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Comparative distribution of ultrasound-detectable forefoot bursae in patients with osteoarthritis and rheumatoid arthritis

LINDSEY HOOPER[1,2,3], CATHERINE J. BOWEN[1,3], LUCY GATES[1,2], DAVID CULLIFORD[2,3], NIGEL K. ARDEN[2,3] AND CHRISTOPHER J EDWARDS[1,2]

Name of department(s) and institution(s) to which the work should be attributed:

1. University Hospital Southampton NHS Foundation Trust, UK

2. University of Southampton, UK

3. University of Oxford, NIHR Musculoskeletal Biomedical Research Unit, UK

Corresponding author

Dr Lindsey S. Hooper

Postal address: Faculty of Health Sciences, University of Southampton,
Building 45, Burgess Road,
Southampton, Hampshire. United Kingdom.
SO17 1BJ

Email: l.hooper@soton.ac.uk Tel: 02380 795279 Fax: 02380 796711

Co-authors

- Dr Catherine J. Bowen; Faculty of Health Sciences, University of Southampton, UK
- Ms Lucy Gates; Faculty of Health Sciences, University of Southampton, Southampton, UK
- Mr David J. Culliford; Faculty of Medicine, University of Southampton, Southampton, UK
- Prof Nigel K. Arden; NIHR Musculoskeletal Biomedical Research Unit, Oxford, UK.
- Dr Christopher J. Edwards; Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, UK.

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ABSTRACT

Objective: To investigate the prevalence and distribution of forefoot bursae (FFB) in individuals with osteoarthritis (OA), rheumatoid arthritis (RA) and healthy controls (HC). Additionally, we sought to identify mechanical or inflammatory factors predicting FFB count.

Methods: A cross-sectional, observational study was completed in three cohorts; 1. OA (n=50), 2. RA (n=56), 3. HC (n=50). FFB were recorded as present if detectable in two ultrasound (US) scanning planes. The comparative probabilities of FFB presence between groups was expressed as odds ratios. Mechanical factors, including joint deformity, range of motion and foot posture, were determined for both patient groups. Inflammatory factors, including serology, DAS28 and US-detected metatarsophalangeal joint hypertrophy and metatarsal head erosion, were determined for RA patients. Multiple linear regression analyses were used to determine factors related to FFB count in patient groups.

Results: FFB were highly prevalent in both OA and RA groups (OA: 94 per 100 patients; RA: 88 per 100 patients), compared to HC (56 per 100 participants). FFB distribution significantly differed between patient groups (RA-OA: X^2=15.64, p≤0.001). In OA patients FFB were commonly located in the medial/lateral forefoot region but across all regions for RA patients. In OA patients reduced ankle joint range of motion predicted FFB count (R^2=0.030, p=0.037). In RA patients erosion presence was related to FFB count (R^2=0.42, p≤0.001).

Conclusion: FFB are highly prevalent in patients with OA and RA. FFB distribution significantly differs between patient groups. FFB in patients with OA may be related to mechanical factors.

The comparative distribution of FFB in OA and RA

SIGNIFICANCE AND INNOVATIONS

- FFB are highly prevalent in patients with OA and RA
- The distribution of FFB across forefoot sites significantly differs between patients with OA and RA
- FFB occurring in OA patients may be related to mechanical factors.

The comparative distribution of FFB in OA and RA

Previous studies have demonstrated a high prevalence of clinically meaningful, ultrasound (US) detected forefoot bursae (FFB) in patients who have rheumatoid arthritis (RA) [1, 2]. We hypothesised that, in patients who have RA, the increased prevalence of FFB may be related to increased inflammation. This concurs with other investigators who have suggested that the synovium, which lines the otherwise inconspicuous intermetatarsal anatomical bursae, becomes hypertrophied as a consequence of excessive disease activity [3-5]. Conversely, other investigators have hypothesised that adverse mechanical pressure and shearing forces may result in the accumulation of interstitial fluid within the subcutaneous tissues, often termed adventitial bursae [6-8]. From our previous investigations of FFB, utilising musculoskeletal ultrasound (US), we have shown that in patients with RA a combination of both mechanical and inflammatory factors may be related to the high prevalence of FFB noted both within the intermetatarsal spaces and in the plantar forefoot region [9]. In order to optimise therapeutic interventions, it would be beneficial to compare the prevalence and distribution of US-detectable FFB between patients with RA and patients with a non-inflammatory arthritis (OA) or healthy controls (HC). Potential differences in the prevalence or distribution of FFB between patient groups will contribute towards an improved understanding of the potential clinical importance and mechanical or inflammatory factors underpinning their presence.

To our knowledge, the prevalence and distribution of FFB have not been investigated in any other musculoskeletal condition than RA. The primary aim of this study was therefore to investigate the prevalence and distribution of forefoot bursae (FFB) in individuals with medial knee osteoarthritis (OA) (i.e. non-inflammatory arthritis), rheumatoid arthritis (RA) (i.e. inflammatory arthritis) and healthy controls (HC) (i.e. comparative control group). Additionally, we sought to identify whether mechanical (in both patient groups) or inflammatory (in RA patients only) factors were significantly related to the presence of FFB.

