**Measuring the musculoskeletal aging phenotype**

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Abstract

The world is aging. The population aged over sixty years worldwide is predicted to rise from 841 million in 2013 to more than 2 billion by 2050. Musculoskeletal (MSK) disease is a significant burden on the aging population, contributing 7.5% of the disease burden in those over 60 years. MSK diseases have a pronounced effect on disability level and independence in old age, with consequent significant public health burden and impact on quality of later life. As numbers of older individuals and their disease burden increases, it is important to examine MSK disease in older life in detail. The musculoskeletal aging phenotype comprises four often interwoven key elements; osteoporosis, osteoarthritis, sarcopenia and frailty and this review will focus on these four themes. It is crucial that we are able to accurately measure each phenotype in order that we might identify those individuals at greatest risk of developing these conditions, and design trials of therapeutic agents that might impact their development. Accurate measurement of the musculoskeletal aging phenotype is necessary firstly to document the burden of each condition, and then to enable factors to be identified which may accelerate or retard their development or progression. In some areas of MSK disease, this work is more advanced (osteoporosis); in other areas (sarcopenia) the field is currently very rapidly evolving. We will explore the tools currently used to measure the musculoskeletal aging phenotype and how they compare, as well as highlight areas where more work is needed.

Introduction

The world is aging. 14% of the UK’s population is sixty five years or older [1] ; worldwide the population over sixty is predicted to rise from 841 million in 2013 to more than 2 billion by 2050 [2]; a proportional rise from 11% to 22% [3]. The question is whether this rise in life expectancy is a rise in healthy life expectancy or whether these extra years are burdened with poor health and disability. There is controversy currently over whether we are seeing a compression or expansion of morbidity with age. Progress with interventions aimed at lethal disease has left many previously fatal conditions survivable but in states of – frequently co-morbid – disability [2].

Global Burden of Disease estimates from 2010 attribute 23.1% of the total disease burden to disorders in those over 60 years in age [1]. Musculoskeletal (MSK) disease is a significant burden on the aging population contributing 7.5% of the disease burden in those over 60 years. MSK disease is more prominent and is increasing in burden in middle to high income countries [1, 2]. With its pronounced effect on disability level and independence in old age it is helpful to examine musculoskeletal aging in detail. It is hence very important that researchers can accurately measure the musculoskeletal aging phenotype; to document the burden of each condition, and to identify factors that might accelerate or retard the development or progression. This review will focus on the four themes common to musculoskeletal aging: osteoporosis, osteoarthritis, frailty and sarcopenia.

Pathophysiology of musculoskeletal aging

There is a significant heterogeneity of aging [4]; different persons at the same chronological age exhibit highly varied psychological and physical effects. There are however common aging processes that can be measured, and may contribute to how we define a phenotype. With age the proportion of body fat increases and its location alters: subcutaneous fat decreases as visceral fat increases. Muscle is infiltrated with fat and collagen is deposited. Motor units are denervated and fast type II muscle fibres are converted to slow type I fibres [3, 5]. These changes lead to a decrease in muscle mass and strength. Muscle mass decreases annually from the age of fifty by 1-2% and muscle strength similarly decreases, by 1.5% from the age of fifty to sixty and by 3% thereafter [6]. Decreases in muscle mass and strength also have a negative effect on bone mineral density, which also decreases with age.

Loss of bone mineral density is also mediated by oestrogen. The loss of oestrogen at menopause is an important factor for musculoskeletal aging in women. It is associated with a rapid decline in bone mineral density (BMD), muscle mass and muscle strength [3]. There is no comparable androgen state of middle life in men, although lower levels of testosterone predict sarcopenia, lower levels of protein synthesis and loss of muscle mass [7].

Protein intake is one stimulus for protein synthesis. However, the phenomenon of anorexia of aging means that older people often have a decreased protein intake. As a recognised state of older age is reduced response to anabolic stimuli [4, 5], aging here effects both availability of the stimulus and the ability to react to it.

The pro-inflammatory nature of aging contributes to the anorexia of aging. As we age the production of pro-inflammatory factors, including IL-6, CRP and TNF-alpha, is increased [7]. This low level increase in serum inflammatory markers is associated with impaired motor and cognitive function and is an independent risk factor for impaired mobility and disability [4]. This natural pro-inflammatory state can exacerbate any previous inflammatory exposure through life and any concurrent inflammatory disease process.

