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Review article

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 aged over 60 years. MSK diseases have a pronounced effect on disability level and independence in old age, with a consequent significant public health burden and impact on quality of later life. As numbers of older individuals and their disease burden increase, 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.

Contents

1. 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 dis-

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ability. 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.

2. 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.

3. Measuring the phenotype

3.1. 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.

3.2. 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 con-