MATERIALS AND METHODS

Study design

A comparative, cross-sectional observational study design was used, in which US-detected FFB presence was defined as the main outcome variable of interest. Ethical approval for the study was obtained from the S.W. Hampshire LREC for the investigation of FFB in OA and RA patient groups. Ethical approval was obtained from the University of Southampton ethics committee for the observation of US-detected FFB in HC. All participants gave written informed consent for inclusion.

Study population

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Participants were required to attend a single data collection appointment only. Data collection took place between January 2010 and September 2011. All data collection occurred within the Wellcome Trust Clinical Research Facility, Southampton General Hospital. A single investigator undertook all the clinical foot and US assessments (LH), and was blinded to the patient reported outcome measures, blood tests and disease activity scores.

Consecutive patients with a diagnosis of unilateral knee OA, of Kellgren and Lawrence grade ≥2 at the time of recruitment [10] and of RA, (consistent with 1987 ACR criteria) were prospectively recruited from a population of patients attending a United Kingdom (UK) rheumatology outpatient clinic. A group of HC adults were recruited from the staff and student population at the University of Southampton for comparative purposes.

Inclusion criteria

Patients with OA were included in the study if they had radiological evidence of early OA in the medial tibio-femoral knee compartment (based upon a modified Kellgren & Lawrence score of 2-3 [11], and Joint space width of <1mm), had pain in the knee for most days of the previous month, were attending a local rheumatology outpatient clinic and were ambulatory at the time of recruitment. Patients with RA were included in the study if they had a diagnosis of RA according to ACR criteria, were attending a rheumatology outpatient clinic, took part in the baseline FeeTURA study [1], and were aged between 18-80 years at the time of initial recruitment into the study. HC were included in the study if they had no diagnosis of a musculoskeletal condition, were a student or staff member at the University of Southampton and were willing and able to participate in the study.

Exclusion criteria

For all three groups (OA, RA and HC) participants were excluded from the study if they had received any corticosteroid injection therapy to the lower limb within the 12 weeks, or injection of hyaluronic acid within the 24 weeks, prior to recruitment; had undergone any surgical procedure to the any joints of the lower limb in the 24 weeks prior to recruitment; were pregnant or were unable to walk a distance of 5 metres or had other concomitant musculoskeletal disease. Participants were also excluded if they had a serious medical or psychological disorder that would affect the study protocol, were unable to comply, understand or were unwilling to give informed consent. OA group participants were recruited from a larger study of vitamin D supplementation, therefore the following exclusion criteria were also applied to this group: the presence of secondary OA subsequent to any of the following: septic arthritis, gout, pseudo-gout, Wilson's disease, Paget's

disease, hyperparathyroidism, hypothyroidism, sarcoidosis, osteomalacia, osteoporotic fracture, a history of inflammatory disease, hypercalcaemia or hypercalciuria**;** were using any of the following at the time of initial recruitment: glucosamine or chondroitin within the 12 weeks prior to recruitment, bisphosphonates, vitamin D supplementation with at total vitamin D content >200iμ, any anti-epileptic medication**.**

Assessment of demographic and clinical characteristics

For all groups, demographic data including age, gender and body mass index (BMI)were recorded. Disease duration was noted for both RA and OA patient groups. Foot characteristics considered representative of mechanical factors and selected based upon the findings of previous work, literature review and potential clinical relevance included assessment of foot joint deformity (hallux abducto-valgus (HAV), or lesser digital deformity (LDD)), range of motion (ankle, subtalar, midfoot, or metatarsophalangeal joint (MTPJ)), and foot posture. Forefoot deformity (including lesser digital deformity and hallux abducto-valgus deformity) was scored as either present (1) or absent (0) for each joint assessed and the cumulative score for each foot generated (thus LDD score range: 0-8, HAV score range: 0-2). Joint range of motion was scored as full (0), limited (1) or rigid (2) for each joint of interest and the score for each foot combined (0-4). The foot posture index (FPI) was selected as a composite measure of weight-bearing foot joint alignment and was scored for both feet combined (0-24) [12].

For participants with RA, variables related to inflammatory joint disease, including serological markers (ESR, CRP), a composite measure of disease activity (DAS28 score) [13], and US-detected metatarsophalangeal joint hypertrophy (JH) and metatarsal head erosion (ER), were determined. JH was noted as present if distension of the dorsal synovial joint membrane, as a consequence of either increased fluid volume or membrane thickening, extended beyond the proximal or distal attachment sites at the metatarsal head or base of the proximal phalanx respectively. Metatarsal head ER was noted as present if a distinct loss in cortical bone was observed in two perpendicular scanning planes.

Assessment of FFB using US

US scans for all participants were completed using a Diasus® diagnostic scanner (System 8, Dynamic imaging, Livingston, Scotland, UK) in grey-scale, B-Mode to provide real-time images. All US scanning was performed in accordance with the British Medical Ultrasound Society guidelines for safe use [14] and completed by a trained researcher (LH). All US scans were performed after completion of a

clinical assessment as per the standardised protocol for the study. The primary study outcome, the presence of FFB, was determined for all participants using a pre-determined US scanning protocol for the forefoot region [4, 15]. Both forefeet were imaged in all participants from plantar and dorsal approaches, in longitudinal and transverse scanning planes, using 8-16MHz and 5-10MHz linear array transducers, and were completed prior to the assessment of mechanical foot characteristics. Inter-rater agreement in the use of US between the primary researcher and a second 'expert' researcher was confirmed as good-excellent on two occasions (kappa 0.6 and 0.8 respectively), suggesting that the likelihood of reporting error is minimal. The reliability of a podiatrist undertaking US examination for the evaluation of FFB prevalence has been reported previously by this research group [15].

