailed); \*Correlation is significant at the 0.05 level (2-tailed).

As well as MSUS detectable bursae, within the baseline study (N=149) significant correlations had also been noted between LFIS$_{IF}$ and global well being VAS, LFIS$_{IF}$ and ESR but not LFIS$_{IF}$ and DAS-28. Non returnee analyses demonstrated no significant differences within the returnee group for these variables therefore the association between LFIS$_{IF}$ and global well being VAS is justified by being significant at two different time points (Chapter five, section 5.8.5.1, page 145).

Similarly, as well as MSUS detectable bursae, within the baseline study (N=149), significant correlations had also been noted between LFIS$_{AP}$ and age, duration of RA, global well being VAS, ESR and CRP but not DAS-28. Non returnee analyses demonstrated no significant differences within the returnee group for these variables therefore the associations between LFIS$_{AP}$ and age, duration of RA, global well being VAS, ESR and CRP are justified by being significant at two different time points (Chapter five, section 5.8.5.1, page 145).

In terms of foot structure, at baseline, only left foot MTP joint subluxation was significantly associated with LFIS$_{AP}$, in contrast to the twelve month data presented in **Table 71** and **Table 72** that shows significant associations between right and left feet MTP joint subluxation and LFIS$_{IF}$ and LFIS$_{AP}$. As mentioned earlier within section 6.7.1.2 (**Table 66**, page 176 ), caution should be heeded in interpreting these results as the measurements undertaken for MTP joint subluxation were by subjective observation and it is possible that the results are due to measurement bias rather than true differences.

**Table 71**. Categorical data correlations between LFIS$_{IF}$ and explanatory variables for RA participants at the twelve month return visit.

| | Spearman's Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| Right MTP joint subluxation (N=120)* | -0.217 | 0.017 |
| Left MTP joint subluxation (N=120)** | -0.243 | 0.008 |
| Right pes planus (N=117) | 0.059 | 0.529 |
| Left pes planus (N=118) | 0.060 | 0.519 |
| Currently on methotrexate (N=120) | 0.015 | 0.867 |
| Currently on anti-TNF-α therapy (N=117) | 0.116 | 0.213 |
| Disease severity (N=117) | 0.002 | 0.981 |

**Key:** ** Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed)

**Table 72**. Categorical data correlations between LFIS$_{AP}$ and explanatory variables for RA participants at the twelve month return visit.

| | Spearman's Correlation Coefficient | Significance (2-tailed) |
|---|---|---|
| Right MTP joint subluxation (N=120)** | -0.245 | 0.007 |
| Left MTP joint subluxation (N=120)** | -0.259 | 0.004 |
| Right pes planus (N=117) | -0.022 | 0.818 |
| Left pes planus (N=118) | -0.023 | 0.803 |
| Currently on methotrexate (N=120) | 0.027 | 0.772 |
| Currently on anti-TNFα therapy (N=117) | 0.098 | 0.294 |
| Disease severity (N=117) | -0.079 | 0.399 |

**Key:** ** Correlation is significant at the 0.01 level (2-tailed)

### 6.7.3.2. Cross sectional univariate linear regression analyses at twelve months

Results using univariate linear regression show the extent of the associations for MSUS detectable bursae such that LFIS$_{IF}$ increases by 0.512 and LFIS$_{AP}$ by 1.04 for a unit increase in MSUS detectable bursae (LFIS$_{IF}$ β=0.512, p=0.009; LFIS$_{AP}$ β=1.040, p=0.010). The r$^2$ (R square) for the LFIS$_{IF}$ model was 0.056 indicating that approximately 5.6% of the variability in LFIS$_{IF}$ can be explained by the model. The r$^2$ (R square) for the LFIS$_{AP}$ model

was 0.055 indicating that approximately 5.5% of the variability in LFIS$_{AP}$ can be explained by the model.

The extent of the associations were also calculated for wellbeing (β=0.095, p<0.001), and DAS-28 (β=1.408, p<0.001) with LFIS$_{IF.}$ For LFIS$_{AP}$ there were significant associations for age (β=0.252, p<0.001), duration of RA (β=0235, p=0.006), wellbeing (β=0.216, p<0.001), ESR (β=0.168, p<0.001), CRP (β=0.084, p=0.020) and DAS-28 (β=3.005, p<0.001). No other associations were significant.

Of note, at baseline, LFIS$_{AP}$ associations appeared to be stronger than LFIS$_{IF}$ associations with both the primary and secondary outcome variables (Chapter five, section 5.8.5.1, page 145). From the above paragraph, it can be seen that this was also the case again at twelve months, although the same caution applies in interpretation of this as the scales for LFIS$_{IF}$ and LFIS$_{AP}$ are not equal, with LFIS$_{IF}$ being nine points less.

### *6.7.3.3. Cross sectional multivariate linear regression analyses at twelve months*

Diagnostic tests for assumptions showed that the use of multiple linear regressions was an appropriate method of investigating further the extent to which MSUS detectable bursae was linearly related to the outcome variable (LFIS) after adjusting for the other explanatory variables. All histograms and normal probability plots of standardised residuals showed that the distribution of the residuals was normal. All constant variance scatter plots showed no particular tendency for residuals to increase or decrease systematically with the fitted values, indicating that the constant variance assumption is almost met. In all scatter plots of residuals versus MSUS detectable bursae there was no particular pattern, indicating a linear relationship between LFIS$_{IF}$ and MSUS detectable bursae and LFIS$_{AP}$ and MSUS detectable bursae. There were no colinearity indications for any of the models.

Using the same multivariate regression modeling technique as for the baseline data analyses (Chapter five, section 5.8.5.3, page 149), after one year, MSUS detectable bursae were still an independent factor associated with LFIS$_{IF}$ (β=0.507, p=0.011) and LFIS$_{AP}$ (β=0.857, p=0.024) when modeled with the confounding explanatory variables of age and disease duration (**Table 73** and **Table 74**). The r$^2$ (R square) for the LFIS$_{IF}$ model was 0.072, indicating that approximately 7.2% of the variability in LFIS$_{IF}$ can be explained by the model. The r$^2$ (R square) for the LFIS$_{AP}$ model was 0.179, indicating that approximately 17.9% of the variability in LFIS$_{AP}$ can be explained by the model.

**Table 73.** Multivariate linear regression model for LFIS impairment subscale scores and confounding explanatory variables at twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | LFIS$_{IF}$ | 0.507 | 0.196 | 0.011 | 0.118 - 0.896 |
| Age | LFIS$_{IF}$ | -0.020 | 0.036 | 0.575 | -0.091 – 0.051 |
| Duration of RA | LFIS$_{IF}$ | 0.057 | 0.042 | 0.176 | -0.026 - 0.140 |

**Table 74.** Multivariate linear regression model for LFIS activity participation limitation subscale scores and confounding explanatory variables at twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | LFIS$_{AP}$ | 0.857 | 0.375 | 0.024 | 0.114 – 1.600 |
| Age | LFIS$_{AP}$ | 0.211 | 0.069 | 0.003 | 0.075 – 0.347 |
| Duration of RA | LFIS$_{AP}$ | 0.190 | 0.080 | 0.019 | 0.032 – 0.348 |

Furthermore, after one year, after adjusting for disease activity confounding variables, a significant linear relationship remained between MSUS detectable bursae and LFIS$_{IF}$ (ß=0.525, p=0.009) at the 0.01 level and LFIS$_{AP}$ (ß=0.732, p=0.029) at the 0.05 level (**Table 75** and **Table 76**). The $r^2$ (R square) for the LFIS$_{IF}$ model was 0.232, indicating that approximately 23.2% of the variability in LFIS$_{IF}$ can be explained by the model. The $r^2$ (R square) for the LFIS$_{AP}$ model was 0.376, indicating that approximately 37.6% of the variability in LFIS$_{AP}$ can be explained by the model.

**Table 75.** Multivariate linear regression model for LFIS impairment subscale scores and confounding explanatory disease activity variables at twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| MSUS Bursae | LFIS$_{IF}$ | 0.525 | 0.198 | 0.009 | 0.131 – 0.918 |
| Age | LFIS$_{IF}$ | -0.031 | 0.041 | 0.445 | -0.113 – 0.050 |
| DAS-28 | LFIS$_{IF}$ | 1.393 | 0.310 | 0.000 | 0.778 – 2.008 |

**Table 76.** Multivariate linear regression model for LFIS activity participation limitation subscale scores and confounding explanatory disease activity variables at twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| MSUS Bursae | $LFIS_{AP}$ | 0.732 | 0.330 | 0.029 | 0.078-1.386 |
| Age | $LFIS_{AP}$ | 0.172 | 0.062 | 0.006 | 0.050 -0.295 |
| Global VAS | $LFIS_{AP}$ | 0.173 | 0.032 | 0.000 | 0.108-0.237 |
| ESR | $LFIS_{AP}$ | 0.102 | 0.037 | 0.007 | 0.028-0.176 |

Within the model for $LFIS_{IF}$ presented in **Table 75**, CRP and ESR were omitted as they were not associated with $LFIS_{IF}$ and global wellbeing VAS was omitted due its colinearity with DAS-28 at twelve months. Within the model for $LFIS_{AP,}$ presented in **Table 76**, CRP and DAS-28 were omitted due to their colinearity with VAS and ESR at twelve months. However, when the same model as the baseline assessments was used that included MSUS detectable bursae, age, global well being VAS and ESR, MSUS detectable bursae were still a significant independent association with $LFIS_{IF}$ (ß=0.451, p=0.015) at the 0.05 level.

The results for the twelve month analyses, for associations of MSUS detectable bursae with foot impairment and activity participation limitation, were therefore consistent with the results at baseline. This indicates that if a new model was to be produced with no prior assumptions on the data the same result for the associations between MSUS detectable bursae and both LFIS subscales would have been achieved at two separate time points, confirming that the association is real and independent of disease activity.

### *6.7.4. Associations of change in presence of MSUS detectable bursae*

To determine associations of change in the presence of MSUS detectable bursae, raw values for change were calculated for individual data for each of the explanatory variables. Although the means for number of bursae were not significantly different between the baseline data and twelve months data (section 6.7.1.2. page 175), when assumptions for raw change values were checked, most values were normally distributed demonstrating a wide range of change within each of the explanatory variables. **Figure 39** and **Figure 40** show the normal distributions for raw change for MSUS detectable bursae and both LFIS subscale values.

**Figure 39.** Histogram showing the raw change in total numbers of MSUS detectable bursae for returning RA participants between baseline and twelve month assessments.
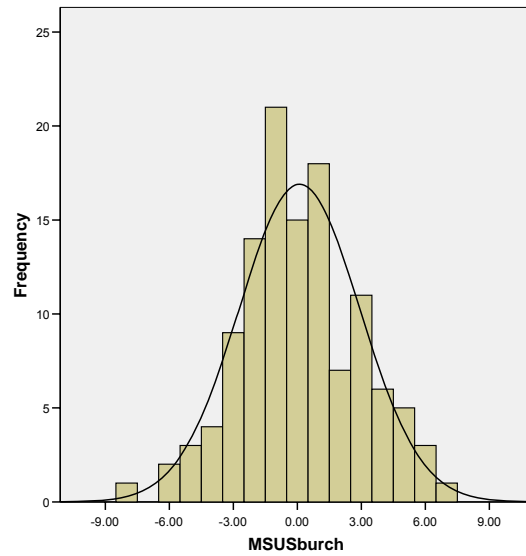


**Key:** MSUSburch: MSUS detectable bursae

**Figure 40.** Histograms showing the distribution of magnitude and direction of change for LFIS$_{IF}$ and LFIS$_{AP}$ subscales for returning RA participants between baseline and twelve month assessments.
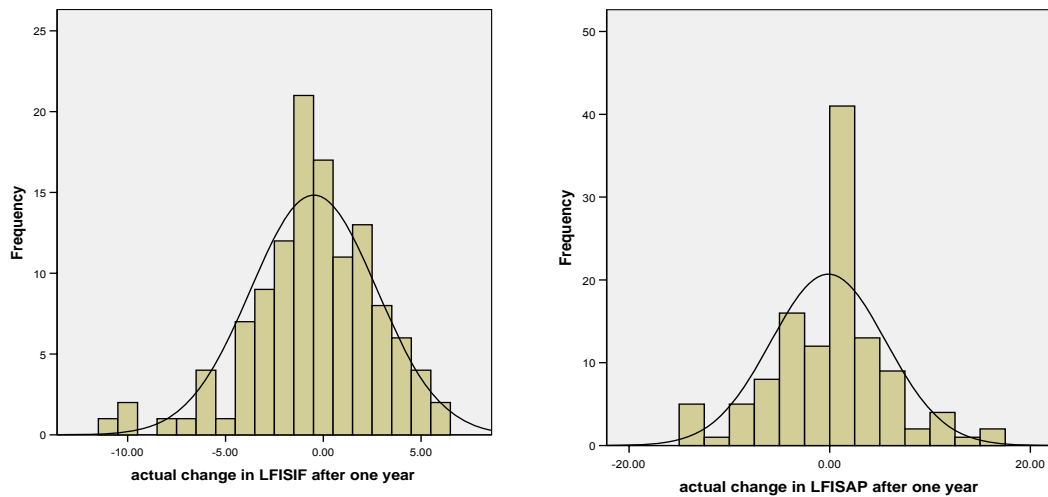


**Key:** LFIS$_{IF}$: Leeds Foot Impact impairment/footwear subscale; LFIS$_{AP}$: Leeds Foot Impact activity limitation/participation subscale.

Within **Figure 39**, it can be seen that the majority of participants did not have much change in total MSUS detectable bursae. However normal distribution shows that a similar number of participants had a reduction in MSUS detectable bursae as those who had an increase.

The normal distribution of foot impact scores, seen in **Figure 40**, shows the same trend for $LFIS_{IF}$ and $LFIS_{AP}$. The majority of participants did not have much change in foot impact scores, but a similar number had a reduction in scores as those who had an increase.

Bowling (2002) suggests that this is probably due to the longitudinal nature of the data as well as sample drop out and that raw individual change should be tested rather than averaging the individual time points. From the statistical tests on the mean changes between baseline and twelve months (presented in section 6.7.1.2, page 174) there was a wide variance of change for MSUS detectable bursae and LFIS subscale scores but these were not significantly different. However, what was not known was whether the raw changes for each of those variables were related.

### *6.7.4.1. Longitudinal correlations*

Following the trend observations, the data was explored further using scatter plots and correlations to determine any significant associations between the raw changes of MSUS detectable bursae and raw changes in each of the explanatory variables. Findings showed that there was a weak significant positive correlation between the changes in MSUS detectable bursae with changes in both $LFIS_{IF}$ (PCC = 0.216, p=0.018) and $LFIS_{AP}$ (PCC = 0.193, p=0.036) but none with changes in global wellbeing VAS, ESR, CRP and DAS-28 (**Table 77**, **Figure 41** and **Figure 42**).

Duration of RA at the twelve month return visit was also tested for association with raw change in MSUS bursae and a significant negative weak correlation was noted (PCC = - 0.269, p=0.003).

**Table 77.** Correlations between the raw changes in explanatory variables from the baseline to the twelve month assessment.

| | | change in LFISIF | change in LFISAP | change in MSUS bursae | change in VAS | change in ESR | change in CRP | change in DAS-28 |
|---|---|---|---|---|---|---|---|---|
| change in LFISIF | Pearson Correlation | 1 | | | | | | |
| | Sig. (2-tailed) | | | | | | | |
| change in LFISAP | Pearson Correlation | 0.410** | 1 | | | | | |
| | Sig. (2-tailed) | 0.000 | | | | | | |
| change in MSUS bursae | Pearson Correlation | 0.216* | 0.193* | 1 | | | | |
| | Sig. (2-tailed) | 0.018 | 0.036 | | | | | |
| change in well being VAS | Pearson Correlation | 0.124 | 0.071 | -0.023 | 1 | | | |
| | Sig. (2-tailed) | 0.178 | 0.442 | 0.802 | | | | |
| change in ESR | Pearson Correlation | 0.163 | 0.002 | -0.079 | 0.322** | 1 | | |
| | Sig. (2-tailed) | 0.087 | 0.987 | 0.406 | 0.001 | | | |
| change in CRP | Pearson Correlation | -0.019 | 0.097 | -0.103 | 0.236* | 0.477** | 1 | |
| | Sig. (2-tailed) | 0.843 | 0.324 | 0.290 | 0.014 | 0.000 | | |
| change in DAS-28 | Pearson Correlation | 0.126 | 0.059 | -0.149 | 0.318** | 0.557** | 0.331** | 1 |
| | Sig. (2-tailed) | 0.259 | 0.599 | 0.180 | 0.004 | 0.000 | 0.003 | |

**Key:** ** Correlation is significant at the 0.01 level (2-tailed); *Correlation is significant at the 0.05 level (2-tailed).

**Table 77** shows the correlations of changes in all clinical outcomes, although the focus of the analysis is the primary outcome of foot impact scores (LFIS$_{IF}$ and LFIS$_{AP}$) and MSUS detectable bursae. For continuity, the same method was used as in the baseline visit to assess correlations of change in clinical outcomes between baseline and twelve months.

**Figure 41.** Scatter plot showing the association between changes in foot impairment (LFIS$_{IF}$) and MSUS detectable bursae from baseline to twelve months.
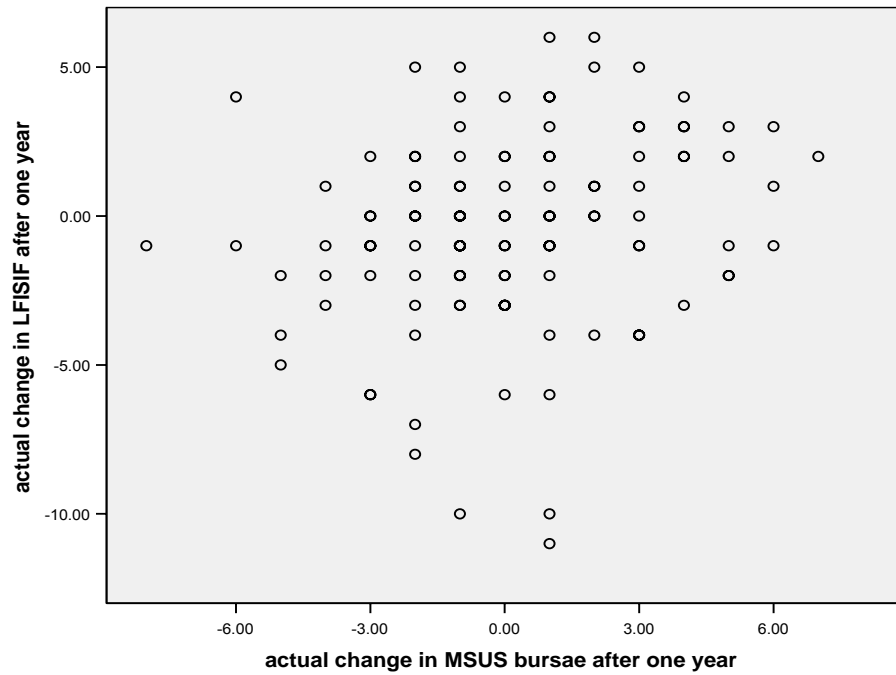


**Figure 42.** Scatter plot showing the association between changes in activity participation limitation (LFIS$_{AP}$) and MSUS detectable bursae from baseline to twelve months.
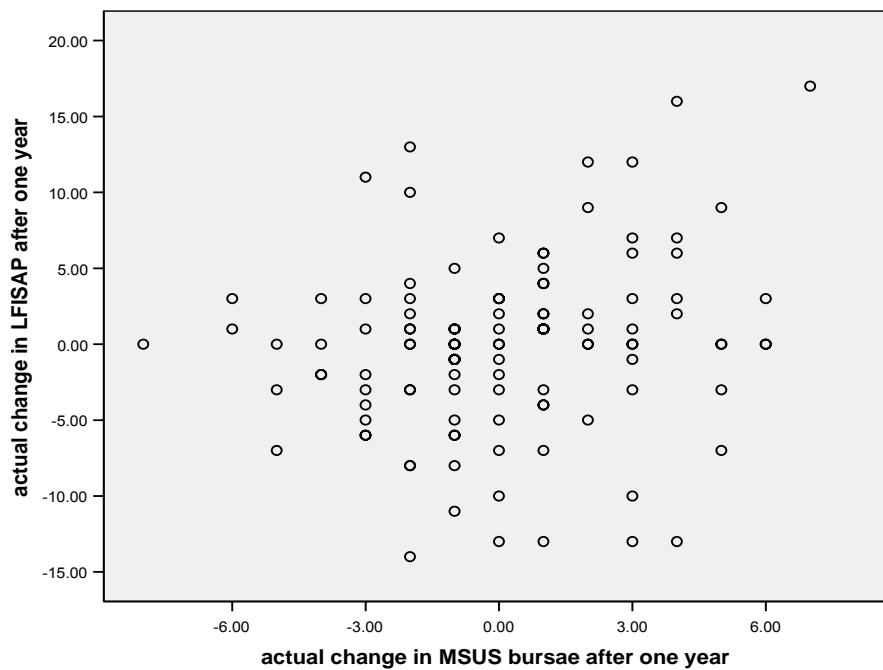
*6.7.4.2. Longitudinal multivariate linear regression analyses*

To determine if changes in MSUS detectable bursae were independently related to changes in foot impact scores, the values of change for each of the explanatory variables were checked for assumptions and entered into same multivariate model as for the twelve month analysis (section 6.7.3.3, page 182). Even though the raw changes in the explanatory variables of global wellbeing VAS, ESR, CRP and DAS-28 were not significantly associated with either LFIS subscale change scores, they were forced into the model for continuity reasons and comparison between studies. After adjusting for age and disease variables (global wellbeing VAS and ESR) the changes in MSUS detectable bursae remained a significant independent factor at the 0.05 level associated with $LFIS_{IF}$ ($\beta$=0.276, p=0.012) and $LFIS_{AP}$ ($\beta$=0.450, p=0.028) (**Table 78** and **Table 79**). The $r^2$ (R square) for the $LFIS_{IF}$ model was 0.118 indicating that approximately 11.8% of the variability in $LFIS_{IF}$ can be explained by the model. The $r^2$ (R square) for the $LFIS_{AP}$ model was 0.050 indicating that approximately 5.0% of the variability in $LFIS_{AP}$ can be explained by the model.

**Table 78**. Multivariate linear regression model for changes in LFIS impairment subscale scores, changes in MSUS detectable bursae and changes in disease activity between baseline and twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| MSUS Bursae | $LFIS_{IF}$ | 0.276 | 0.108 | 0.012 | 0.062 – 0.491 |
| Age at baseline | $LFIS_{IF}$ | -0.062 | 0.026 | 0.022 | -0.114 - -0.009 |
| Global VAS | $LFIS_{IF}$ | 0.012 | 0.012 | 0.333 | -0.012 – 0.036 |
| ESR | $LFIS_{IF}$ | 0.037 | 0.019 | 0.059 | 0.001 – 0.075 |

**Table 79**. Multivariate linear regression model for changes in LFIS activity participation limitation subscale scores, changes in MSUS detectable bursae and changes in disease activity between baseline and twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| MSUS Bursae | $LFIS_{AP}$ | 0.450 | 0.203 | 0.028 | 0.048 – 0.852 |
| Age at baseline | $LFIS_{AP}$ | -0.033 | 0.050 | 0.510 | -0.132 – 0.068 |
| Global VAS | $LFIS_{AP}$ | 0.018 | 0.023 | 0.436 | -0.027 – 0.063 |
| ESR | $LFIS_{AP}$ | -0.001 | 0.036 | 0.969 | -0.070 – 0.073 |

### 6.7.5. Predictors of change

From the multivariate regression analyses changes in both LFIS$_{IF}$ and LFIS$_{AP}$ appear to be predicted fairly well by the changes in the number of MSUS detectable forefoot bursae, after adjusting for age, global wellbeing VAS and ESR. The p-values (0.013 and 0.021) are not outstanding, but can be deemed good, given the sample size and the fact that count data for MSUS detectable bursae are being used as continuous.

### 6.7.5.1. Comparison of baseline associations of MSUS detectable bursae with associations at twelve months

These findings are further confirmed when baseline values for each of the predictor variables are analysed against MSUS detectable bursae for the cohort data at both baseline and twelve months. Both subscales of LFIS are significantly positively correlated with MSUS detectable bursae at baseline and again at twelve months (Table 80).

**Table 80.** Correlations between cohort MSUS detectable bursae and relevant clinical variables for RA participants at baseline and twelve months.

| | Baseline | | Twelve months | |
|---|---|---|---|---|
| | Pearson Correlation Coefficient | Significance (2-tailed) | Pearson Correlation Coefficient | Significance (2-tailed) |
| Age years(N=120) | -0.030 | 0.744 | 0.106 | 0.248 |
| Duration of RA years (N=119) | 0.404** | 0.000 | 0.063 | 0.496 |
| Weight(kgs) (N=120) | 0.072 | 0.433 | -0.069 | 0.451 |
| Height(cms) (N=119) | 0.062 | 0.552 | -0.030 | 0.748 |
| Global wellbeing 100mmVAS (N=120) | -0.001 | 0.988 | 0.114 | 0.217 |
| ESR mm/hr (N=115) | 0.140 | 0.133 | 0.043 | 0.644 |
| CRP mg/l (N=113) | 0.050 | 0.595 | -0.120 | 0.204 |
| DAS-28 (N=97) | -0.114 | 0.276 | 0.041 | 0.693 |
| LFIS$_{IF}$ (N=120) ** | 0.226* | 0.013 | 0.236** | 0.009 |
| LFIS$_{AP}$ (N=12) ** | 0.254** | 0.005 | 0.235** | 0.010 |

However, when the data were analysed further to determine if LFIS$_{IF}$ or LFIS$_{AP}$ values at baseline were related with MSUS detectable bursae at twelve months no significant associations were found (**Figure 43** and **Figure 44**).

**Figure 43.** Scatter plot showing the association between foot impairment at baseline and MSUS detectable bursae at twelve months.
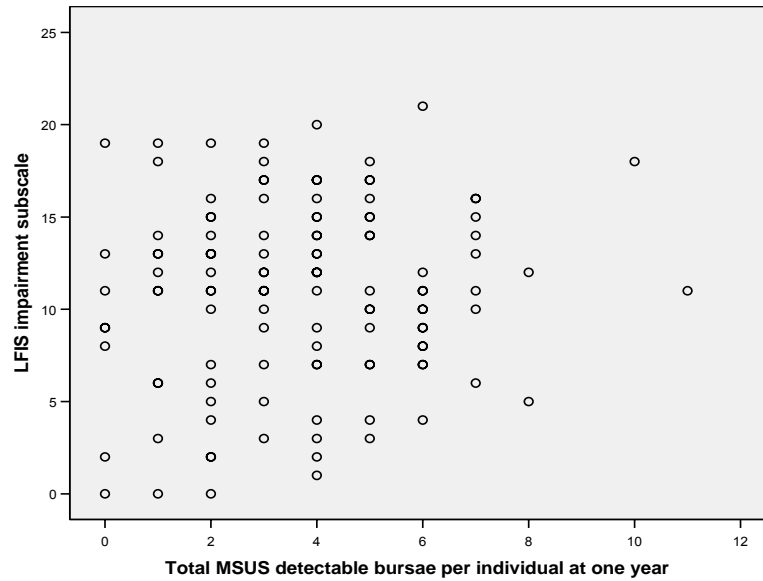


**Figure 44.** Scatter plot showing the association between activity participation limitation at baseline and MSUS detectable bursae at twelve months.
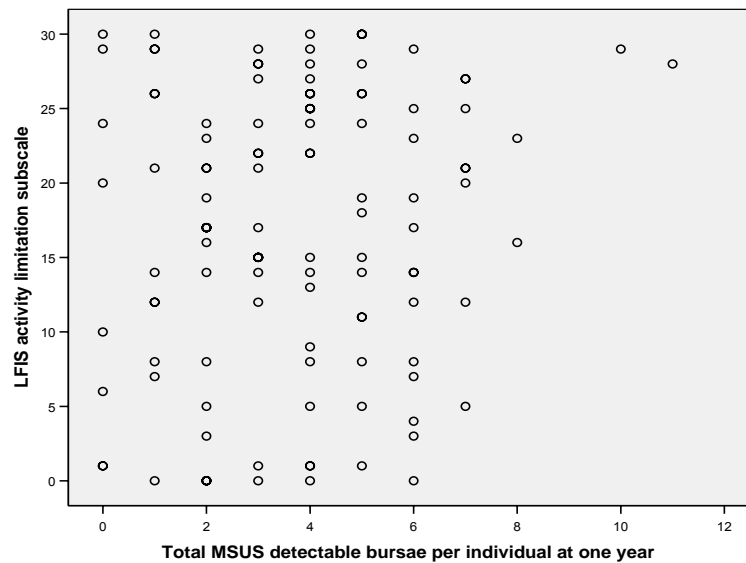


The scatter plots show a random pattern between LFIS scores at baseline and MSUS detectable bursae at one year indicating a lack of association between these variables.

### 6.7.5.2. Regression to the mean

Bowling (2002) highlights that detection of any change in variables could be due to the regression to the mean phenomenon. This is also known as a regression threat or "regression artefact" and may occur with a non-random sample from a population and two measures that are imperfectly correlated. It is an important phenomenon to take note of because it affects the internal validity of the study design (Bowling 2002; Petrie and Sabin 1998).

