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A clinical guide to the pathophysiology, diagnosis and treatment of osteosarcopenia

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ABSTRACT

Advances in medicine have paved the way for older persons to live longer, but with more years spent living with disability and dependency. Many older persons are living with comorbidities such as osteoporosis (loss of bone mass) and sarcopenia (loss of muscle mass and function), two diseases that, when concurrent, form osteosarcopenia, a newly identified musculoskeletal syndrome. Osteosarcopenia impedes mobility and diminishes independence and thus quality of life. Evidence suggests the pathology of this syndrome comprises genetic polymorphisms, alterations in mechanotransduction, and localized or systemic crosstalk between growth factors and other proteins (myokines, osteokines, adipokines). As a direct result of an aging society, health outcomes such as falls and fractures will rise as the prevalence of osteosarcopenia increases. Two major risk factors for osteosarcopenia (other than age itself) are physical inactivity and poor nutrition. Addressing these modifiable risk factors can prevent, or at least delay, the onset of osteosarcopenia. Pharmaceutical treatments for osteosarcopenia are currently unavailable, although research trials are underway. This review provides an update from basic and clinical sciences on the biology, epidemiology (prevalence, risk factors and diagnosis) and treatments for osteosarcopenia, and recommends future research priorities to improve health outcomes for those living with or at risk of osteosarcopenia.

1. Introduction

The importance of preserving musculoskeletal health into old age is marked by the adverse outcomes sarcopenia (loss of muscle mass and function) and osteoporosis (bone loss) may confer such as an increased risk of falls, fractures, frailty, disability and premature death [1]. The role of these metabolically active tissues also extends beyond maintaining mobility and independence. For instance, skeletal muscle insulin resistance has been identified as the largest defect in type II diabetes [2], and the loss of muscle mass and strength correlates with cardiovascular disease in older adults [3]. Likewise, the skeleton provides a reservoir for mesenchymal stem cell (MSC) production in bone marrow and facilitates nutrient storage. Declines in bone microarchitecture have been related to MSC exhaustion [4]. Any compromise to the structure or function of muscle and bone tissue, such as that which accompanies aging [5], leads to a deterioration in health span and an increase in healthcare dependence as well as expenditure [6]. Based on demographic changes, which will see an increase in the oldest old, the burdening of osteoporosis and sarcopenia on socioeconomic resources are projected to rise [1].

Osteoporosis and sarcopenia are both risk factors for falls and fractures. In older women (> 80 years), the incidence of osteoporotic fractures of the vertebrae and hip are estimated at 30 and 40 %, respectively [7]. Similarly in those with sarcopenia (> 65 years), the risk of falls and fractures are significantly elevated compared to their aged- and sex-matched counterparts [8]. Health care costs related to these diseases are overwhelming. In the United Kingdom, muscle weakness was estimated to cost the public health system £2.5 billion in 2018 [9]. In sarcopenic patients admitted to hospital, median health care costs are also significantly higher compared to non-sarcopenic patients

Abbreviations: ALM, appendicular lean mass; BMD, bone mineral density; MSC, mesenchymal stem cell; SARC-F, strength, assistance in walking, rise from a chair, climb stairs, falls; FRAX, fracture risk assessment tool; SPPB, Short Physical Performance Battery; TUG, Timed Up and Go test; DXA, dual-energy X-ray Absorptiometry; QCT, quantitative computed tomography; QUS, quantitative ultrasound; MRI, magnetic resonance imaging; BIA, bioimpedance analysis; IMAT, intramuscular adipose tissue; RE, resistance exercise; FDA, food and drug administration

