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Osteoporosis and Sarcopenia in Older Age

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Abstract

Osteoporosis and sarcopenia are common in older age and associated with significant

morbidity and mortality. Consequently, they are both attended by a considerable

socioeconomic burden. Osteoporosis was defined by the World Health Organisation (WHO)

in 1994 as a bone mineral density of less than 2.5 standard deviations below the sex-specific

young adult mean and this characterisation has been adopted globally. Subsequently, a

further step forward was taken when bone mineral density was incorporated into fracture risk

prediction algorithms, such as the Fracture Risk Assessment Tool (FRAX®) also developed

by the WHO. In contrast, for sarcopenia there have been several diagnostic criteria

suggested, initially relating to low muscle mass alone and more recently low muscle mass

and muscle function.   However, none of these have been universally accepted. This has

led to difficulties in accurately delineating the burden of disease, exploring geographic

differences, and recruiting appropriate subjects to clinical trials. There is also uncertainty

about how improvement in sarcopenia should be measured in pharmaceutical trials.

Reasons for these difficulties including the number of facets of muscle health available, e.g.

mass, strength, function, and performance, and the various clinical outcomes to which

sarcopenia can be related such as falls, fracture, disability and premature mortality. It is

imperative that a universal definition of sarcopenia is reached soon to facilitate greater

progress in research into this debilitating condition.

Introduction

Osteoporosis and sarcopenia are common diseases that predominantly affect older

individuals [1, 2].   They are both associated with significant morbidity and can therefore lead

to considerable health and social costs [3, 4]. Specially, sarcopenia is associated with

increased rates of disability, poor mobility, frailty, and hospitalisation [5, 6] and it has been

estimated that, in the United States, sarcopenia resulted in additional healthcare costs of

over $18 billion in 2001 [4]. Furthermore, in common with hip and vertebral fracture

fractures, a decline in muscle health has also been shown to predict future mortality from

middle-age into later life [7]. Given current secular trends in population demographics with

greater longevity, the burden of both osteoporosis and sarcopenia may continue to increase.

In addition to the similar population in which they occur, there is also growing evidence of a

link between the two conditions. Studies have shown associations between bone and

muscle health by dual energy x-ray absorptiometry (DXA) and more recently using cross-

sectional imaging techniques [8, 9]. DXA studies have focussed on relationships between

facets of muscle health and either bone mass or density and have tended to show positive

relationships [10-12]. The use of peripheral quantitative computed tomography (pQCT) has

additionally shown bone size and strength to be associated with muscle size, and to a lesser

extent, muscle strength. Relationships of muscle with cortical and trabecular volumetric

bone mineral density (vBMD) have been less consistent [8, 9].

There are several potential explanations for these interrelationships (Figure 1). The mechanostat hypothesis describes the action of muscle contraction providing a direct mechanical stimulus to bone which promotes osteogenesis [13]. Hormones, such as growth hormone, can have positive effects on the growth of muscle and bone [14, 15]. Furthermore, exercise and levels of activity clearly augment both of these components of the musculoskeletal system. There are also likely to be common genetic and developmental components to muscle and bone health [16, 17].

Despite their similarities and interrelationships, study into these diseases is at very different stages of evolution, with research into osteoporosis considerably ahead. This review describes the progress that has been made in defining these conditions and explores the reasons for the discrepancy in progress made.

The history of osteoporosis

Osteoporosis is a skeletal disease characterised by low bone mass and microarchitectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture [18]. The term literally means "porous bone" and was first introduced in France and Germany when it described a histological diagnosis. We now know this to represent bone

tissue which is normally mineralised but reduced in quantity. This abnormality is the

mechanism through which bones become weaker, increasing the risk of fractures occurring.