A regression artefact occurs when participants have extreme measurements on variables of interest or there are normal fluctuations in the variable of interest over time. The net effect of regression toward the mean is that the lower scores (or measurements) on the pre-test tend to be higher on the post-test, and the higher scores (or measurements) on the pre-test tend to be lower on the post-test (Bowling 2002; Petrie and Sabin 1998). To test this effect, the regression models were recalculated with the addition of the baseline values of both LFIS subscale scores (**Table 81** and **Table 82**).

After adjusting for age and disease variables (global wellbeing VAS and ESR) and baseline LFIS subscale scores, the changes in MSUS detectable bursae remained a significant independent factor at the 0.05 level associated with $LFIS_{IF}$ ($\beta$=0.248, p=0.016) but not with $LFIS_{AP}$ ($\beta$=0.3740, p=0.063). The $r^2$ (R square) for the $LFIS_{IF}$ model was 0.238 indicating that approximately 23.8% of the variability in $LFIS_{IF}$ can be explained by the model. The $r^2$ (R square) for the $LFIS_{AP}$ model was 0.110 indicating that approximately 11.0% of the variability in $LFIS_{AP}$ can be explained by the model.

**Table 81**. Multivariate linear regression model for changes in LFIS impairment subscale scores, changes in MSUS detectable bursae and changes in disease activity between baseline and twelve months including baseline $LFIS_{IF}$.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| MSUS Bursae | $LFIS_{IF}$ | 0.248 | 0.101 | 0.016 | 0.047 – 0.448 |
| Age at baseline | $LFIS_{IF}$ | -0.055 | 0.025 | 0.029 | -0.047 – 0.448 |
| Global VAS | $LFIS_{IF}$ | 0.003 | 0.012 | 0.778 | -0.020 – 0.026 |
| ESR | $LFIS_{IF}$ | -0.041 | 0.018 | 0.026 | -0.005 – 0.077 |
| $LFIS_{IF}$ baseline | $LFIS_{IF}$ | -0.233 | 0.057 | 0.000 | -0.346 – -0.120 |

**Table 82**. Multivariate linear regression model for changes in LFIS activity participation limitation subscale scores, changes in MSUS detectable bursae and changes in disease activity between baseline and twelve months including baseline LFIS$_{AP}$.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| MSUS Bursae | LFIS$_{AP}$ | 0.374 | 0.178 | 0.063 | -0.021 – 0.769 |
| Age at baseline | LFIS$_{AP}$ | 0.014 | 0.052 | 0.791 | -0.089 – 0.116 |
| Global VAS | LFIS$_{AP}$ | 0.013 | 0.022 | 0.567 | -0.031– 0.057 |
| ESR | LFIS$_{AP}$ | 0.007 | 0.035 | 0.835 | -0.063 – 0.077 |
| LFIS$_{AP}$ baseline | LFIS$_{AP}$ | -0.166 | 0.063 | 0.009 | -0.290 – (-0.042) |

This suggests that the association of change between MSUS detectable bursae and foot impairment (LFIS$_{IF}$) is real and not due to regression artefact. However the association between change in MSUS detectable bursae and activity participation limitation just dropped out of the model for significance when baseline LFIS$_{AP}$ data was included. It is therefore possible that changes within LFIS$_{AP}$ may be attributed to the natural variation or random fluctuation in the impact of RA disease on the foot over time rather than MSUS detectable bursae. Results therefore should be interpreted with caution. However, the confidence intervals for MSUS detectable bursae within the LFIS$_{AP}$ model did only just cross zero and it might be that the sample size of returnee participants was too small to determine the association.

### 6.7.5.3. Person specific analyses according to changes in MSUS detectable bursae over twelve months

The variance of the data for changes in MSUS detectable bursae was further examined as person specific data to investigate what, if anything, predicted those changes. **Figure 45** shows the MSUS scan images of a participant whose bursae count decreased from the baseline to the twelve month visit. To determine predictors of changes this data was grouped according to occurrences of MSUS bursae per individual (group A: 0-2 MSUS detectable bursae; group B: 3-6 MSUS detectable bursae; group C: 7-11 MSUS detectable bursae) at both baseline and twelve months. An increase in the number of MSUS detectable bursae was observed in 31 (25.8%) participants, whilst in 28 (23.3%) participants MSUS detectable bursae decreased and in 61 (50.8%) participants the number of MSUS detectable bursae remained the same after twelve months (**Table 83**).

**Figure 45.** MSUS images of the left plantar forefoot area of the same study participant with RA demonstrating enlarged bursae as anechoic areas between the second and third metatarsal heads and the third and fourth metatarsal heads (white arrows) (A) at baseline. (B) the same foot demonstrating a homogenous signal between the second and third metatarsal heads and third and fourth metatarsal heads at the twelve month visit.
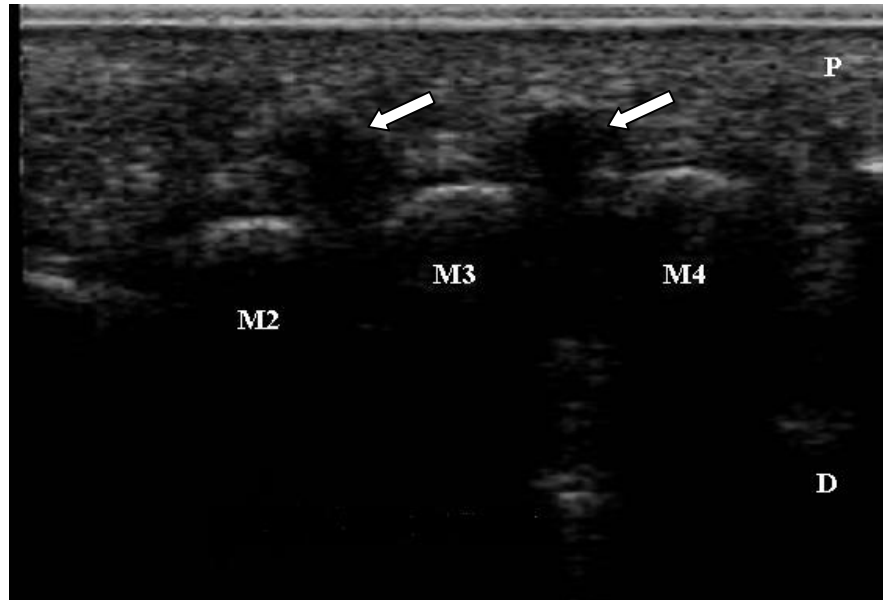


A
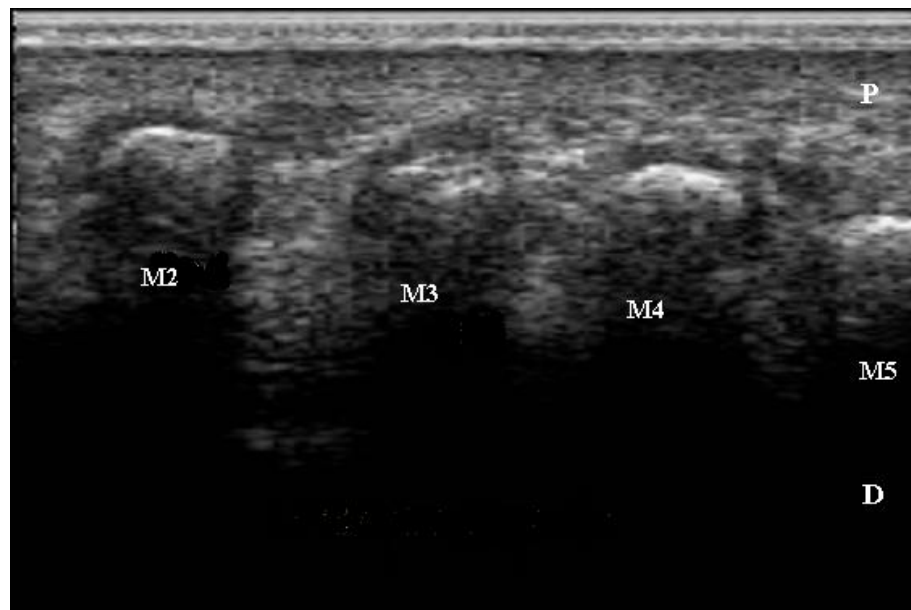


B

**Key:** M2 = second metatarsal; M3 = third metatarsal; M4 = fourth metatarsal;
M5 = fifth metatarsal; P = plantar surface; D = dorsal surface

**Table 83.** A contingency table showing results for the comparisons between MSUS detectable bursae at baseline and after twelve months.

| | | Categories of MSUS detectable bursae at twelve months | | | |
| --- | --- | --- | --- | --- | --- |
| | | GroupA 0-2 | Group B 3-6 | Group C 7-11 | Total |
| Categories of MSUS detectable bursae at baseline | GroupA | 20 | 21 | 3 | 44 |
| | GroupB | 15 | 39 | 7 | 61 |
| | GroupC | 4 | 9 | 2 | 15 |
| | Total | 39 | 69 | 12 | 120 |

The data was then analysed for mean change of the predictor variables according to the direction and magnitude of change of MSUS detectable bursae for each of the groups A, B and C.

**Table 84** shows the descriptive results indicating that there was a trend towards those individuals who exhibited a decrease in the number of MSUS detectable bursae to have longer mean disease duration but to have an improvement in well being and foot impact scores observed by a reduction in those scores. However they showed a mean increase in disease variables ESR, CRP and DAS-28. Those who exhibited an increase in MSUS detectable bursae tended to have shorter disease duration and deterioration in foot impact scores (observed by an increase in those scores) but a reduction in mean disease variable scores for ESR, CRP and DAS-28

The data was further tested for significance of between-group effects using analysis of variance. Significant differences at the 0.05 level between groups were observed for change in LFIS$_{TOT}$ (p=0.036), ESR (p=0.016) and CRP (p=0.014). After adjusting the p values for the number of tests performed using Bonferroni correction the results were significant for ESR (p=0.012) and CRP (p=0.011) between those who had no change in MSUS detectable bursae state and those who exhibited an increase in MSUS detectable bursae. For LFIS$_{TOT}$ the differences were also between those who had no change in MSUS detectable bursae state and those who exhibited an increase in MSUS detectable bursae, however this became marginally non significant (p=0.053).

**Table 84.** Analysis of variance for the mean change observed for individuals in each of the predictor variables according to the direction and magnitude of change of MSUS detectable bursae.

| | Increase in bursae N=31 | No change in bursae N=61 | Decrease in bursae N=28 | ANOVA Statistical values |
|---|---|---|---|---|
| Age (baseline) | 61.1 (12.5) 33 - 85 | 58.8 (12.1) 25-87 | 60.1 (11.9) 32 - 82 | f=0.409 p=0.666 |
| Duration of RA (baseline) | 8.6 (6.7) 2 - 30 | 12.7 (9.8) 0.5 - 38 | 14.3 (14.1) 2 - 43 | f=2.539 p=0.083 |
| Raw change in LFIS* | 2.4 (9.6) -24 – 19 | -1.6 (6.1) -19 - 10 | -2.1 (8.1) -23 – 18 | f=3.414 p=0.036 |
| Raw change in LFISIF | 0.5 (3.9) -11 – 6 | -0.6 (2.8) -8.0 – 6.0 | -1.3 (3.2) -10 – 5 | f=2.245 p=0.111 |
| Raw change in LFISAP | 1.8 (6.7) -13 – 17 | -1.0 (5.3) -14 - 12 | -0.4 (5.1) -8 – 13 | f=2.629 p=0.076 |
| Raw change in VAS | -3.5 (27.5) -57 – 60 | -1.9 (26.0) -80.0 – 57.0 | -9.7 (22.8) -55 – 29 | f=0.893 p=0.412 |
| Raw change in ESR* | -5.1 (17.5) -42 – 55 | 5.6 (14.5) -20.0 – 71.0 | 0.62 (17.7) -33 – 56 | f=4.297 p=0.016 |
| Raw change in CRP* | -9.1 (24.2) -115 – 16 | 9.7 (33.4) -45 - 216 | 1.1 (14.2) -31 – 42 | f=4.442 p=0.014 |
| Raw change in DAS-28 | -0.4 (1.6) -3 – 3 | 0.3 (1.9) -4.1 – 4.9 | 0.5 (1.4) -2 – 4 | f=1.528 p=0.223 |

**Key:** *Significant at the 0.05 level

Using chi squared analyses there were no significant differences between the groups for disease severity, use of medication at baseline and twelve months, previous podiatry treatment, podiatry treatment at baseline and foot structure at baseline. A significant difference was noted between the groups for current podiatry treatment at twelve months, with those who exhibited an increase in MSUS detectable bursae having the least podiatric treatment (**Table 85**, **Table 86** and **Table 87**).

**Table 85.** The disease severity and use of disease modifying medication at baseline and twelve months for individuals in each of the predictor variables according to the direction and magnitude of change of MSUS detectable bursae.

| | Increase in bursae (N=31) | No change in bursae (N=61) | Decrease in bursae (N=28) | Statistical values |
|---|---|---|---|---|
| Disease severity | +ve 23 (74.2%) <br> -ve 7 (22.6%) <br> Missing 1 (3.2%) | +ve 46 (75.4%) <br> -ve 13 (21.3%) <br> Missing 2 (3.3%) | +ve 24 (85.7%) <br> -ve 4 (14.3%) | $\chi^2$=0.896 <br> p=0.639 |
| TNF baseline | No 21 (67.7%) <br> Yes 10 (32.3%) | No 19 (31.1%) <br> Yes 42 (68.9%) | No 14 (50%) <br> Yes 14 (50%) | $\chi^2$=3.108 <br> p=0.211 |
| TNF 1yr | No 17 (54.8%) <br> Yes 13 (41.9%) <br> Missing 1 (3.2%) | No 32 (52.5%) <br> Yes 28 (45.9) <br> Missing 1 (1.6%) | No 14 (50%) <br> Yes 13 (46.4%) <br> Missing 1 (3.6%) | $\chi^2$=0.146 <br> p=0.930 |
| MTX baseline | No 14 (45.2%) <br> Yes 17 (54.8%) | No 19 (31.1%) <br> Yes 42 (68.9%) | No 9 (32.1%) <br> Yes 19 (67.9%) | $\chi^2$=1.905 <br> p=0.386 |
| MTX 1yr | No 10 (32.3%) <br> Yes 21 (67.7%) | No 17 (27.9%) <br> Yes 44 (72.1%) | No 8 (28.6%) <br> Yes 20 (71.4%) | $\chi^2$= 0.198 <br> p=0.906 |

**Key:** $\chi^2$=Chi square statistic; pres=presence; abs=absence; TNF=antiTNFα therapy; MTX=methotrexate.

**Table 86.** Clinical foot care at baseline and twelve months for individuals in each of the predictor variables according to the direction and magnitude of change of MSUS detectable bursae.

| | Increase in bursae (N=31) | No change in bursae (N=61) | Decrease in bursae (N=28) | Statistical values |
|---|---|---|---|---|
| Past pod baseline | No 12 (38.7%) <br> Yes 19 (61.3%) | No 28 (45.9%) <br> Yes 33 (54.1%) | No 6 (21.4% ) <br> Yes 22 (78.6%) | $\chi^2$=4.865 <br> p=0.088 |
| Current Pod at baseline | No 21 (67.7%) <br> Yes 10 (32.3%) | No 46 (75.4%) <br> Yes 15 (24.6%) | No 15 (53.6%) <br> Yes 13 (46.4.6%) | $\chi^2$=4.236 <br> p=0.120 |
| Current Pod at twelve months* | No 20 (64.5%) <br> Yes 11 (35.5%) | No 33 (57.4%) <br> Yes 24 (39.3%) <br> Missing 2 (3.3%) | No 9 (32.1%) <br> Yes 19 (67.9%) | $\chi^2$=7.441 <br> p=0.024 |

**Key:** *Significant at the 0.05 level; $\chi^2$=Chi square statistic; pres=presence; abs=absence

**Table 87.** Foot structure deformity at baseline for individuals in each of the predictor variables according to the direction and magnitude of change of MSUS detectable bursae.

| | Increase in bursae (N=31) | No change in bursae (N=61) | Decrease in bursae (N=28) | Statistical values |
|---|---|---|---|---|
| Right MTP joint subluxation | Pres 25 (80.6%) Abs 6 (19.4%) | Pres 45 (73.8%) Abs 15 (24.6%) Missing 1 (1.6%) | Pres 21 (75%) Abs 7 (25%) | $\chi^2$=0.406 p=0.816 |
| Left MTP joint subluxation | Pres 25 (80.6%) Abs 6 (19.4%) | Pres 46 (75.4%) Abs 14 (23.0%) Missing 1 (1.6%) | Pres 21 (75%) Abs 7 (25%) | $\chi^2$=0.296 p=0.862 |
| Right pes planus | Pres 25 (80.6%) Abs 1 (3.2%) Missing 5 (16.1%) | Pres 55 (90.2%) Abs 2 (3.3%) Missing 4 (6.6%) | Pres 26 (92.9%) Abs 1 (3.6%) Missing 1 (3.6%) | $\chi^2$=0.006 p=0.977 |
| Left pesplanus | Pres 25 (80.6%) Abs 1 (3.2%) Missing 5 (16.1%) | Pres 55 (90.2%) Abs 2 (3.3%) Missing 4 (6.6%) | Pres 26 (92.9%) Abs 1 (3.6%) Missing 1 (3.6%) | $\chi^2$=0.006 p=0.977 |

**Key:** $\chi^2$=Chi square statistic; pres=presence; abs=absence

The findings that podiatry treatment may influence the presence of MSUS detectable bursae within the forefeet of patients with RA were analysed further. To determine if changes in podiatric treatment status of individuals influenced the relationship between changes in foot impact scores and changes in MSUS detectable bursae the regression model (section 6.7.3.3, page 182) was repeated with these variables (**Table 88**, **Table 89**, **Table 90**, **Table 91**, **Table 92**, **Table 93**).

**Table 88.** Multivariate linear regression model for LFIS impairment subscale scores and confounding explanatory variables at baseline.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{IF}$ | 0.441 | 0.199 | 0.028 | 0.047 - 0.834 |
| Age | $LFIS_{IF}$ | 0.006 | 0.039 | 0.885 | -0.072 – 0.083 |
| Podiatry treatment | $LFIS_{IF}$ | 1.955 | 1.022 | 0.058 | -0.070 - 3.980 |

**Table 89.** Multivariate linear regression model for LFIS activity participation limitation subscale scores and confounding explanatory variables at baseline.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{AP}$ | 1.000 | 0.355 | 0.006 | 0.296 - 1.704 |
| Age | $LFIS_{AP}$ | 0.229 | 0.070 | 0.001 | 0.091 - 0.367 |
| Podiatry treatment | $LFIS_{AP}$ | 3.418 | 1.838 | 0.065 | -0.222 - 7.058 |

**Table 90.** Multivariate linear regression model for LFIS impairment subscale scores and confounding explanatory variables at twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{IF}$ | 0.539 | 0.192 | 0.006 | 0.158 -0.920 |
| Age | $LFIS_{IF}$ | -0.036 | 0.036 | 0.323 | -0.107 - 0.036 |
| Podiatry treatment | $LFIS_{IF}$ | 2.334 | 0.874 | 0.009 | 0.603 - 4.065 |

**Table 91.** Multivariate linear regression model for LFIS activity participation limitation subscale scores and confounding explanatory variables at twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{AP}$ | 0.948 | 0.360 | 0.010 | 0.235 - 1.660 |
| Age | $LFIS_{AP}$ | 0.181 | 0.068 | 0.009 | 0.047 - 0.315 |
| Podiatry treatment | $LFIS_{AP}$ | 6.111 | 1.636 | 0.000 | 2.871 - 9.352 |

**Table 92.** Multivariate linear regression model for changes in LFIS impairment subscale scores and changes in MSUS detectable bursae and changes in podiatry treatment between baseline and twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{IF}$ | 0.261 | 0.101 | 0.012 | 0.060 - 0.462 |
| Age | $LFIS_{IF}$ | -0.043 | 0.024 | 0.071 | -0.090 - 0.004 |
| Podiatry treatment | $LFIS_{IF}$ | -0.565 | 0.631 | 0.372 | -1.815 - .685 |

**Table 93.** Multivariate linear regression model for changes in LFIS activity participation limitation subscale scores and changes in MSUS detectable bursae and changes in podiatry treatment between baseline and twelve months.

| Explanatory Variable | Outcome variable | Regression coefficient β | Standard Error | P Value | 95% CI |
|---|---|---|---|---|---|
| Total Bursae | $LFIS_{AP}$ | 0.382 | 0.183 | 0.039 | 0.019 - 0.744 |
| Age | $LFIS_{AP}$ | -0.009 | 0.043 | 0.828 | -0.095 - 0.076 |
| Podiatry treatment | $LFIS_{AP}$ | -0.062 | 1.137 | 0.956 | -2.315 - 2.191 |

After adjusting for age and podiatric treatment at baseline, MSUS detectable bursae remained a significant independent factor at the 0.05 level associated with $LFIS_{IF}$ (β=0.441, p=0.028) and $LFIS_{AP}$ (β=1.000, p=0.006) (**Table 88** and **Table 89**).

After adjusting for age and podiatric treatment at twelve months, MSUS detectable bursae remained a significant independent factor at the 0.05 level associated with $LFIS_{IF}$ (β=0.539, p=0.006) and $LFIS_{AP}$ (β=0.948, p=0.010) (**Table 90** and **Table 91**).

After adjusting for age and podiatric treatment the changes in MSUS detectable bursae remained a significant independent factor at the 0.05 level associated with $LFIS_{IF}$ (β=0.261, p=0.012) and $LFIS_{AP}$ (β=0.382, p=0.039) (**Table 92** and **Table 93**).

This indicates that the association between the presence of MSUS detectable bursae and foot impact scores is probably also independent of podiatric treatment.

### 6.8. Summary of results

#### 1. Descriptive changes in prevalence of MSUS detectable bursae

At twelve months, there were no statistically significant changes in mean numbers of MSUS detectable bursae per individual, mean $LFIS_{IF}$ and mean $LFIS_{AP}$ scores between baseline and twelve months. The intermetatarsal space 4/5 remained as the most common site for MSUS detectable bursae. There were no significant differences in the means of clinical characteristics or demographic variables between baseline and twelve months assessments but the changes exhibited a wide variance and were normally distributed.

Statistically significant differences were noted for regular podiatry treatment (more receiving care at twelve months) and use of DMARDs and anti TNF-α therapy.

#### 2. Associations with MSUS detectable forefoot bursae at twelve months

Results at twelve months were consistent with those at baseline. MSUS detectable bursae remained a significant and independent factor (of disease activity) in its association with patient reported foot impact outcome measures.

#### 3. Associations with changes in presence of MSUS detectable forefoot bursae

Changes in MSUS detectable bursae were significantly positively associated with changes in $LFIS_{IF}$ and $LFIS_{AP}$ and significantly negatively associated with duration of RA although in both instances this was a weak correlation. The association of changes in MSUS detectable bursae with changes in $LFIS_{IF}$ and $LFIS_{AP}$ remained independent of disease activity.

#### 4. Predictors of change in presence of MSUS detectable bursae

Those individuals who had an increase in MSUS detectable bursae over time displayed greater deterioration in foot impact scores and tended to have had a reduction in podiatric treatment. However, they also displayed decreases in ESR and CRP and were more likely to have shorter disease duration.

**6.9. Discussion**

The results from this study provide new prospective evidence for the prevalence and natural history of bursae within the forefoot in a large cross sectional cohort of patients with RA. We have confirmed that MSUS detectable bursae in the study patients with RA were significantly associated with patient reported foot impact outcome measures, independent of overall disease activity as hypothesized in the previous cross sectional study (Chapter 5, page 125). The analyses within this study also provide evidence that foot impairment, activity limitation and participation restriction do change over time and that these changes may be associated with changes in the presence of MSUS detectable bursae.

Most current evidence for the manifestations of RA disease within the foot and ankle is attributable to cross-sectional analytical data with small sample sizes. The lack of foot specific longitudinal data has consequently been criticised as limiting the understanding of the full pathophysiology of RA within the foot, which has led to an inadequate evidence base for currently used clinical interventions (Bowen, Burridge and Arden 2005; Farrow, Kingsley et al 2005; Clark, Rome et al 2006; van der Leeden, Steultjens et al 2008). A recently published study was the first to longitudinally evaluate foot symptoms in a cohort of newly diagnosed patients with RA over a period of eight years (van der Leeden, Steultjens et al 2008). From a large sample of patients (N=848) forefoot involvement in patients with RA was emphasized as being important, with an increase in prevalence of forefoot erosion associated with RA disease progression (van der Leeden, Steultjens et al 2008).

Within this study results at twelve months were consistent with those at baseline. MSUS detectable bursae remained a significant and independent factor (of disease activity) in the contribution to foot impairment, activity limitation and participation restriction. Cross sectional findings showed that total numbers of MSUS detectable bursae were significantly correlated with impact of RA disease on the foot for both the impairment and the activity limitation and participation restriction subscales of the LFIS. If the baseline data presented in Chapter five (page 125) is compared, then some differences between baseline and twelve months existed where duration of RA, ESR, disease severity and left MTP joint subluxation were correlated with MSUS detectable bursae at baseline but not twelve months. However, when the variables were compared as a cohort, the data was largely consistent, with $LFIS_{IF}$ and $LFIS_{AP}$ being correlated with MSUS detectable bursae at both time points.

The intermetatarsal space 4/5 remained the most common site for MSUS detectable bursae and there were no statistically significant differences in mean numbers of MSUS detectable bursae per individual and mean $LFIS_{IF}$ and $LFIS_{AP}$ scores between baseline and twelve months. There were no significant differences either in the means of clinical characteristics or demographic variables between baseline and twelve months assessments but the changes in all variables appeared to be parallel exhibiting a wide variance that were normally distributed. This suggests that analysing means at baseline and twelve months may have masked the raw person specific changes observed in the variables or may have been due to normal fluctuations that may occur in clinical variables over time, described by Bowling (2002).

To our knowledge, this is the first study that has investigated forefoot bursae in RA detected by ultrasound over a period of time. When the data was grouped according to person specific numbers of MSUS detectable bursae, an increase in the number of MSUS detectable bursae was observed in 31 (25.8%) participants, whilst in 28 (23.3%) participants MSUS detectable bursae decreased and in 61 (50.8%) participants the number of MSUS detectable bursae remained the same after twelve months. These findings imply that MSUS detectable bursae in the forefeet do change over time. Interestingly, this was true of all the other predictor variables consistent with the well documented variability of RA disease over time (Boers, van Riel et al 1995; Fortin, Stucki and Katz 1995; Hulsmans, Jacobs et al 2000; Singh, Solomon et al 2006).

This highlights the use of longitudinal cohort data providing better statistical power against cross sectional data studied at different time points. van der Hejde, Landewe et al (2008) highlight that longitudinal data utilizes all available data within a prospectively followed cohort that allows adjustment for misleading intra-patient correlation. This is confirmed in longitudinal studies that have demonstrated that radiographic damage and radiographic progression of the hands and feet independently contribute to changes in physical function (Welsing, van Gestel et al 2001; Ødegard, Landewe et al 2006; van der Heijde, Landewe et al 2008).

Further evidence from this study, of the association between MSUS detectable bursae and patient reported foot impact, was provided when raw change values between baseline and

twelve months were analysed. There was a significant positive correlation between the changes in MSUS detectable bursae, with changes in both subscales of the LFIS but no significant associations with changes in disease activity variables (ESR, VAS and DAS-28). After adjusting for age and changes in disease activity the changes in MSUS detectable bursae remained an independent factor associated with patient reported foot impact. Although no previous study has examined forefoot bursae in RA in a longitudinal cohort, other investigators have found that foot related impairment and disability assessed by the LFIS is common amongst RA patients and independent of disease duration and global disease activity (Turner, Helliwell et al 2008). In that study, foot status was measured by structural deformity and biomechanical foot function and no account was taken of identification of pathology by imaging techniques (Turner, Helliwell et al 2008). This emphasizes the importance of studying the forefoot separately to general measures of disease activity.

The data from this study therefore provides reasonable longitudinal cohort evidence to support previous propositions from small sample cross sectional data of the relationship between MSUS detectable bursae and RA foot related symptoms (Koski 1998). Changes in patient reported foot impact appear to be predicted fairly well by the changes in the number of MSUS bursae over a twelve month period. However, analyses of regression to the mean showed that some of the variance in LFIS$_{AP}$ scores may be due to natural fluctuation in activity participation limitation over time. It is also possible that the smaller sample size of the returnee participants may not have enough statistical power, a common problem in longitudinal studies (Bowling 2002) so these findings should be interpreted with caution to avoid the possibility of rejection of a true null hypothesis.

In investigating predictors of change in the presence of MSUS detectable bursae over time, findings indicated that those who had an increase in MSUS detectable bursae tended to have shorter disease duration with deterioration in foot impact scores. Conversely, they were more likely to experience a significant improvement in ESR and CRP but had a significant reduction in podiatric treatment and were significantly less likely to be under the regular of care of a podiatrist. This implies that deterioration in foot status would not be detected by the usual clinical methods and that the forefoot requires additional attention in RA patients.