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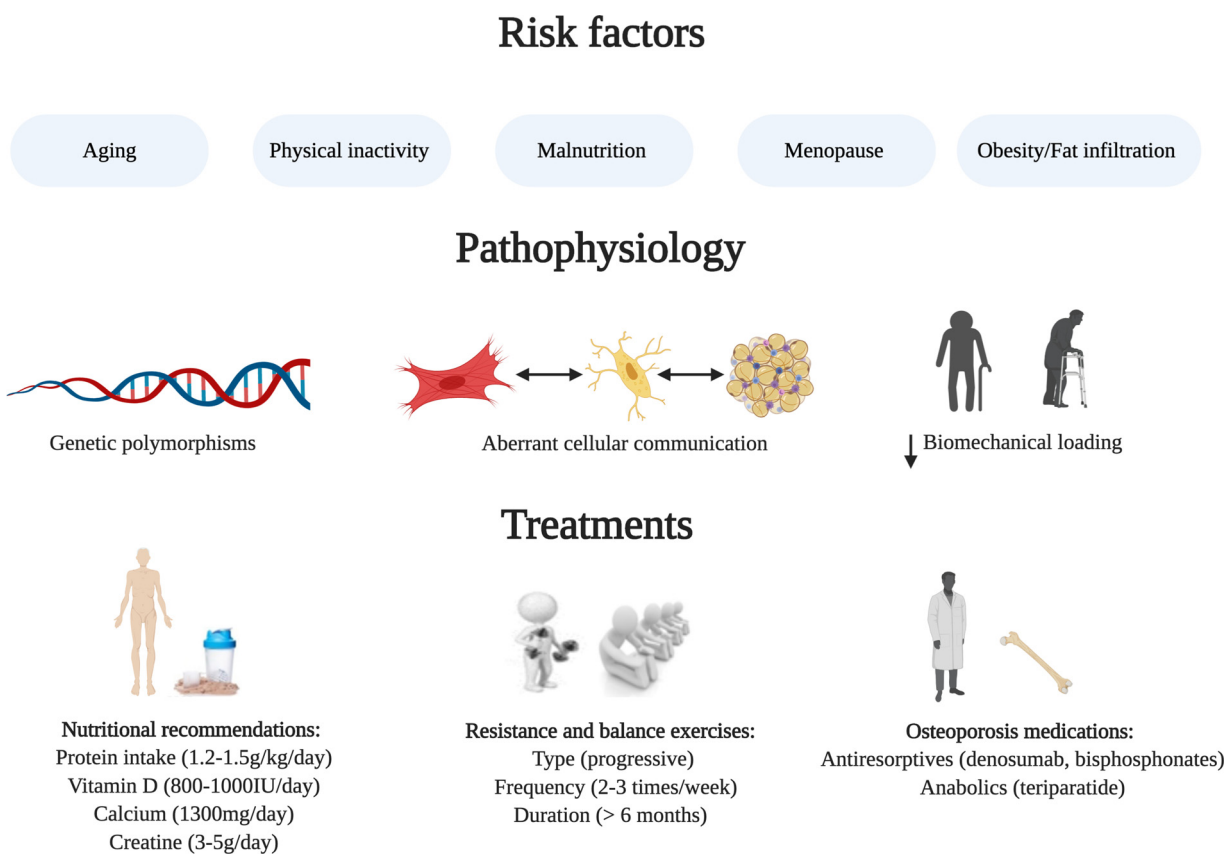

Fig. 1. Osteosarcopenia: risk factors, pathophysiology and treatment options.

(€3150 vs €2170) [10]. In Europe alone, osteoporotic fractures were estimated to cost an upwards of €37 billion in 2018 [11]. The impact of sarcopenia and osteoporosis on a patients' quality of life is substantial with a reduction in the ability to perform activities of daily living and an increased length of hospital stay just some of the negative health outcomes reported [12,13].

In more recent times, there has been an increase in the number of studies illustrating the link between muscle and bone loss [14,15], which is partly due to the number of older adults presenting with osteoporosis and sarcopenia [16]. Indeed, data indicates that risk factors for falls or fractures such as reduced grip strength [17], poor balance [18], gait speed [19], chair rise time [17] and lean body and bone mass [16], further decline in individuals with concurrent osteoporosis and sarcopenia (or osteosarcopenia, as coined by our team [20]). Given that recent reports demonstrate that falls prevention and fragility fractures are neglected and underprioritized by healthcare systems [7], there is an urgent need to educate researchers and clinicians on the importance of identifying and managing osteosarcopenia.