As illustrated in figure one, FFB were classified as inter-metatarsal (IM) lesions if a defined region of hypo-echogenicity was noted as occurring within the IM spaces, either inferiorly or superiorly to the deep transverse inter-metatarsal ligament. FFB were classified as plantar lesions if a defined region of hypo-echogenicity, occurring inferior to the level of the base of the metatarsal heads, was observed. Thus the total number of possible IM lesions observed in a single foot was four, whilst the total number of plantar lesions was five, yielding a total of nine possible lesions per foot. Participants with one or more FFB were considered as a positive 'case' for the purposes of prevalence analysis.

Statistical Analysis

All analysis was completed using Stata version 11.0 (Stata Corp, USA), or SPSS version 18.0 (Chicago, USA). Prior to analysis, data distribution was checked for inconsistencies, outliers, missing information and normalcy. The demographic and clinical characteristics of the study participants are presented as the mean, standard deviation (SD) and range. Statistically significant differences in demographic and clinical characteristics between groups were determined using independent sample t-tests. Statistical significance was reported at the 5% confidence level, based upon two-tailed analysis ($p \leq 0.05$).

The total number of US-detectable FFB for both feet combined was calculated for each participant; these count scores were treated as continuous variables for the purposes of analysis, although they were bounded between 0-18. For RA participants, the total number of US-detectable JH and ER was also calculated and scores bounded between 0-10. The point prevalence proportion (PP) of US-detectable FFB was calculated by the division of the sum of identified cases by the sum of the total studied population and expressed per 100 patients. The probability of FFB presence was determined for each group and comparatively expressed as an odds ratio (inclusive of 95% confidence interval and p-value). Linear regression analysis, with ordinary least squares estimation, was used to explore

statistical relationships between FFB count as the primary outcome of interest and potential explanatory variables (mechanical and inflammatory factors) in the patient groups. Significant factors for each participant group were subsequently entered into a multiple linear regression model, which was adjusted for age and BMI, to identify potential confounding or colinearity within the study findings.

FFB were grouped into medial (sites 1-3), central (sites 4-6) or lateral (sites 7-9) scores (figure 1). Trends between medial, central and lateral FFB scores were then coded into one of four categories: 1. equal distribution of FFB across all sites, 2. increased distribution laterally, 3. increased distribution centrally, 4. other distribution. Categories were selected based upon observations of overall trends within the data for each group. It is noteworthy that few patients demonstrated an increasing distribution medially therefore this was not included as a category. Chi^2 analyses were used to determine statistically significant differences in pattern category between patient groups.

RESULTS

Study populations

156 participants were recruited to the study, 50 with OA, 56 with RA and 50 HC. A summary of the demographic and clinical characteristics of the study participants is shown in table 1. A summary of measured mechanical and inflammatory factors is shown in Table 2. Between the three groups, participant age significantly differed (RA-HC $p \leq 0.001$; OA-HC $p \leq 0.001$; RA-OA $p=0.006$). Additionally, weight, BMI and disease duration significantly differed between participants with OA and RA ($p \leq 0.001$, $p \leq 0.001$, $p=0.043$ respectively).

FFB prevalence

The overall prevalence of FFB (combined IM and plantar lesions) in patients with OA was 94 per 100 participants (mean=2.8, SD=1.5, range-0-5). Similarly, the prevalence of FFB in patients with RA was 88 per 100 participants (mean=3.05, SD-2.14, range=0-11), whilst in HC was 56 per 100 participants (mean=1.3, SD=1.5, range=0-6).

Participants with OA were 1.7 times more likely to have at least one FFB than HC (0.94/0.56); the relative risk ratio for FFB occurrence in patients with OA was therefore 1.68 (95% CI=1.40-2.01, $p \leq 0.001$). Participants with RA were 1.6 times more likely to have at least one FFB than HC (0.88/0.56); the relative risk ratio for FFB occurrence in patients with RA was therefore 1.57 (95% CI=1.30-1.90, $p \leq 0.001$).

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FFB distribution

The distribution pattern of FFB significantly differed between all groups (RA-HC: X^2=26.37, p≤0.001; RA-OA: X^2=15.64, p≤0.001; OA-HC: X^2=16.02, p≤0.001). FFB were commonly located in the medial or lateral forefoot region in OA and HC groups, and across all regions in patients with RA (figure 2). Differences in the shape of detected FFB were also observed and are illustrated in figure 3.

Factors relating to FFB presence in patients with OA or RA

For patients with OA reduced ankle joint range of motion was determined to be significantly independently related to US-detected FFB count (R^2=0.09, p=0.037, table 3a). Lesser digital deformity was approaching significance following univariate analysis and this was therefore also included in the further multiple regression model. Subsequently, both explanatory variables remained significant when entered into a multiple regression analysis, with the resultant model explaining 15% of the variability in the observed number of FFB in this patient group (table 3b).

For patients with RA, an increased presence of metatarsal head ER and reduced ankle joint range of motion were determined to be significantly related to FFB count (R^2=0.18, p≤0.001; R^2=0.08, p=0.039 respectively, table 3a). Metatarsal head ER remained significant when entered into a multiple regression analysis, with the resultant model explaining 18% of the variability in the observed number of FFB (table 3b).