The scenario of increases in MSUS detectable bursae in those with early disease implies

that bursae are not related to disease progression. From the close relationship between MSUS detectable bursae and patient reported foot impact, independent of disease activity, we can hypothesize that mechanical trauma to the forefoot region due to higher levels of activity or altered foot mechanics may be key to the increase in numbers of MSUS detectable bursae for those with early disease. Some investigators have demonstrated correlations of MTP joint deformity in patients with RA with peak pressure and pressure time integrals for the first and fourth MTP joints (van der Leeden, Steultjens et al 2006). Others have also found that foot pain, swollen foot joint count and walking speed were independent predictors of foot related impairment and disability assessed by the LFIS (Turner, Helliwell et al 2008). No investigators have, to date, incorporated the use of MSUS imaging techniques to identify foot pathology with the use of biomechanical and clinical structural assessment techniques in understanding the burden of foot disease in patients who have RA and this area of research warrants further investigation.

In explaining synovitis within joints, Brown, Conaghan et al (2008) highlight that grey scale MSUS primarily detects hypertrophy of the synovium but does not differentiate between inflammatory and non inflammatory synovitis. They also report that synovium may become chronically thickened and less reversible in established disease (Brown, Conaghan et al 2008). The same pathophysiology also may apply to anatomical bursae in RA (refer back to Chapter two, section 2.2. page 18) although in this study due to limitations of the MSUS technique we were not able to distinguish between active hypertrophied synovium of bursae and non active synovium. Furthermore, no techniques have yet been developed to detect differences between mechanically related inflamed hypertrophied synovium and active inflammatory synovium related to disease activity in RA within the foot. For future studies the use of power Doppler MSUS, Gadolinium enhanced MRI and/or biopsy for histological analysis of forefoot bursae would be needed to achieve this.

A final point of interest was that the longitudinal data from the preliminary study (Chapter four, section 4.8.6, page 114) indicated that there was a trend towards reduction in the presence of MSUS detectable MTP joint synovitis and MSUS detectable bursae within the forefoot after twelve weeks of anti-TNF-α therapy, although the sample was small and the perceived reduction was not statistically significant. Others have also demonstrated significant reduction in synovitis of MCP (metacarpo-phalangeal) joints in patients with

RA starting anti-TNF-α therapy using MSUS (Hau, Kneitz et al 2002; Taylor, Steuer et al 2006; Iagnocco, Naredo and Tripodo 2008). Within this longitudinal study statistically significant differences were noted in the use of DMARDs and anti-TNF-α therapy by the RA participants between baseline and twelve months, however when the group data was analysed according to changes in MSUS detectable bursae, no significant differences between the groups were noted. This discrepancy can probably be explained by the lack of documentation over when participants started or stopped taking DMARDs and/or anti-TNF-α therapy.

## 6.10. Strengths and potential limitations

This study has several strengths and a number of limitations.  Its strengths include:

- a longitudinal cohort follow up design
- the large sample size
- a pragmatic clinical study representative of secondary care in the UK
- the use of patient reported clinical outcomes including disease activity and foot specific measures

This study has several potential limitations, firstly, the lack of availability of Power Doppler within this study to determine activity of synovium in bursae and therefore bursitis has already been highlighted in Chapter four (section 4.11, Page 121). As has also already been highlighted and discussed within Chapter five (section 5.11, page 162) the lack of MR imaging, biopsy and histology and / or fresh cadaver dissection to validate the presence of bursae within the forefoot limits the ability to accurately differentiate MSUS detectable bursae from MTP joint synovitis or tenosynovitis.

Secondly, the use of two time points spanning a one year period, although providing useful information, may have missed much of the variance and change in variables associated with fluctuations in disease state of RA. More time points would have allowed variations to be monitored and sensitivity of MSUS imaging to change in forefoot bursae to be measured by calculating the intra-observer variation and the smallest detectable difference between repeated measures (Østergaard and Wiell 2004; Ejberjerg, Vestergaard et al 2005)

Thirdly, a large cohort of patients (N=120 from a baseline of N=149) with RA was

investigated longitudinally over one year. The sample at the twelve month visit was representative of the original cohort as analyses showed that there were no significant differences between returnees and non returnees. However, although the response rate of 80.5% is generally considered to be acceptable within clinical studies (Bowling 2002) the reduction in returnees within this study may have affected statistical power (refer to sample size power calculations in Chapter three, section 3.7.1, page 69). Weak correlations may be due to sample size and lack of statistical power, particularly when the MSUS detectable bursae sub groups of the cohort were analysed. Bowling (2002) regards this as a common problem in longitudinal clinical cohort studies where the return sample is usually lower than the initial sample recruited according to power calculations. The reduced power thus limits the inferences that can be made from the statistical analyses regarding the associations between MSUS detectable bursae and patient reported foot impact outcome measures.

Fourthly, there was evidence of a significant decrease in the presence of MTP joint subluxation noted between baseline and twelve months that could not be biologically explained. Our study was conducted in accordance with daily clinical practice and the recognition of measurement error and recall bias cannot be discounted. The assessment of MTP joint subluxation within the study was by subjective observation and, although conducted by an experienced podiatrist, there were no other reliability checks.

To our knowledge there are no reliable clinical methods for assessing level of deformity at the MTP joints other than by radiographic scoring of MTP joint damage (van der Leeden, Steultjens et al 2006). The structural index score is a composite measure of seven items that includes the grading of MTP joint subluxation severity from 0 – 12 however there is still reliance on the clinician's subjective assessment (Platto, O'Connell et al 1991).

Clinical judgement of foot deformity is subjective and susceptible to poor reliability (Turner, Helliwell and Woodburn 2007; Turner, Helliwell et al 2008) and makes defining a complete foot status a limiting factor. Future investigations of the foot in RA are proposed with the use of established measurements to determine foot status. For example, the Foot Posture Index that has been well validated to determine foot type (Redmond, Crosibie, Ouvrier e et al 2006; Redmond, Crane and Menz 2008), plantar foot pressure measurement (van der Leeden, Steultjens et al 2006) and three dimensional kinematic analysis of gait (Turner, Helliwell et al 2008).

Finally, as also mentioned in Chapter five (section 5.11, page 162) patients treated in primary care only who may have less severe RA disease were not included.

**6.11. Conclusion**

The findings provide new evidence that MSUS detectable bursae within the forefeet of participants with RA do change over time, increasing more in those individuals with early disease and those who are also less likely to be under the routine care of a podiatrist. The findings at twelve months indicate that the results from the baseline study of the association between MSUS detectable bursae within the forefeet and patients' perception of their foot impairment and disability that was independent of overall RA disease activity were real. However, further study is required to confirm whether the association is also independent of MTP joint synovitis and plantar forefoot tenosynovitis.

The data therefore supports the baseline study recommendations that clinicians should consider giving additional attention to the forefoot in RA patients. The findings also support the baseline recommendations for the use of specific techniques, such as MSUS, to determine a more precise evaluation of the effects of RA disease within the foot and how these change over time.

# 7.0 Chapter Seven: Discussion

The primary aim of this doctoral thesis was to develop a reliable MSUS imaging technique to be performed by a podiatrist to assess the prevalence and natural history of bursae occurring within the forefeet of patients in secondary care who were being managed for RA. In doing so, it was anticipated that the MSUS technique and new knowledge of the prevalence of forefoot bursae may inform a more precise diagnosis of metatarsalgia in this patient group. It follows that this could potentially facilitate more timely and targeted treatment approaches for metatarsalgia.

Chapters four, five and six have therefore outlined and discussed the results of the reliability of the proposed MSUS technique and subsequent prospective investigation of forefoot bursae in patients with RA using MSUS performed by a podiatrist. Chapter seven draws together the overarching results and discusses the implications for clinical practice. Some time is given to debating the reliability issues surrounding this doctoral study and the challenges of conducting clinical research in the clinical setting.

## 7.1. Musculoskeletal ultrasound technique performed by a podiatrist

Within this doctoral thesis MSUS has been identified as a suitable tool to locate bursae within the forefoot in RA patients and, following appropriate training and mentorship from radiologists, the technique was shown to be reliable when performed by a podiatrist. The null hypothesis ($H_0$) stated in Chapter three (section 3.2, page 66) that 'a podiatrist performing MSUS is not reliable in the detection of forefoot bursae in patients with RA' can be rejected and the alternative hypothesis ($H_1$) that 'a podiatrist performing MSUS is reliable in the detection of forefoot bursae in patients with RA' can therefore be accepted.

This may be controversial amongst radiologists, but in the current climate of health policy, Lord Darzi's intention to "establish a health service that is responsive to patients and local communities whatever the circumstances" reasons that traditional distinctions between professional roles will change (DOH 2008). By 2020 there will be 20 million people living with long term conditions who at present account for 70% of acute and primary care spending, 58% of GP appointments and 77% of inpatient bed stays (DOH 2007). A flexible, multi-skilled health workforce will therefore be required.

A number of changes have occurred over the past decade in the provision of health care delivery. Most of the changes are the result of Government policy including 'The NHS Plan' (DOH 2000), 'Agenda for Change' (DOH 1999) and 'Modernising Regulation' (DOH 2000), others have been brought about by the changing role of the allied health professional within health care teams. The NHS Plan (DOH 2000) recognised that delivery of modern health care would require crossing of traditional professional boundaries and extending professional practice.

The scope of practice for podiatrists has constantly been in flux (Potter 2007; Graham 2007; Bowen 2008; Vernon 2008). Most significant of these changes was the development of local anaesthesia in the late 1960s leading to the development of nail surgery techniques and the evolution of podiatric surgery (Borthwick 2001). During the 1980s and early 1990s a graduate profession was established along with the transition from a technical skills approach to learning to one of problem based learning and critical thinking (Camp 1996). A new type of graduate who was challenged to question and analyse the traditional podiatric treatment methods thus emerged. Many of these graduates have continued to grow and create an evidence base for the profession as they have progressed further with Masters degrees, doctorates of philosophy and a growing number of consultant and professorial posts.

The extended roles of podiatrist in orthopaedics and rheumatology may include the administration of local steroid injections. The ability of podiatrists with this acquired new skill to use MSUS in guiding needle placement for the management of conditions such as morton's neuroma, achilles tendonitis and plantar fasciitis, would undoubtedly improve the effectiveness of this therapy (Koski 2000).

Results from the reliability study indicate that there is evidence that MSUS performed by a podiatrist is effective in the diagnosis of musculoskeletal pathology occurring within the forefoot. We confirmed good inter-observer agreement between a podiatrist and radiologist on MSUS assessment of the forefoot, particularly for MTP joint erosions and plantar forefoot bursae in patients with RA (Bowen, Dewbury et al 2008).

Although we reported good sensitivity for the podiatrist detecting MTP joint synovitis, specificity was low (Bowen, Dewbury et al 2008). Difficulties were encountered in using

MSUS to detect MTP joint synovitis from the plantar aspect of the foot where deformities such as MTP joint subluxation were present, which have also been reported by others (radiologists and rheumatologists) experienced in MSUS imaging (Szkudlarek, Court-Payen et al 2003; D'Agostino, Maillefert et al 2004; Scheel, Schmidt et al 2005; Naredo, Moller et al 2006).

It was also clear from the conceptual stage that, in the preliminary study, due to forefoot structural deformity in some participants, tenosynovitis was too difficult to assess using the proposed Diasus MSUS machine. As well as MTP joint synovitis, the appearance of flexor tenosynovitis on MSUS is a key differential diagnosis for metatarsalgia (Koski 1995). A dorsal approach to the MSUS scan protocol may have been preferable however those who advocate this technique did not state whether deformity and subluxation of the MTP joints was excluded (D'Agostino, Maillefert et al 2004).

At the time of this study there was no definition for detecting clinically apparent plantar forefoot bursae. Lack of standardization and variation in scanning technique amongst sonographers has been deliberated as contributing to disagreement between experts (Scheel, Schmidt et al 2005).We therefore decided to use a plantar approach to determine the prevalence of bursae within the forefoot.

Koski (1998) also utilised a plantar approach to detect intermetatarsal bursae sonographically and clinically by palpation, however the reason for this and the limitations were not discussed in his paper. Our justification for using a plantar approach was based on the work by Koski (1998) and on previous clinical observations of pain and palpable swollen bursae occurring within the plantar forefoot area. Cadaver studies investigating forefoot bursae had been conducted via a plantar approach (Chauveaux, Le Huec and Midy 1987; Studler et al 2008) as had MSUS and surgical studies of Morton's neuroma (Irwin, Konstantoulakis et al 2000; Jones, Bygrave et al 1999).

The preliminary study within this doctoral thesis confirmed that one podiatrist can utilize MSUS techniques to reliably detect forefoot pathology that is clinically under detected but highly prevalent on MSUS in patients who have RA. It is evident that further work on establishing reliability of protocols for MSUS assessment of the forefoot is required and to determine if others can also reliably use these techniques.

Before this new skill may be encompassed within extended scope podiatric practice a number of issues must be considered. These include, but are not restricted to:

- The essential of having expert anatomical knowledge of the foot and ankle.
- The reported steep learning curve in the interpretation of the on-screen grey scale images
- The selection of equipment.
- The resolution of medico-legal issues and professional indemnity

## 7.2. The prevalence and natural history of MSUS detectable bursae

In 2008, the current health secretary for the UK, declared the intention to focus on preventative health shifting the focus for the health professions, including podiatry, to prevent health problems rather than just responding to crises (DOH 2008). The current evidence base for prevention of foot health problems associated with RA is inadequate due to a previous lack of longitudinal cohort data. Results from a recently published eight year cohort study (N=848) indicate that forefoot involvement, detected radiologically and clinically in patients with RA is important in early RA disease (van der Leeden, Steultjens et al 2008). In our own one year prospective longitudinal cohort study, we have specifically identified a high prevalence of bursae detectable by MSUS that are not detectable by clinical assessment or prevalent in normal control participants.

The null hypothesis ($H_0$) stated in Chapter three (section 3.2, page 66) that 'MSUS detectable bursae within the forefoot are not a prevalent factor in patients with RA' can be rejected and the alternative hypothesis ($H_1$) that 'MSUS detectable bursae within the forefoot are a prevalent factor in patients with RA' can therefore be accepted.

As techniques in MSUS have advanced, knowledge of the effect of RA on the hand and foot joints has improved and consequently approaches to treatment of synovitis have improved (Hau, Kneitz et al 2002; Brown, Quinn et al 2006; Taylor, Steuer et al 2006). Traditionally, radiography has been the method through which the progression of RA disease has been assessed by demonstrating cartilage loss or bony erosion (Bushberg, Seibert et al 2002). In clinical trials the Sharp/van der Heijde score (van der Heijde 1996) and Larsen/Scott index (Scott, Houssien 1995) remain the most widely used methods of

scoring systems of radiographs that provide objective measures for investigators to determine RA disease progression. Both scoring systems are limited by the ability of x-ray imaging to detect actual disease activity. Radiography is further limited by the inability of x-rays to detect soft tissue changes (Bushberg, Seibert et al 2002).

Similarly, clinical assessment techniques are proven relatively insensitive in assessment of RA disease within the foot, as clinically under reported manifestations of RA within the foot appear to be common a common finding in imaging studies (Koski 1998; Brown, Quinn et al 2006; Wakefield, Freeston et al 2008). Using MSUS, changes in MTP joint synovitis have been detected in patients who have RA but had been diagnosed clinically as in remission (Brown, Conaghan et al 2008). Data from our studies concur with these findings, suggesting that the current measures used to assess forefoot bursae, which largely rely on clinical assessment, are not sufficiently sensitive to exclude ongoing changes in forefoot bursae, especially in those with earlier RA disease.

Data from this doctoral thesis therefore contributes to the growing body of evidence that modern imaging modalities such as MSUS appear to be superior in detection of temporal changes in the manifestations of RA than radiography and clinical assessment (Backhaus, Burmester et al 2002; Hau, Kneitz et al 2002; Ejbjerg, Vestergaard et al 2005; Naredo, Collado et al 2007; Iagnocco, Naredo and Tripodo 2008; Brown, Conaghan et al 2008). Furthermore, our findings confirm suggestions from others that bursae in the forefoot are poorly documented, may be difficult to detect clinically and may be the cause of foot symptoms (Olivieri, Scarano et al 2004).

Loss of function of the intermetatarsal spaces, due to symptomatic bursae within RA, has received little attention in the conceptual thoughts of mechanical dysfunction of the foot. The presence of adventitious bursae within the plantar forefoot area has been even less well considered. Foot deformities and abnormally concentrated forefoot pressures are usually reported as being related to the combined effects of repeated episodes of synovitis that weakens the joints and eventually destroys of the integrity of the feet (Woodburn, Helliwell et al. 2002; Turner, Helliwell et al 2006). This is probably due to the lack of suitable clinical tools that have been available to identify bursae within the forefoot. Mechanically, the role of the intermetatarsal bursae is said to be as shock absorbers that facilitate the metatarsal heads to glide in a dorso-plantarly direction, enabling the forefoot to adapt to

irregularities of the ground surfaces, particularly during walking or running (Bossley and Cairney 1980; Awerbuch, Shephard et al 1982; Claustre, Bonnel et al 1983; Chauveaux, Le Huec et al 1987; Theumann, Pfirrmann et al 2001). The association of MSUS detectable bursae with patient reported foot impact outcome measures that we detected may therefore be related to the destruction of the normal shock absorbency mechanisms of the forefoot and subsequent malfunction of the forefoot during walking.

Whilst we did demonstrate that the association between MSUS detectable bursae and patient reported foot impact outcome measures was independent of RA disease activity and was consistent at both time points there are a number of factors that need to be considered. The associations, although significant resulted in weak correlation coefficients as well as low $r^2$ values within the regression models indicating that only a small percentage of the model could be explained by MSUS detectable bursae. Analysis of regression to the mean also suggested that the association of change between MSUS detectable bursae and activity participation limitation could be attributed to the natural variation or random fluctuation in the impact of RA disease on the foot over time. However, the confidence intervals for MSUS detectable bursae within the $LFIS_{AP}$ model did only just cross zero and it might be that the sample size of returnee participants was too small to determine the association.

The null hypothesis ($H_0$) stated in Chapter three (section 3.2, page 66) that 'MSUS detectable bursae within the forefoot are not associated with patient reported foot impact outcome measures in patients with RA' cannot therefore be completely rejected.
It may be that the association between MSUS detectable bursae and patient reported foot impact outcome measures were independent of RA disease activity but not independent of MTP joint synovitis and / or flexor tenosynovitis. It may also be that the power of the sample was to low to confirm the associations.

We recommend that future studies of foot related symptoms in RA should therefore include identification of forefoot bursae as well as MTP joint synovitis by MSUS when defining extraneous variables and developing strategies to control for confounding factors. Furthermore, refinement of the technique to differentiate forefoot bursae from MTP joint synovitis and tenosynovitis within the forefoot is also essential and MSUS with power Doppler and / or MRI would be appropriate tools for this.

With insights gained from assessment of the forefoot using MSUS there is therefore potential for better targeting of treatment and preventative foot health. This would allow more targeted therapeutic approaches such as corticosteroid injection. Bursae within other anatomical areas responds well to injection (Koski 2000, Grassi, Filipucci et al 2001) and our own clinical experiences to date have indicated that MSUS guided steroid injection for swollen forefoot bursae is beneficial (**Figure 46**).

Within the remit of the study, identification of symptomatic forefoot bursae by MSUS has also informed treatment decisions. Other treatment methods that participants have been referred for have included intramuscular Depomedrone injection and/or dose adjustment of DMARDs for better control, where there has been a high prevalence of symptomatic bursae and other joint involvement. At the current time, treatment approaches to symptomatic MSUS detectable forefoot bursae remain anecdotal and have yet to be rigorously investigated.

**Figure 46**. MSUS images of the right plantar forefoot area of a study participant with RA demonstrating an enlarged bursa between the third and fourth metatarsal heads (A) and the same bursa immediately after injection with hydrocortisone (B).
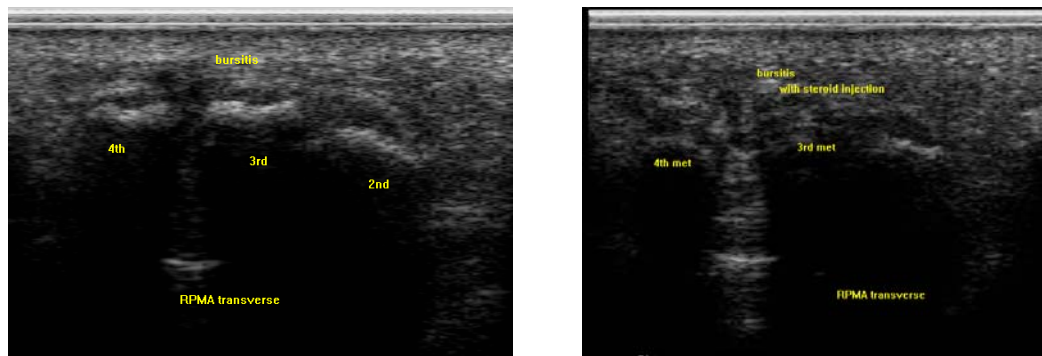


A: The patient complained of a painful right forefoot that was limiting her activity.

B: the right forefoot immediately after injection of hydrocortisone

**NB.** At a one month check, symptoms had resolved and the patient was able to return to their regular activities.

A final point of interest was that the longitudinal data from the preliminary study (Chapter four, section 4.8.6, page 144) indicated that there was a trend towards reduction in the presence of MSUS detectable MTP joint synovitis and MSUS detectable bursae within the forefoot after twelve weeks of anti-TNF-α therapy, although the sample was small and the perceived reduction was not statistically significant. However, significant changes were observed in ESR, CRP, DAS-28 and MFPDQ. These findings suggested that although the treatment switches off the disease process, twelve weeks may not have been long enough for MSUS detectable synovitis and bursal hypertrophy within the foot to regress.

Others have also demonstrated significant reduction in synovitis of MCP joints in patients with RA starting anti-TNF-α therapy using MSUS (Hau, Kneitz et al 2002; Taylor, Steuer et al 2006; Iagnocco, Naredo and Tripodo 2008). Within this doctoral thesis longitudinal study, statistically significant differences were noted in the use of DMARDs and anti-TNF-α therapy by the RA participants between baseline and twelve months, however when the group data was analysed according to changes in MSUS detectable bursae no significant differences between the groups were noted. This discrepancy can probably be explained by the lack of documentation over when participants started or stopped taking DMARDs and/or anti-TNF-α therapy. A key consideration in imaging studies should be whether with more sensitive tools to detect synovitis 'is more pathology observed?' or 'is pathology observed in more detail?'

There is clearly evidence to support the use of MSUS imaging of the foot as an essential component in the refinement of diagnosis and the development and implementation of effective care pathways for the assessment and treatment of foot and ankle pain and disability associated with RA.  The further development and use of MSUS assessment of the foot and ankle as a discrete field in clinical practice could be beneficial to patients with RA as well as conferring lower costs in service provision.


## 7.3. Critique of research methodologies

The studies that form this doctoral thesis have several strengths and a number of potential limitations, most of which have been highlighted previously (Chapter four, section 4.11, page 121, Chapter five, section 5.11, page 162 and Chapter six, section 6.10, page 206).

Key strengths include:

- Preliminary reliability testing of the MSUS technique against a radiologist
- the large sample sizes at the baseline and twelve month studies with an 80% response rate and the investigation of a comparator control at baseline
- the study sample was representative of secondary care in the UK and the study was conducted in accordance with general clinical practice to facilitate transference of results for patient benefit.
- the use of patient reported outcomes including disease activity and a measure of foot impact that had been developed and classified according to the WHO ICF (World Health Organisation International Classification of Functioning, Disability and Health) classification of impairment.

A number of potential limitations within the studies that form the doctoral thesis should be acknowledged and these are grouped according to the following themes:-

- Participant samples
- MSUS imaging technique
- MSUS measurement of forefoot bursae
- Measurement of clinical activity and foot structure
- Measurement of patient related foot disability using LFIS
- Assessment of foot mechanics

### 7.3.1. Participant samples

For the cross sectional data in the main study there was a 45.8% none response rate (Chapter five, section 5.8.1, page 135) from the initial recruitment such that only 54.2% of the population were investigated. If non-responders were people without foot pain or foot symptoms this could over inflate our estimates of foot symptoms, foot disability and MSUS detectable bursae. We did perform a non-response analysis and found no significant differences in parameters of age, gender, seropositivity and DMARDs between responders and none responders, suggesting this was not a major issue, although we cannot be certain of this. However, as participants may have been selected on the basis of foot symptoms and not MSUS detectable bursae, none differential bias effects are not likely to have affected

results.

We recruited only patients who were treated in secondary care clinics in the UK. Patients who were treated in primary care only, who may have less severe RA disease, were not included within the studies and this may limit the generalizibility of the results. Other authors have commented on the lack of UK studies of foot disease impact in RA based in primary care, but at the same time acknowledged that within the UK, most patients with RA currently receive their foot treatment within secondary care setting (Turner, Helliwell and Woodburn 2007). Studies within the secondary care environment are currently therefore more likely to be representative of current foot care for patients who have RA in the UK.

In all studies the population investigated was homogenous for RA which was required to be diagnosed according to the ACR criteria (Arnett, Edworthy et al 1988) and the clear eligibility criteria (section 4.4.2. page 97, section 5.4.2.1, page 128, section 6.4.2.1 page 166) ensured that members of both samples were representative of the wide spectrum of adults who have RA. However, within the samples for studies two and three there was a wide variation in disease state and manifestations of disease on the foot.

To our knowledge, there was no other existing longitudinal data that had investigated the prevalence of forefoot bursae in RA and it had received little attention in the literature (see Section 2.2, Chapter 2, page 18). The inclusion of participants with different severities of RA disease was therefore necessary within studies two and three. Interpretation of results, however, have to be noted with caution as, it is possible that, splitting the participants into groups for the analyses of associations of MSUS detectable forefoot bursae may have reduced the statistical power.

Furthermore, with a mean disease duration of 12.3 years, it is possible that foot problems within this group may have been high and thus the reported prevalence of forefoot bursae within this patient group may have been over inflated. Future work regarding other populations, such as early RA and non-inflammatory arthritis would therefore be interesting.

Within the baseline study (study two), the healthy control participants were not age matched with the RA participants due to difficulties in recruitment of the control sample

from a population of convenience. This may have introduced bias in the comparative analyses of explanatory variables; however we did conduct extra analyses on the sample data that showed that this did not appear to significantly alter the findings.

### 7.3.2. Musculoskeletal imaging technique

The presence of bursae within the forefoot was not validated by any other 'gold standard' imaging technique, such as MRI. As well as intermetatarsal bursae, and adventitious bursae, soft tissue swelling at the level of the MTP joints can be related to MTP joint synovitis or tenosynovitis that could be better differentiated using MRI. Most previous studies have not used MRI either, due to its limited availability (Szkudlarek, Court-Payen et al 2003; D'Agostino, Maillefert et al 2004; Naredo, Moller et al 2006). The OMERACT MSUS special interest group highlighted limited data in terms of comparisons of MRI with MSUS (Wakefield, Balint et al 2005), however within the preliminary study (Chapter four, page 96) we attempted to address this issue by demonstrating reliability through testing of the podiatrist's MSUS technique against an expert radiologist using a high level MSUS machine and the results of this work have since been published (Bowen, Dewbury et al 2008).

It could be that bursae detectable by MSUS in the studies presented within this doctoral thesis have hypertrophied synovium that may not be inflammatory active. Gadolinium enhanced MRI would provide clearer information relating to both synovial thickness and increased blood flow enabling better definition of bursitis (Gaffney, Cookson et al 1995). More recently power Doppler mode is advocated to determine whether synovium is actively inflamed, allowing a more precise definition of active synovitis (Brown, Quinn et al 2006; Balint, Mandl and Kane 2008).

Previously MSUS detectable bursae in the forefoot have been referred to as bursitis (Koski 1998) and the technique for the use of power Doppler in assessment of changes in synovial perfusion has been a development subsequent to the commencement of this doctoral thesis. Whilst the MSUS machine utilised by the radiologists (KD and MS) in the validation study did have power Doppler mode, the MSUS machine utilised by the podiatrist (CB) did not. To avoid complication in the use of terminology, following analysis of the results from the technique validation, we decided to refrain from using the term bursitis in the baseline and twelve month studies, preferring the term 'MSUS detectable bursae' instead. For future

studies, a MSUS machine with power Doppler is recommended as a prerequisite.

A further potential limitation in the MSUS imaging technique is that we could not accurately measure MTP joint synovitis and erosion or tenosynovitis. However, this was not the research question which was focused on whether forefoot bursae were common and if so, whether they were associated with patient reported foot impact outcome measures. We have satisfactorily demonstrated that forefoot bursae are common in patients with RA and that this may be associated with patient reported foot impact outcome measures independent of generalized disease measures (DAS- 28, CRP and ESR).

The lack of data on MTP joint synovitis and erosion or tenosynovitis limits our ability to determine whether the association between MSUS detectable forefoot bursae and patient reported foot impact outcome measures is independent of these potential collinear / confounding variables. To answer this question one would almost certainly have to perform MRI of the feet, probably with gadolinium enhancement, however this was out-with the scope of the thesis. We do hope to follow this up as part of a post-doctoral research plan.

### 7.3.3. Musculoskeletal ultrasound measurement of forefoot bursae

During the reliability and preliminary studies, it became evident that measurement of the size of MSUS detectable bursae was unachievable with the MSUS equipment utilised. Measurement was difficult due to the three dimensional nature of bursae and the two dimensional output of MSUS. Dichotomising the data into absence or presence of individual bursae may have limited the ability to detect true change between the baseline and twelve month visits. There may have been bursae that either reduced or increased in size and this effect will have been missed in our analyses. Actual measurement of forefoot structures detected by MSUS will require more attention within future work and new technology such as 3D and 4D MSUS or MRI would be more appropriate to accomplish this. In addition, determination of the smallest detectable difference that was clinically meaningful would be useful to enhance clinical management decisions.