**Measuring the phenotype**

OSTEOPOROSIS

Osteoporosis is a skeletal disorder characterised by diminished bone strength, microarchitectural deterioration and increased propensity to fracture. Fragility fracture is its major clinical consequence [8]. It affects over 22 million women aged over 50 years in Europe, or 22% of the female population in 2010 [3]. Although women bear the greatest burden of this disease it is not solely a female concern: 13% of men will experience an osteoporotic fracture [9].

Osteoporosis is defined by the WHO using bone mineral density (BMD) cut-offs: the presence of a DXA T score of ≤-2.5. However, a definition using BMD alone misses many other risk factors for fracture and does not enable all of those at risk of osteoporotic fracture to be identified [10]: the majority of fragility fractures occur in postmenopausal women who do not have osteoporosis by WHO definitions [11].

Fracture risk calculators exist to help guide clinicians in managing osteoporosis and understanding likelihood of fracture tailored to individual patients. Osteoporosis tools have been studied in different populations. The three most commonly used are FRAX, QFracture (both original and 2012 revised version) and Garvan. All the tools vary in number of risk factors taken into account; from 4 to 33. This affects not only their sensitivity and specificity, but also their pragmatic clinical use. They differ also in predictive time period from 5 to ten years, which has implications for their review e.g. when they are judged in a follow up period shorter than that for which they are designed to predict [12]. Different countries have different thresholds for intervention: often determined on a cost basis [11]. In the UK FRAX is often paired with National Osteoporosis Guideline Group (NOGG) recommendations on treatment initiation. However, in a paper looking at fracture risk estimation tools in clinical practice, significant disparity was found between FRAX with and FRAX without NOGG in comparison to Qfracture [13]. This highlights the need to always consider the patient and their own appreciation of risk and benefit, as even the tools designed to assist are not conclusive.

Weight-bearing exercise should usually be recommended as it helps not only in terms of bone strength but improves muscle strength and helps mediate falls risk. When pharmacological intervention is indicated, it focuses primarily on antiresorptive agents such as bisphosphonates and denosumab rather than pro-anabolic therapies. Agents which appear to stimulate bone formation, such as sclerostin antibody treatment [9], are currently in development and results awaited with interest.

OSTEOARTHRITIS

The Royal College of General Practitioners estimated in 2006 that over 1 million adults annually consult their GP with symptoms of osteoarthritis. The UK department of work and pensions estimated 36 million work days were lost to osteoarthritis in 2002 alone, with an estimated loss of economic productivity of £3.2 billion. Osteoarthritis is the most frequent cause of hip and knee replacements in the UK (93% of hip and 97% of primary knee replacements in 2010) at a cost of £852 million in 2010 [14].

Osteoarthritis is a multifactorial degenerative disease of the joints, characterised by cartilage degradation, bone remodelling, osteophyte formation, joint inflammation and loss of normal joint function, affecting over half of adults over 65 years [15, 16]. As global rates of obesity rise (with one third of the adult population over sixty obese in the USA [4]) obesity is an increasingly important predisposing factor to symptomatic OA. It has multiple routes of potential damage, as a proinflammatory state with increased adipokines and as a state which produces increased mechanical loading stress. Prevalence of OA varies dependent on mode of definition: clinical, radiological or reported symptoms. However it is estimated that 10-20% of adults over 60 have significant clinical problems attributable to OA [1]. Hip and knee OA was ranked by the Global Burden of Disease 2010 study as the 11th highest contributor to global disability [16]. In terms of joint prevalence OA appears in decreasing order: hand, knee, hip [17].

There have been many attempts to accurately identify and grade radiographic disease in OA. Of these, the classification by Kellgren and Lawrence (K&L) is the most widely accepted and used. Overall grades of severity are determined from 0 to 4 and are related to the presumed sequential appearance of osteophytes, joint space loss, sclerosis and cysts [18]. The World Health Organization (WHO) adopted these criteria as the standard for epidemiological studies on OA. Cross-sectional imaging methods, such as magnetic resonance imaging (MRI), can visualize joint structures in more detail and continue to undergo evaluation to determine if they will provide a means by which the definition of OA can be refined. Many studies now report the prevalence of self-reported or symptomatic OA; these differing approaches may go some way toward explaining part of the heterogeneity in OA estimates [19]. A recent systematic review [19] attempted to understand the differences in prevalence and incidence of OA according to case definition in knee, hip and hand joints and concluded that radiographic case definition afforded the highest estimates, while self-reported and symptomatic OA definitions presented similar estimates.