A significant leap forward was made with the development of non-invasive techniques able

to assess bone mineral density (BMD) *in vivo*. Up to that point, attempts had been made to

quantify bone health purely using plain radiographs, such as assessments of cortical

morphometry [19]. Single photon absorptiometry was introduced in the 1960s and was

subsequently replaced by dual photon absorptiometry. Both relied on radionuclide sources

[20] and took over 15 minutes to complete (per site). The radionuclide decayed and

consequently had a finite lifespan, needing to be changed at regular intervals. Around 25

years ago, the radionuclide source was superseded by an X-ray source and DXA scanners

were born with faster scanning times and greater spatial resolution. This technique allows

measurement of areal bone mineral density (aBMD) primarily at the hip and lumbar spine.

In 1994, the next step change in the definition of osteoporosis occurred, when a working

group of the World Health Organisation (WHO) used bone density measurements by DXA to

provide a practical definition of osteoporosis as an aBMD of less than 2.5 standard

deviations (SD) below the young normal mean [21]. As earlier definitions had incorporated

fracture, in order to provide comparability, the subset of women with osteoporosis who had

also suffered one or more fragility fractures were deemed to have severe (established)

osteoporosis. Osteopenia was defined as an aBMD level between 1 and 2.5 SD below the

young normal mean.

This definition has been adopted throughout the world and has allowed great strides forward

within this disease area. Prevalence was compared between different geographical

locations and this led to hypotheses regarding likely aetiology. Study participants could be

more easily selected and beneficial effects on bone could be quantified facilitating research

into pharmaceutical agents to treat osteoporosis. This has led to the licensing of several

medications with good evidence for efficacy in fracture risk reduction.

Overall within a population, higher aBMD is associated with greater bone strength.

Specifically, it has been shown that there is an almost doubling of fracture risk for every one

standard deviation reduction in aBMD [22]. However, these measures alone do not explain

all of the variance in fracture risk. This is partly related to the inability to measure cortical

and trabecular bone separately, and to take into consideration the bone's material quality or

structural geometry [23, 24]. Recent studies have shown some additional fracture

discrimination using cross-sectional imaging techniques but the incremental gains tend to be

relatively small [25, 26]. These techniques may however allow better understanding of the

specific pathogenesis of osteoporosis at the structural level. In contrast, a considerable

improvement in fracture prediction has been achieved with the development of fracture risk

prediction algorithms, such as the Fracture Risk Assessment Tool (FRAX®).

FRAX® uses clinically available risk factors, with or without aBMD, to determine an

individual's risk of major osteoporotic fracture and hip fracture in the next 10 years [27]. As

this is more accurate than using aBMD alone, it allows better targeting of treatments to those

at greatest risk with positive effects on the ratio of risk to benefit. Therefore, we are now at a

point where we can evaluate whether or not to treat an individual and have several effective

therapies to do so, with more in the pipeline.

The history of sarcopenia

The term sarcopenia was first coined in 1989 by Irwin Rosenberg who used it to pertain to

the loss of muscle mass with age [28, 29]. It has since become apparent that muscle

function, in addition to muscle mass, is necessary to describe sarcopenia and so the

definition has undergone an evolution to reflect this. Although muscle mass would intuitively

be thought to be the central factor, it is only weakly associated with function and disability. It

does, however, relate to low muscle strength which is strongly associated with these clinical

outcomes [30]. Furthermore, although both muscle mass and muscle function decline from

the age of 35 years [31], muscle strength and power decrease more rapidly than muscle

mass [32] implying that they may be more sensitive to the changes that are occurring.

Several consensus definitions have been proposed to define sarcopenia clinically [33-35],

most recently from the Foundation of the National Institute of Health (FNIH) sarcopenia

project [30]. Although they all differ to some extent, each includes a measurement of both

muscle size and muscle function. The assessment of muscle size utilised in the European

Working Group on Sarcopenia in Older People (EWGSOP) and International Working Group

on Sarcopenia (IWGS) definitions is that of skeletal mass index (appendicular mass relative

to height squared) [33, 34]. This mitigates against defining individuals as sarcopenic or not

based solely on their size. In contrast, the FNIH definition recommends use of muscle mass

relative to body mass index (BMI) focussing more on the importance of adequate muscle for

a given level of adiposity [30]. This is in keeping with the concept of sarcopenic obesity

which has been developed to describe those individuals with both low muscle mass/function

and excess adiposity. This combination is important as there is evidence that it may

adversely affect health to a greater extent than either condition alone [36].