DISCUSSION

To our knowledge, this is the first study to comparatively determine the prevalence of US-detectable forefoot bursae (FFB) between patients who have osteoarthritis (OA), rheumatoid arthritis (RA) and healthy controls (HC). Interestingly, FFB were highly prevalent in both OA and RA patient groups compared to the healthy control group (i.e. patients with OA and RA were shown to be 1.6 and 1.7 times more likely to have at least one FFB than a HC respectively). Furthermore, the results of this study suggest that patients with OA have a higher prevalence of US detectable FFB than those with RA. However, the sensitivity and specificity of US for detecting and differentiating between FFB and fibrotic changes within the forefoot has not yet been established. It is possible therefore that misclassification of FFB and fibrotic lesions could be contributing to an over-reporting of FFB presence. Future work which determines the construct validity of US-reported FFB, with comparative histopathological analysis, would be of significant benefit to this area of study. When considering the clinical importance of this work it is pertinent to note that all conclusions drawn are based upon the outcome of US investigation for which validity has not been proven. It is also noteworthy that It was not our intention to reference US as a 'gold standard' technique, rather to

see if the phenomenon that was previously found in patient with RA, was similar in patients with knee OA or in HC.

None the less, following an extensive literature review no previous studies investigating the presence of US-detectable FFB in patients with OA have been reported. As such, the surprisingly high prevalence of FFB cannot be directly compared to other works. In a similar lower limb study, Silva [16] has reported the presence of bursal hypertrophy in the absence of active inflammation in patients with mechanically elicited trochanteric pain. In this investigation the authors hypothesise that mechanical irritation contributed to both the hypertrophy of the bursa and the fibrotic changes seen in the associated histopathological analysis of the excised tissue. It is possible that a similar rationale of mechanical irritation to the plantar forefoot, subsequent to proximal/distal joint degradation and kinetic dysfunction, may account for the high presence of FFB reported in this study [17-19].

The observed pattern of FFB distribution significantly differed between the OA and RA participants of this study. FFB were commonly located in the lateral or medial forefoot region in OA participants, and across all forefoot regions in RA participants (figure 2). These findings could suggest that the distribution pattern of FFB is related to underlying musculoskeletal pathology however further work is required to substantiate this theory. It is noteworthy however, that both OA and RA groups had the highest prevalence of FFB observed in the 4/5 inter-metatarsal space, which was also noted to be proportionally similar to in the HC group. This could suggest that lesions identified in this region are not related to underlying musculoskeletal pathology, and in this sense are of less clinical relevance. Similarly, although a high prevalence of FFB was observed in both patient groups, a high proportion were also noted in the control group, indicating that some FFB may be present yet clinically 'silent' within a general population. The observations of overall FFB distribution made in this study do nonetheless appear to reinforce those of previous authors indicating that FFB can be found in both the intermetatarsal and plantar metatarsal head regions of the forefoot [7, 20, 21]. Future investigation of potential associations between FFB and self-reported pain or disability, as an indication of clinical relevance in OA or HC groups would be of additional clinical benefit.

Despite similarities between the prevalence and distribution of FFB in patients with RA in this study and those of previous works, our investigation of predictive factors demonstrated minimal support for the theoretical contribution of excessive inflammation to the development of FFB [22]. The presence of metatarsal head erosion remained the only significant independent predictor of FFB

count in patients with RA, after multiple linear regression analysis. However, reduced ankle joint range of motion was initially identified as a significant factor in first phase univariate regression analyses. These findings suggest, that erosion and reduced ankle joint range of motion are perhaps colinear, and the rationale for the consistent significance of erosion is its' confounding relationship with joint function rather than acute inflammation. It is arguably unclear to what extent erosion should be considered as representative of inflammatory disease activity, disease chronicity or mechanical impairment of the MTP joints in this experimental context. Interestingly this concept is arguably reinforced by the findings of Woodburn *et al*. [23], who demonstrate changes in forefoot kinetics associated with impaired ankle joint architecture in patients with RA. Future use of Power Doppler (PD) US or Magnetic Resonance Imaging to identify active inflammation would enhance subsequent study of the clinical importance of FFB in patients with RA.

This study has a number of strengths and limitations. The participants with OA or RA were consecutively, prospectively recruited from an outpatient secondary care setting and as such the study findings may be considered generalisable to similar patients within the UK. There is no known pathophysiological mechanism that would lead to regional variation in the reported prevalence of FFB in such patient groups. However, the generalisability of the study results to patients not reviewed within a secondary care setting should be considered [24].

The patients with OA included within this study had a greater BMI than RA and HC groups. Previous research has suggested a link between elevated BMI and mechanical impairment in terms of both kinematic and kinetic joint loading parameters [25-27]. The additional loading and torsional stress exerted upon the soft tissues of the forefoot as a consequence of elevated BMI are unclear, although such theoretical links provide a plausible pathophysiological rationale for an association between BMI and FFB presence [18]. It is possible that the overall elevation in BMI present in patients with OA may contribute to the increased presence of FFB recorded. It is currently unclear whether elevated BMI may be an aetiological, putative or confounding factor in the development of FFB. This is a common problem when comparing OA and RA. In an attempt to adjust for this, BMI was included within the regression model, but was not significantly related to FFB count in either group. Improved understanding of the relationship between FFB and BMI would help inform the further determination of the clinical importance of FFB in differing patient groups. Furthermore, it should be acknowledged that the HC group were pragmatically recruited and as such, differ essentially in many aspects from the patient groups. Ideally, these groups could have been better fit and theoretically,

the differences between the OA/RA and HC participants could have been explained by the differences in baseline characteristics.

