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Chapter 3

Chronology of age-related disease definitions: Osteoporosis and Sarcopenia

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Abstract

Low muscle mass at older age has been associated with functional impairments, cognitive decline and mortality. The term sarcopenia, coined in 1988, has been used interchangeably to describe low muscle mass, strength, and function. Without a well defined definition, results of studies using the term sarcopenia cannot be compared. Difficulties in defining sarcopenia parallel the history of defining osteoporosis. To understand critical steps that are needed to reach consensus in defining age-related diseases, we have identified milestones in the history of defining osteoporosis and compared these to sarcopenia. As a result, the main missing steps in the process of defining sarcopenia are: specific treatment options, pharmaceutical interest, and public awareness. Similar to osteoporosis being defined as ‘low bone mineral density’, the term sarcopenia should be reserved for ‘low muscle mass’. Consensus must be reached regarding the diagnostic criteria to quantify muscle mass, correction factors, and reference populations used to define cut-off values of muscle mass.
Introduction

Over the past decades, scientists have reached consensus on an exclusive definition of osteoporosis, which was instrumental in developing clinical protocols for early diagnosis and tailored treatment. Sarcopenia, a much younger term, was first used in 1988 to describe the deficiency of muscle tissue often observed in older age (1). The term sarcopenia is still largely unknown among clinicians and researchers. Identifying and treating sarcopenia is becoming increasingly important, since research has shown that low muscle mass is associated with functional and cognitive impairment (2-4) and increased mortality (5). After the age of 50 years, an average annual decline of 1 to 2 percent of muscle mass has been reported (6), leading to a 50 percent reduction of muscle mass among those aged 80 years and older (3). It is estimated that a 10.5 reduction of the prevalence of sarcopenia could lead to a reduction of healthcare costs by 1.1 billion US dollars per year in the United States (7). However, the prevalence and measurable impact of sarcopenia depends crucially on how sarcopenia is defined. A proper definition is the necessary base for clinical diagnosis and development of tailored treatment.

Over the past years the term sarcopenia has been used interchangeably to describe low muscle mass as well as low muscle strength and physical performance. Loss of muscle mass cannot fully explain loss of muscle strength and vice versa (8). While it has been proposed to define sarcopenia based on the presence of low muscle mass together with low muscle strength or function (9), it has also been suggested to restrict the term sarcopenia to low muscle mass and to use another term for low muscle strength: ‘dynapenia’ (10). The prevalence of sarcopenia in elderly populations was found to vary substantially (11;12). The use of various diagnostic criteria of sarcopenia is most likely to account for the differences. Consequently, difficulties arise when comparing different cohorts and individual patients (13).

The medical community did not agree on a definition of osteoporosis from its first medical interest in the early 1940s until the mid 1990s. The aim of this paper is to learn from the similarities and differences in defining sarcopenia with respect to osteoporosis. By identifying and comparing milestones in the process of decision making we aim to get insights into the required steps to be taken to reach a clinically applicable definition of sarcopenia.
Chronology of osteoporosis and sarcopenia

Milestones in the definition of osteoporosis
The term ‘osteoporosis’ (porous bone) was most probably launched by the French pathologist Lobstein ‘the Younger’ in 1830 (milestone 1: coining of a term, figure 1). This term was derived from the Greek ‘osteon’ (bone) and ‘poros’ (little hole), and was initially used to describe cavities observed in human bone of his patients during autopsy (14). Though the term was widely accepted and described in medical dictionaries from that moment on, it was not until the 20th century that osteoporosis was considered a treatable disorder instead of an unavoidable condition just occurring with ageing. This was probably due to Albright and colleagues, who first made a medical definition for osteoporosis and described conditions associated with osteoporosis (milestone 2: understanding of consequences, figure 1). Since the presence of osteoporosis was mainly observed in postmenopausal women, treatment with estrogen was suggested (15) (milestone 3: available medication, figure 1). Albright defined osteoporosis as “too little formation of calcified bone”, with the bone itself being normally calcified, and exhibiting a normal rate of bone destruction (16;17).