In terms of treatment analgesia and anti-inflammatories remain the mainstay for symptomatic relief of OA. Many studies have found that moderate intensity physical exercise is associated with lower risk of joint pain and disability [16]. Moderate physical activity has the added benefit of contributing toward weight loss and muscle strengthening.

FRAILTY

Like the musculoskeletal conditions described above, frailty is significant in its social impact: 71% of frail patients in one study were found to require some assistance with activities of daily living compared to 31% of non-frail patients [20]. It is significant too in its association with mortality: greater than age alone, the Canadian study of Health and Aging found those with mild frailty have a 5-year-risk-of-death odds ratio of 4.82; this increases to 7.34 in those with severe frailty [21].

Frailty is not an inevitable consequence of aging. Frailty is defined as a state of poor physiological reserve of more than one body system, which induces a state of vulnerability; even minor health insults can precipitate significant deterioration to overall health, including falls, hospitalisation, institutionalisation and mortality [22, 23]. Fried et al proposed five criteria for frailty: weakness (assessed by grip strength), slowness (assessed by gait speed), low levels of physical activity, low levels of energy (self-reported) and unintentional weight loss. Possessing one to two criteria indicates a pre-frail state while three or more is diagnostic of frailty [24]. The Frailty Index, a cumulative deficit approach in contrast to Fried’s phenotype approach, was proposed by Clegg, Young, Iliffe, Rikkert and Rockwood [25]. It allows for a gradeable rather than binary absent/present approach to frailty. Prevalence among 60-69 year olds in the UK is estimated at 6.5% [20] and increases with age; 65% of those over 90 are frail. At present, while diagnostic tools have been developed to identify those with the condition (e.g. the PRISMA 7 questionnaire), as there are many conditions which frailty mimics, the problem of low specificity remains.

Exercise and nutrition interventions are the focus of most frailty treatment plans, although this is dependent on the particular frailty domain exhibited by the individual patient.

SARCOPENIA

Like frailty, sarcopenia is strongly associated with loss of function. Up to 3% of functional capacity is lost each year beyond the age of 60 [26]. This has a negative effect on people’s ability for independent living. This of course brings its own burdens in terms of consequent isolation, effect on mental health, and cost of assistance care.

Sarcopenia is considered to comprise the loss of muscle strength, muscle mass and muscle function with increasing age. At a histopathological level, sarcopenic muscle samples display muscle atrophy, particularly of type II fibres; necrosis and between-fibre reductions in cross bridging elements; as well as a reduction in mitochondria [5]. The consensus definition of sarcopenia is still under debate, a factor which has adversely affected study design and comparability. The two main sets of criteria are those proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) and The Foundation for the National Institutes of Health (FNIH) Sarcopenia Project. Other proposed criteria include those from International Working Group (IWG), European Society for Clinical Nutrition and Metabolism Special Interest Group on cachexia-anorexia in chronic wasting diseases (ESPEN) and Society of Sarcopenia, Cachexia, and Wasting Disorders (SCWD) [27].

Low lean mass, muscle strength and weakness are considered in the criteria. Different performance measures can be used: commonly grip strength, gait speed and muscle mass as derived from DXA scans are used. Gait speed has recently been questioned as an indicator as in the older population causes of slower walking speed may not always be related to lower muscle mass or quality [28, 29].

EWGSOP seeks to differentiate presarcopenia (low mass) from sarcopenia (low mass + low strength or low performance) and severe sarcopenia (low mass + low strength + low performance). Weakness, as applied to grip strength, has a differing cut-off defined by FNIH: <26kg in men <16kg in women; to EWGSOP: <30kg in men <20kg in women. Slowness is consistent between groups with <0.8m/s recognised as predicting sarcopenia. Regarding low lean mass, FNIH criteria looks at appendicular lean mass divided by BMI. All other criteria use Appendicular Lean Mass (ALM) divided by height squared. The difference in FNIH causes their criteria to identify patients who are older; have higher BMI; have higher lean mass and those who have greater functional impairment (slower gait and more inability to rise from sitting) [30,31]. In a cohort of British community-dwelling men and women in early old age the prevalence of sarcopenia was found to be 3.1% of men, 2.7% of women according the FNIH criteria, whereas prevalence using EWGSOP criteria was: 4.4% of men, 7.3% of women [23, 31] demonstrating the impact of using different tools. There is a need for consensus definition to enable research to progress, as its validation in cohorts is required to enable recruitment to studies.