Throughout the course of data collection the researcher undertaking the US assessment was not blinded to the group of each participant, and as such there is potential for observer bias within the reported results [24]. Additionally, the researcher completing the US assessment also completed the foot assessment. However to minimise subjectivity in observation, a strict protocol of US procedure and FFB identification was adhered to throughout data collection and US examination was always performed after the completion of a clinical assessment in order to standardised the study methodology, minimising bias where possible. Additionally, the researcher undertaking the investigation completed a comprehensive formal training programme in the use of US. Inter-rater agreement in the use of US between the primary researcher and a second 'expert' researcher was confirmed as good-excellent on two occasions, suggesting that the likelihood of reporting error is minimal. None the less, validation of a method of characterising FFB is warranted to strengthen future work in this area. Furthermore, the use of Power Doppler (PD) was not available at the time of this study, however it is strongly recommended that any future investigation in this area should incorporate this within its' US protocol. It is unclear to what extent current systemic measures such as CRP, ESR or the 28-joint disease activity score accurately reflect ongoing disease activity within the foot and as such localised PD examination is particularly warranted in any subsequent work.

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Conclusion

FFB are highly prevalent in both patients with OA and RA. The distribution of FFB across forefoot sites significantly differs between these two patient groups. The findings of this study suggest that FFB occurring in patients with OA may be related to mechanical factors. Further investigation of localised inflammation using US Power Doppler and dynamic mechanical analyses are recommended, in order to optimise future treatments.

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AUTHORS CONTRIBUTIONS

All authors contributed to the development and review of the final transcript.
Study conception and design: Hooper, Bowen, Arden, Edwards
Acquisition of data: Hooper, Gates
Analysis and interpretation of data: Hooper, Culliford, Bowen, Arden, Edwards

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TABLES

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Table 1: Cohort demographic, inflammatory & mechanical characteristics
Where SD = standard deviation, BMI = body mass index, ROM = range of motion, MTPJ = metatarsophalangeal joint, HAV = hallux abducto-valgus deformity. Forefoot deformity (including LDD and HAV) was scored as either present (1) or absent (0) for each joint assessed and the cumulative score for each foot generated. Joint range of motion was scored as full (0), limited (1) or rigid (2) for each joint of interest and the score for each foot combined (0-4). The foot posture index (FPI) was selected as a composite measure of weight-bearing foot joint alignment and was scored for both feet combined (0-24) [12].

	HEALTHY CONTROLS (N=50)	KNEE OA (N=50)	RA (N=56)
	Mean, (SD), Range	**Mean**, (SD), Range	**Mean**, (SD), Range
age (years)	**41**, (13), 20-65	**66.3**, (12.2), 53-80	**62**, (11.8), 28-89
BMI	**24.6**, (4.5), 18.9-38.4	**28.6**, (5), 19.3-41.5	**25.5**, (3.9), 19.1-33.4
disease duration (years)	-	**11.2**, (9.3), 1-40	**15.1**, (10.3), 3-45
Ankle ROM	**2.1**, (0.5), 2-4	**2.7**, (1.0), 2-4	**3.2**, (1.1), 2-4
Subtalar ROM	**2.1**, (0.5), 2-4	**2.5**, (1.0), 2-4	**3.2**, (1.1), 2-4
Midfoot ROM	**2.1**, (0.5), 2-4	**2.7**, (1.0), 2-4	**3.5**, (1.4), 2-4
MTPJ ROM	**2.2**, (0.6), 1-4	**2.9**, (1.1), 2-4	**3.6**, (1.3), 2-4
HAV	**0.2**, (0.6), 0-2	**0.6**, (0.9), 0-2	**1.0**, (1.0), 0-2
Lesser digital deformity	**0.6**, (1.4), 0-6	**4.1**, (1.2), 2-8	**5.5**, (1.7), 2-8
Foot posture index	**1.2**, (3.8), -6-16	**3.1**, (3.8), 0-16	**9.6**, (8.0), -2-24
CRP (mg/L)	-	-	**8.8**, (13.2), 1-73
ESR (mm/hr)	-	-	**20.1**, (20.5), 0-111
DAS 28-CRP	-	-	**2.9**, (1.2), 1-5.4
DAS 28-ESR	-	-	**3.1**, (1.3), 0.3-6

The comparative distribution of FFB in OA and RA

Table 3: Predictors of FFB count: age-adjusted, linear regression analyses
3a shows results of univariate, age-adjusted, linear regression analyses for all dependent variables; 3b shows results of a multiple linear regression analyses for previously identified independent predictors of FFB count.
Where BMI = body mass index; jROM = joint range of motion; CI = confidence interval. *= Significant at the 0.05 level.

3a.