After Albright’s definition, the interest of researchers in osteoporosis increased. However, researchers assigned different meanings to ‘osteoporosis’, with varying emphases on clinical, physiological, and biochemical factors. Until 1994, different definitions of osteoporosis were described in medical dictionaries (interchangeable use of the term osteoporosis, figure 1)(18). Furthermore, the definition of osteoporosis in Harrison’s ‘Principles of internal medicine’ varied over the years. In the Harrison of 1950, age was considered as one of the causal factors leading to atrophy of tissue. It was recognized that all tissues atrophy with age, and skeletal atrophy was termed osteoporosis (19). An age based distinction was made between ‘senile’ and ‘postmenopausal’ osteoporosis. Women under the age of 65 years were diagnosed with postmenopausal osteoporosis; above 65 years of age they were diagnosed with senile osteoporosis (19-21). This definition was held until 1970, when osteoporosis was distinguished from ‘normal age-related bone loss’ and recognized as a disease (22). Age was considered the causal factor in ‘primary’ osteoporosis. If an underlying cause was identified such as immobilization, steroid use or gonadal insufficiency, it was called ‘secondary’ osteoporosis (22). Although there was no universal definition of osteoporosis, besides the estrogen therapy introduced by Albright, other drug therapies (e.g. bisphosphonates in 1960) were developed and introduced in patient care (23).
Figure 1: Chronology of osteoporosis and sarcopenia. Milestones in defining osteoporosis / sarcopenia: (1) coining of a term, (2) understanding of consequences, (3) available medication, (4) pharmaceutical interest, (5) public awareness, (6) imaging, (7) criteria for quantification, (8) World Health Organisation (WHO) definition, (9) definition including risk stratification. For the definition of sarcopenia, crucial milestones are missing such as (3) available medication, (4) pharmaceutical interest and (5) public awareness. First definitions for sarcopenia have been proposed, using criteria to quantify muscle mass, strength and function (7). There is no universal consensus on which criteria to use to define sarcopenia.
Before the introduction of dual-energy x-ray absorptiometry (DXA) scanners in 1987, osteoporosis was diagnosed in a rather crude way, for example, when there was evidence of deformity of a vertebral body or fracture or other bone from minor trauma, or the bones were extensively demineralized, readily recognized on routine diagnostic x-ray films. Without the ability to detect osteoporosis in an early stage, osteoporosis was a disease with a sudden onset after a fracture in patients. Without a proper method to measure bone mineral density, no consensus was reached on how to define osteoporosis without the presence of fractures. In the 1980s, a massive public awareness campaign regarding osteoporosis was launched in the United States, largely funded by the pharmaceutical industry producing hormone replacement therapy and dairy industry promoting their products as bone-building treatments (milestone 4: pharmaceutical interest, figure 1) (18). The awareness was so widespread that by 1987, 85% of Americans knew what osteoporosis was, as compared to 15% in 1982 (milestone 5: public awareness, figure 1) (18). Investments were also made in imaging technology to measure bone-density in routine clinical practice, leading to the introduction of the DXA scanners in 1987 (milestone 6: imaging) (24). Effort was made to define a reference standard against which a certain bone mineral density could be measured. Fracture risk was taken into account to define osteoporosis, to be able to start treatment before the onset of adverse events (milestone 7: criteria for quantification, figure 1) (25).

After the introduction of DXA, it was recognized that the clinically important cut-off points for bone mineral density varied according to a number of parameters such as sex, age, and racial origin (25;26). A definition was formulated at the WHO Consensus Conference of Osteoporosis in Copenhagen in 1990, where osteoporosis was defined ‘a disease characterized by low bone mass, microarchitectural deterioration of bone tissue leading to enhanced bone fragility, and a consequent increase in fracture risk’ (27). In 1994 the World Health Organization (WHO) operationally defined osteoporosis as a bone density measured with DXA, 2.5 standard deviations (SD) below the mean for healthy women aged 20 – 29 years, also referred to as a T-score of -2.5 (milestone 8: WHO definition, figure 1) (28). These cut-off points, although arbitrarily defined based on sensitivity and specificity of the occurrence of fractures, are still being used today.

Optimal risk assessment in osteoporosis still remains under debate in research. When the WHO diagnostic criteria were provided, the prevalence of osteoporosis was considered roughly equal whether assessed at the hip, lumbar spine or forearm (high degree of agreement between sites). However, with the introduction of new technologies (peripheral DXA, quantitative ultrasound, quantitative computed
tomography, and other radiographic techniques) applied to different skeletal sites of the body, it became clear that the same T-score from different skeletal sites and techniques yielded different information on the prevalence of osteoporosis and on fracture risk (29). Moreover, it has been recognized that using the same reference values for different races is far from optimal (29-31). After the introduction of a clinically applicable WHO definition of osteoporosis, other risk factors of fractures have been assessed to optimize the assessment of fracture risk in osteoporosis. The fracture risk depends not only on the bone mineral density but also on other factors like the level of being at risk for trauma (risk behavior or cognitive functioning), severity of the trauma, and underlying conditions such as rheumatoid arthritis (32). The Fracture Risk Assessment Tool (FRAX) was initiated and enables physicians to assess the 10-year probability of fracture for individual patients based on information about a patient’s clinical risk factors combined with a hip DXA scan (milestone 9: definition including risk stratification, figure 1) (32). While convenient in risk assessment, the definition of osteoporosis as defined by the WHO in 1994 remained unchanged.

### Milestones in the definition of sarcopenia

In 1988, Rosenberg coined the term ‘sarcopenia’ to describe ‘deficiency of muscle mass’ as a literal translation from Greek, where ‘sarx’ means ‘flesh’ and ‘penia’ means ‘deficiency’ (milestone 1: coining of a term, figure 1) (1). Since the introduction of the term, the attention of the medical community to sarcopenia has grown. Nowadays the use of the term sarcopenia in literature has reached a level comparable to the use of the term osteoporosis 50 years ago (figure 2).