Limitations relating to the analysis of presence or absence of MSUS detectable bursae during the validation of the technique should also be noted.  Using MSUS as an outcome measure for research is different to using MSUS for clinical diagnosis. Kappa agreements

are based on dichotomous categorical variables (Petrie and Sabin 2005) and so analysis of agreements for bursae were reduced to either presence or absence of bursae in either foot. Matching actual locations of bursae would have provided more credibility for reliability of the technique, although this did prove difficult in the preliminary study (Chapter four, page 96) due to the three dimensional nature of bursae and the two dimensional output of MSUS. However, by not classifying MSUS detectable bursae according to exact location this could have biased results towards higher levels of agreement between the podiatrist and radiologist. We attempted to attenuate this by conducting the consensus meeting where exact anatomical regions were tested for agreement.

Furthermore, with a number of confounding variables that potentially could distort the effect of the association between MSUS detectable bursae and patient reported foot impact scores, regression modelling techniques were used to discern meaning. Analysis of correlations and regression models revealed statistically significant associations between MSUS detectable bursae and patient reported foot disability scores, however, the correlation coefficients were not very strong. These correlations were probably limited by the fact that count data for MSUS detectable bursae was used as continuous data. The range of MSUS detectable bursae was from 0 -11 which, on the one hand is a continuous scale, but due to the small size of the scale may have impacted on the statistical power of the test.

### 7.3.4. Measurement of clinical activity and foot structure

Within the preliminary (reliability) study clinical activity was measured via the DAS-28 score that was performed independently by a trained joint assessor. Clinical foot status was determined by the podiatrist (CB) so that the radiologists (KD and MS) were blinded to the results of the foot assessment. However, this meant that the ultrasound measurements performed by the podiatrist (CB) were not performed independently to the clinical foot assessments. The same approach was used within the main studies (Chapter five, page 125 and Chapter six, page 164), that is the clinical activity and clinical foot assessments were performed by the same individual (CB) and not determined by an independent assessor. For the second and third studies it was not feasible to have numerous independent investigators and as such investigator bias and recall bias therefore need to be taken account when interpreting the data. Investigator bias is common in social research on human beings (Bowling 2002) and we attempted to reduce the effect of this bias by maintaining a

systematic order to the data collection (see study protocol flow charts, Chapter five, page 133, Chapter six, page 169) and using experienced independent data handlers to double enter and clean all the information onto the SPSS data sheet.

In study three, the investigator (CB) was trained in DAS-28 technique and also performed these assessments. The fact that there was a change in personnel performing the DAS-28 obviously had no impact between studies one and two as the data between those studies was not used interchangeably. During study three, the DAS-28 assessment was always performed before the MSUS foot assessments and it is possible that at a purely subconscious level that this may have affected the interpretation of the MSUS images leading to a greater reporting of MSUS detectable forefoot bursae. Whilst we cannot fully rule this out, the prevalence of MSUS detectable forefoot bursae and the association between MSUS detectable forefoot bursae and DAS-28 did not differ significantly between studies two and three. This would argue against a major bias.

The effect of investigator bias is related to the results of the clinical foot assessments and not LFIS scores. LFIS scores remained blinded to the podiatrist (CB) and therefore it is unlikely that the results from the main studies for the associations between LFIS scores and MSUS detectable bursae would be affected. It could be that results of the clinical foot assessments may have inflated the presence of MSUS detectable bursae. However, this bias could be attenuated by the fact that during the validation study the podiatrist (CB) underestimated the presence of MSUS detectable bursae compared to the radiologists (KD and MS) who used a more sensitive machine.


### 7.3.5. Measurement of patient reported foot impact using the LFIS

Results from the regression modeling techniques within the baseline and twelve month studies confirmed that the associations between MSUS detectable bursae and patient reported foot impact may be independent of overall disease activity. Whilst MSUS detectable bursae do explain some of the biological variance in both $LFIS_{IF}$ and $LFIS_{AP}$ scores, these values are probably lower due to measurement error of the MSUS technique and of the LFIS.

The LFIS was selected as the primary outcome measure for the prediction of the impact of

MSUS detectable bursae on patient related foot disability due to its validation for use in detecting change in foot status in patients with RA. At the time of the development of this doctoral study, the LFIS was published as a new instrument that had been validated to measure the effectiveness of interventions for foot disability in patients who have RA (Helliwell, Reay et al 2005). The instrument had, however, not been used in any other previous studies and therefore power calculations for the main studies were performed using results from the MFPDQ in the preliminary study (Chapter four, page 96).

In considering the use of LFIS for use in a randomised controlled trial, Turner, Helliwell and Woodburn (2007) report that a minimally clinically important difference for $LFIS_{IF}$ would be 3 points (Standard deviation=5), but did not report on $LFIS_{AP}$. They did suggest that for a two treatment parallel-design randomised controlled trial of podiatry led foot care versus no foot care, that 85 per group would be required to detect a difference between the groups of three points based on 90% and 1% significance level (Turner, Helliwell and Woodburn 2007). If we apply these calculations to the main studies within this thesis, then with a sample of 149 at baseline and 120 at follow up there should be adequate statistical power to make inferences about the associations of $LFIS_{IF}$ with the predictor variables.

Measurement error may have been introduced, as difficulties were experienced by some participants in their interpretation of some of the LFIS statements. Respondents were asked to tick the statements that applied best to them at the time of the data collection about their feet as either "true" if the statement applied to them or "not true" if it did not. Some participants required clarification of questions and some asked whether they could have responses that were sometimes true. Many participants were unsure of how to interpret the statement "Please choose the response that applies best to you at the moment". Therefore responses to the statements may have varied between thoughts and feelings during the past couple of weeks to that day only.

With the current limited published data that has used LFIS there appears to be no other available data on which to compare these participant reported difficulties. The authors of the LFIS did use rigorous item response techniques, Rasch analysis, in the validation of the LFIS and did report good test-retest results (Helliwell, Reay et al 2005). The data generated within the main studies of this doctoral thesis will therefore inform robust sample size calculations for future work.

### 7.3.6. Foot mechanics

Throughout the development of the studies we chose to focus on assessment of foot pathology and foot disability and no account was taken of the mechanical forces of foot function during gait. In a systematic review of measurement of foot related measures, van der Leeden, Steultjens et al (2008) recommend considering both self report and performance based instruments when investigating foot problems associated with RA. In an earlier study, van der Leeden, Steultjens et al (2006) demonstrated correlations of radiographic MTP joint deformity with peak pressure and pressure time integrals for the first and fourth MTP joints and correlations of high forefoot pressures with pain. Others have investigated the association between foot disabilities, assessed by both subscales of the LFIS, mechanics of function and foot mechanics and recommended that future prediction models may be enhanced by imaging based identification of foot pathology (Turner, Helliwell et al 2007). Following results from the studies that form this doctoral thesis, the development of a technique to investigate the effect of foot mechanics in the relationship between MSUS detectable forefoot bursae in RA and foot disability is proposed for future investigations.

Data from both baseline and twelve month visits of our studies showed that there was a significant association between MTP joint subluxation and patient related foot disability but not MSUS detectable bursae. We also performed further regression models that showed MSUS detectable bursae remained independent of the association between MTP joint subluxation and patient related foot disability. However, a significant decrease in the presence of MTP joint subluxation was noted between baseline and twelve months that could not be biologically explained. Our study was conducted in accordance with daily clinical practice and the recognition of measurement error and recall bias cannot be discounted. The assessment of MTP joint subluxation within the study was by subjective observation and although conducted by an experienced podiatrist there were no other reliability checks. To our knowledge there are no reliable clinical methods for assessing level of deformity at the MTP joints other than by radiographic scoring of MTP joint damage (van der Leeden, Steultjens et al 2006). The structural index score is a composite measure of seven items that includes the grading of MTP joint subluxation severity from 0 – 12 however there is still reliance on the clinician's subjective assessment (Platto, O'Connell et al 1991).

It is important to use established measurements to determine foot status and for future investigations of the foot in RA, the use of the Foot Posture Index that has been well validated to determine foot type (Redmond, Crosibie, Ouvrier et al 2006; Redmond, Crane and Menz 2008), plantar foot pressure measurement (van der Leeden, Steultjens et al 2006) and three dimensional kinematic analysis of gait (Turner, Helliwell et al 2008) should be considered.


## 7.4. Plans for future work

The foot remains an under investigated area in the rheumatology literature. The investigations presented within this doctoral thesis have not only confirmed this but have provided robust data that contributes to the body of knowledge and understanding of pathology within the foot in RA. Further investigation of the foot in RA by MSUS has been justified and reliability issues of this being performed by a podiatrist identified. This is unique longitudinal data highlighting the high prevalence of MSUS detectable forefoot bursae that are susceptible to change over time.

In order to optimize the management of these patients, it is essential to conduct further work on validation of the MSUS technique, confirmation of the association between MSUS detectable bursae and patient reported foot impact outcome measures and to differentiate the aetiology in terms of mechanical trauma and/or RA systemic inflammatory response.

Given unlimited resources, this would ideally involve:-

- A study that allowed MSUS imaging of fresh cadaver feet from individuals who had RA with confirmation of detected bursae by dissection
- The use of MRI as an external validator for location of forefoot bursae in patients with RA
- The use of MSUS guided biopsy of forefoot bursae in patients with RA to confirm tissue type through histological analysis.
- Or the use of microbubble contrast agents in MSUS imaging to quantify or show 'hot spots' of active inflammation within the RA forefoot
- A study that incorporated assessment of the lower limb biomechanics and the assessment of metatarsal movement through the gait cycle.

The objectives that we consider are feasible to pursue within our research department for further study are:

1. To further develop the technique of identifying bursae within the forefoot in patients with RA and differentiating those that are in an active flare from those that are chronically hypertrophied, using Power Doppler MSUS imaging and magnetic resonance imaging.

2. To investigate mechanical function of the foot and ankle in patients with RA using computerised foot pressure technology and three dimensional gait analysis technologies to determine relationships between mechanical function and forefoot bursae.

3. To investigate the systemic inflammatory impact of RA using laboratory serology indicators and histopathology analyses of inflamed forefoot bursae to determine relationships between inflammatory flare and forefoot bursae.

4. To improve current clinical decision making and treatment pathways for patients with painful forefeet who have RA and thus impact positively on patient mobility, and activity participation.

A cohort of patients with RA is now established who have been assessed at two time points. Further prospective investigation of forefoot bursae as independent markers and associations of change in patient reported foot impact in patients with RA would not only strengthen the data but allow changes in forefoot bursae to be compared over several time points.

Foot pressure measurements have been recorded by an FScan® system (Tekscan Inc. USA) at both the baseline and return visit. The FScan® automatically records the amount of pressure occurring on the soles of the feet during each footstep, storing data on the system for later analysis. It was not feasible to interpret this data within the remit of this doctoral thesis, however future analyses will focus on the associations of foot pressure variables with the presence of MSUS detectable forefoot bursae. The addition of three dimensional kinematic analysis of rearfoot and forefoot motion in future studies will also enhance the predictive model.

To differentiate active inflammatory synovium from non active synovium in forefoot bursae in RA, future work will involve the assessment of the foot by a portable MSUS system that has both Colour and Doppler mode functions. A sub section of participants will also undergo MRI assessment of the foot to validate the MSUS power Doppler findings. It

is also proposed that in participants who, after undergoing MRI scans of their feet, are identified as having forefoot bursitis a biopsy is taken of the bursa for histo-pathological examination

With further insights and enhanced predictive modeling it is anticipated that a clinical treatment algorithm for forefoot symptoms due to bursae in RA patients will be determined. It is hoped that this will assist foot health clinicians to improve clinical treatment decisions that ultimately benefits patients who have RA in terms of improvement in foot impairment, activity limitation and participation restriction.

## 7.5 Conclusions

This doctoral thesis has introduced the research problem of investigation of the prevalence of forefoot bursae in the forefeet in patients with RA, by MSUS performed by a podiatrist, and the research questions and hypotheses. The study of bursae in the feet of patients who have RA was justified, definitions were presented and the methodology and results for each of the studies that form the thesis were described and discussed. Limitations were given and proposals for future work presented.

This study was the first to attempt to investigate inter-observer agreement in the use of MSUS between an allied health professional (podiatrist) and an expert radiologist. Performance of MSUS in image acquisition and interpretation by the podiatrist was of an acceptable standard during the primary investigation and, following further training, levels of agreement increased to a good standard. MSUS imaging was also confirmed as a key modality for assessing forefoot bursae at baseline and changes in the presence of forefoot bursae over time.

Further longitudinal study of patients with RA in a hospital setting confirmed that bursae within the forefoot was a common finding on MSUS but under-detected clinically and rare in healthy comparator control subjects. The findings that MSUS detectable bursae within the forefeet of participants with RA were related to patients' perception of their foot impact that was independent of overall disease activity were unique, although could not be completely confirmed by the methodology used. These findings were strengthened by the

results that changes in MSUS detectable bursae were significantly associated with changes in patient reported impact at twelve months. However, more work is required to differentiate foot symptoms that could be related to bursae, MTP joint synovitis and tenosynovitis before the associations between MSUS detectable bursae and patient reported foot symptoms can be accepted.

The data suggests that clinicians need to consider regular foot assessments and supports the use of specific techniques such as MSUS to determine a more precise evaluation of the effects of RA disease within the foot and the prediction of patient reported foot impact. The results of the studies that form this doctoral thesis therefore contribute to clinical practice in providing further information that helps in understanding of the disease process of RA within the foot. The key benefit for patients and service delivery lies within the possibility of podiatrists being able to image bursae within the foot in patients with RA in the clinical environment, facilitating timely treatment decisions.

Finally, further work has been recommended to be undertaken in establishing reliable protocols for MSUS assessment of the foot in patients who have RA. In addition, recommendations have been made regarding the further development of techniques that facilitate the prediction of foot impairment, activity limitation and participation restriction, especially in the identification of forefoot bursae in patients who have RA.

# APPENDICES

# Appendix 1

**Literature review**

**Electronic Search Strategy**

The following databases were electronically searched for all articles related to musculoskeletal imaging of bursitis in the RA forefoot (1984 up to present):

- PubMed
- Embase
- Cinahl
- The Cochrane Database of Systematic Reviews
- The Cochrane Database of Abstracts of Reviews of effects
- The Cochrane Central Register of Controlled Trials
- The Cochrane Database of methodology reviews
- The Cochrane Methodology Register, the Health Technology assessment database

**Hand Search Strategy**

The following Journals were hand searched:

- The Foot (1992 – present)
- The Journal of British Podiatric Medicine (1991- 1997)
- The British Journal of Podiatry (1998 – 2008)

Only English Language studies and studies that were less than twenty years old were considered. Date limitations from 1984 – June 2004 were applied in order to obtain currency from the evidence. Non-human studies were not considered as applicable for inclusion in this review.

Unpublished work, such as conference presentations, both aural and poster and consultations with 'expert' colleagues in the field, were not included in this review. Although the consequence of this is that very recent and ongoing work is not reviewed, to include all relevant conference presentations (essential to avoid bias) would have resulted in a very large database. Furthermore, the peer review process is an effective gateway for screening research and selecting only high quality work.

Citations within key papers that fit the remit of the review were identified and included.

**Search Terms**

Keywords related to musculoskeletal imaging, bursitis, rheumatoid arthritis and the foot and ankle were combined using Boolean logic to make the search more effective. Keywords used to search the current literature for the review were as follows:-

- ➢ Rheumatoid Arthritis AND bursitis
- ➢ Rheumatoid Arthritis AND bursitis AND foot
- ➢ Rheumatoid Arthritis AND bursae
- ➢ Rheumatoid Arthritis AND bursae AND foot
- ➢ Rheumatoid Arthritis AND diagnostic imaging
- ➢ Rheumatoid Arthritis AND diagnostic imaging AND foot
- ➢ Rheumatoid Arthritis AND diagnostic imaging AND foot AND ankle
- ➢ Rheumatoid Arthritis AND musculoskeletal ultrasound
- ➢ Rheumatoid Arthritis AND musculoskeletal ultrasound AND foot
- ➢ Rheumatoid Arthritis AND musculoskeletal ultrasound AND foot AND ankle
- ➢ Rheumatoid Arthritis AND musculoskeletal ultrasound AND forefoot
- ➢ Musculoskeletal ultrasound AND foot
- ➢ Musculoskeletal ultrasound AND foot AND ankle
- ➢ Musculoskeletal ultrasound AND forefoot
- ➢ Rheumatoid Arthritis AND Magnetic Resonance imaging
- ➢ Rheumatoid Arthritis AND Magnetic Resonance imaging AND foot
- ➢ Rheumatoid Arthritis AND Magnetic Resonance imaging AND foot AND ankle
- ➢ Magnetic Resonance imaging AND foot
- ➢ Magnetic Resonance imaging AND foot AND ankle
- ➢ Magnetic Resonance imaging AND forefoot
- ➢ Rheumatoid Arthritis AND X-ray AND foot
- ➢ Rheumatoid Arthritis AND erosion AND foot

## Appendix 2

**NHS**

19 June 2006

**SOUTHAMPTON & SOUTH WEST HAMPSHIRE
RESEARCH ETHICS COMMITTEES (A)**

1ST Floor, Regents Park Surgery
Park Street, Shirley
Southampton
Hampshire
SO16 4RJ

Mrs Catherine Bowen
Lecturer, Podiatry
School of Health Professions and Rehabilitation Sciences
Building 45
University of Southampton
Southampton
SO17 1BJ

Tel:    023 8036 2466
          023 8036 3462
Fax:    023 8036 4110

Email: GM.E.hio-au.SWHRECA@nhs.net

Dear Mrs Bowen

**Full title of study:**    Investigation of bursitis within the forefoot of patients
with rheumatoid arthritis as determined by non-invasive
diagnostic ultrasound.

**REC reference number:**    06/Q1702/57

Thank you for your letter of 06 June 2006, responding to the Committee's request for further
information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Chair.

### Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above
research on the basis described in the application form, protocol and supporting documentation as
revised.

**Note: The letter of invitation should be signed by Dr Arden as the patients clinician and not the
researcher.**

### Ethical review of research sites

The favourable opinion applies to the research sites listed on the attached form.

### Conditions of approval

The favourable opinion is given provided that you comply with the conditions set out in the attached
document. You are advised to study the conditions carefully.

### Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

| Document | Version | Date |
|---|---|---|
| Application | | 07 April 2006 |
| Investigator CV For Miss C Bowen | | 31 March 2006 |
| Investigator CV For Dr N Arden | | 07 April 2006 |
| Protocol | 4 | 30 March 2006 |
| Covering Letter | | 07 April 2006 |

| Summary/Synopsis | 1 | 28 March 2006 |
|---|---|---|
| Letter from Sponsor | | 06 April 2006 |
| Peer Review | | 15 March 2006 |
| Questionnaire - Leeds Foot Impact Scale | | |
| Advertisement | 1 | 30 March 2006 |
| Letter of invitation to participant | 3 | 05 June 2006 |
| GP/Consultant Information Sheets | 1 | 30 March 2006 |
| Participant Information Sheet | 6 | 05 June 2006 |
| Participant Consent Form: . | 3 | 30 March 2006 |
| Response to Request for Further Information | | 06 June 2006 |
| Reply Slip | 4 | 05 June 2006 |
| Confirmation of Data Protection | | 10 April 2006 |

## Research governance approval

The study should not commence at any NHS site until the local Principal Investigator has obtained final research governance approval from the R&D Department for the relevant NHS care organisation.

## Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees (July 2001) and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

| 06/Q1702/57 | Please quote this number on all correspondence |
|---|---|

With the Committee's best wishes for the success of this project

Yours sincerely

Mr Edward Carter
Chair

Email: GM.E.hio-au.SWHRECA@nhs.net

*Enclosures:*

*Standard approval conditions, SL-AC2*

*Site approval form*

Copy to:

Dr Martina Dorward
University of Southampton Research Governance Office
Building 27 Room 3043
University of Southampton, Highfield
Southampton
SO17 1BJ

SF1 list of approved sites

An advisory committee to Hampshire and Isle of Wight Strategic Health Authority

# Appendix 3

University
of Southampton

Email: jbk1@soton.ac.uk
Secretary: 023 8059 5905

**School of Health Professions & Rehabilitation Sciences**

Dr Paula Kersten, Head of School

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Mrs Cathy Bowen
School of Health Professions and Rehabilitation Sciences
University of Southampton

17 December 2007

Dear Cathy

Submission No: SO6/11-01

Title: Bursitis in the forefoot

Thank you for your letter dated 12 December 2007 detailing the proposed changes to your study.

I confirm that the requested amendments to your study have been approved by the School of Health Professions and Rehabilitation Sciences Ethics Committee.

Please forward details of your proposed changes along with a copy of this signed letter to Dr Martina Prude in the Research Governance Office (RGO, University of Southampton, Highfield Campus, Bldg. 37, Southampton SO17 1BJ).

Yours sincerely

Dr Emma Stack
Chair, SHPRS Ethics Committee

**Appendix 4**

# Dynamic Imaging

## Diasus Ultrasound Scanning System
## Technical Specification

| Probe types | Ultra Wideband Electronic Linear Array | |
|---|---|---|
| Probe frequencies | 5-10MHz, 40mm active length<br>8-16MHz, 26mm active length<br>10-22MHz, 26mm active length | |
| Scan modes | B-Mode | |
| Screen format | Single/Dual image | |
| Resolution | 640 x 440 pixels, 8 bits | |
| External interface | Seven slide potentiometer gain controls<br>2 rotary potentiometers controlling Transmit Power and Overall Gain<br>86 key QWERTY keyboard and 29 dedicated function keys<br>trackerball for measurements and text positioning<br>15" Digital Autoscan Colour Monitor, high resolution, flicker free, low emission MPR-II compliance, screen resolution 800x600<br>Standard PC communications ports | |
| B-Mode features | Depth of view | 100mm max |
| | Frame rate | 30fps max |
| | Magnification | 6 step zoom |
| | Inversion | black-white/white-black, left-right/right-left |
| Signal processing | 4.0 - 26.0MHz bandwidth, swept frequency, 4 post processing curves (gamma correction), 2D filtering, frame averaging, selectable multiple transmit focus positions | |
| Display information | Patient ID, Hospital ID, Clinicion ID, measurement mode, post processing status, current scale, frame averaging status, transpose status, frozen status, time & date, transmit focus indicators, body mark, text annotation | |
| Software package | Distance (4) traced or ellipse area (2) curved line length (2) | |
| Power | Input | 115V AC/60Hz, 230V AC/50Hz, rated power 300VA max |
| | Output | 230V AC, 50/60Hz 230VA max for additional accessories |
| Operating conditions | Temperature | +10°C to +40°C |
| | Relative | 30% to 80% |

## Appendix 4

| | | |
|---|---|---|
| | humidity | |
| Storage/transport | Temperature | -10°C to +60°C |
| | Relative humidity | 30% to 90% (non condensing) |
| Physical | Weight | 65Kg approx |
| | Dimensions | 537 x 1285 x 765mm (WxHxD) |
| Standards | Electrical safety | EN60601-1-1, UL2601-1, Class 1, Type BF |
| | EMC | EN60601-1-2 |
| | Acoustic power | EN61157, on screen indication in accordance with Acoustic Output Display Standard |
| | Quality | Dynamic Imaging is committed to a Total Quality Culture and has been assessed and registered as meeting the requirements of BS EN46001, the application of BS EN ISo 9001 to the manufacture of medical devices, under Annex II of EC Council Directive 93/42/EEC, the Medical Device Directive |
| | CE$_{0120}$ | Diasus is identified with this CE Mark in compliance with EC Directive 93/42/EEC (Medical Devices Directive) Dynamic Imaging is registered as complying with EN46001, the internationally recognised quality system standard for medical devices. |
| Accessories | Video printers, needle guide attachments | |
| Consumables | Gel, video printer paper, needle guides | |

Dynamic Imaging Ltd
9 Cochrane Square, Brucefield Industrial Park, Livingston, EH54 9DR, UK
Telephone : +44 (0)1506 415282
Fax : +44 (0)1506 415282
email : sales@dynamicimaging.co.uk
www.dynamicimaging.co.uk

## Appendix 5

**Ultrasound report / data sheet    RIGHT FOOT**        Wk No:……

Pt ID No:………………………. …        Date …………………………

Footwear ……………………………

*Please tick the appropriate boxes:-*

| Anatomical location | Synovitis hyperaemia detectable with PD | | Synovitis thickness grading | | |
|---|---|---|---|---|---|
| | Yes | no | Mild | Moderate | Severe |
| MPJ 2 | | | | | |
| MPJ 5 | | | | | |

| | Bursitis | | | Bursitis measurements (mm) | | |
|---|---|---|---|---|---|---|
| | anatomical | adventitious | unidentifiable | longitudinal | transverse | Distance of bulging under the met head |
| Sub met 1 | | | | | | |
| Inter met 1 / 2 | | | | | | |
| Sub met 2 | | | | | | |
| Inter met 2 / 3 | | | | | | |
| Sub met 3 | | | | | | |
| Inter met 3 / 4 | | | | | | |
| Sub met 4 | | | | | | |
| Inter met 4 / 5 | | | | | | |
| Sub met 5 | | | | | | |
| *Comments:* | | | | | | |

**Key:** PD = power Dopplar; mmt = measurement; MPJ = metatarsophalangeal joint; sub met = plantar metatarsal area; inter met = intermetatarsal capita space.

Pto…

## Appendix 5

**Ultrasound report / data sheet**     **LEFT FOOT**          Wk No:……

Pt ID No:…………………………. …          Date …………………………

*Please tick the appropriate boxes:-*

| Anatomical location | Synovitis hyperaemia detectable with PD | | Synovitis thickness grading | | |
|---|---|---|---|---|---|
| | Yes | no | Mild | Moderate | Severe |
| MPJ 2 | | | | | |
| MPJ 5 | | | | | |

| | Bursitis | | | Bursitis measurements (mm) | | |
|---|---|---|---|---|---|---|
| | anato mical | advent itious | uniden tifiable | longitudinal | transverse | Distance of bulging under the met head |
| Sub met 1 | | | | | | |
| Inter met 1 / 2 | | | | | | |
| Sub met 2 | | | | | | |
| Inter met 2 / 3 | | | | | | |
| Sub met 3 | | | | | | |
| Inter met 3 / 4 | | | | | | |
| Sub met 4 | | | | | | |
| Inter met 4 / 5 | | | | | | |
| Sub met 5 | | | | | | |
| *Comments:* | | | | | | |

**Key:** PD = power Dopplar; mmt = measurement; MPJ = metatarsophalangeal joint; sub met = plantar metatarsal area; inter met = intermetatarsal capita space.

**Pto..**

**Version 3**                                                          238

## Appendix 6

**Self administered questionnaire on disability associated with foot pain.**

Below are some statements about problems people have because of **pain in their feet**.

For each statement indicate if this has applied to you during the **past month**. If so, was this only on some days or on most or every day in the past month?

### PLEASE TICK A BOX FOR EACH STATEMENT

**During the past month this has applied to me:**

| | None of the time | On some days | On most / every day |
|---|---|---|---|

**Because of pain in my feet:**

| | None of the time | On some days | On most / every day |
|---|---|---|---|
| I avoid walking outside at all | ☐ | ☐ | ☐ |
| I avoid walking long distances | ☐ | ☐ | ☐ |
| I don't walk in a normal way | ☐ | ☐ | ☐ |
| I walk slowly | ☐ | ☐ | ☐ |
| I have to stop and rest my feet | ☐ | ☐ | ☐ |
| I avoid hard or rough surfaces where possible | ☐ | ☐ | ☐ |

|  | **None of the time** | **On some days** | **On most / every day** |
|---|---|---|---|
| **Because of pain in my feet:** | | | |
| I avoid standing for a long time | ☐ | ☐ | ☐ |
| I catch the bus or use the car more often | ☐ | ☐ | ☐ |
| I need help with housework/shopping | ☐ | ☐ | ☐ |
| I still do everything but with more pain or discomfort | ☐ | ☐ | ☐ |
| I get irritable when my feet hurt | ☐ | ☐ | ☐ |
| I feel self conscious about my feet | ☐ | ☐ | ☐ |
| I get self conscious about the shoes I have to wear | ☐ | ☐ | ☐ |
| I have constant pain in my feet | ☐ | ☐ | ☐ |
| My feet are worse in the morning | ☐ | ☐ | ☐ |
| My feet are more painful in the evening | ☐ | ☐ | ☐ |
| I get shooting pains in my feet | ☐ | ☐ | ☐ |

## Appendix 6

| | None of the time | On some days | On most / every day | not applicable |
|---|---|---|---|---|

**Because of pain in my feet:**

I am unable to carry out my previous work

☐ ☐ ☐ ☐

I no longer do all my previous activities (sport, dancing, hill-walking etc)

☐ ☐ ☐ ☐

**TICK HERE WHEN YOU HAVE READ ALL THE STATEMENTS ON THIS PAGE**  ☐

## LEEDS FOOT IMPACT SCALE

On the following pages you will find some statements which have been made by people who have arthritis in their feet. We would like you to tick **"true"** if the statement applies to you, and tick **"not true"** if it does not.