EXPLANATORY VARIABLES	HC			OA			RA		
	Coefficient	p-value (95% CI)	Adjusted R^2	Coefficient	p-value (95% CI)	Adjusted R^2	Coefficient	p-value (95% CI)	Adjusted R^2
BMI	-0.004	0.934 (-0.10-0.09)	0.00	-0.00	0.948 (-0.09-0.09)	0.00	-0.01	0.888 (-0.17-0.14)	0.00
MTP Joint hypertrophy	0.88	0.107 (-0.2-2.0)	0.05	-0.01	0.979 (-0.48-0.47)	0.00	0.14	0.175 (-0.06-0.34)	0.03
erosion	0.41	0.072 (-0.04-0.86)	0.07	0.03	0.766 (-0.20-0.26)	0.00	0.27	0.001 (0.11-0.43)*	0.18
foot posture	0.17	0.003 (0.06-0.27)*	0.17	-0.04	0.497 (-0.15-0.07)	0.10	0.04	0.272 (-0.03-0.11)	0.02
hallux abducto-valgus	0.88	0.024 (0.12-1.63)*	0.10	-0.22	0.334 (-0.66-0.23)	0.02	0.50	0.088 (-0.08-1.07)	0.05
lesser digital deformity	0.53	0.001 (0.25-0.80)*	0.23	0.31	0.057 (-0.01-0.64)*	0.07	0.23	0.174 (-0.10-0.56)	0.03
ankle jROM	1.09	0.016 (0.22-1.97)*	0.12	-0.44	0.037 (-0.85- -0.03)*	0.09	0.52	0.039 (0.03-1.01)*	0.08
subtalar jROM	1.27	0.004 (0.42-2.12)*	0.16	-0.05	0.829 (-0.51-0.41)	0.00	0.41	0.111 (-0.10-0.92)	0.05
midfoot jROM	1.27	0.004 (0.42-2.12)*	0.16	0.09	0.675 (-0.33-0.50)	0.00	0.35	0.090 (-0.06-0.76)	0.05
MTP jROM	0.61	0.084 (-0.08-1.3)	0.06	0.20	0.302 (-0.18-0.58)	0.02	0.40	0.077 (-0.05-0.84)	0.06

3b.

EXPLANATORY VARIABLES	HC			OA			RA		
	Coefficient	p-value (95% CI)	Adjusted R^2	Coefficient	p-value (95% CI)	Adjusted R^2	Coefficient	p-value (95% CI)	Adjusted R^2
BMI	0.01	0.96 (-0.1-0.12)		-0.01	0.88 (-0.11-0.10)		-0.02	0.79 (-0.16-0.12)	
MTP Joint hypertrophy	-	-		-	-		-	-	
erosion	-	-		-	-		0.24	0.004 (0.08-0.41)	
foot posture	0.15	0.022* (0.02-0.27)	0.24	-	-	0.15	-	-	0.18
hallux abducto-valgus	-0.42	0.398 (-1.4-0.57)		-	-		-	-	
lesser digital deformity	0.77	0.026* (0.1-1.43)		0.37	0.022 (0.06-0.68)		-	-	
ankle jROM	-0.20	0.742 (-1.4-1.0)		-0.50	0.014 (-0.90- -0.11)		0.36	0.137 (-0.12-0.83)	

The comparative distribution of FFB in OA and RA

subtalar jROM				-	-		-	-	
midfoot jROM	-0.77	0.343 (-2.4-0.85)		-	-		-	-	
MTP jROM	-	-		-	-		-	-	

The comparative distribution of FFB in OA and RA

FIGURE LEGENDS

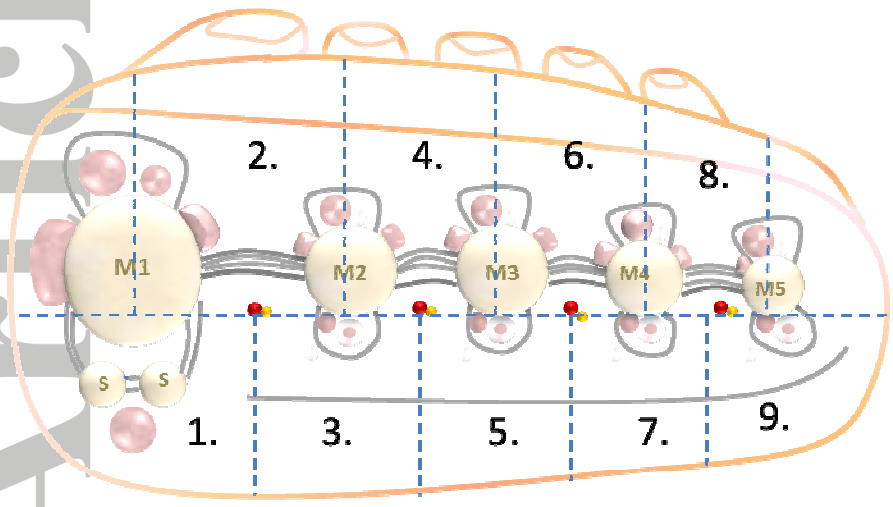


Figure 1: Lesion site definitions
Segmentation of intermetatarsal sites is by bisection of the midline of the metatarsal head, relative to the short axis of the foot, for medial-lateral boundaries and the base of the lesser metatarsal heads for plantar boundaries. Segmentation of plantar sites is by vertical bisection of the midline of the intermetatarsal space, relative to the short axis of the foot, for medial-lateral boundaries and the base of the lesser metatarsal heads for dorsal boundaries. 1-9 = derived intermetatarsal and plantar foot segments.