Herein, we discuss the pathophysiology underpinning osteosarcopenia, its epidemiological roots, as well as upstream prevention and downstream treatment options for this musculoskeletal syndrome.

2. The pathophysiology of osteoporosis and sarcopenia

Sarcopenia is a progressive degenerative disease with a multifactorial etiology. Age-related immunological changes (hormonal imbalances, chronic inflammation and increase in oxidative stress), imbalances in protein turnover (degradation exceeding synthesis), increases in adiposity (particularly intra- and inter-muscular fat), reductions in physical activity and poor nutritional status contribute to sarcopenia [21]. On the other hand, osteopenia/osteoporosis is characterized as the age-related decline in bone mineral density (BMD) and microarchitecture [22]. Compared to sarcopenia, the pathophysiology of osteoporosis is better understood, which likely reflects this condition being recognised by the World Health Organisation over two decades ago. Declines in bone density are thought to stem from imbalances between bone forming (osteoblasts) and resorbing (osteoclasts) cells, with the latter exceeding the former over time [22]. Hormonal factors particularly estrogen, parathyroid hormone and testosterone (all essential for optimal bone growth), decline after menopause and are implicated in the development of osteoporosis [22]. Reductions in physical activity and poor nutritional status (low intake of protein, vitamin D and calcium) also contribute to this skeletal disease [23].

3. Similarities between osteoporosis and sarcopenia

There are several similarities between muscle and bone wasting conditions such as osteoporosis and sarcopenia. Indeed, both tissues can regulate one another, and the loss of muscle and bone mass coincide with aging [5]. Polymorphisms of the genes family with sequence similarity 210 member A (*FAM210A)*, Growth/differentiation factor 8 (*GDF8),* Methyltransferase Like 21C *(METTL21C)*, and sterol regulatory element binding transcription factor 1/ target of myb1-like 2 (*SREBF1/ TOM1L2)*are associated with muscle and bone wasting [24]. Of these, *GDF8* (also known as myostatin) is the most well-characterized and overexpression of this protein has shown to induce protein degradation in muscle and inhibit osteoblastic differentiation in bone, resulting in a net loss of muscle and bone mass [24].

Muscle and bone are also highly malleable tissues and respond similarly to environmental stimuli. Following prolonged physical loading, significant increases in muscle mass, strength and physical functioning [25,26], as well as bone density and microarchitecture are evident [27]. In periods of bed rest/disuse, the opposite occurs with rapid declines in muscle mass and function and slower declines in bone density [28]. Overlapping with this, increased adiposity and the accumulation of inter- and intra-muscular fat and bone marrow adipose

tissue are hallmarks of osteoporosis and sarcopenia [29]. In both tissues, lipid infiltrations results in lipotoxicity, defined as fat products-induced cellular dysfunction and death [30]. Again, physical activity decreases whole body adiposity and ectopic fat in aged muscle and bone [31]. Systemic factors such as a decline in estrogen and testosterone predisposes to the risk of osteoporosis and sarcopenia (respectively), and high parathyroid hormone and insufficient vitamin D levels are considered risk factors for both diseases [20]. Lastly, cellular senescence and the release of proinflammatory cytokines, chemokines and proteases contribute to muscle and bone loss [32]. Given these overlapping features, in addition to work displaying worse health outcomes in those with osteosarcopenia [33], more recent work has focused on the role of systemic and localized factors regulated by MSCs.

3.1. Possible humoral factors driving osteosarcopenia

Muscle and bone are active organs which interact via auto-, para- and endocrine mechanisms. This communication system is governed by the secretion of myokines, osteokines and adipokines from their respective precursor cell (myocytes, osteocytes and adipocytes) (Fig. 1). Biomedical studies demonstrate that some myokines (insulin-like growth factor 1, fibroblast growth factor, follistatin, osteonectin, osteoglycin, irisin and interleukin-15) exert anabolic actions on bone, while other myokines (myostatin and interleukin-6) initiate bone catabolism [34]. Bone-derived osteokines (osteocalcin, connexin 43 and sclerostin) can also impact muscle in a positive or negative manner [34]. In both tissues, the infiltration of adipose tissue results in the secretion of adipokines and other fatty acids which are toxic to muscle and bone cells [30].