Muscle mass cut points have been suggested for each of the definitions. In the IWGS

definition it equates to an appendicular lean mass divided by height squared of <7.23kg/m^2

in men and <5.67kg/m^2 in women [34]. The EWGSOP offers several DXA cut points all of

which are of a similar magnitude [33]. From their large observational dataset, the FNIH

definition suggests cut offs of appendicular lean mass over BMI of <0.789 for men and

<0.512 in women, both of which predicted impaired mobility as assessed by a gait speed of

<0.8 m/s [30].

Usual gait speed is the measure of muscle function in both the IWGS and ESPEN SIG

definitions and this can be assessed using a 4 metre walk test. Interestingly, the cut offs

differ by study group being <1m/s for the IWGS definition but more stringent at <0.8m/s for

the ESPEN SIG definition [34, 35]. The EWGSOP definition is similar in that it suggests

sarcopenia is present with the occurrence of low muscle mass along with low gait speed

(<0.8m/s) but differs in that the later could be replaced by low muscle strength (grip strength)

[33]. In contrast, the FNIH definition uses low grip strength (<26kg for men and <16 kg for

females) alone as the required measure of muscle function [30]. Cut offs were higher in the

EWGSOP definition and rates of sarcopenia were correspondingly greater [37].

In addition to those measures of muscle function already explored, there are other related

parameters, such as muscle endurance and levels of habitual activity. Although both may

relate to functional ability, they will clearly also be strongly influenced by factors other than

sarcopenia. Furthermore, there are few published data concerning these outcomes and a

lack of consistency in the way they are defined. Consequently they have not been included

in current consensus definitions.

Although there are certainly similarities between the four consensus definitions described

above, the subtle differences result in different groups of individuals being identified as

sarcopenic [37]. Currently, there is therefore no universally accepted way to determine

which patients are sarcopenic. This leads to several difficulties in investigating the condition.

The importance of defining sarcopenia

As sarcopenia is associated with significant morbidity and is a predictor of premature

mortality, it is clearly important for further research in this area to take place. A universal

consensus definition of sarcopenia would allow an evaluation of prevalence across different

geographical areas. This would allow a more accurate quantification of the burden of

disease and, as in the case of osteoporosis, potentially provide further clues to the aetiology.

It would also allow identification of individuals at risk of the disease in order to evaluate its

natural history and to target treatment where appropriate. Interventions may include diet,

exercise and, in the future, pharmaceutical agents.

Furthermore, a universal definition of sarcopenia would also simplify participant selection for

studies, including those of therapeutic agents, and would likely facilitate regulatory approval.

In addition, it is also imperative to produce an easily measureable and clinically important

study outcome. Options would include change in muscle size, muscle strength, or physical

performance. However, as will be discussed, there are benefits and limitations to each of

these. Furthermore, in line with fracture risk reduction in osteoporosis, it would also be

beneficial if a drug could be shown to ameliorate one or more of the adverse clinical

outcomes of sarcopenia.

Difficulties in defining sarcopenia

When a definition of sarcopenia is developed in clinical practice, it is important that it is

practical, affordable, and acceptable to patients. Although it may be possible to use a more

complicated and expensive method within research, it would be favourable to have a

definition that could be used in both settings allowing results of studies to be more easily

translatable into clinical practice.

The principle reason that progress in sarcopenia research has not advanced as rapidly as

osteoporosis research, is the difficulty in establishing a consensual definition of sarcopenia

that achieves the objective of a diagnostic criterion, as well as serving as an appropriate

outcome measure for clinical trials of treatment. It is clear that any definition could use

various combinations of muscle mass, strength and physical performance. However, the

extent to which these three measures may be combined in a universal definition remains

controversial. Some approaches attempt to incorporate all three components (EWGSOP)

while others focus on simply one measure, such as gait speed.