**Please choose the response that applies best to you at the moment.**

|   |   | TRUE | NOT TRUE |
|---|---|---|---|
| 1. | My feet get painful when I'm standing………………. | ☐ | ☐ |
| 2. | My feet hurt me…………………………………………. | ☐ | ☐ |
| 3. | I find the pain in my feet frustrating…………………. | ☐ | ☐ |
| 4. | The pain is worse when I've been on my feet all day………………………………………………………. | ☐ | ☐ |
| 5. | At the end of the day there is pain and tension in my feet………………………………………………. | ☐ | ☐ |
| 6. | I never get rid of the stiffness in the background…… | ☐ | ☐ |

**Please remember to read each statement thinking about your feet.**
**Please choose the response that applies best to you at the moment.**

|   |   | TRUE | NOT TRUE |
|---|---|---|---|
| 7. | My feet throb at night…………………………………... | ☐ | ☐ |
| 8. | My feet wake me up at night…………………………… | ☐ | ☐ |
| 9. | I feel as though I've got pebbles in my shoes……….. | ☐ | ☐ |
| 10. | I get pain every time I put my foot down…………… | ☐ | ☐ |
| 11. | I get a burning sensation all the time………………… | ☐ | ☐ |
| 12. | I cry with pain…………………………………………… | ☐ | ☐ |

**Please check you have ticked a box for every statement on this page**

**Please remember to read each statement thinking about your feet.**
**Please choose the response that applies best to you <u>at the moment</u>.**

|  |  | **TRUE** | **NOT TRUE** |
|---|---|---|---|
| 13. | I can only walk in certain shoes……………………. | ☐ | ☐ |
| 14. | I need shoes with plenty of room in them…………… | ☐ | ☐ |
| 15. | I am limited in my choice of shoes…………………. | ☐ | ☐ |
| 16. | I need a wider fit of shoes…………………………… | ☐ | ☐ |
| 17. | I feel I need a lot of padding under my feet………… | ☐ | ☐ |
| 18. | My footwear always feels heavy…………………….. | ☐ | ☐ |
| 19. | I have to keep swapping and changing my shoes…… | ☐ | ☐ |
| 20. | I can't get any shoes on……………………………… | ☐ | ☐ |
| 21. | I walk bare foot all the time………………………… | ☐ | ☐ |

**Please remember to read each statement thinking about your feet.**
**Please choose the response that applies best to you <u>at the moment</u>.**

|  |  | **TRUE** | **NOT TRUE** |
|---|---|---|---|
| 22. | I feel unsafe on my feet……………………………… | ☐ | ☐ |
| 23. | I have to walk for a bit and sit for a bit…………… | ☐ | ☐ |
| 24. | I can't run…………………………………………… | ☐ | ☐ |
| 25. | I find I shuffle around……………………………….. | ☐ | ☐ |
| 26. | I am limping about all the time…………………….. | ☐ | ☐ |
| 27. | I have to use a walking stick or walking frame…….. | ☐ | ☐ |

> **Please check you have ticked a box for every statement on this page**

**Please remember to read each statement thinking about your feet.**
**Please choose the response that applies best to you <u>at the moment</u>.**

|  |  | **TRUE** | **NOT TRUE** |
|---|---|---|---|
| 28. | It takes me all my time to climb the stairs…………… | ☐ | ☐ |
| 29. | I need help to climb stairs…………………………… | ☐ | ☐ |
| 30. | I can't walk on cobbles……………………………… | ☐ | ☐ |
| 31. | I am unsteady on uneven surfaces…………………… | ☐ | ☐ |
| 32. | I can't walk as far as I would like to………………. | ☐ | ☐ |
| 33. | It takes me longer to do things……………………… | ☐ | ☐ |
| 34. | My whole life has been adapted……………………… | ☐ | ☐ |

**Please remember to read each statement thinking about your feet.**
**Please choose the response that applies best to you <u>at the moment</u>.**

|  |  | **TRUE** | **NOT TRUE** |
|---|---|---|---|
| 35. | My feet restrict my movement……………………… | ☐ | ☐ |
| 36. | I get annoyed because I'm slower…………………… | ☐ | ☐ |
| 37. | I get frustrated because I can't do things so quickly… | ☐ | ☐ |
| 38. | My whole life has slowed down……………………. | ☐ | ☐ |
| 39. | It's reduced the range of things I can do…………... | ☐ | ☐ |
| 40. | I have to plan everything out……………………… | ☐ | ☐ |
| 41. | I can't keep up like I used to……………………… | ☐ | ☐ |
| 42. | Socially its affected me a lot……………………. | ☐ | ☐ |
| 43. | I am ashamed of how I walk……………………… | ☐ | ☐ |
| 44. | I'm nervous of missing a curb edge………………. | ☐ | ☐ |

| **Please check you have ticked a box for every statement on this page** |
|---|

**Please remember to read each statement thinking about your feet.**
**Please choose the response that applies best to you <u>at the moment</u>.**

|  |  | TRUE | NOT TRUE |
|---|---|---|---|
| 45. | I feel isolated because I can't go very far…………… | ☐ | ☐ |
| 46. | I feel I slow other people down……………………… | ☐ | ☐ |
| 47. | I can't do some of the things I take for granted……… | ☐ | ☐ |
| 48. | I can't go for walks with the people close to me……. | ☐ | ☐ |
| 49. | I'm finding it difficult to be independent…………… | ☐ | ☐ |
| 50. | I dread finishing up in a wheelchair………………. | ☐ | ☐ |
| 51. | I get frustrated because I can't do things for myself.. | ☐ | ☐ |

**Please check you have ticked a box for every statement on this page**

Score =

**Appendix 8**

# Demographic data collection

1.

| Patient Addressograph | Patient Code |
|---|---|
| | Participant number: |

2.  Date of visit: ........./.............../..........     Age ………

3.  Year of diagnosis........./.............../..........     RA duration ………

4.  Does Patient have ACR diagnosis of Rheumatoid arthritis?
    Yes ☐      No ☐

    4a. Are they Seropos. ☐     Seroneg. ☐ ?

5.  Weight:..................kgs      Height..................cms

6.  Diabetic    Yes ☐    No ☐

7.  Limb dominance:   Left ☐    Right ☐

8.  Have you had any lower limb/foot surgery in the past year *(either limb)*?
    Yes ☐ *(please specify limb/date of surgery)*     No ☐

    ...................................................................................................................................

9.  Have you had any foot/ankle steroid injections within the four weeks *(either limb)*?
    Yes ☐ *(please specify limb/date of surgery)*   No ☐

    ...............................................................................................................................

10. Have you had any steroid injections (intramuscular) in the past eight weeks?

    Yes ☐      No ☐

11. Are you currently on Anti TNF therapy?
    Yes ☐      No ☐

    If yes, which one? ………………………….

12. Are you currently on Methotrexate (MTX)?
    Yes ☐      No ☐

## Appendix 8

13.    Which other arthritis drugs are you currently using (do not include anti-TNF therapy)?
        Gold injections/tablets
        Sulphasalazine
        Azathioprine
        Penacillamine
        Cyclosporin
        Other (please specify)

14.    Which other arthritis drugs have you used in the past?
        Gold injections/tablets
        Sulphasalazine
        Azathioprine
        Penacillamine
        Cyclosporin
        Other (please specify)

15.    Present Medication *(please list)*

        ..............................................................................................................

        ..............................................................................................................

        ..............................................................................................................

16. Is there any documentation of foot symptoms in the patients medical records?
        Yes   ☐       No   ☐
        If yes specify details:

        ..............................................................................................................

        ..............................................................................................................

17.    Has the patient ever seen a chiropodist/podiatrist in the past?
        Yes   ☐       No   ☐

        Are they using a chiropodist/podiatrist now?
        Yes   ☐       No   ☐

Investigator Signature:...............................................

Print name:.......................................

d d m m y y y y

Date: ………………….

# Modified Swollen and Tender Joint Count

Patient ID  _____

Which joints are **tender**? (Please tick)

Which joints are **swollen?** (please tick)

MCPs →

MTPs →

Bursitis

R        L        R        L

| 5 | 4 | 3 | 2 | 1 | 1 | 2 | 3 | 4 | 5 | 5 | 4 | 3 | 2 | 1 | 1 | 2 | 3 | 4 | 5 |

Global VAS: Overall wellbeing: please indicate on the scale below

0                                                              100

|--------------------------------------------------------------------|

Best Imaginable                    Worst Imaginable
Health State                       Health State

_____

ESR………………Date:………..
CRP………………Date:………..
DAS………………Date:………..

**Appendix 10**

## Demographic data collection

1.

| Patient Addressograph | | Patient Code |
|---|---|---|
| | | Age ……… |

2.  Date of 2$^{nd}$ visit: ........./............./..........

3.  Weight:..................kgs          Height..................cms

4.  Diabetic          Yes ☐          No ☐

5.  Have you had any lower limb/foot surgery in the past year *(either limb)*?
    Yes ☐ *(please specify limb/date of surgery)*          No ☐

    .............................................................................................................................

6.  Have you had any foot/ankle steroid injections within the four weeks *(either limb)*?
    Yes ☐ *(please specify limb/date of surgery)*      No ☐

    ..........................................................................................................................

7.  Have you had any steroid injections (intramuscular) in the past eight weeks?

    Yes ☐          No ☐

8.  Are you currently on Anti TNF therapy?
    Yes ☐          No ☐

    If yes, which one? …………………………….

9.  Are you currently on Methotrexate (MTX)?
    Yes ☐          No ☐

## Appendix 10

10.   Which other arthritis drugs are you currently using (do not include anti-TNF therapy)?
      Gold injections/tablets
      Sulphasalazine
      Azathioprine
      Penacillamine
      Cyclosporin
      Other (please specify)


11.   Present Medication *(please list)*

      ....................................................................................................................

      ....................................................................................................................

      ....................................................................................................................


12.   Is the patient using a chiropodist/podiatrist now?
      Yes     ☐              No     ☐


Investigator Signature:...............................................

Print name:.......................................

| | Year 03/04 | Year 04/05 | Year 06/07 | Year 08/09 |
|---|---|---|---|---|
| **Preliminary study** | | | | |
| Attendance at msk ultrasound list | ←→ (orange) | ←→ (blue) | | |
| Ethics submission (anti tnf trial) | | ←→ (blue) | | |
| Participant recruitment (stage 1) | | ←→ (blue) | | |
| Ultrasound reliability/sensitivity | | ←——————————→ (red) | | |
| Analysis of results | | | ←→ (blue) | |
| Discussion & Write Up | | | ←→ (blue) ⌂ | |
| **Baseline RA** | | | | |
| Ethics submission (stage 2) | | | ←→ (blue) | |
| Participant recruitment (stage 2 ) | | | ←→ (red) | |
| Data collection (stage 2) | | | ←——————→ (red) | |
| Analysis of results | | | ←→ (blue) | |
| Discussion & Write Up | | | ←→ (blue) | ⌂ |
| **Baseline Healthy** | | | | |
| Ethics submission (stage 3) | | | ←→ (blue) | |
| Participant recruitment (stage 3 ) | | | ←→ (red) | |
| Data collection (stage 3) | | | ←→ (red) | |
| Analysis of results | | | ←→ (blue) | |
| Discussion & Write Up | | | ←→ (blue) | |
| **Twelve month RA** | | | | |
| Participant recruitment (stage 4 ) | | | ←→ (red) | |
| Data collection (stage 4) | | | ←——————————→ (red) | |
| Analysis of results | | | ←——————————→ (blue) | |
| Discussion & Write Up | | | | ←——→ (blue) ⌂ |

Legend

←——→ ……… theoretical writing

←——→ ………… activities / data collection etc.

⌂ ………… milestones eg. Abstract/paper submissions for conference presentations / articles etc.

RHEUMATOLOGY RESEARCH UNIT
Mailpoint 64, Level F, West Wing
Tremona Road,
SOUTHAMPTON, S016 6YD.

Tel/Fax: 023 8079 6711/8532
E-mail: rheum_research@hotmail.com

Southampton **NHS**

University Hospitals NHS Trust

Submission No: 046/04/t

## Can anti-TNF therapy for rheumatoid arthritis improve insulin resistance and foot pain?

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

### What is the purpose of the study?

Rheumatoid arthritis (RA) causes pain and damage to many joints. The joints most likely to be involved are in the feet and hands. Most studies have concentrated on the involvement of joints in the hands. The inflammation associated with RA can also cause other problems. Recently it has been noticed that inflammation affects the way blood sugar (glucose) levels in the blood are controlled by the hormone insulin. This lack of a normal response to insulin is called "insulin resistance". This does not mean that patients with RA have diabetes but may increase the risk of cardiovascular disease such as heart attacks.

In the last few years a new group of treatments for RA called TNF-blockers have been introduced. This study will find out if these new medicines may improve insulin resistance and reduce foot inflammation and damage in patients with RA.

### Why have I been chosen?

You have been chosen for one of two reasons.

1) You have RA and are about to start treatment with a TNF-blocking treatment.

2) Or, you have osteoarthritis (OA) and are under routine care in the Rheumatology department. Patients with OA are needed to form a control group. OA is not an inflammatory disease and is very different from RA. Patients with OA make a good control group as inflammation will not have altered their insulin resistance.

## Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

## What will happen to me if I take part?

If you agree to take part in the study what happens will vary depending on whether you have rheumatoid arthritis or osteoarthritis. If you have rheumatoid arthritis you will be involved in the study for 3 months. There will be two extra appointments in addition to your routine appointments. These appointments will be about one hour longer than normal. Before you receive the first injection of the TNF-blocking treatment you will be given three questionnaires to fill in about foot pain. You will also have an ultrasound scan, bone density scan and MRI scan of your feet. The ultrasound scan will take about 15 minutes. A probe will be placed on your foot. The bone density measurement is like having an X-ray taken. It takes 15 minutes. The MRI scan will take 20 minutes. You will be asked to lay on a narrow bed that moves into the machine. There will be a gentle banging sound. None of the above procedures will hurt. You will also be asked to give an extra 5 mls (about a tablespoonful) of blood so we can measure glucose and insulin. Four weeks after the TNF-blocking treatment you will have a further 5 mls of blood taken to measure glucose and insulin. Then at 12 weeks after the TNF-blocking treatment you will be given three questionnaires about foot pain to fill in and have a further ultrasound scan, bone density scan and MRI scan of your feet. You will also be asked to give an extra 5 mls of blood so we can measure glucose and insulin.

If you have osteoarthritis you will only be asked to give an extra 5mls of blood on one occasion.

## What do I have to do?

Taking part in the study does not alter any of your standard care. You do not need to alter your lifestyle or diet in any way.

## What are the possible disadvantages and risks of taking part?

It is possible that measuring blood glucose may uncover unexpected diabetes. This is unlikely as all patients attending the Rheumatology clinic have urine tests for diabetes performed. However, if this was discovered we would arrange further treatment by your general practitioner or other doctor as necessary. Future insurance status e.g. for life insurance or private medical insurance, could be affected by taking part if diabetes is detected.

## What are the possible benefits of taking part?

It is unlikely that taking part in this study will directly benefit your medical treatment. However, the information we get from this study may help us to treat future patients with rheumatoid arthritis better.

## What happens when the research study stops?

After the study you will continue with your normal treatment in the rheumatology department.

## What if something goes wrong?

It is extremely unlikely that taking part in this research project will harm you. However, if this occurred there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

## Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

## What will happen to the results of the research study?

We hope the results are useful and we intend to publish them in a rheumatological journal. You will not be identified in any report/publication.

## Who is organising and funding the research?

Rheumatologists at Southampton General Hospital and Southampton University are carrying out the study. The study is funded by the charity "Southampton Rheumatology Trust".

## Who has reviewed the study?

The study has been peer reviewed by the Southampton University Hospitals NHS Trust Research and Development Department and Southampton University. The Southampton and South West Hampshire Local Research Ethics Committee have also reviewed the study.

## Contact for Further Information

Further information can be obtained from Dr Chris Edwards in the Department of Rheumatology on: 023 8079 8723/8532/6711

Thank you for reading this.

**If you agree to take part you will be given a copy of the information sheet and a signed consent form to keep.**

Version 3 – 21/06/04

**Appendix 13**

<div align="right">

**RHEUMATOLOGY RESEARCH UNIT**
**Mailpoint 63**
**Level G**
**West Wing**
**Southampton General Hospital**

</div>

**Tel: 023 8079 6711/8532**
**Fax: 023 8079 6711**
**Email: pamela.freeman@suht.swest.nhs.uk**


Study Number: RHM MED 0691
Ethics Submission No: 06/Q1702/57


**PATIENT INFORMATION SHEET:**

**Part 1**

**1. Study title**
The 'FeeTURA' study

**Full title:** Investigation of swelling in the feet due to rheumatoid arthritis using
ultrasound scanning.


**2. Invitation to participate in the study**

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- *Part 1 tells you the purpose of this study and what will happen to you if you take part.*
- *Part 2 gives you more detailed information about the conduct of the study.*

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

**Appendix 13**

### 3. What is the purpose of the study?

The main purpose of this study is to investigate swelling (inflammation) in the forefoot of patients with Rheumatoid Arthritis using musculoskeletal ultrasound.

Rheumatoid arthritis (RA) causes pain and damage to many joints. The joints most likely to be involved are in the feet and hands. Most studies have concentrated on problems in the hands, but the disease can also cause other problems.

Imaging using ultrasound is increasing in popularity within rheumatology as it allows observation of anatomical structures at the time of the clinical visit. The technique used for ultrasound imaging of these structures is the same as that used when unborn babies are scanned within the womb. There are other advantages of ultrasound over X-Rays which are usually used to assess the status of your joints and these are that it is painless and harmless (no ionising radiation).

Swelling in the forefoot due to RA may be caused by bursitis. Bursitis is the inflammation of a fluid filled sac that usually occurs between the long bones and the toes of the feet. Being able to see lesions using ultrasound such as bursitis occurring in the feet and understand how they change over time when you attend your rheumatology outpatients or podiatry appointments would help us to decide on the best course of treatment for you and for future patients. For example, this may involve deciding on what medicines and/or doses to use for you or providing you with or adjusting your existing orthotic device / joint splint, thus preventing further pain, disability or mobility loss for yourself or future patients.

### 4. Why have I been chosen?
You have been chosen because you have rheumatoid arthritis and are due to attend the Department of Rheumatology, Southampton General Hospital (Southampton University Hospitals NHS Trust) as part of your usual care.

### 5. Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

## 6. What will happen to me if I take part?

If you agree to participate in this study your regular appointment will be extended by forty five minutes. You will be required to participate in the study on two separate occasions, once now and again in twelve months time. For both occasions when you participate in the study it will be as part of your normal clinical visit so that you do not have to make any extra trips into the hospital. During your appointment we will scan the sole of your foot using a diagnostic ultrasound scanner in the same way that unborn babies are scanned within the womb.

During the scan you will be asked to sit on a couch with your feet facing the investigator. The investigator will scan the soles of both your feet. Following each scan recording the investigator will note all areas of inflammation within that part of your feet.

A clinical examination of your feet will involve the examination of the soles of both your feet by the investigator and any observations will be recorded on a pictorial diagram. The position of any lesions will be recorded and photographs of the soles of your feet will be taken. Foot pressure measurements will be recorded by a computerised system, FScan® Pressure sensitive insoles will be placed within your footwear and these are attached via a long cable to a computer. You will be asked to walk ten steps forward away from the computer so that any cable trip hazard is avoided. The computer automatically records the amount of pressure occurring on the soles of your feet during each footstep.

You will also be asked to complete a questionnaire that asks you about foot pain and walking ability. The questionnaire will take you approximately five minutes to complete.

The rheumatology nurse will assess your RA in the usual way and the information will be used within this study. A small number of people (10%) will be asked to undergo traditional ultrasound foot scan performed by a radiologist using the normal ultrasound equipment (Philips HDI 5000 System broadband linear 5 - 12 MHz probe) in the Department of Ultrasound and Radiology, Southampton General Hospital (Southampton University Hospitals NHS Trust). The same scanning protocol will be used as for the Diasus scanner. These scans allow us to compare the two different ultrasound machines.

About twelve months from your first appointment we will repeat the study and examine your feet in exactly the same way.

**7. What do I have to do?**
Taking part in the study does not alter any of your standards of care. You do not need to alter your lifestyle or diet in any way.

**8. What are the possible disadvantages and risks of taking part?**
In laboratory trials some risk of ultrasound exposure damage to tissues has been documented. The risk, however, is attributed to levels of exposure that are never used within clinical practice. An excellent safety record exists in that, after many years of clinical use, there is no known instance of human injury as a result of exposure to diagnostic ultrasound. During clinical assessments with new ultrasound equipment such as that being used in this study, the total ultrasound exposure is kept as low as reasonably achievable and this is known as the ALARA principle. Implementing ALARA within the study has required the chief investigator, Catherine Bowen, to attend a recognised training course in the use of ultrasound imaging. Mrs Bowen has further support for scanning technique supervision from the Dr Keith Dewbury, Consultant Radiologist, Department of Ultrasound at Southampton General Hospital (Southampton University Hospitals NHS Trust).

It is possible that the Foot pressure measurements recorded by the FScan® system may pose some risk of trip or fall as the pressure sensitive insoles are placed within the your footwear and these are attached via a long cable to a personal computer. There is also a minor risk of you walking too far and toppling over the FScan® system. To avoid these hazards, the exact distance of the walkway will be explained to you and you will be supervised by the investigator at all times during this activity.

**9. What are the benefits of taking part?**
The information that we get from this study may help us to treat patients with rheumatoid arthritis better in the future. There may not be any direct benefits to you associated with taking part in this study; however, taking part in this study may identify bursitis, swelling or pain within your feet which would lead us to initiate appropriate treatment for you.

**10. What if there is a problem?**
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

The contact number for any complaints is: Dr Martina Dorward, Research Support Office, University of Southampton, Building 27, Highfield Campus, Southampton, SO17 1BJ. Telephone: 023 8059 8848

**11. Will my taking part in this study be kept confidential?**
Yes. All the information about your participation in this study will be kept confidential. The details are included in Part 2.

**12. Contact for further information**
Further information can be obtained from

Mrs Catherine Bowen in the Rheumatology Research Unit, Southampton General Hospital. Tel. 023 8079 8532 / 6711
OR the School of Health Professions and Rehabilitation Sciences. Tel. 023 8059 7637.

*And / or*
Dr Nigel Arden in the Department of Rheumatology, Southampton General Hospital on: 023 8079 8723 / 8523 / 6711.

***Thank you for reading this.***

**This completes Part 1 of the Information Sheet.**

***If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.***

**Appendix 13**


**PATIENT INFORMATION SHEET:**     **Part 2**

### 18.  What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time but if you give your permission information and any ultrasound images collected may still be used.

### 19. What if there is a problem or something goes wrong?

It is extremely unlikely that taking part in this research project will harm you. If this did occur, however, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action for compensation against (The University of Southampton or Southampton University Hospitals NHS Trust) but you may have to pay your legal costs.  The normal National Health Service complaints mechanisms will still be available to you.

Regardless of this, if you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact number; 023 8059 7637).  If you remain unhappy and wish to complain formally, you can do this through the NHS Complaints Procedure.  Details can be obtained from the Patient Advice and Liaison Service (PALS) information point within the hospital or you can telephone them on 023 8079 8498 or email PALS@suht.swest.nhs.uk

Alternatively, the consumers for ethics in research (CERES) http://www.ceres.org.uk/ is a recommended third independent participant support body.

### 20. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the hospital/surgery will be coded so that at no time will any of your personal details be revealed. The procedures for handling, processing, storage and destruction of any data collected during the study are compliant with the Data Protection Act 1998 and in line with the Southampton University Hospitals NHS Trust policy.

### 21. What will happen to the results of the research study?

We hope the results are useful and we intend to publish them in a rheumatological journal and to present them at scientific conferences. The results will also be utilised by the chief investigator for part completion of a PhD thesis to be submitted to the University of Southampton. You will not be identified in any reports or publications.

**22. Who is organizing and funding the research?**
The study is cosponsored by the University of Southampton and Southampton University Hospitals NHS Trust and is organised by investigators from the School of Health Professions and Rehabilitation Sciences, University of Southampton and the Rheumatology and Radiology departments at Southampton General Hospital (Southampton University Hospitals NHS Trust) .

**23. Who has reviewed the study?**
The study has been peer reviewed by the Research division of School of Health Professions and Rehabilitation Sciences, University of Southampton and the Southampton University Hospitals NHS Trust research and development department. The Southampton and South West Hampshire Local Research Ethics Committee have also reviewed the study.

If you agree to take part you will be given a copy of the information sheet and a signed consent form to keep. If you have read this information sheet and are happy to participate in the proposed study please sign the attached reply slip and return it in the stamped addressed envelope.

*Thank you for considering taking part and taking time to read this sheet.*

# The 'FeeTURA' study

We are looking for **volunteers** to take part in a **study** which is investigating foot problems in patients who have Rheumatoid Arthritis.

We know that Rheumatoid Arthritis commonly affects the feet causing swelling and pain within the foot joints reducing a person's ability to walk. Not much is known, however, about the appearance and progression of these swellings within the feet.

This study has therefore been designed to investigate the presence of **swelling within the feet** using diagnostic **ultrasound** imaging and to see if there are any links with the disease process of **rheumatoid arthritis** and/or symptoms of foot pain and function.

If you are interested in taking part in the study please ask at the rheumatology outpatient reception desk.

*Alternatively, please contact either:*
Dr Nigel Arden, Reader & Consultant Rheumatologist, telephone 023 8079 8532/6711.
*Or*
Mrs Catherine Bowen, Lecturer Podiatry, telephone 02380 597637.

**Appendix 15**

**RHEUMATOLOGY RESEARCH UNIT**
**Mailpoint 63**
**Level G**
**West Wing**
**Southampton General Hospital**
**Tel: 023 8079 6711/8532**
**Fax: 023 8079 6711**
**Email: pamela.freeman@suht.swest.nhs.uk**

**Study Number: RHM MED 0691**
**Ethics Submission No: 06/Q1702/57**
**Patient identification Number for this study:**

# CONSENT FORM

**Title of Project:** Investigation of swelling in the feet due to rheumatoid arthritis using ultrasound scanning / The 'FeeTURA' Study.

**Name of Researcher:** Mrs Catherine Bowen

**Please initial box**

1. I confirm that I have read and understand the information sheet dated 05.06.06 (version6) for the above study and have had the opportunity to ask questions and have had these answered satisfactorily.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.

3. I understand that sections of my medical notes may be looked at by responsible individuals from the University of Southampton and Southampton University Hospitals NHS Trust or from regulatory authorities where it is relevant to my taking part in research. I give permission for these individuals to have access to my records.

4. I agree to take part in the above study

| _____ | _____ | _____ |
|---|---|---|
| Name of Patient | Date | Signature |

| _____ | _____ | _____ |
|---|---|---|
| Name of Person taking consent *(if different from researcher)* | Date | Signature |

| _____ | _____ | _____ |
|---|---|---|
| Researcher | Date | Signature |

*1 for patient; 1 for researcher; 1 (original) to be kept with hospital notes*

Version 3 / 30.03.06

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# The 'FeeTUH' study

We are looking for **volunteers** to take part in a **study** which is investigating bursitis in the forefeet of healthy persons.

Bursitis is inflammation (swelling) of a bursa and can occur in the forefoot causing pain and /or discomfort during walking. Numerous disorders may give rise to discomfort in the metatarsal region of the forefoot, however not much is known, about the appearance of bursitis within the feet.

This study has therefore been designed to investigate the presence of **bursitis within the forefeet** of healthy persons using diagnostic **ultrasound** imaging and to see if there are any links with symptoms of forefoot pressures, foot swelling and foot pain.

If you are interested in taking part in the study please contact:

Mrs Catherine Bowen, Lecturer Podiatry,

Telephone 02380 597637.

# Appendix 17

Study Number:
Patient identification Number for this study:

## PARTICIPANT INFORMATION SHEET:

### Part 1

### 1. Study title
The 'FeeTUH' study

**Full title:** Investigation of bursitis within the forefoot of healthy subjects as determined by non-invasive diagnostic ultrasound.

### 2. Invitation to participate in the study

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish.

- *Part 1 tells you the purpose of this study and what will happen to you if you take part.*
- *Part 2 gives you more detailed information about the conduct of the study.*

Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

Thank you for reading this.

### 3. What is the purpose of the study?

Bursitis is inflammation (swelling) of a bursa and can occur in the forefoot causing pain and /or discomfort during walking. We know that bursae are pouches of fluid that facilitate movement between adjacent structures by reducing friction and that four anatomical connective tissue bursae have been identified between the metatarsal heads in the forefoot. Numerous disorders may give rise to discomfort in the metatarsal region of the forefoot, however not much is known, about the appearance of bursitis within the forefeet.

Our previous study results have demonstrated that diagnostic ultrasound is capable of detecting changes within the forefoot tissues and joints due to Rheumatoid

# **Appendix 17**

Arthritis and that these are clinically underreported.  We do not yet know whether bursitis of the forefoot is also present in healthy persons.

Imaging using ultrasound is increasing in popularity within clinical practice as it allows observation of anatomical structures at the time of the clinical visit. The technique used for ultrasound imaging of these structures is the same as that used when unborn babies are scanned within the womb. There are other advantages of ultrasound over X-Rays which are usually used to assess the status of bones and joints and these are that it is painless and harmless.

The main purpose of this study is therefore to investigate the presence of bursitis within the forefeet of healthy people using diagnostic ultrasound imaging and to see if there are any associated links with symptoms of forefoot pressure, foot pain and foot swelling.