For sarcopenia, the techniques to measure the amount of muscle mass were already in use at the time the term was coined, but there was little intention for application, since the clinical consequences were unknown. In 1998, Baumgartner et al. suggested a formula to define sarcopenia as appendicular lean mass (sum of lean mass of both arms and legs) divided by height squared. Values more than two standard deviations below the mean of a young reference population were classified as sarcopenia (3). Other researchers introduced different formulas to define sarcopenia using muscle mass corrected for a combination of height, fat mass, or total body mass (milestone 7: criteria for quantification, figure 1) (4;33;34).

The introduction of diagnostic criteria contributed to the understanding of the consequences of having low muscle mass. There is a growing body of evidence that muscle mass is associated with self-reported physical disability (3;4;35) and functional impairment (4;35) (milestone 2, understanding of consequences).
Sarcopenia has also been defined by muscle strength represented by knee extension isometric torque or handgrip strength, lower extremity muscle power or physical performance such as gait speed (36) (milestone 7: criteria for quantification, figure 1). It has also been proposed to define sarcopenia by combining muscle mass with muscle strength or function, such as a combination of low muscle mass with low gait speed (9;37;38). Interchangeable use of the term sarcopenia makes it impossible to compare studies on sarcopenia due to very little concordance between different used diagnostic criteria (13).

**Reflection**

We have identified milestones in the history of the definition of osteoporosis and compared these to milestones that have been reached for the definition of sarcopenia. Both disease definitions relate to chronological age and started with the identification, recognition, and branding of a phenomenon (milestone 1, coining of a term, figure 1). A relevant question is at what stage to consider the gradual decline in bone mass or muscle mass as a disease, instead of a condition normal for

*Figure 2: Amount of hits in the MEDLINE database with the term “osteoporosis” (white bars) and “sarcopenia” (black bars). Both terms were entered as a single term in the MEDLINE database search engine per year with 5 year intervals.*
chronological ageing. In the past, the terms ‘disease’, ‘disorder’, and ‘condition’ have been used as synonyms in literature for osteoporosis, while they describe different phenomena. ‘Disease’ is a definite morbid process with characteristic symptoms, whereas a ‘disorder’ describes an abnormality of function and a ‘condition’ is a state or mode of being, especially a state of health (39). The severity and development of the process and the underlying pathophysiological process determines the term to be chosen. The detrimental outcome associated with sarcopenia justifies defining sarcopenia as a disease, comparable to osteoporosis (milestone 2: understanding of consequences, figure 1).

The difficulty in defining cut-off points for the amount of bone mineral density and muscle mass accounts for both osteoporosis and sarcopenia. Which reference populations should be used to decide whether the amount of muscle mass or bone mineral density is normal or abnormal? Concerning osteoporosis, cut-off points are based on the optimal combination of sensitivity and specificity to determine the occurrence of fractures. As in osteoporosis, for sarcopenia it is crucial to define reference groups, based on gender, ethnicity, and race.

An important difference between osteoporosis and sarcopenia is a clearly defined clinical consequence, which is needed for evaluation of the diagnostic criteria and development of treatment. In case of osteoporosis the risk of fractures is used as clinical outcome parameter. For sarcopenia, a clear clinical outcome parameter is still lacking. It is undesirable to evaluate muscle quality in terms of physical performance and strength, since this is also dependent on other parameters such as the neural controller, cardiovascular fitness and joint function. Although the amount of muscle mass is associated with muscle strength (4;33;34;40), there is accumulating evidence that muscle mass and muscle strength are two different entities (10;41;42) and therefore the term ‘dynapenia’ was coined by Clark in 2008 to describe the loss of muscle strength occurring with age (10). Besides a generator of strength, muscle tissue is an important internal organ. Next to mechanical consequences, loss of muscle mass has physiological consequences. These include protein storage, glucose regulation, hormone production and other cellular mechanisms (6). Recent studies have shown that the ability to recover from life-threatening disease is dependent on a higher amount of muscle mass, as sarcopenia was associated with higher mortality rates after liver transplantation (43) and higher chemotoxicity, independent of confounding factors (44). This might also be of clinical relevance in determining whether or not a patient is suitable for organ transplantation or chemotherapy.

In conclusion, it appears that crucial milestones are missing in the development of a clinically applicable definition of sarcopenia. Obvious main lacking milestones are
the availability of specific drug therapy (and therewith pharmaceutical interest), public awareness of clearly defined disease consequences, and a universally accepted definition. Interchangeable use of the definition of sarcopenia makes it impossible to compare studies, to understand the pathophysiological process and to develop targeted therapies. Since muscle tissue is involved in multiple processes, we suggest defining sarcopenia as ‘low muscle mass’ without use of functional or metabolic outcome parameters. Consensus must be reached regarding reference values of the general population of different ethnicities and race and applied correction factors. Furthermore, proper outcome measures should be defined for valid risk assessment. Understanding of the underlying pathophysiological processes will lead to first treatment possibilities and introduction of the disease in clinical care. It is necessary to create public awareness and accelerate the process of reaching a universally accepted definition of sarcopenia.

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