The comparative distribution of FFB in OA and RA

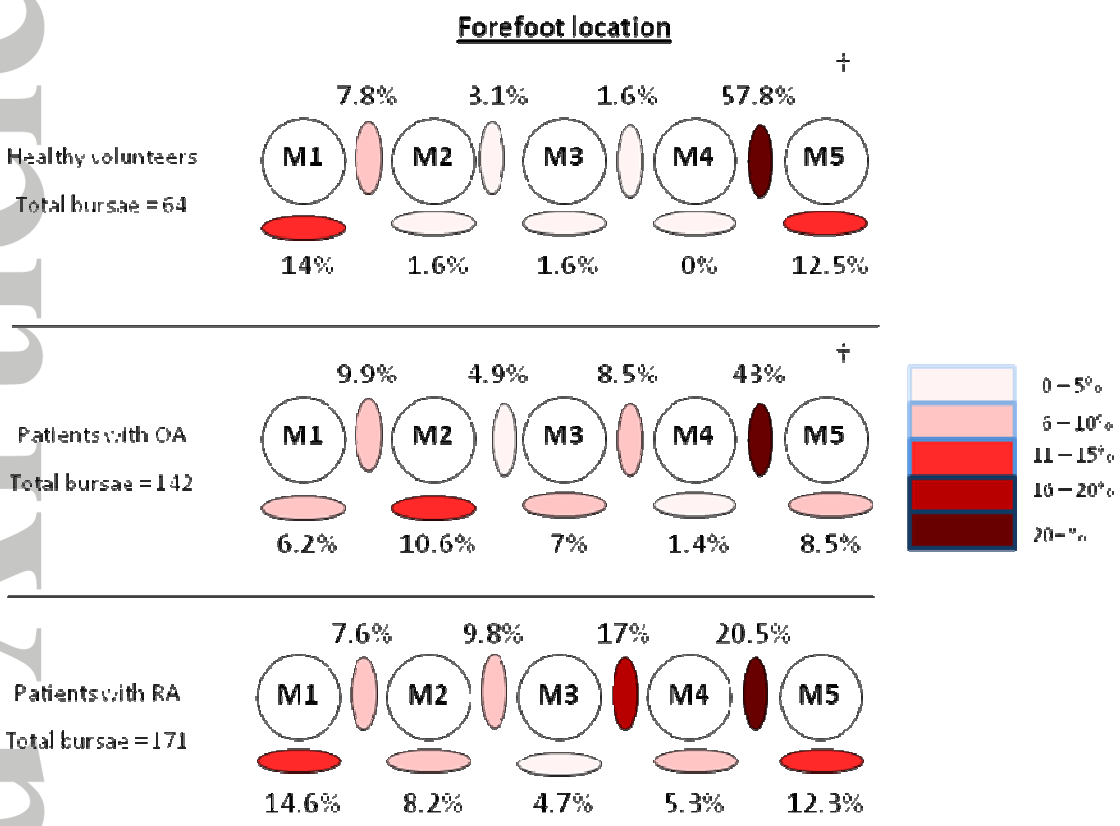


Figure 2: The distribution of FFB across forefoot sites in HC and patients with OA or RA
Values are expressed as percentage of sample with FFB in this location.
Where M1-5 = plantar metatarsophalangeal joint region.