Physical exercise in middle age appears protective against sarcopenia in older age and effective in maintaining muscle strength and physical performance in older age [29]. Interventions in sarcopenia have trialled nutrition and physical exercise in concert. More research is required but findings for dual component interventions see to have a positive outcome [26]. Pharmacological therapies with potential in sarcopenia may include myostatin inhibitors and type II activin receptor inhibitors; follistatin; selective androgen receptor modulator (SARMs); angiotensin-coverting-enzyme (ACE) inhibitors and ghrelin mimetics [30].

Conclusion

The musculoskeletal aging phenotype comprises four often interwoven key elements; osteoporosis, osteoarthritis, sarcopenia and frailty. Together they represent a very significant public health burden and impact on quality of life in later life. Within the musculoskeletal phenotype there are agents able to retard progression of disease at different stages of development. There are currently more agents available for bone disorders such as osteoporosis, than those targeting muscle such as in sarcopenia. This reflects the challenge in the musculoskeletal phenotype: those with more agreed diagnostic framework are further along an intervention development path. In order that we might identify those individuals at greatest risk of developing these conditions, agree framework around outcomes of interest and design trials of therapeutic agents that might impact that development, it is crucial that we are able to accurately measure each phenotype. In some areas described above, this work is more advanced (osteoporosis); in other areas (sarcopenia) the field is currently very rapidly evolving.

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TABLE 1: Comparison of measurements in musculoskeletal aging [8, 27, 31-36]

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| --- | --- | --- | --- |
| FRAILTY |  |  |  |
| Canadian Study of Health and Aging (CSHA) Frailty Scale | 7 point labelled scale | ‘Very fit’ – ‘severely frail’ |  |
| Frailty Index | Cumulative deficit score. Index = sum of deficits over total score based on number of items used (e.g. 36) | 0 - 0.2 no frailty0.2 – 0.4 mild frailty0.4 – 1.0 frailty |  |
| Phenotype model (Fried et al criteria) | 5 criteria | 1 – 2 pre-frail≥ 3 frail |  |
|  |  |  |  |
| SARCOPENIA | Low muscle mass: | Low muscle strength: | Low physical performance: |
| IWG | ALM/ht²Men: <7.23kg/ m²Women: <5.67kg/m² | Low grip strength(undefined) | Gait speed <1.0 m/s |
| EWGSOP | ALM/ht²Men: <7.23kg/ m²Women: <5.67kg/m² | Low grip strengthMen: <30kgWomen: < 20kg | Gait speed < 0.8m/s |
| SCWD | Low ALM/ht² (undefined) | \_ | Gait speed < 1.0 m/s or 6min walk < 400m |
| FNIH | ALM:BMI ratioMen: <0.789Women: <0.512 | Low grip strengthMen: <26kgWomen: <16kg | Gait speed < 0.8 m/s |
| ESPEN/SIG | ≥ 2 standard deviations below the mean measured in young adults | \_ | Gait speed < 0.8 m/s |
|  |  |  |  |
| OSTEOARTHRITIS |  |  |  |
| Radiological: Kellgren and Lawrence system | 0-4 grades severity |  |  |
| Symptomatic: Western Ontario and McMaster Universities Arthritis Index (WOMAC) | Self-report questions:5 pain 2 stiffness 17 functional limitation | Score out of 96:tertiles can be used with the lowest, middle, and highest groups representing mild, moderate, and severe OA |  |
| Clinical: American College of Rheumatology (ACR) criteria | Variable signs and symptoms criteria dependent on joint |  |  |
|  |  |  |  |
| OSTEOPOROSIS |  |  |  |
| WHO | BMD ≤2.5 T score |  |  |
| Risk calculators: | Number of risk factors | Age range | Gender | BMD | Timescale |
| QFracture 2012 | 31 | 30-99 | Male/female | no | 1-10 year time points of prediction |
| FRAX | 11 | 40-90 | Female | optional | 10 year |
| Garvan | 5 | 60-96 | Male/female | no | 5 and 10 year |

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