## **4. Why have I been chosen?**
You have been chosen because you are healthy and are a student currently enrolled on the BSc Hons Podiatry programme and about to take part in a workshop on ultrasound imaging.

## **5. Do I have to take part?**
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of teaching/ teaching support you receive.

## **6. What will happen to me if I take part?**
If you agree to participate in this study it will be as part of your normal Podiatry teaching schedule so that you do not have to make any extra trips into the University. During the workshop we will scan the sole of your foot using a diagnostic ultrasound scanner in the same way that unborn babies are scanned within the womb.

During the scan you will be asked to sit on a couch with your feet facing the investigator. The investigator will scan the soles of both your forefeet. Following each scan recording the investigator will note all areas of swelling within that part of your feet.

A clinical examination of your feet will involve the examination of the soles of both your feet by the investigator and any observations will be recorded on a pictorial diagram. The position of any lesions will be recorded and photographs of the soles of your feet will be taken. Foot pressure measurements will be recorded by a

## Appendix 17

computerised system, FScan® Pressure sensitive insoles will be placed within your footwear and these are attached via a long cable to a computer. You will be asked to walk ten steps forward away from the computer so that any cable trip hazard is avoided. The computer automatically records the amount of pressure occurring on the soles of your feet during each footstep.

You will also be asked to complete a questionnaire that asks you about foot pain and walking ability. The questionnaire will take you approximately five minutes to complete.

### 7. What do I have to do?
Taking part in the study does not alter any of your regular studies. In order to take foot pressures using the FScan® system we will require you to ensure that you attend wearing / bring with you suitable closed in footwear and socks (ie. Not sandals) for the ultrasound workshop.

### 8. What are the possible disadvantages and risks of taking part?
In laboratory trials some risk of ultrasound exposure damage to tissues has been documented. The risk, however, is attributed to levels of exposure that are never used within clinical practice. An excellent safety record exists in that, after many years of clinical use, there is no known instance of human injury as a result of exposure to diagnostic ultrasound. During clinical assessments with new ultrasound equipment such as that being used in this study, the total ultrasound exposure is kept as low as reasonably achievable and this is known as the ALARA principle. Implementing ALARA within the study has required the chief investigator, Catherine Bowen, to attend a recognised training course in the use of ultrasound imaging. Mrs Bowen has further support for scanning technique supervision from the Dr Keith Dewbury, Consultant Radiologist, Department of Ultrasound at Southampton General Hospital (Southampton University Hospitals NHS Trust).

It is possible that the Foot pressure measurements recorded by the FScan® system may pose some risk of trip or fall as the pressure sensitive insoles are placed within the your footwear and these are attached via a long cable to a personal computer. There is also a minor risk of you walking too far and toppling over the FScan® system. To avoid these hazards, the exact distance of the walkway will be explained to you and you will be supervised by the investigator at all times during this activity.

### 9. What are the benefits of taking part?
The information that we get from this study may help us to treat patients with rheumatoid arthritis better in the future. There may not be any direct benefits to you associated with taking part in this study; however, taking part in this study may identify bursitis, swelling or pain within your feet which would lead us to initiate appropriate treatment for you.

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### 10. What if there is a problem?
Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

The contact number for any complaints is: Dr Martina Dorward, Research Support Office, University of Southampton, Building 27, Highfield Campus, Southampton, SO17 1BJ.  Telephone: 023 8059 8848

### 11. Will my taking part in this study be kept confidential?
Yes.  All the information about your participation in this study will be kept confidential.  The details are included in Part 2.

### 12. Contact for further information
Further information can be obtained from

Mrs Catherine Bowen in the School of Health Professions and Rehabilitation Sciences on 023 8059 7637.

***Thank you for reading this.***

### This completes Part 1 of the Information Sheet.

***If the information in Part 1 has interested you and you are considering participation, please continue to read the additional information in Part 2 before making any decision.***

### <u>PATIENT INFORMATION SHEET:</u>        Part 2

### 18.  What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time but if you give your permission information on any ultrasound images collected may still be used.

### 19. What if there is a problem or something goes wrong?
It is extremely unlikely that taking part in this research project will harm you. If this did occur, however, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action for compensation against The University of Southampton but you may have to pay your legal costs.

Regardless of this, if you have a concern about any aspect of this study, you should ask to speak with the researchers who will do their best to answer your questions (Contact number; 023 8059 7637).  If you remain unhappy and wish to complain

formally, please contact Mr. Mike Potter, Head of Podiatry, School of Health Professions and Rehabilitation Sciences on 02380 595268*.*

Alternatively, the consumers for ethics in research (CERES) http://www.ceres.org.uk/ is a recommended third independent participant support body.

## 20. Will my taking part in this study be kept confidential?

All information that is collected about you during the course of the research will be kept strictly confidential. Any information about you that leaves the University building will be coded so that at no time will any of your personal details be revealed. The procedures for handling, processing, storage and destruction of any data collected during the study are compliant with the Data Protection Act 1998 and in line with the Southampton University policy.

## 21. What will happen to the results of the research study?

We hope the results are useful and we intend to publish them in a clinically relevant journal and to present them at scientific conferences. The results will also be utilised by the chief investigator for part completion of a PhD thesis to be submitted to the University of Southampton. You will not be identified in any reports or publications.

## 22. Who is organizing and funding the research?

The study is sponsored by the University of Southampton and is organised by investigators from the School of Health Professions and Rehabilitation Sciences, University of Southampton and the Rheumatology and Radiology departments at Southampton General Hospital (Southampton University Hospitals NHS Trust) .

## 23. Who has reviewed the study?

The study has been peer reviewed by the Research division of School of Health Professions and Rehabilitation Sciences, University of Southampton and the Southampton University Hospitals NHS Trust rheumatology research department. The School of Health Professions and Rehabilitation Sciences Undergraduate Research Committee have reviewed this study.

If you agree to take part you will be given a copy of the information sheet and a signed consent form to keep. If you have read this information sheet and are happy to participate in the proposed study please sign the attached reply slip and return it in the stamped addressed envelope.

***Thank you for considering taking part and taking time to read this sheet.***

## Appendix 18

| Participant code | Date |
|---|---|

### Foot Structure Assessment  mark as appropriate

|  | **RIGHT** | **LEFT** |
|---|---|---|
| **Hallux Abducto Valgus** | present / absent | present / absent |
| **5th MPJ Exostosis** | present / absent | present / absent |
| **Lesser Toe Deformity** | present / absent | present / absent |
| **MPJ Subluxation** | present / absent | present / absent |
| **Pes Cavus** | present / absent | present / absent |
| **Pes Planus** | present / absent | present / absent |

### Joint Assessment  mark as appropriate

| **R.O.M** | **RIGHT** | **LEFT** |
|---|---|---|
| **Ankle Joint** | Full / Limited / Rigid | Full / Limited / Rigid |
| **Sub Talar Joint** | Full / Limited / Rigid | Full / Limited / Rigid |
| **Mid Tarsal Joint** | Full / Limited / Rigid | Full / Limited / Rigid |
| **1st MPJ** | Full / Limited / Rigid | Full / Limited / Rigid |

### Foot Pressure Assessment  mark as appropriate

|  | **LEFT** | **RIGHT** |
|---|---|---|
| **Location of peak pressure (A,B,C,D,E,F)** |  |  |
| **Value of peak pressure (KPa)** |  |  |
| **Time of peak pressure** |  |  |
| **Total footstep time** |  |  |
| **Force time-integral** |  |  |
| **Mean force** |  |  |

**Sensor size: ……………**

### Comments (inc tissue viability, skin and nail condition)

**Footwear**       Patients Own       Bespoke       Stock
Suitable / Not Suitable

**Orthoses**       Simple Insole       Moulded Device       TCI       None

**Ulceration**       present / absent / past history
*If present state site, duration, appearance*

*Other comments:*

### Outcome/ any actions  delete as appropriate

| **Ref for Biomech Assess.** | Yes / No | **Ref to Orthotist** | Yes / No |
|---|---|---|---|
| **Ref to Consultant / GP** | Yes / No | | |
| **Ref for Vascular / Neurological Assess.** | Yes / No | | |
| **Podiatric Treatment** | Regular Appointment /  SR / SOS / Annual Recall / No | | |

**Researcher's Signature:**                                        **Date**

**Ultrasound report / data sheet**      **RIGHT FOOT**      Wk No:……
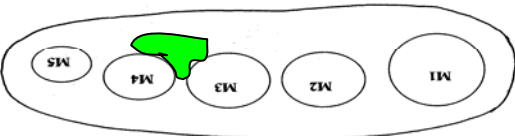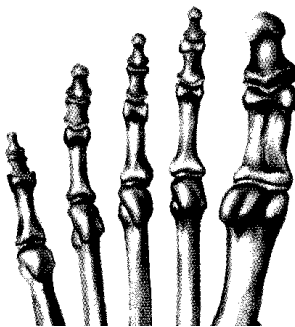
Pt ID No:………………………. …      Date …………………………

*Please tick the appropriate boxes:-*

| Anatomical location | Synovitis presence | | Erosion present | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| MPJ 1 | | √ | | √ |
| MPJ2 | | √ | | √ |
| MPJ3 | | √ | | √ |
| MPJ4 | | √ | | √ |
| MPJ 5 | | √ | √ | |

| Bursitis | *Please tick if present* | **Bursitis presence** *Please mark on the diagram where the bursae are* |
|---|---|---|
| Sub met 1 | | |
| Inter met 1 / 2 | | **Plantar aspect** |
| Sub met 2 | | |
| Inter met 2 / 3 | | |
| Sub met 3 | | |
| Inter met 3 / 4 | √ | |
| Sub met 4 | | **Dorsal aspect** |
| Inter met 4 / 5 | | |
| Sub met 5 | | **Plantar View** |
| **Other** *(please specify)* | | |

*Comments:*

**Key:** MPJ = metatarsophalangeal joint; sub met = plantar metatarsal area; inter met = intermetatarsal capita space, M1 = 1<sup>st</sup> metatarsal head.

**Pto…**     

**Ultrasound report / data sheet**     **LEFT FOOT**          Wk No:……

Pt ID No:……………………. …          Date …………………………

*Please tick the appropriate boxes:-*

| Anatomical location | Synovitis presence | | Erosion present | |
|---|---|---|---|---|
| | Yes | No | Yes | No |
| MPJ 1 | | | | |
| MPJ2 | | | | |
| MPJ3 | | | | |
| MPJ4 | | | | |
| MPJ 5 | | | | |

| Bursitis | *Please tick if present* | **Bursitis presence** *Please mark on the diagram where the bursae are* |
|---|---|---|
| Sub met 1 | | **Plantar aspect** |
| Inter met 1 / 2 | | |
| Sub met 2 | | |
| Inter met 2 / 3 | | |
| Sub met 3 | | |
| Inter met 3 / 4 | | **Dorsal aspect** |
| Sub met 4 | | |
| Inter met 4 / 5 | | **Plantar View** |
| Sub met 5 | | |
| **Other** *(please specify)* | | |
| *Comments:* | | |

**Key:** MPJ = metatarsophalangeal joint; sub met = plantar metatarsal area; inter met = intermetatarsal capita space, M1 = 1$^{st}$ metatarsal head.

**Pto…**

# References

AIUM (1994) *Medical Ultrasound Safety*. O'Brien W.D. and Sweeney T. USA: The American Institute of Ultrasound in Medicine.

AIUM (2007) Practice Guideline for the Performance of the Musculoskeletal Ultrasound Examination. The American Institute of Ultrasound in Medicine. http://www.aium.org/publications/guidelines/musculoskeletal.pdf accessed 4<sup>th</sup> August 2009.

Akil, M. and Amos, R.S. (1999) *Rheumatoid Arthritis: clinical features and diagnosis*. In: *ABC of Rheumatology 2nd Edition*. London: BMJ books. pp 40 - 43.

ARMA (2008) *Standards of Care for people with Musculoskeletal Foot Health problems*. London: The Arthritis and Musculoskeletal Alliance.

Arnett, F.C., Edworthy, S.M., Bloch, D.A., McShane, D.J., Fries, J.F., Cooper, N.S., Healey, L.A., Kaplan, S.R., Liang, M.H., Luthra, H.S., et al. (1988). 'The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis*', Arthritis Rheum,* 31(3), pp 315-24.

Ashman C.J., Klecker, R.J. and Yu, J.S. (2001). 'Forefoot pain involving the metatarsal region: differential diagnosis with MR imaging', *Radiographics,* 21(6), pp 1425-40.

Avouac, J., Gossec, L. and Dougados, M. (2006) 'Diagnostic and predictive value of anti-cyclic citrullinated protein antibodies in rheumatoid arthritis: a systematic literature review', *Ann Rheum Dis,* 65(7), pp 845-51.

Awerbuch, M.S., Shephard, E. and Vernon-Roberts, B. (1982). 'Morton's metatarsalgia due to intermetatarsophalangeal bursitis as an early manifestation of rheumatoid arthritis', *Clin Orthop Relat Res,* (167), pp 214-21.

Backhaus, M., Kamradt, T., Sandrock, D., Loreck, D., Fritz, J., Wolf, K.J., Raber, H., Hamm, B,, Burmester, G.R. and Bollow, M. (1999) 'Arthritis of the finger joints: a comprehensive approach comparing conventional radiography, scintigraphy, ultrasound, and contrast-enhanced magnetic resonance imaging', *Arthritis Rheum,* 42(6), pp 1232-45.

Backhaus, M., Burmester, G.R., Gerber, T., Grassi, W., Machold, K.P., Swen, W.A., Wakefield, R.J. and Manger, B. (2001) 'Guidelines for musculoskeletal ultrasound in rheumatology', *Ann Rheum Dis,* 60(7), pp 641-9.

Backhaus, M., Sandrock, D. and Schmidt, W.A. (2002) '[Imaging in rheumatology]', *Dtsch Med Wochenschr,* 127(37), pp 1897-903.

Baeten, D., Demetter, P., Cuvelier, C., Van Den Bosch, F., Kruithof, E., Van Damme, N., Verbruggen, G., Mielants, H., Veys, E.M. and De Keyser, F. (2000) 'Comparative study of the synovial histology in rheumatoid arthritis, spondyloarthropathy, and osteoarthritis: influence of disease duration and activity', *Ann Rheum Dis,* 59(12), pp 945-53.

Balint, P. and Sturrock, R.D. (1997) 'Musculoskeletal ultrasound imaging: a new diagnostic tool for the rheumatologist?', *Br J Rheumatol,* 36(11), pp 1141-2.

Balint, P.V., Kane, D. and Sturrock, R.D. (2001) 'Modern patient management in rheumatology: interventional musculoskeletal ultrasonography', *Osteoarthritis Cartilage*, 9(6), pp 509-11.

Balint, P.V., Kane, D., Hunter, J., McInnes, I.B., Field, M. and Sturrock, R.D. (2002) 'Ultrasound guided versus conventional joint and soft tissue fluid aspiration in rheumatology practice: a pilot study', *J Rheumatol*, 29(10), pp 2209-13.

Balint, P.V., Mandl, P. and Kane, D. (2008) 'All that glistens is not gold- separating artefacts from true Doppler signals in rheumatological ultrasound', *Ann Rheum Dis*, 67(2), pp 141-2.

Bancroft, L.W., Peterson, J.J., Kransdorf, M.J. (2008) 'Imaging of soft tissue lesions of the foot and ankle'. Radiol Clin North Am. 46(6), pp 1093-103, vii. Review.

Barnett, S., Campbell, R. and Harvey, I. (2005) 'The Bristol Foot Score: developing a patient-based foot-health measure', *J Am Podiatr Med Assoc*, 95(3), pp 264-72.

Beggs, I. (2002) 'Ultrasound of soft tissue masses', *Imaging*, 14, pp 202-208.

Bell, M. and McNally E.G.M. (2002) 'Ultrasound of the Foot and Ankle', *BMUS Bulletin*, 10(3), pp 28-32.

Bennett, P.J., Patterson, C., Wearing, S. and Baglioni, T. (1998) 'Development and validation of a questionnaire designed to measure foot-health status', *J Am Podiatr Med Assoc,* 88(9), pp 419-28.

Bianchi, S., Martinoli, C., Keller, A. and Bianchi-Zamorani, M.P. (2002) 'Giant iliopsoas bursitis: sonographic findings with magnetic resonance correlations', *J Clin Ultrasound,* 30(7), pp 437-41.

BMUS (2000) 'Guidelines for the safe use of Diagnostic Ultrasound Equipment', *British Medical Ultrasound Society Bulletin*, August, pp 29-33.

BMUS (2000). Statement on the Safe Use, and Potential Hazards of Diagnostic Ultrasound. The British Medical Ultrasound Society.
http://www.bmus.org/about-ultrasound/au-safetystatement.asp
accessed August 14th 2009.

Boers, M., Tugwell, P., Felson, D.T., van Riel, P.L., Kirwan, J.R., Edmonds, J.P., Smolen, J.S., Khaltaev, N. and Muirden, K.D. (1994) 'World Health Organization and International League of Associations for Rheumatology core endpoints for symptom modifying antirheumatic drugs in rheumatoid arthritis clinical trials', *J Rheumatol Suppl.,* Sep;41, pp 86-9.

Boers, M., van Riel, P.L., Felson, D.T. and Tugwell, P. (1995) 'Assessing the activity of rheumatoid arthritis', *Baillieres Clin Rheumatol*, 9(2), pp 305-17.

Boers, M., Brooks, P., Strand, C.V., Tugwell, P. (1998) 'The OMERACT filter for Outcome Measures in Rheumatology'. J Rheumatol. 25(2):198-9.

Borthwick, A. (2001) 'Editorial - Occupational Imperialism at work: the case of podiatric surgery', *British Journal of Podiatry*, 4(3), pp 70-79.

Borthwick, A. (2004) 'The politics of allied health prescribing: Reflections on a new discourse', *British Journal of Podiatry*, 7(2), p 31.

Bossley, C.J. and Cairney P.C. (1980) 'The intermetatarsophalangeal bursa--its significance in Morton's metatarsalgia', *J Bone Joint Surg Br*, 62-B(2), pp 184-7.

Boutry, N., Larde, A., Lapegue, F., Solau-Gervais, E., Flipo, R.M. and Cotton, A. (2003) 'Magnetic resonance imaging appearance of the hands and feet in patients with early rheumatoid arthritis', *Journal of Rheumatology*; 30(4), pp 671-679.

Bowen, C.J. (2003) 'Extending the Scope of Practice for Podiatrists: A consideration of the use of Diagnostic Ultrasound Imaging', *British Journal of Podiatric Medicine*, 6(4), pp 92-95.

Bowen, C.J., Burridge, J. and Arden, N.K. (2005) 'Critical Review: Podiatry interventions in the rheumatoid foot', *Br J Podiatry*, 8(3), pp 76-82.

Bowen, C.J., Dewbury, K., Sampson, M., Sawyer, S., Burridge, J., Edwards, C.J. and Arden, N.K. (2008) 'Musculoskeletal ultrasound imaging of the plantar forefoot in patients with rheumatoid arthritis: inter-observer agreement between a podiatrist and a radiologist', *J Foot Ankle Res*, Jul 28;1(1), p 5.

Bowen, C.J. (2008) 'Podiatry: A vision for the future', *Podiatry Now*, 11(10), pp 33-34. Bowling, A. (2002) *Handbook of health research methods : investigation, measurement and analysis.* Maidenhead: Open University Press.

Bresnihan, B. and Kane D. (2004) 'Sonography and subclinical synovitis', *Ann Rheum Dis* 63(4), pp 333-4.

Brill, K., Eckes, D., Weiler, E. and Lord ,G. (2004) 'Chronic inflammatory pain control with omega-5$^{eTM}$ (CHIPCO5)' Available at: http://alphaflex.com/research.html. (Accessed September 2008).

Brooks, P.M. (1998) 'The Heberden Oration 1997. Treatment of rheumatoid arthritis: from symptomatic relief to potential cure', *Br J Rheumatol*, 37(12), pp 1265-71.

Brown, A.K., O'connor, P.J., Roberts, T.E., Wakefield, R.J., Karim, Z. and Emery, P. (2005) 'Recommendations for musculoskeletal ultrasonography by rheumatologists: setting global standards for best practice by expert consensus', *Arthritis Rheum*, 53(1), pp 83-92.

Brown, A.K., O'Connor, P.J., Roberts, T.E., Wakefield, R.J., Karim, Z. and Emery. P. (2006) 'Ultrasonography for rheumatologists: the development of specific competency based educational outcomes', *Ann Rheum Dis*, 65(5) pp 629-36.

Brown, A.K., Quinn, M.A., Karim, Z., Conaghan, P.G., Peterfy, C.G., Hensor, E., Wakefield, R.J., O'Connor, P.J. and Emery, P. (2006) 'Presence of significant synovitis in rheumatoid arthritis patients with disease-modifying antirheumatic drug-induced clinical remission: evidence from an imaging study may explain structural progression', *Arthritis Rheum*, 54(12), pp 3761-73.

Brown, A.K., Roberts, T.E., O' Connor, P.J., Wakefield, R.J., Karim, Z. and Emery, P. (2007) 'The development of an evidence-based educational framework to facilitate the training of competent rheumatologist ultrasonographers', *Rheumatology*, 46(3), pp 391-7.

Brown, A.K., Conaghan, P.G., Karim, Z., Quinn, M.A., Ikeda, K., Peterfy, C.G., Hensor, E., Wakefield, R.J., O'Connor, P.J. and Emery, P. (2008) 'An explanation for the apparent dissociation between clinical remission and continued structural deterioration in rheumatoid arthritis', *Arthritis Rheum*, 58(10), pp 2958-67.

Brown, J.N., Betts, R.P. and Bygrave, C.J. (1994) 'The use of ultrasound in the cause of persistent pain following a metatarsal shortening osteotomy', *The Foot*, 4, pp 159-162.

Budiman-Mak, E., Conrad, K.J. and Roach, K.E. (1991) 'The Foot Function Index: a measure of foot pain and disability', *J Clin Epidemiol*, 44(6), pp 561-70.

Budiman-Mak, E., Conrad, K.J., Roach, K.E., Moore, J.W., Lertratanakulm Y., Kochm A.E., Skoseym J.L., Froelichm C. and Joyce-Clarkm N. (1995) 'Can foot orthoses prevent hallux valgus deformity in rheumatoid arthritis? A randomized clinical trial', *Journal of Clinical Rheumatology*, 1(6), pp 313-321.

Bukhari, M., Harrison, B., Lunt, M., Scott, D.G., Symmons, D.P. and Silman, A.J. (2001) 'Time to first occurrence of erosions in inflammatory polyarthritis: results from a prospective community-based study', *Arthritis Rheum*, 44(6), pp 1248-53.

Bus, S.A., Maas, M., Cavanagh, P.R., Michels, R.P. and Levi, M. (2004) 'Plantar fat-pad displacement in neuropathic diabetic patients with toe deformity: a magnetic resonance imaging study', *Diabetes Care*, 27(10), pp 2376-81.

Bushberg, J.T., Seibert, J.A., Leidholdt, E.M. and Boone, J.M. (2002) *The Essential physics of medical imaging*. 2nd Edition. USA: Lippincott Williams and Wilkins.

Bygrave, C.J., Betts, R.P. and Saxelby, J. (1998) 'Diagnosing plantar fasciitis with ultrasound using Planscan', *The Foot*, 8, pp 141-146.

Byrne, D.W. (1998) *Publishing your medical research paper*. Canada: Lippincott Williams and Wilkins.

Camp, G. (1996) Problem-based learning: A paradigm shift or passing fad? *Medical Education Online*, 1:2. Available at: http://www.med-ed-online.org/f0000003.htm.

Canoso, J.J. (1997) *Rheumatology in Primary Care*. Philadelphia: WB Saunders Company.

Canoso, J.J., Liu, N., Traill, M.R., Runge, V.M. (1988) 'Physiology of the retrocalcaneal bursa'. Ann Rheum Dis. 47(11), pp 910-2.

Cantini, F., Salvarani, C., Olivieri, I., Niccoli, L., Padula, A., Macchioni, L., Boiardi, L., Ciancio, G., Mastrorosato, M., Rubini, F., Bozza, A. and Zanfranceschi, G. (2001) 'Shoulder ultrasonography in the diagnosis of polymyalgia rheumatica: a case-control study', *J Rheumatol*, 28(5), pp 1049-55.

Chalmers, A.C., Busby, C., Goyert, J., Porter, B. and Schulzer, M. (2000) 'Metatarsalgia and rheumatoid arthritis--a randomized, single blind, sequential trial comparing 2 types of foot orthoses and supportive shoes', *J Rheumatol,* 27(7), pp 1643-7.

Chauveaux, D., Le Huec, J.C. and Midy, D. (1987) 'The supra-transverse intermetatarsocapital bursa: a description and its relation to painful syndromes of the forefoot', *Surg Radiol Anat,* 9(1), pp 13-8.

Chen, M.J., Lew, H.L., Hsu, T.C., Tsai, W.C., Lin, W.C., Tang, S.F., Lee, Y.C., Hsu, R.C. and Chen, C.P. (2006) 'Ultrasound-guided shoulder injections in the treatment of subacromial bursitis', *Am J Phys Med Rehabil,* 85(1), pp 31-5.

Choy, E.H. and Panayi, G.S. (2001) 'Cytokine pathways and joint inflammation in rheumatoid arthritis', *N Engl J Med*, 344(12), pp 907-16.

Clark, H., Rome, K., Plant, M., O'Hare, K. and Gray, J. (2006) 'A critical review of foot orthoses in the rheumatoid arthritic foot', *Rheumatology*, 45(2) pp 139-45.

Claustre, J., Bonnel, F., Constans, J.P. and Simon, L. (1983) '[The intercapital metatarsal space. Anatomical and pathological aspects]' *Rev Rhum Mal Osteoartic,* 50(6), pp 435-40.

Coakley, F.V., Samanta, A.K. and Finlay, D.B. (1994) 'Ultrasonography of the tibialis posterior tendon in rheumatoid arthritis', *Br J Rheumatol*, 33(3), pp 273-7.

Conaghan, P.G., O'Connor, P., McGonagle, D., Astin, P., Wakefield, R.J., Gibbon, W.W., Quinn, M., Karim, Z., Green, M.J., Proudman, S., Isaacs, J. and Emery, P. (2003) 'Elucidation of the relationship between synovitis and bone damage: a randomized magnetic resonance imaging study of individual joints in patients with early rheumatoid arthritis', *Arthritis Rheum*, 48(1), pp 64-71.

Conrad, K.J., Budiman-Mak, E., Roach, K.E., Hedeker, D., Caraballada, R., Burks, D. and Moore, H. (1996) 'Impacts of foot orthoses on pain and disability in rheumatoid arthritics', *J Clin Epidemiol*, 49(1), pp 1-7.

Cooper, N.J. (2000) 'Economic burden of rheumatoid arthritis: a systematic review', *Rheumatology*, 39(1), pp 28-33.

Costa, M., Rizack, T. and Zimmermann, B. (2004) 'Rheumatologic conditions of the foot', *J Am Podiatr Med Assoc*, 94(2), pp 177-86.

Crawford, F. and Thomson C. (2003) 'Interventions for treating plantar heel pain', *Cochrane Database Syst Rev*, (3), p CD000416.

D'Agostino, M.A., Maillefert, J.F., Said-Nahal, R., Breban, M., Ravaud, P. and Dougados, M. (2004) 'Detection of small joint synovitis by ultrasonography: the learning curve of rheumatologists', *Ann Rheum Dis,* 63(10), pp 1284-7.

Daker-White, G., Carr, A.J., Harvey, I., Woolhead, G., Bannister, G., Nelson, I. and Kammerling, M. (1999) 'A randomised controlled trial. Shifting boundaries of doctors and physiotherapists in orthopaedic outpatient departments', *J Epidemiol Community Health*, 53(10), pp 643-50.

Darzi A. (2008) *High Quality Health Care for all: NHS next stage.* London: Department of Health.

Davys, H.J,, Turner, D.E., Helliwell, P.S., Conaghan, P.G., Emery, P. and Woodburn, J. (2005) 'Debridement of plantar callosities in rheumatoid arthritis: a randomized controlled trial', *Rheumatology*, 44(2), pp 207-10.

Demp, P.H. (2001) 'Biomechanics: A mathematical perspective', *Clin Podiatr Med Surg*, 18(4), pp 703-4, vi.

DOH (1999) *Agenda for Change: Modernising the NHS Pay System*. London: Department of Health.

DOH. (2000) *The NHS Plan: A Plan for Investment, A Plan for Reform.* London: Department of Health.

DOH (2000) *A Health Service of All The Talents: Developing the NHS Workforce. Health.* London: Department of Health.

DOH (2000) *Modernising Regulation, The New Health Professions Council.* London: Department of Health.

DOH (2007) *Horizon Scanning: Future threats and opportunities.* London: Department of Health.

DOH (2008) *The Darzi Report: High quality care for all: NHS Next Stage Review final report.* London: Department of Health.

Donatelli, R.A. and Wolf, S.L. Editors (1990) *The biomechanics of the foot and ankle*. Philadelphia: F.A. Davis Company.

Doran, M.F., Pond, G.R., Crowson, C.S., O'Fallon, W.M. and Gabriel, S.E. (2002) 'Trends in incidence and mortality in rheumatoid arthritis in Rochester, Minnesota, over a forty-year period', *Arthritis Rheum,* 46(3), pp 625-31.