Another difficulty has been a decision on which measures of muscle mass, strength and

physical performance are most appropriate. Which is chosen may depend on what clinical

outcomes are felt to be most important. For example, gait speed would be most closely

associated with mobility and both gait speed and grip strength have been associated with

several other outcomes including premature death [7].

This question also arises when assessing for clinical improvement. In osteoporosis, aBMD

has been universally adopted as a good proxy for bone strength. Whereas in sarcopenia the

most appropriate measure is not as apparent. Each possible endpoint has its own

advantages and disadvantages (table 1). Similarly, the important clinical event in

osteoporosis is obviously fracture. However, sarcopenia is associated with several adverse

outcomes including falls, fractures, disability and death. Choosing the primary clinical

outcome to include in clinical trials is therefore more problematic.

The move towards a consensus is urgently needed and it may be that the two objectives

(classification of individuals as disease or non-disease, and an outcome measure for clinical

trials of novel therapies) require distinct definitional approaches [38].

Conclusion

There are many similarities between osteoporosis and sarcopenia including patient

demographics, high prevalence, and great socioeconomic cost. There is also evidence of a

mechanistic interrelationship between muscle and bone with sarcopenic individuals at greater risk of osteoporosis and vice versa. Although both are well recognised, there is a considerable difference in the progress that has been made in managing the two conditions.

A universal definition was established for osteoporosis in 1994 and this has allowed thorough assessment of its epidemiology, aetiology and fracture risk assessment, and for treatments to be developed. In contrast, there is still ongoing debate regarding how best to define sarcopenia. Although it tends to be accepted that this should include a measure of muscle size and muscle function, the precise nature of these measures and the cut offs to be used have not be confirmed.

It is imperative that a definition is agreed on soon to drive forward progress in this field. A better understanding of the prevalence and burden of sarcopenia will potentially build the case for further funding and interest from industry. It will also facilitate appropriate recruitment to studies and allow optimal measurement of improvement in muscle health in therapeutic trials.