The comparative distribution of FFB in OA and RA

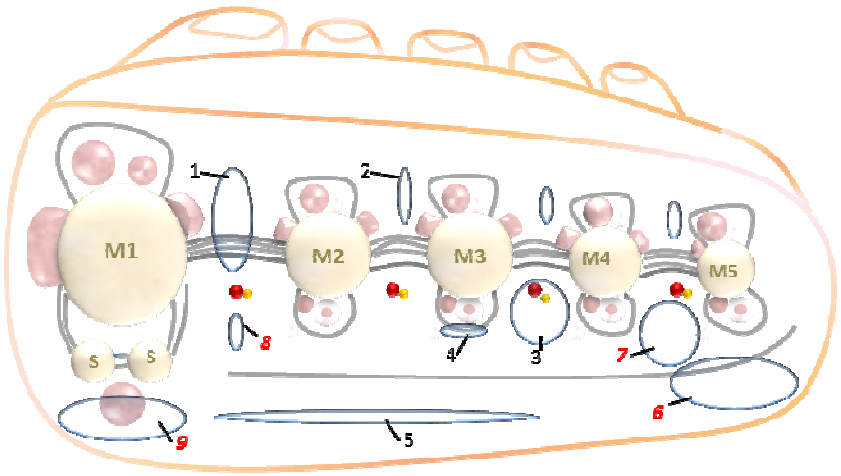
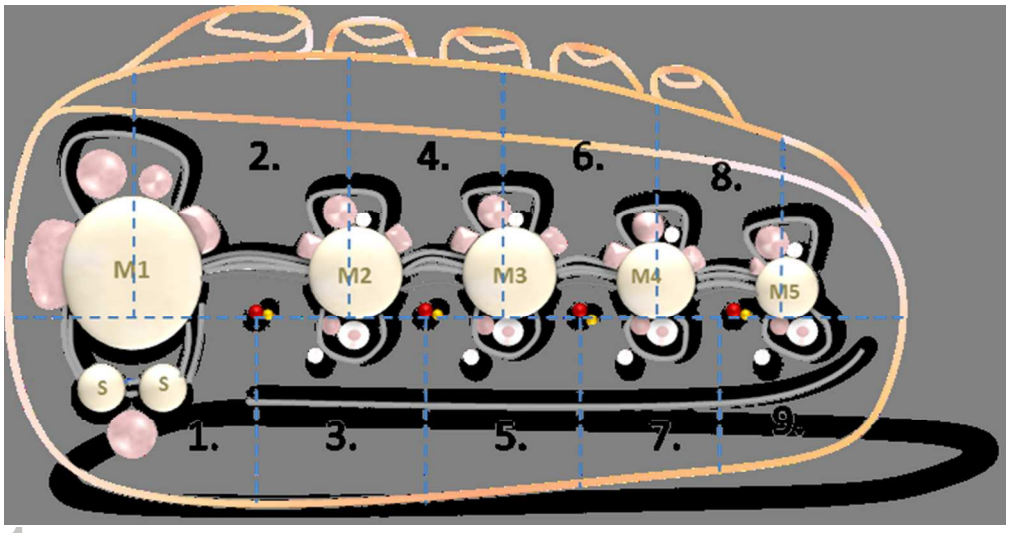
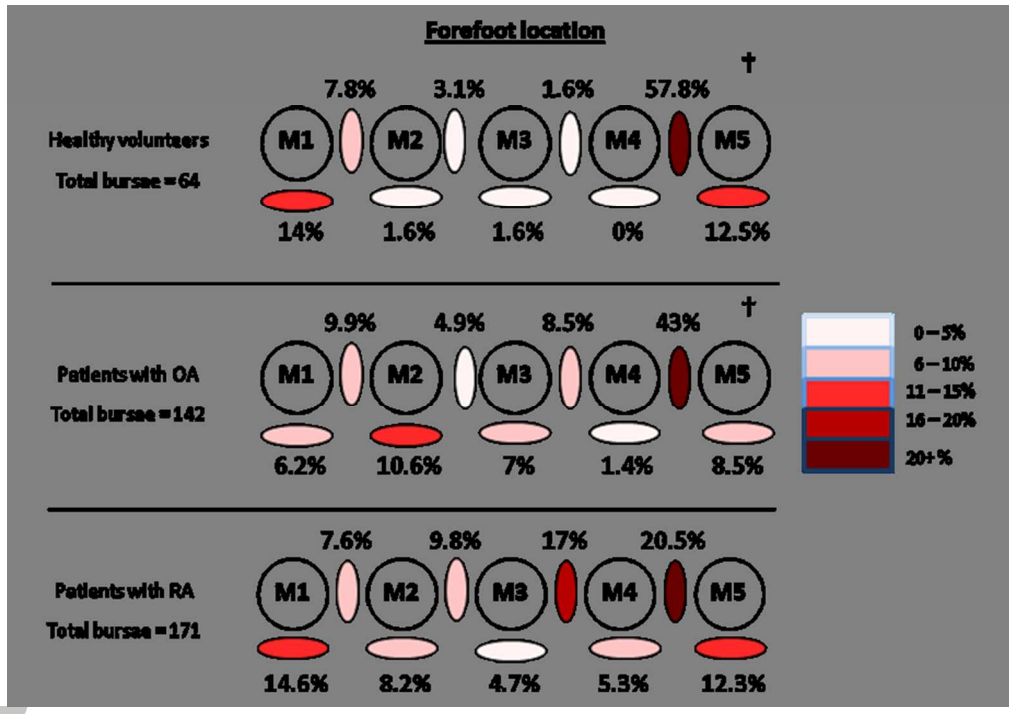


Figure 3: Forefoot anatomy & identification of observed bursae
Where FFB 1-5 were previously identified, FFB 6-9 are additionally identified within this study.
1 = 1-2 intermetatarsal bursa coursing adjacent to adductor hallucis tendon that may extend beyond the deep transverse intermetatarsal ligament, 2 = intermetatarsal bursae that may become hypertrophied extending beyond the deep transverse intermetatarsal ligament, 3 = bursae associated with neurovascular bundle, 4 = bursae associated with superior aspect of flexor digitorum brevis tendon, 5 = plantar mechanical bursae, 6 = large 'billowing' intermetatarsal bursae located plantar to the deep transverse intermetatarsal ligament, may appear as either an organised homogeneous hypoechoic mass, or diffuse hypoechoic region with or without an anechoic centre, 7 = large spherical encapsulated intermetatarsal bursae, may appear as either a hypoechoic mass with or without an anechoic centre, 8 = small intermetatarsal bursae, appearing as a well-defined region with hypoechoic signal, 9 = large encapsulated spherical bursae located plantar to the 1st MTPJ, often found plantar to the medial sesamoid bone.




Forefoot location
Healthy volunteers
Total bursae = 64
7.8%
3.1%
1.6%
57.8%
†
M1
M2
M3
M4
M5
14%
1.6%
1.6%
0%
12.5%
Patients with OA
Total bursae = 142
9.9%
4.9%
8.5%
43%
†
6.2%
10.6%
7%
1.4%
8.5%
Patients with RA
Total bursae = 171
7.6%
9.8%
17%
20.5%
14.6%
8.2%
4.7%
5.3%
12.3%
0–5%
6–10%
11–15%
16–20%
20+%