Edwards, J.C. (1988) *'Pathophysiology of chronic synovitis'*, Br J Rheumatol, 27 Suppl 2, pp 116-9.

Ejbjerg, B.J., Vestergaard, A., Jacobsen, S., Thomsenm H.S. and Østergaard, M. (2005) 'The smallest detectable difference and sensitivity to change of magnetic resonance imaging and radiographic scoring of structural joint damage in rheumatoid arthritis finger, wrist, and toe joints: a comparison of the OMERACT rheumatoid arthritis magnetic resonance imaging score applied to different joint combinations and the Sharp/van der Heijde radiographic score', *Arthritis Rheum*, 52(8) pp 2300-6

Ellis, J.R.C., McNally ,E.G. and Scott, P.M. (2002) 'Ultrasound of peripheral nerves', *Imaging*, 14(3), pp 217-222.

Ellis, J.R.C., Teh, J.L. and Scott, P.M. (2002) 'Ultrasound of tendons' *Imaging*, 14(3), pp 223-228.

Evangelisto, A., Wakefield, R.J. and Emery, P.(2004) 'Imaging in early arthritis', *Best Pract Res Clin Rheumatol*, 18(6, pp: 927-43.

Evans, A.M., Copper, A.W., Scharfbillig, R.F., Scutter, S.D. and Williams, M.T. (2003) 'Reliability of the foot posture index and traditional measures of foot position'. *Journal of the American Podiartric Medical Assosciation*, 93(3), pp 203-213.

Farrant, J.M., O'Connor, P.J. and Grainger, A.J. (2007) 'Advanced imaging in rheumatoid arthritis. Part 1: synovitis', *Skeletal Radiol*, 36(4), pp 269-79.

Farrow, S.J., Kingsley, G.H. and Scott, D.L. (2005) 'Interventions for foot disease in rheumatoid arthritis: a systematic review', *Arthritis Rheum*, 53(4), pp 593-602.

Fessell, D.P. and van Holsbeeck, M.T. (1999) 'Foot and ankle sonography'. Radiol Clin North Am. 37(4), pp 831-58, x. Review.

Filippucci, E., Unlu, Z., Farina, A.and Grassi, W. (2003) 'Sonographic training in rheumatology: a self teaching approach', *Ann Rheum Dis*, 62(6), pp 565-7.

Filippucci, E., Meenagh, G., Ciapetti, A., Iagnocco, A., Taggart, A. and Grassi, W. (2007) 'E-learning in ultrasonography: a web-based approach', *Ann Rheum Dis,* 66(7), pp 962-5.

Finlay, K. and Friedman, L. (2006) 'Ultrasonography of the lower extremity', *Orthop Clin North Am*, 37(3), pp 245-75

Firestein, G.S. (2003) 'Evolving concepts of rheumatoid arthritis', *Nature*, 15;423(6937), pp 356-61.

Fish, P. (1990). *Physics and instrumentation of diagnostic medical ultrasound*. Chichester: Wiley.

Fortin, L. and Belanger R. (1995) 'Bursitis of the iliopsoas: four cases with pain as the only clinical indicator', *J Rheumatol*, 22(10), pp 1971-3.

Fortin, P.R., Stucki, G. and Katz, J.N. (1995) 'Measuring relevant change: an emerging challenge in rheumatologic clinical trials', *Arthritis Rheum*, 38(8), pp 1027-30.

Fransen, M. and Edmonds J. (1997) 'Off-the-shelf orthopedic footwear for people with rheumatoid arthritis', *Arthritis Care Res,* 10(4), pp 250-6.

Fredberg, U., Bolvig, L., Pfeiffer-Jensen, M., Clemmensen, D., Jakobsen, B.W. and Stengaard-Pedersen, K. (2004) 'Ultrasonography as a tool for diagnosis, guidance of local steroid injection and, together with pressure algometry, monitoring of the treatment of athletes with chronic jumper's knee and Achilles tendinitis: a randomized, double-blind, placebo-controlled study', *Scand J Rheumatol*, 33(2), pp 94-101.

French, S., Neville, S. and Laing, J. (1994) *Teaching and learning: A Guide for Therapists.* Oxford, UK: Butterworth, Heinmann.

Fries, J.F., Spitz, P., Kraines, R.G. and Holman, H.R. (1980) 'Measurement of patient outcome in arthritis', *Arthritis Rheum*, 23(2), pp 137-45.

Fuller, E.A. (1999) 'Center of pressure and its theoretical relationship to foot pathology', *J Am Podiatr Med Assoc*, 89(6), pp 278-91.

Gabriel, S.E., Crowson, C.S., Kremers, H.M., Doran, M.F., Turesson, C., O'Fallon, W.M. and Matteson, E.L. (2003) 'Survival in rheumatoid arthritis: a population-based analysis of trends over 40 years', *Arthritis Rheum*, 48(1), pp 54-8.

Gaffney, K., Cookson, J., Blake, D., Coumbe, A. and Blades, S. (1995) 'Quantification of rheumatoid synovitis by magnetic resonance imaging', *Arthritis Rheum*, 38(11), pp 1610-7.

Garrow, A.P., Papageorgiou, A.C., Silman, A.J., Thomas, E., Jayson, M.I. and Macfarlane, G.J. (2000) 'Development and validation of a questionnaire to assess disabling foot pain', *Pain*, 85(1-2), pp 107-13.

Genc, H., Saracoglu, M., Nacir, B., Erdem, H.R. and Kacar, M. (2005) 'Long-term ultrasonographic follow-up of plantar fasciitis patients treated with steroid injection', *Joint Bone Spine*, 72(1), pp 61-5.

Gibbon, W.W. (1996) 'Musculoskeletal ultrasound', *Baillieres Clin Rheumatol*, 10(4), pp 561-88.

Gibbon, W.W. and Wakefield R.J. (1999) 'Ultrasound in inflammatory disease' *Radiol Clin North Am*, 37(4), pp 633-51.

Gordon, P., Jones, H.W. and Gibson, T. (1997) 'Clinical improvement and radiological deterioration in rheumatoid arthritis', *Br J Rheumatol*, 36(11), pp 1231-2.

Goupille, P., Roulot, B., Akoka, S., Avimadje, A.M., Garaud, P., Naccache, L., Le Pape, A. and Valat, J.P. (2001) 'Magnetic resonance imaging: a valuable method for the detection of synovial inflammation in rheumatoid arthritis', *J Rheumatol,* 28(1), pp 35-40.

Graham, P. (2007) 'The future is Generalist Practice', *Podiatry Now,* 10(9), pp 220-21.

Grassi, W. and Cervini, C. (1998) 'Ultrasonography in rheumatology: an evolving technique', *Ann Rheum Dis*, 57(5), pp 268-71.

Grassi, W., Filippucci, E., Farina, A., Salaffi, F. and Cervini, C. (2001) 'Ultrasonography in the evaluation of bone erosions', *Ann Rheum Dis*, 60(2), pp 98-103.

Grassi, W., Filippucci, E., Farina, A., Salaffi, F., Cervini, C. (2001) 'Ultrasonography in the evaluation of bone erosions'. Ann Rheum Dis. 60(2), pp 98-103.

Grassi, W., Filippucci, E. and Busilacchi P. (2004) 'Musculoskeletal ultrasound', *Best Pract Res Clin Rheumatol,* 18(6), pp 813-26.

Gregg, J.M., Schneider, T. and Marks, P. (2008) 'MR imaging and ultrasound of metatarsalgia--the lesser metatarsals', *Radiol Clin North Am*, 46(6), pp 1061-78, vi-vii.

Haavardsholm, E.A., Ostergaard, M., Ejbjerg, B.J., Kvan, N.P., Uhlig, T.A., Lilleås, F.G. and Kvien, T.K. (2005) 'Reliability and sensitivity to change of the OMERACT rheumatoid arthritis magnetic resonance imaging score in a multireader, longitudinal setting', *Arthritis Rheum*, 52(12), pp 3860-7.

Harris, E.D. Jr. (1990) 'Rheumatoid arthritis. Pathophysiology and implications for therapy', *N Engl J Med,* 3;322(18), pp 1277-89.

Harrison, B.J., Symmons, D.P., Barrett, E.M. and Silman, A.J. (1998) 'The performance of the 1987 ARA classification criteria for rheumatoid arthritis in a population based cohort of patients with early inflammatory polyarthritis. American Rheumatism Association', *J Rheumatol*, 25(12), pp 2324-30.

Hau, M., Kneitz, C., Tony, H.P., Keberle, M., Jahns, R. and Jenett M. (2002) 'High resolution ultrasound detects a decrease in pannus vascularisation of small finger joints in patients with rheumatoid arthritis receiving treatment with soluble tumour necrosis factor alpha receptor (etanercept)', *Ann Rheum Dis,* 61(1), pp 55-8.

Hernandez, P.A., Hernandez, W.A. and Hernandez, A. (1991) 'Clinical aspects of bursae and tendon sheaths of the foot', *J Am Podiatr Med Assoc,* 81(7), pp 366-72.

Helliwell, P.S. (2003) 'Lessons to be learned : review of a multidisciplinary foot clinic in rheumatology', *Rheumatology*, 42(11), pp 1426-1427.

Helliwell, P., Reay, N., Gilworth, G., Redmond, A., Slade, A., Tennant, A., and Woodburn, J. (2005) 'Development of a foot impact scale for rheumatoid arthritis', *Arthritis Rheum*, 15;53(3), pp 418-22.

Helliwell, P., Woodburn, J., Redmond, A., Turner, D.E. and Davys, H. (2007) *The Foot and Ankle in Rheumatoid Arthritis*. Edinburgh: Churchill Livingstone.

Hermann, K.G., Backhaus, M., Schneider, U., Labs, K., Loreck, D., Zühlsdorf, S., Schink, T., Fischer, T., Hamm, B. and Bollow, M. (2003) 'Rheumatoid arthritis of the shoulder joint: comparison of conventional radiography, ultrasound, and dynamic contrast-enhanced magnetic resonance imaging', *Arthritis Rheum,* 48(12), pp 3338-49.

Heron C.W. (1993) 'Magnetic resonance imaging of the ankle and foot' *The Foot*, 3, pp 1-10.

Hodge, M.C., Bach, T.M. and Carter, G.M. (1999) 'novel Award First Prize Paper. Orthotic management of plantar pressure and pain in rheumatoid arthritis', *Clin Biomech*, 14(8), pp 567-75.

Hulsmans, H.M., Jacobs, J.W., van der Heijde, D.M., van Albada-Kuipers, G.A., Schenk, Y. and Bijlsma, J.W. (2000) 'The course of radiologic damage during the first six years of rheumatoid arthritis', *Arthritis Rheum*, 43(9), pp 1927-40.

Iagnocco, A., Coari, G., Palombi, G. and Valesini, G. (2001) 'Sonography in the study of metatarsalgia', *J Rheumatol*, 28(6), pp 1338-40.

Iagnocco, A., Naredo, E. and Tripodo, E. (2008) 'Etanercept in the treatment of rheuamtoid arthritis: clinical follow up over one year by ultrasonography', *Clin Rheumatol*, 27, pp 491-496.

Irwin, L.R., Konstantoulakis, C., Hyder, N.U. and Sapherson, D.A. (2000) 'Ultrasound in the diagnosis of Morton's Neuroma', *The Foot*, 10, pp 186-189.

Isomäki, H., Kaarela, K. and Martio, J. (1988) 'Are hand radiographs the most suitable for the diagnosis of rheumatoid arthritis?' *Arthritis Rheum*, 31(11), pp 1452-3.

Jacob, H.A. (2001) 'Forces acting in the forefoot during normal gait--an estimate' Clin Biomech. 16(9), pp 783-92

Jawaheer, D. and Gregersen, P.K. (2002) 'Rheumatoid arthritis. The genetic components', *Rheum Dis Clin North Am*, 28(1), pp 1-15, v.

Jones, S., Bygrave, C.J., Betts, R.P. and Smith, T.W.D. (1999) 'Morton's Neuroma: a Sonographic-surgical evaluation', *The Foot*, 9, pp 189-192.

Joshua, F., Lassere, M., Bruyn, G.A., Szkudlarek, M., Naredo, E., Schmidt, W.A., Balint, P., Filippucci, E., Backhaus, M., Iagnocco, A., Scheel, A.K., Kane, D., Grassi, W., Conaghan, P.G., Wakefield, R.J. and D'Agostino, M.A. (2007) 'Summary findings of a systematic review of the ultrasound assessment of synovitis', *J Rheumatol,* 34(4), pp 839-47.

Kalsi, J. and Isenberg D. (1993) 'Rheumatoid factor: primary or secondary event in the pathogenesis of RA?', *Int Arch Allergy Immunol*, 102(3), pp 209-15.

Kane, D., Greaney, T., Bresnihan, B., Gibney, R. and FitzGerald, O. (1998) 'Ultrasound guided injection of recalcitrant plantar fasciitis', *Ann Rheum Dis*, 57(6), pp 383-4.

Kane, D., Greaney, T., Shanahan, M., Duffy, G., Bresnihan, B., Gibney, R. and FitzGerald, O. (2001) 'The role of ultrasonography in the diagnosis and management of idiopathic plantar fasciitis', *Rheumatology*, 40(9), pp 1002-8.

Kane, D., Balint, P.V., Sturrock, R. and Grassi, W. (2004) 'Musculoskeletal ultrasound--a state of the art review in rheumatology. Part 1: Current controversies and issues in the development of musculoskeletal ultrasound in rheumatology', *Rheumatology*, 43(7), pp 823-8.

Kane, D., Grassi, W., Sturrock, R. and Balint, P.V. (2004) 'Musculoskeletal ultrasound--a state of the art review in rheumatology. Part 2: Clinical indications for musculoskeletal ultrasound in rheumatology', *Rheumatology,* 43(7), pp 829-38.

Karim, Z., Wakefield, R.J., Conaghan, P.G., Lawson, C.A., Goh, E., Quinn, M.A., Astin, P., O'Connor, P., Gibbon, W.W. and Emery, P. (2001) 'The impact of ultrasonography on diagnosis and management of patients with musculoskeletal conditions', *Arthritis Rheum*, 44(12), pp 2932-3.

Kataria, R.K., Chaiamnuay, S., Jacobson, L.D. and Brent, L.H. (2003) 'Subacromial bursitis with rice bodies as the presenting manifestation of rheumatoid arthritis', *J Rheumatol*, 30(6), pp 1354-5.

Keenan, M.A., Peabody, T.D., Gronley, J.K. and Perry, J. (1991) 'Valgus deformities of the feet and characteristics of gait in patients who have rheumatoid arthritis', *J Bone Joint Surg Am*, 73(2), pp 237-47.

Kerry, R.M., Holt, G.M. and Stockley, I. (1994) 'The foot in chronic rheumatoid arthritis : A continuing problem', *The Foot*, 4, pp 201-203.

Kinnear, P.R. and Gray, C.D. (2006) *SPSS14 made simple.* Hove UK: Psychology press.

Kirby, K.A. (2001). 'Subtalar joint axis location and rotational equilibrium theory of foot function', *J Am Podiatr Med Assoc*, 91(9), pp 465-87.

Kirwan, J.R. (1997) 'The relationship between synovitis and erosions in rheumatoid arthritis', *Br J Rheumatol*, 36(2), pp 225-8.

Kirwan, J.R. (2004) 'The synovium in rheumatoid arthritis: evidence for (at least) two pathologies', *Arthritis Rheum*, 50(1), pp 1-4.

Klarlund, M., Ostergaard, M., Jensen, K.E., Madsen, J.L., Skjødt, H. and Lorenzen, I. (2000) 'Magnetic resonance imaging, radiography, and scintigraphy of the finger joints: one year follow up of patients with early arthritis. The TIRA Group', *Ann Rheum Dis*, 59(7), pp 521-8.

Klenerman, L. (1995) 'The foot and ankle in rheumatoid arthritis', *Br J Rheumatol*, 34(5), pp 443-8.

Korda, J. and Balint, G.P. (2004) 'When to consult the podiatrist', *Best Pract Res Clin Rheumatol*, 18(4), pp 587-611.

Koski, J.M. (1990) 'Ultrasonography of the metatarsophalangeal and talocrural joints', *Clin Exp Rheumatol,* 8(4), pp 347-51.

Koski, J.M. (1995) 'Detection of plantar tenosynovitis of the forefoot by ultrasound in patients with early arthritis', *Scand J Rheumatol*, 24(5), pp 312-3.

Koski, J.M. (1998) 'Ultrasound detection of plantar bursitis of the forefoot in patients with early rheumatoid arthritis', *J Rheumatol*, 25(2), pp 229-30.

Koski J.M. (2000) 'Ultrasound guided injections in rheumatology', *The Journal of Rheumatology*; 27 (9), pp 2131-2138.

Koski, J.M. and Hermunen H. (2001) 'Intra-articular glucocorticoid treatment of the rheumatoid wrist. An ultrasonographic study', *Scand J Rheumatol*, 30(5), pp 268-70.

Kremkau, F. W. (1998) *Diagnostic Ultrasound.* 6th Ed. Philadelphia: W.B. Saunders.

Kuper, H.H., van Leeuwen, M.A., van Riel, P.L., Prevoo, M.L., Houtman, P.M., Lolkema, W.F. and van Rijswijk, M,H. (1997) 'Radiographic damage in large joints in early rheumatoid arthritis: relationship with radiographic damage in hands and feet, disease activity, and physical disability', *Br J Rheumatol,* 36(8), pp 855-60.

Kvien, T.K., Uhlig, T., Ødegård, S. and Heiberg, M.S. (2006) 'Epidemiological aspects of rheumatoid arthritis: the sex ratio', *Ann N Y Acad Sci*, 1069, pp 212-22.

Laroche, D., Pozzo, T., Ornetti, P., Tavernier, C. and Maillefert, J.F. (2006) 'Effects of loss of metatarsophalangeal joint mobility on gait in rheumatoid arthritis patients' *Rheumatology*, 45(4), pp 435-40.

Lin, J.P., Cash, J.M., Doyle, S.Z., Peden, S., Kanik, K., Amos, C.I,, Bale, S.J. and Wilder, R.L. (1998) 'Familial clustering of rheumatoid arthritis with other autoimmune diseases', *Hum Genet,* 103(4), pp 475-82.

Luukkainen, R.K., Saltyshev, M., Koski, J.M. and Huhtala, H.S. (2003) 'Relationship between clinically detected joint swelling and effusion diagnosed by ultrasonography in metatarsophalangeal and talocrural joints in patients with rheumatoid arthritis', *Clin Exp Rheumatol,* 21(5), pp 632-4.

Luukkainen, R., Ekman, P., Luukkainen, P. and Koski, J.M. (2009) 'Ultrasonographic findings in metatarsophalangeal and talocrural joints in healthy persons', *Clin Rheumatol.,* 28(3), pp 311-3.

Machin, D., Campbell, M.J., Fayers, P. and Pinol, A.P.Y. (1997) *Sample size tables for clinical studies*. 2nd ed. Oxford: Blackwell Science Ltd.

MacGregor, A.J., Riste, L.K., Hazes, J.M. and Silman, A.J. (1994) 'Low prevalence of rheumatoid arthritis in black-Caribbeans compared with whites in inner city Manchester', *Ann Rheum Dis*, 53(5), pp 293-7.

Macsween, A., Brydson, G. and Hamilton, J. (1999) 'The effect of custom moulded ethyl vinyl acetate foot orthoses on the gait patterns of patients with rheumatoid arthritis', *The Foot,* 9, pp 128-133.

Mathieson, I. (2001) 'Reconstructing Root. An argument for objectivity', *Clin Podiatr Med Surg,* 18(4), pp 691-702, vi.

McCance, K.L. and Huether, S.E. (2002) Pathophysiology : the biologic basis for disease in adults & children, 4th edition. St. Louis: Mosby.

McGinn, T., Wyer, P.C., Newman, T.B., Keitz, S. and Leipzig, R., For GG (2004) 'Tips for learners of evidence-based medicine: 3. Measures of observer variability (kappa statistic)', *CMAJ,* 171(11), pp 1369-73.

McGonagle, D. and Conaghan P. (1999) 'Magnetic Resonance Imaging in Rheumatology', *ARC Reviews*, (17), pp 159-164.

McGonagle, D., Conaghan, P.G., Wakefield, R.J., Emery, P. (2001) 'Imaging the joints in early rheumatoid arthritis', *Best Pract Res Clin Rheumatol,* 15(1), pp 91-104.

McIntosh, E. (1996) 'The cost of rheumatoid arthritis', *Br J Rheumatol,* 35(8), pp 781-90.

Meenagh, G., Iagnocco, A., Filippucci, E., Riente, L., Delle Sedie, A., Bombardieri, S., Valesini, G. and Grassi, W. (2006) 'Ultrasound imaging for the rheumatologist IV. Ultrasonography of the knee', *Clin Exp Rheumatol,* 24(4), pp 357-60.

Meenan, R.F., Mason, J.H., Anderson, J.J., Guccione, A.A. and Kazis, L.E. (1992) 'AIMS2. The content and properties of a revised and expanded Arthritis Impact Measurement Scales Health Status Questionnaire', *Arthritis Rheum,* 35(1), pp 1-10.

Melchiorre, D., Calderazzi, A., Maddali Bongi, S., Cristofani, R., Bazzichi, L., Eligi, C., Maresca, M. and Ciompi, M. (2003) 'A comparison of ultrasonography and magnetic resonance imaging in the evaluation of temporomandibular joint involvement in rheumatoid arthritis and psoriatic arthritis', *Rheumatology*, 42(5), pp 673-6.

Michelson, J., Easley, M., Wigley, F.M. and Hellmann, D. (1994) 'Foot and ankle problems in rheumatoid arthritis', *Foot Ankle Int*, 15(11), pp 608-13.

Molenaar, E., van der Heijde, D. and Boers, M. (2000) 'Update on outcome assessment in rheumatic disorders', *Curr Opin Rheumatol*, 12(2), pp 91-8.

Mulder, J.D. (1951) 'The causative mechanism in morton's metatarsalgia', *J Bone Joint Surg Br,* 33-B(1), pp 94-5.

Mulherin, D., Fitzgerald, O. and Bresnihan, B. (1996) 'Clinical improvement and radiological deterioration in rheumatoid arthritis: evidence that the pathogenesis of synovial inflammation and articular erosion may differ', *Br J Rheumatol*, 35(12), pp 1263-8.

Naraghi, A.M., White, L.M., Patel, C., Tomlinson, G., Keystone, E.C. (2009) 'Comparison of 1.0-T extremity MR and 1.5-T conventional high-field-Strength MR in patients with rheumatoid arthritis', Radiology, 251(3), pp 829-37.

Naredo, E., Bonilla, G., Gamero, F., Uson, J., Carmona, L. and Laffon, A. (2005) 'Assessment of inflammatory activity in rheumatoid arthritis: a comparative study of clinical evaluation with grey scale and power Doppler ultrasonography', *Ann Rheum Dis*, 64(3), pp 375-81.

Naredo, E., Möller, I., Moragues, C., de Agustín, J.J., Scheel, A.K., Grassi, W., de Miguel, E., Backhaus, M., Balint, P., Bruyn, G.A., D'Agostino, M.A., Filippucci, E., Iagnocco, A., Kane, D., Koski, J.M., Mayordomo, L., Schmidt, W.A., Swen, W.A., Szkudlarek, M., Terslev, L., Torp-Pedersen, S., Uson, J., Wakefield, R.J. and Werner, C; EULAR Working Group for Musculoskeletal Ultrasound. (2006) 'Interobserver reliability in musculoskeletal ultrasonography: results from a "Teach the Teachers" rheumatologist course', *Ann Rheum Dis*, 65(1), pp 14-9.

Naredo, E., Collado, P., Cruz, A., Palop, M.J., Cabero, F., Richi, P., Carmona, L. and Crespo, M. (2007) 'Longitudinal power Doppler ultrasonographic assessment of joint inflammatory activity in early rheumatoid arthritis: predictive value in disease activity and radiologic progression' *Arthritis Rheum*, 15;57(1), pp 116-24.

Naredo, E., Bijlsma, J.W., Conaghan, P.G., Acebes, C., Balint, P., Berner-Hammer, H., Bruyn, G.A., Collado, P., D'Agostino, M.A., de Agustin, J.J., de Miguel, E., Filippucci. E., Grassi, W., Iagnocco, A., Kane, D., Koski, J.M., Manger, B., Mayordomo, L., Möller, I., Moragues, C., Rejón, E., Szkudlarek, M., Terslev, L., Uson, J., Wakefield, R.J. and Schmidt. W.A. (2008) Recommendations for the content and conduct of European League Against Rheumatism (EULAR) musculoskeletal ultrasound courses', *Ann Rheum Dis,* 67(7), pp 1017-22.

Narváez, J.A., Narváez, J., Roca, Y. and Aguilera, C. (2002) 'MR imaging assessment of clinical problems in rheumatoid arthritis', *Eur Radiol*, 12(7), pp 1819-28.

Navarro-Cano, G., Del Rincón, I., Pogosian, S., Roldán, J.F. and Escalante, A. (2003) 'Association of mortality with disease severity in rheumatoid arthritis, independent of comorbidity', *Arthritis Rheum*, 48(9), pp 2425-33.

NICE (2009) *Clinical Guidelines for Rheumatoid arthritis: the management of rheumatoid arthritis in adults.* London: National Institute for Clinical Excellence.

NWCEG (2002). *Guidelines for the Management of the Foot in Rheumatic Diseases*. Salford UK: North West Podiatry Services Clinical Effectiveness Group.

O'Brien, T.S., Hart, T.S. and Gould, J.S. (1997) 'Extraosseous manifestations of rheumatoid arthritis in the foot and ankle', *Clin Orthop Relat Res*, (340), pp 26-33.

O'Dell, J.R. (2003) 'Rheumatoid Arthritis: Clinical aspects', in Koopman, W.J B. Heudebert, D.W (eds) *Clinical Primer of Rheumatology*. Philadelphia: Lippincott, Williams and Wilkins, 97-115.

O'Connor, P.J. and Grainger A.J. (2002) 'Ultrasound Imaging of Joint Disease' *Imaging*, 14, pp 188-201.

Ødegård, S., Landewé, R., van der Heijde, D., Kvien, T.K., Mowinckel, P. and Uhlig, T. (2006) 'Association of early radiographic damage with impaired physical function in rheumatoid arthritis: a ten-year, longitudinal observational study in 238 patients', *Arthritis Rheum*, 54(1), pp 68-75.

Olivieri, I., Scarano, E., Ciancio, G., Padula, A. and Benjamin, M. (2004) 'Involvement of an inconstant bursa under the head of the second metatarsal bone in spondyloarthritis', *Clin Rheumatol,* 23(1), pp 93-4.

Ostendorf, B., Scherer, A., Mödder, U. and Schneider, M. (2004) 'Diagnostic value of magnetic resonance imaging of the forefeet in early rheumatoid arthritis when findings on imaging of the metacarpophalangeal joints of the hands remain normal', *Arthritis Rheum,* 50(7), pp 2094-102.

Ostergaard, M. and Wiell C. (2004) 'Ultrasonography in rheumatoid arthritis: a very promising method still needing more validation', *Curr Opin Rheumatol*, 16(3), pp 223-30.

Otter, S.J., Bowen, C.J. and Young, A.K. (2004) 'Forefoot plantar pressures in rheumatoid arthritis', *J Am Podiatr Med Assoc,* 94(3), pp 255-60.

Paimela, L. (1992) 'The radiographic criterion in the 1987 revised criteria for rheumatoid arthritis. Reassessment in a prospective study of early disease', *Arthritis Rheum*, 35(3), pp 255-8.

Palmer, D.G. (1995) 'The anatomy of the rheumatoid lesion', *Br Med Bull,* 51(2), pp 286-95.

Palosaari, K., Vuotila, J., Takalo, R., Jartti, A., Niemelä, R.K., Karjalainen, A., Haapea, M., Soini, I., Tervonen, O. and Hakala, M. (2006) 'Bone oedema predicts erosive progression on wrist MRI in early RA--a 2-yr observational MRI and NC scintigraphy study', *Rheumatology*, 45(12), pp 1542-8.

Panayi, G.S. (1994) 'The pathogenesis of Rheumatoid Arthritis', in Wolfe F.P. and Pincus T. (eds) *Rheumatoid Arthritis: Pathogenesis, Assessment, Outcome and Treatment.* New York: Marcel Dekker Inc 75 -99.

Pando, J.A., Duray, P., Yarboro, C., Gourley, M.F., Klippel, J.H. and Schumacher, H.R.. (2000) 'Synovitis occurs in some clinically normal and asymptomatic joints in patients with early arthritis', *J Rheumatol,* 27(8), pp 1848-54.

Parker, J., Nester, C.J., Long, A.F. and Barrie, J. (2003) 'The problem with measuring patient perceptions of outcome with existing outcome measures in foot and ankle surgery', *Foot Ankle Int*, 24(1), pp 56-60.

Payne, C., Turner, D. and Miller, K (2002) 'Determinants of plantar pressures in the diabetic foot', *J Diabetes Complications*, 16(4), pp 277-83.
Petrie, A. and Sabin, C. (2005) *Medical Statistics at a glance*. 2nd Ed. Oxford: Blackwell Publishing Ltd.

Pincus, T. and Wolfe, F. (1994) 'Introduction: Updating a reassessment of traditional paradigms concerning rheumatoid arthritis', in Wolfe F.P. and Pincus T. (eds) *Rheumatoid Arthritis: Pathogenesis, Assessment, Outcome and Treatment.* New York: Marcel Dekker Inc, 1 - 74.