One way to aid in the determination of which definition of sarcopenia should be adopted may be to more thoroughly examine their relationships, and those of their individual facets, to adverse clinical outcomes such as falls, fracture, disability, and death. This may allow an approach based on a more comprehensive evidence base.
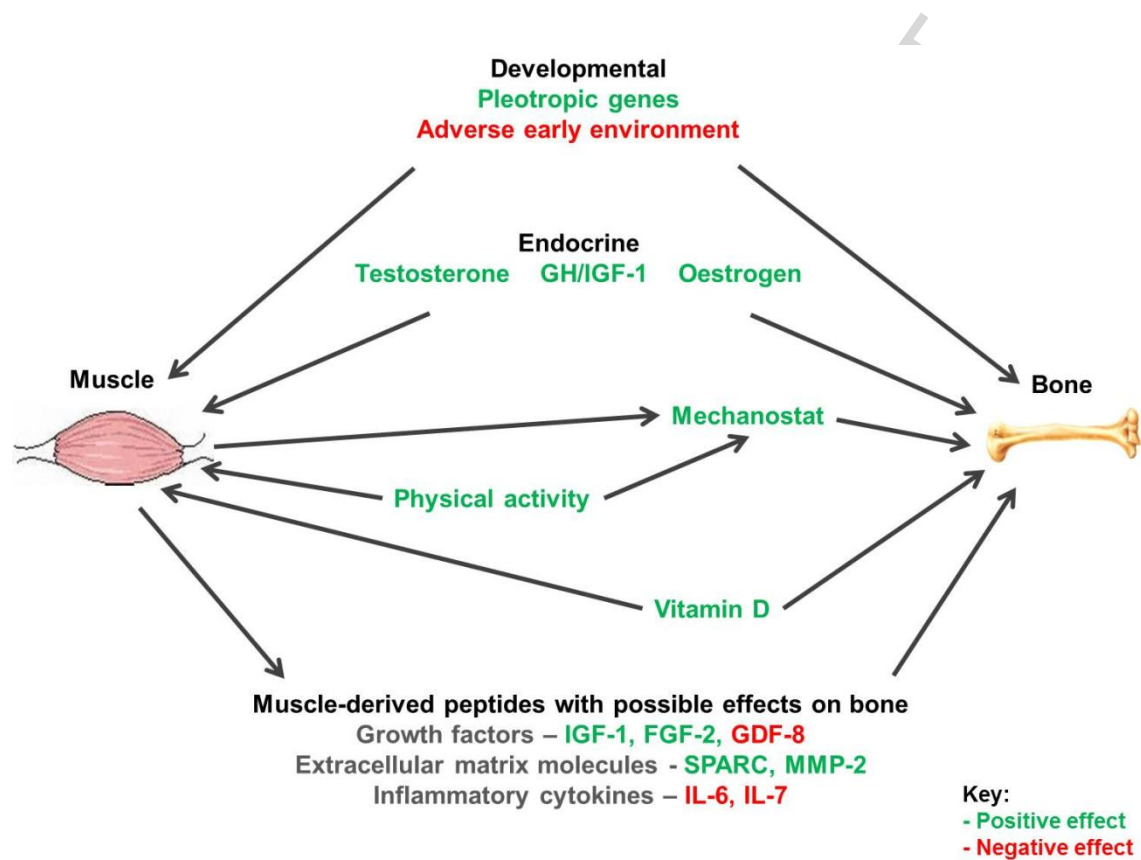
Table 1: Potential endpoints in trials of interventions for sarcopenia and osteoporosis.

Adapted with permission from Cooper *et al.* [38].

	Advantages	Disadvantages
Sarcopenia		
Muscle mass	1. Specific to skeletal muscle 2. Responsive to change 3. Easy to implement with the established use of DXA	1. Not as powerful a predictor of physical capability as muscle strength or gait speed 2. Difficult to detect small changes using DXA (CT or MRI should be used)
Muscle strength	1. Powerful predictor of physical capability 2. Includes a neuromuscular component 3. Good correlation with gait speed	1. Not reflected in the term 'sarcopenia' 2. Possibly restricted in the clinical trial context by frequency of visits
Muscle power	1. Specific to skeletal muscle 2. Includes a neuromuscular component 3. Strongly predictive of functional mobility and risk of falls among older adults	1. Generally requires expensive equipment
Muscle fatigue	1. Important determinant of force production	1. Few published data 2. Lack of definitional consistency
Osteoporosis		
Bone mineral density	1. Predicts fracture risk 2. Easily measured by DXA 3. DXA scanners are widely available	1. Lumbar spine readings subject to artefact 2. Timing of repeat measures limited by scan precision
Fracture	1. Important clinical	1. Occult vertebral fractures

	outcome		may be missed
	2. Associated with morbidity and mortality	2.	Relatively rare outcome

Figure 1: Interrelationships between muscle and bone.

Developmental
Pleotropic genes
Adverse early environment

Endocrine
Testosterone   GH/IGF-1   Oestrogen

Muscle

Mechanostat

Physical activity

Bone

Vitamin D

Muscle-derived peptides with possible effects on bone
Growth factors – **IGF-1, FGF-2, GDF-8**
Extracellular matrix molecules - **SPARC, MMP-2**
Inflammatory cytokines – **IL-6, IL-7**

Key:
- Positive effect
- Negative effect

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Highlights

- Osteoporosis has been clearly defined and fracture risk prediction tools allow accurate evaluation of the likelihood of adverse outcomes.

- Although several consensus definitions of sarcopenia have been suggested, none have been universally adopted.

- A universal definition of sarcopenia is required to facilitate advancement of research in this area.