Pincus, T. and Sokka T. (2003) 'Uniform databases in early arthritis: specific measures to complement classification criteria and indices of clinical change', *Clin Exp Rheumatol,* 21(5 Suppl 31), pp S79-88.

Platto, M.J., O'Connell, P.G., Hicks, J.E. and Gerber, L.H. (1991) 'The relationship of pain and deformity of the rheumatoid foot to gait and an index of functional ambulation', *J Rheumatol,* 18(1), pp 38-43.

Potter, M.J. (2007) 'Discussing and debating the future of Podiatry', *Podiatry Now*, 10(9), p 19.

Prevoo, M.L., van 't Hof, M.A., Kuper, H.H., van Leeuwen, M.A., van de Putte, L.B. and van Riel, P.L. (1995) 'Modified disease activity scores that include twenty-eight-joint counts. Development and validation in a prospective longitudinal study of patients with rheumatoid arthritis', *Arthritis Rheum*, 38(1), pp 44-8.

Pullar, T. (1997) 'Joint inflammation and erosion: different mechanisms?' *Br J Rheumatol,* 36(7), pp 821-2.

Puttemans, T. and Nemery C. (1998) 'Diabetes: the use of color Doppler sonography for the assessment of vascular complications', *Eur J Ultrasound*, 7(1), pp 15-22.
QAA (2001) *Benchmark Statements: Health Care Programmes: Podiatry (chiropody).* London: Department of Health.

Quinn, M.A., Gough, A.K., Green, M.J., Devlin, J., Hensor, E.M., Greenstein, A., Fraser, A. and Emery, P. (2005) 'Anti-CCP antibodies measured at disease onset help seronegative rheumatoid arthritis and predict radiological and functional outcome', *Rheumatology*, 45(4), pp 478-480.

Rawool, N.M. and Nazarian L.N. (2000) 'Ultrasound of the ankle and foot', *Semin Ultrasound CT MR,* 21(3), pp 275-84.

RCR (2003). *Skills Course in Musculoskeletal Ultrasound*, Royal College of Radiologists, Oxford, UK.

Redmond, A.C., Waxman, R. and Helliwell, P.S. (2006) 'Provision of foot health services in rheumatology in the UK', *Rheumatology*, 45(5), pp 571-6.

Redmond, A.C., Crosbie, J. and Ouvrier, R.A (2006) 'Development and validation of a novel rating system for scoring standing foot posture: the Foot Posture Index', *Clin Biomech,* 21(1), pp 89-98.

Redmond, A.C., Crane, Y.Z. and Menz. H.B. (2008) 'Normative values for the Foot Posture Index', *J Foot Ankle Res,* Jul 31;1(1), p 6.

Ridola, C. and Palma A. (2001) 'Functional anatomy and imaging of the foot', *Ital J Anat Embryol,* 106(2), pp 85-98.

Ringen, H.O., Dagfinrud, H., Mowinckel, P. and Kvien, T. (2008) 'Patients with rheumatoid arthritis report greater physical functional deterioration in lower limbs compared to upper limbs over 10 years', *Scand J Rheumatol,* 37(4), pp 255-9.

Rockett, M.S. (1999) 'The Use of Ultrasound in the Foot and Ankle', *Journal of the American Podiatric Medical Association,* 89(7), pp 331-338.

Roemer, F.W., van Holsbeeck M. and Genant, H.K. (2005) 'Musculoskeletal ultrasound in rheumatology: a radiologic perspective', *Arthritis Rheum*, 53(4), pp 491-3.

Romanes, G.J. (1986) *Cunningham's manual of practical anatomy. Volume one : Upper and lower limbs.* Oxford: Oxford University Press.

Root, M.I. (1973) 'Biomechanical examination of the foot', *Journal of the American Podiatric Medical Association*, 63(1), pp 28-9.

Saag, K.G., Saltzman, C.L., Brown, C.K. and Budiman-Mak E. (1996) 'The Foot Function Index for measuring rheumatoid arthritis pain: evaluating side-to-side reliability', *Foot Ankle Int*, 17(8), pp 506-10.

Saladin, K.S. (2004) 'Support and Movement', in: Saladin, K.S. (ed) Anatomy & physiology: the unity of form and function, 3rd edition. New York: McGraw-Hill Companies inc, 299 – 300.

Sangha, O. (2000) 'Epidemiology of rheumatic diseases', *Rheumatology*, 39 Suppl 2, pp 3-12.

Sarrafian, S.K. (1983) *Anatomy of the foot and ankle*. Philadelphia: Lipppincott, J.B.

Savnik, A., Malmskov, H., Thomsen, H.S., Graff, L.B., Nielsen, H., Danneskiold-Samsøe, B., Boesen, J. and Bliddal, H. (2001) 'Magnetic resonance imaging of the wrist and finger joints in patients with inflammatory joint diseases', *J Rheumatol,* 28(10), pp 2193-200.

Scheel, A.K., Schmidt, W.A., Hermann, K.G., Bruyn, G.A., D'Agostino, M.A., Grassi, W., Iagnocco, A., Koski, J.M., Machold, K.P., Naredo, E., Sattler, H., Swen, N., Szkudlarek, M., Wakefield, R.J., Ziswiler, H.R., Pasewaldt, D., Werner. C. and Backhaus, M. (2005). 'Interobserver reliability of rheumatologists performing musculoskeletal ultrasonography: results from a EULAR "Train the trainers" course', *Ann Rheum Dis,* 64(7), pp 1043-9.

Schmidt, W.A., Völker, L., Zacher, J., Schläfke, M., Ruhnke, M. and Gromnica-Ihle, E.. (2000) 'Colour Doppler ultrasonography to detect pannus in knee joint synovitis', *Clin Exp Rheumatol,* 18(4), pp 439-44.

Schmidt WA, Backhaus M. (2008) 'What the practising rheumatologist needs to know about the technical fundamentals of ultrasonography'. Best Pract Res Clin Rheumatol. 22(6), pp 981-99. Review.

Scott, D.L., Shipley, M., Dawson, A., Edwards, S., Symmons, D.P. and Woolf, A.D. (1998) 'The clinical management of rheumatoid arthritis and osteoarthritis: strategies for improving clinical effectiveness', *Br J Rheumatol,* 37(5), pp 546-54.

Scott, D.L., Houssien, D.A. and Laasonen, L. (1995) 'Proposed modification to Larsen's scoring methods for hand and wrist radiographs', *Br J Rheumatol,* 34(1), p 56.

Scutellari, P.N. and Orzincolo C. (1998) 'Rheumatoid arthritis: sequences', *Eur J Radiol*, 27 Suppl 1, pp S31-8.

Semple, R., Turner, D.E., Helliwell, P.S. and Woodburn, J. (2007) 'Regionalised centre of pressure analysis in patients with rheumatoid arthritis', *Clin Biomech*, 22(1), pp 127-9.

Shi, K., Tomita, T., Hayashida, K., Owaki, H. and Ochi, T. (2000) 'Foot deformities in rheumatoid arthritis and relevance of disease severity', *J Rheumatol*, 27(1), pp 84-9.

Singh, J.A., Solomon, D.H., Dougados, M., Felson, D., Hawker, G., Katz, P., Paulus, H. and Wallace, C. (2006) 'Classification and Response Criteria Subcommittee of the Committee on Quality Measures, American College of Rheumatology. Development of classification and response criteria for rheumatic diseases', *Arthritis Rheum*, 55(3), pp 348-52.

Spector, T.D. and MacGregor , A.J. (2001). 'Epidemiology of rheumatic diseases', in Spector, T.D. and MacGregor , A.J. (Eds) *ABC of Rheumatology*. London: BMJ books.

Spiegel, T.M. and Spiegel J.S. (1982) 'Rheumatoid arthritis in the foot and ankle--diagnosis, pathology, and treatment. The relationship between foot and ankle deformity and disease duration in 50 patients', *Foot Ankle*, 2(6), pp 318-24.

Stokes, M., Hides, J., Nassiri, D.K. (1997) 'Musculoskeletal ultrasound imaging: diagnostic and treatment aid in rehabilitation'. Physical Therapy Reviews. 2, (2) , pp. 73-92(20).

Studler, U., Mengiardi, B., Bode, B., Schöttle, P.B., Pfirrmann, C.W., Hodler, J., Zanetti, M. (2008) 'Fibrosis and adventitious bursae in plantar fat pad of forefoot: MR imaging findings in asymptomatic volunteers and MR imaging-histologic comparison'. Radiology. 246(3), pp 863-70.

Swen, W.A., Jacobs, J.W., Bussemaker, F.E., de Waard, J.W. and Bijlsma, J.W. (2001) 'Carpal tunnel sonography by the rheumatologist versus nerve conduction study by the neurologist', *J Rheumatol*, 28(1), pp 62-9.

Symmons, D., Turner, G., Webb, R., Asten, P., Barrett, E., Lunt, M., Scott, D. and Silman, A. (2002) 'The prevalence of rheumatoid arthritis in the United Kingdom: new estimates for a new century', *Rheumatology*, 41(7), pp 793-800.

Symmons, D.P., Hazes, J.M. and Silman A.J. (2003) 'Cases of early inflammatory polyarthritis should not be classified as having rheumatoid arthritis', *J Rheumatol*, 30(5), pp 902-4.

Szkudlarek, M., Court-Payen, M., Strandberg, C., Klarlund, M., Klausen, T. and Ostergaard, M. (2001) 'Power Doppler ultrasonography for assessment of synovitis in the metacarpophalangeal joints of patients with rheumatoid arthritis: a comparison with dynamic magnetic resonance imaging', *Arthritis Rheum*, 44(9), pp 2018-23.

Szkudlarek, M., Court-Payen, M., Jacobsen, S., Klarlund, M., Thomsen, H.S. and Østergaard M. (2003) 'Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis', *Arthritis Rheum,* 48(4), pp 955-62.

Szkudlarek, M., Narvestad, E., Klarlund, M., Court-Payen, M., Thomsen, H.S. and Østergaard, M. (2004) 'Ultrasonography of the metatarsophalangeal joints in rheumatoid arthritis: comparison with magnetic resonance imaging, conventional radiography, and clinical examination', *Arthritis Rheum*, 50(7), pp 2103-12.

Taggart, A., Filippucci, E., Wright, G., Bell, A., Cairns, A., Meenagh, G., Pendleton, A., Rooney, M., Wright, S., Grey, A. and Grassi W. (2006) 'Musculoskeletal ultrasound training in rheumatology: the Belfast experience', *Rheumatology*, 45(1), pp 102-5.

Tak, P.P., Smeets, T.J., Daha, M.R., Kluin, P.M., Meijers, K.A., Brand, R., Meinders, A.E. and Breedveld, F.C. (1997) 'Analysis of the synovial cell infiltrate in early rheumatoid synovial tissue in relation to local disease activity', *Arthritis Rheum*, 40(2), pp 217-25.

Tan, A.L., Tanner, S.F., Conaghan, P.G., Radjenovic, A., O'Connor, P., Brown, A.K., Emery, P. and McGonagle, D. (2003) 'Role of metacarpophalangeal joint anatomic factors in the distribution of synovitis and bone erosion in early rheumatoid arthritis', *Arthritis Rheum,* 48(5), pp 1214-22.

Tarner, I.H., Härle, P., Müller-Ladner, U., Gay, R.E. and Gay, S. (2005) 'The different stages of synovitis: acute vs chronic, early vs late and non-erosive vs erosive', *Best Pract Res Clin Rheumatol,* 19(1), pp 19-35.

Taylor, P.C., Steuer, A., Gruber, J., McClinton, C., Cosgrove, D.O., Blomley, M.J., Marsters, P.A., Wagner, C.L. and Maini, R.N. (2006) 'Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis', *Arthritis Rheum,* 54(1), pp 47-53.

Terslev, L., Torp-Pedersen, S., Savnik, A., von der Recke, P., Qvistgaard, E., Danneskiold-Samsøe, B. and Bliddal, H. (2003) 'Doppler ultrasound and magnetic resonance imaging of synovial inflammation of the hand in rheumatoid arthritis: a comparative study', *Arthritis Rheum*, 48(9), pp 2434-41.

Theumann, N.H., Pfirrmann, C.W., Chung, C.B., Mohana-Borges, A.V., Haghighi, P., Trudell, D.J. and Resnick, D. (2001) 'Intermetatarsal Spaces: Analysis with MR Bursography, Anatomic Correlation, and Histopathology in Cadavers', *Radiology,* 221(2), pp 478-484.

Tuna, H., Birtane, M., Taştekin, N. and Kokino, S. (2005) 'Pedobarography and its relation to radiologic erosion scores in rheumatoid arthritis', *Rheumatol Int*, 26(1), pp 42-7.

Turner, D.E., Helliwell, P.S., Emery, P. and Woodburn, J. (2006) 'The impact of rheumatoid arthritis on foot function in the early stages of disease: a clinical case series', *BMC Musculoskelet Disord,* 7, p 102.

Turner, D.E., Helliwell, P.S. and Woodburn, J. (2007) 'Methodological considerations for a randomised controlled trial of podiatry care in rheumatoid arthritis: lessons from an exploratory trial', *BMC Musculoskelet Disord,* Nov 6;8, pp 109.

Turner, D.E., Helliwell, P.S., Lohmann Siegel, K. and Woodburn, J. (2008) 'Biomechanics of the foot in rheumatoid arthritis: identifying abnormal function and the factors associated with localised disease impact', *Clin Biomech*, 23(1), pp 93-100.

Uhlig, T. and Kvien, T.K. (2005) 'Is rheumatoid arthritis disappearing?', *Ann Rheum Dis,* 64(1), pp 7-10.

Uhlig, T., Heiberg, T., Mowinckel, P. and Kvien, T.K. (2008) 'Rheumatoid arthritis is milder in the new millennium: health status in patients with rheumatoid arthritis 1994-2004', *Ann Rheum Dis*, 67(12), pp 1710-5.

Vainio, K. (1991) 'The rheumatoid foot. A clinical study with pathological and roentgenological comments 1956 ', *Clin Orthop Relat Res,* (265), pp 4-8.

Valentin, L. and Jager K. (2003) 'Minimum Training Requirements for the Practice of Medical Ultrasound in Europe' EFSUMB Newsletter January.
van der Heijde, D.M., van 't Hof, M., van Riel, P.L. and van de Putte, L.B. (1993) 'Development of a disease activity score based on judgment in clinical practice by rheumatologists', *J Rheumatol,* 20(3), pp 579-81.

van der Heijde, DM. (1996) 'Plain X-rays in rheumatoid arthritis: overview of scoring methods, their reliability and applicability', *Baillieres Clin Rheumatol,* 10(3), pp 435-53

van der Heijde, D., Landewé, R., van Vollenhoven, R., Fatenejad, S. and Klareskog, L. (2008) 'Level of radiographic damage and radiographic progression are determinants of physical function: a longitudinal analysis of the TEMPO trial', *Ann Rheum Dis*, 67(9), pp 1267-70.

van der Leeden, M., Steultjens, M., Dekker, J.H., Prins, A.P. and Dekker, J. (2006) 'Forefoot joint damage, pain and disability in rheumatoid arthritis patients with foot complaints: the role of plantar pressure and gait characteristics', *Rheumatology,* 45(4), pp 465-9.

van der Leeden, M., Steultjens, M.P., Terwee, C.B., Rosenbaum, D., Turner, D., Woodburn, J. and Dekker, J. (2008) 'A systematic review of instruments measuring foot function, foot pain, and foot-related disability in patients with rheumatoid arthritis', *Arthritis Rheum,*. 59(9), pp 1257-69.

van der Leeden, M., Steultjens, M.P., Ursum, J., Dahmen, R., Roorda, L.D., Schaardenburg, D.V. and Dekker, J. (2008) 'Prevalence and course of forefoot impairments and walking disability in the first eight years of rheumatoid arthritis', *Arthritis Rheum*, 15;59(11), pp 1596-602.

van Gestel, A.M., Anderson, J.J., van Riel, P.L., Boers, M., Haagsma, C.J., Rich, B., Wells, G., Lange, M.L. and Felson, D.T. (1999) 'ACR and EULAR improvement criteria have comparable validity in rheumatoid arthritis trials. American College of Rheumatology European League of Associations for Rheumatology', *J Rheumatol,* 26(3), pp 705-11.

Van Gheluwe, B. and Dananberg H.J. (2004) 'Changes in plantar foot pressure with in-shoe varus or valgus wedging', *Journal of the American Podiatric Medical Association*, 94(1), pp 1-11.

van Vugt, R.M., van Dalen, A. and Bijlsma, J.W. (1998) 'The current role of high-resolution ultrasonography of the hand and wrist in rheumatic diseases', *Clin Exp Rheumatol,* 16(4), pp 454-8.

Vernon, W. (2008) 'The future of the profession', *Podiatry Now*, 11(9), pp 23-26.

Vos, K., Van der Linden, E. and Pauwels, E.K. (1999) 'The clinical role of nuclear medicine in rheumatoid arthritis patients. A comparison with other diagnostic imaging modalities', *Q J Nucl Med*, 43(1), pp 38-45.

Wakefield, R.J., Gibbon, W.W. and Emery, P. (1999) 'The current status of ultrasonography in rheumatology', *Rheumatology*, 38(3), pp 195-8.

Wakefield, R.J., Gibbon, W.W., Conaghan, P.G., O'Connor, P., McGonagle, D., Pease, C., Green, M.J., Veale, D.J., Isaacs, J.D. and Emery, P. (2000) 'The value of sonography in the detection of bone erosions in patients with rheumatoid arthritis: a comparison with conventional radiography', *Arthritis Rheum,* 43(12), 2762-70.

Wakefield, R.J., Brown, A., O'Connor, P., Grainger, A., Karim, Z., McGonagle, D., Conaghan, P. and Emery, P. (2003) 'Rheumatological ultrasound', *Rheumatology*, 42(8), p 1001.

Wakefield, R.J., Brown, A.K., O'Connor, P.J. and Emery, P. (2003) 'Power Doppler sonography: improving disease activity assessment in inflammatory musculoskeletal disease', *Arthritis Rheum*, 48(2), pp 285-8.

Wakefield, R.J., Kong, K.O., Conaghan, P.G., Brown, A.K., O'Connor, P.J. and Emery, P. (2003) 'The role of ultrasonography and magnetic resonance imaging in early rheumatoid arthritis', *Clin Exp Rheumatol*, 21(5 Suppl 31), pp S42-9.

Wakefield, R.J., Brown, A.K., O'Connor, P.J., Karim, Z., Grainger, A. and Emery, P. (2004) 'Musculoskeletal ultrasonography: what is it and should training be compulsory for rheumatologists?', *Rheumatology*, 43(7), pp 821-2.

Wakefield, R.J., Green, M.J., Marzo-Ortega, H., Conaghan, P.G., Gibbon, W.W., McGonagle, D., Proudman, S. and Emery P. (2004) 'Should oligoarthritis be reclassified? Ultrasound reveals a high prevalence of subclinical disease', *Ann Rheum Dis*, 63(4), pp 382-5.

Wakefield, R.J., Balint, P.V., Szkudlarek, M., Filippucci, E., Backhaus, M., D'Agostino, M.A., Sanchez, E.N., Iagnocco, A., Schmidt, W.A., Bruyn, G.A., Kane, D., O'Connor. P.J., Manger, B., Joshua, F., Koski, J., Grassi, W., Lassere, M.N., Swen, N., Kainberger, F., Klauser, A., Ostergaard, M., Brown, A.K., Machold, K.P. and Conaghan, P.G.; OMERACT 7 Special Interest Group. (2005) 'Musculoskeletal ultrasound including definitions for ultrasonographic pathology', *J Rheumatol*, 32(12), pp 2485-7.

Wakefield, R.J., D'Agostino, M.A., Iagnocco, A., Filippucci, E., Backhaus, M., Scheel, A.K., Joshua, F., Naredo, E., Schmidt, W.A., Grassi, W., Moller, I., Pineda, C., Klauser, A., Szkudlarek, M., Terslev, L., Balint, P., Bruyn, G.A., Swen, W.A., Jousse-Joulin, S., Kane. D., Koski, J.M., O'Connor, P., Milutinovic. S. and Conaghan, P.G; OMERACT Ultrasound Group. (2007) 'The OMERACT Ultrasound Group: Status of Current Activities and Research Directions', *J Rheumatol*, 34(4), pp 848-51.

Wakefield, R.J., Freeston, J.E., O'Connor, P., Reay, N., Budgen, A., Hensor, E.M., Helliwell, P.S., Emery, P. and Woodburn, J. (2008) 'The optimal assessment of the rheumatoid arthritis hindfoot: a comparative study of clinical examination, ultrasound and high field MRI', *Ann Rheum Dis*, 67(12), pp 1678-82.

Wall, B. (1997) 'Assessment of ischaemic feet in diabetes', *J Wound Care*, 6(1), pp 32-8.
Warwick, R. Williams, P.L., Llewellyn, P., Davies, D.V. Editors (1973) *Gray's anatomy.* 5th ed. Harlow: Longman.

Weijers ,R.E., Walenkamp, G.H.I.M.,. van Mameren, H, Joost A.A.M. and van den Hout (2003) 'Changes in soft tissue of the forefoot during loading: a volumetric study', *The Foot,* 13, pp 70-75.

Weishaupt, D., Treiber, K., Kundert, H.P., Zollinger, H., Vienne, P., Hodler, J., Willmann, J.K., Marincek, B. and Zanetti, M. (2003) 'Morton neuroma: MR imaging in prone, supine, and upright weight-bearing body positions', *Radiology,* 226(3), pp 849-56.

Welsing, P.M., van Gestel, A.M., Swinkels, H.L., Kiemeney, L.A. and van Riel, P.L. (2001) 'The relationship between disease activity, joint destruction, and functional capacity over the course of rheumatoid arthritis', *Arthritis Rheum*, 44(9), pp 2009-17.

Weyand, C.M. and Goronzy J. J. (1997) 'Pathogenesis of rheumatoid arthritis', *Med Clin North Am,* 81(1), pp 29-55.

Weiner-Ogilvie, S. and Rome, K. (1998) 'The reliability of three techniques for measuring foot position', *Journal of the American Podiatric Medical Association*, 88(8), pp 381-386.
Weiner-Ogilvie, S. (1999) 'The foot in rheumatoid arthritis', *The Foot,* 9, pp 169-174.
Wiles, N., Symmons, D.P., Harrison, B., Barrett, E., Barrett, J.H., Scott, D.G. and Silman. A.J.(1999) 'Estimating the incidence of rheumatoid arthritis: trying to hit a moving target?', *Arthritis Rheum*, 42(7), pp 1339-46.

Williams, A.E. and Bowden P.B. (2004) 'Meeting the Challenge for Foot Health in Rheumatic Diseases', *The Foot*, 14, pp 154-158.

Wolfe, F. and Hawley, D.J. (1998) 'The longterm outcomes of rheumatoid arthritis: Work disability: a prospective 18 year study of 823 patients', *J Rheumatol,* 25(11), pp 2108-17.

Woodburn, J., Barker, S. and Helliwell, P.S. (2002). 'A randomized controlled trial of foot orthoses in rheumatoid arthritis', *J Rheumatol*, 29(7), pp 1377-83.

Woodburn, J. and Helliwell P.S. (1996) 'Relation between heel position and the distribution of forefoot plantar pressures and skin callosities in rheumatoid arthritis', *Ann Rheum Dis,* 55(11), pp 806-10.

Woodburn, J. and Helliwell P.S. (1997) 'Foot problems in rheumatology', *Br J Rheumatol,* 36(9), pp 932-4.

Woodburn, J. and West S.G. (1999). 'Pain in the foot' in Snaith M.L. (ed) *ABC of Rheumatology*. London: BMJ Books, 18-23.

Woodburn, J., Stableford, Z., Helliwell, P.S. (2000) 'Preliminary investigation of debridement of plantar callosities in rheumatoid arthritis', Rheumatology, 39(6), pp 652-4.

Woodburn, J., Helliwell, P.S. and Barker, S. (2002) 'Three-dimensional kinematics at the ankle joint complex in rheumatoid arthritis patients with painful valgus deformity of the rearfoot', *Rheumatology*, 41(12), pp 1406-12.

Woodburn, J., Udupa, J.K., Hirsch, B.E., Wakefield, R.J., Helliwell, P.S., Reay, N., O'Connor, P., Budgen, A. and Emery, P. (2002) 'The geometric architecture of the subtalar and midtarsal joints in rheumatoid arthritis based on magnetic resonance imaging', *Arthritis Rheum* 46(12), pp 3168-77.

Wordsworth, P. (1995) 'Genes and arthritis', *Br Med Bull*, 51(2), pp 249-66.

Wrobel, J.S. (2000) 'Outcomes research in podiatric medicine', *Journal of the American Podiatric Medical Association*, 90, pp 403-410.

Young, M.J., Coffey, J., Taylor, P.M. and Boulton A.J.M. (1995) 'Weight bearing ultrasound in diabetic and rheumatoid arthritis patients', *The Foot,* 5, pp 76-79.

Young-Min, S., Cawston, T., Marshall, N., Coady, D., Christgau, S., Saxne, T., Robins, S. and Griffiths, I. (2007) 'Biomarkers predict radiographic progression in early rheumatoid arthritis and perform well compared with traditional markers', *Arthritis Rheum,* 56(10), pp 3236-47.

Youssef, P.P., Kraan, M., Breedveld, F., Bresnihan, B., Cassidy, N., Cunnane, G., Emery, P., Fitzgerald, O., Kane, D., Lindblad, S., Reece, R., Veale, D. and Tak, P.P. (1998) 'Quantitative microscopic analysis of inflammation in rheumatoid arthritis synovial membrane samples selected at arthroscopy compared with samples obtained blindly by needle biopsy', *Arthritis Rheum*, 41(4), pp 663-9.

Zanetti, M., Strehle, J.K., Zollinger, H. and Hodler, J. (1997) 'Morton neuroma and fluid in the intermetatarsal bursae on MR images of 70 asymptomatic volunteers', *Radiology*, 203(2), pp 516-520.

Zendman, A.J.W., Van Venroij, W.J. and Pruijn G.J.M. (2006) 'Use and Significance of anti-CCP autoantibodies in rheumatoid arthritis', *Rheumatology*, 45, pp 20-25.

Zvaifler, N.J., Boyle, D and, Firestein, G.S. (1994) 'Early synovitis--synoviocytes and mononuclear cells', *Semin Arthritis Rheum*, 23(6 Suppl 2), pp 11-6.

# Bibliography

Akil, M. and Amos, R.S. (1999) *ABC of Rheumatology 2nd Edition*. London: BMJ books.

Bowling, A. (2002) *Handbook of health research methods : investigation, measurement and analysis.* Maidenhead: Open University Press.

Bushberg, J.T., Seibert, J.A., Leidholdt, E.M. and Boone, J.M. (2002) *The Essential physics of medical imaging*. 2nd Edition. USA: Lippincott Williams and Wilkins.

Byrne, D.W. (1998) *Publishing your medical research paper*. Canada: Lippincott Williams and Wilkins.

Canoso, J.J. (1997) *Rheumatology in Primary Care*. Philadelphia: WB Saunders Company.

Donatelli, R.A. and Wolf, S.L. Editors (1990) *The biomechanics of the foot and ankle*. Philadelphia: F.A. Davis Company.

Fish, P. (1990). *Physics and instrumentation of diagnostic medical ultrasound.* Chichester: Wiley.

French, S., Neville, S. and Laing, J. (1994) *Teaching and learning: A Guide for Therapists.* Oxford, UK: Butterworth, Heinmann.

Helliwell, P., Woodburn, J., Redmond, A., Turner, D.E. and Davys, H. (2007) *The Foot and Ankle in Rheumatoid Arthritis*. Edinburgh: Churchill Livingstone.

Kinnear, P.R. and Gray, C.D. (2006) *SPSS14 made simple.* Hove UK: Psychology press. Kremkau, F. W. (1998) *Diagnostic Ultrasound.* 6th Ed. Philadelphia: W.B. Saunders.

Machin, D., Campbell, M.J., Fayers, P. and Pinol, A.P.Y. (1997) *Sample size tables for clinical studies*. 2nd ed. Oxford: Blackwell Science Ltd.

McCance, K.L. and Huether, S.E. (2002) Pathophysiology : the biologic basis for disease in adults & children, 4th edition. St. Louis: Mosby.

Petrie, A. and Sabin, C. (2005) *Medical Statistics at a glance*. 2nd Ed. Oxford: Blackwell Publishing Ltd.

Romanes, G.J. (1986) *Cunningham's manual of practical anatomy. Volume one : Upper and lower limbs.* Oxford: Oxford University Press.

Saladin, K.S. (2004) Anatomy & physiology: the unity of form and function, 3rd edition**.** New York: McGraw-Hill Companies inc.

Sarrafian, S.K. (1983) *Anatomy of the foot and ankle*. Philadelphia: Lipppincott, J.B. Spector, T.D. and MacGregor , A.J. (2001). *ABC of Rheumatology*. London: BMJ books.

Warwick, R. Williams, P.L., Llewellyn, P., Davies, D.V. (1973) *Gray's anatomy.* 5th ed. Harlow: Longman.

Wolfe F.P. and Pincus T. (1994) *Rheumatoid Arthritis: Pathogenesis, Assessment, Outcome and Treatment.* New York: Marcel Dekker Inc.