Overall, while the study of animal models has certainly shed light on the interaction between muscle and bone at the molecular and cellular level, a limitation of current research is the lack of human data to corroborate this evidence. Thus, further studies are needed to identify the impact of myokines on bone and osteokines on muscle in response to physical loading, aging and disuse. In turn, this may enable the development of pharmaceutical treatments for osteosarcopenia targeting these proteins.

4. Epidemiology

4.1. Prevalence

The estimated prevalence of osteosarcopenia varies widely. This variation is primarily due to classification differences such as fracture history vs. BMD to define osteoporosis, and the definition of sarcopenia applied. Further differences in prevalence estimates are observed in hospitalized older adults, compared with those living in residential care and in the community. Increased prevalence is observed when osteopenia and osteoporosis are included in the definition, as opposed to osteoporosis alone [35]. In a recent systematic review and meta-analysis, using 17 studies, five definitions were applied to suggest 5–40% prevalence in osteosarcopenia across inpatient and community settings [35]. High risk groups such as those with falls or fractures show the greatest prevalence rates (27.2–40 %) [35].

4.2. Clinical outcomes

Numerous cross-sectional and longitudinal studies have examined important outcomes in older adults. The key clinical outcomes include mobility, disability (of which falls and fractures are surrogate outcomes), and mortality. There is a strong association of increased risk of falls (odds ratio 2.83–3.63; $p < .05$) and fractures (odds ratio from 3.86 to 4.38; $p < .05$) in older adults living with osteosarcopenia, compared with non-osteosarcopenic individuals when using various sarcopenia definitions [36]. Findings from the MrOS study also showed that men with combined osteopenia and sarcopenia (osteosarcopenia) (hazard ratio (HR) = 3.79, 95 % confidence interval (CI) = 2.65–5.41) and men with osteopenia only (HR = 1.67, 95 % CI = 1.45–1.93), but not sarcopenia alone (HR = 1.14, 95 % CI = 0.62–2.09), have a greater risk of non-vertebral fractures than those with normal bone density and no sarcopenia [37]. It should be noted that these findings were not replicated in women with no significant difference in risk of fractures between the osteosarcopenia group and low BMD group found [37]. In addition, the Concord Health and Ageing in Men project found that individuals with combined osteopenia and sarcopenia (osteosarcopenia) do not have an increased risk of falls and fractures compared to either osteopenia or sarcopenia alone [38].

Increased mortality at one year has been observed in those experiencing a hip fracture with osteosarcopenia (15.1 %), as compared with matched non-hip fracture patients with sarcopenia (10.3 %) or osteoporosis (5.1 %) alone [39]. After adjusting for covariates, osteosarcopenic individuals were at a 1.8 greater risk of mortality compared to non-osteosarcopenic patients [39]. Another prospective study in community-dwelling older adults found an increased mortality risk in osteosarcopenic older persons (relative risk = 1.49, 95 % CI: 1.01–2.21) compared to those without sarcopenia or osteopenia [40]. However, again, these studies did not find a greater risk of mortality in those with osteosarcopenia vs sarcopenia or osteoporosis alone.

Given the conflicting findings in outcomes, which is likely attributed to methodological differences and non-universal sarcopenia definitions between studies, further longitudinal trials are required to better understand the risk of clinical outcomes in different population groups and amongst diverse ethnicities.

4.3. Diagnosis, assessment and risk factors

Contemporary, comprehensive care of the older adult should include an assessment for osteosarcopenia. A thorough medical history (including falls history), risk factor identification, physical examination, functional assessments, and person-specific investigations must consider:

- Possible causes of osteosarcopenia (low activity, comorbidities, poor nutrition or medications), symptoms (weakness, fatigue, reduced mobility, decreased function, falls and fractures) and impact (reduced quality of life, mood disorders, institutionalization).
- Collateral history from the next of kin, or other health professionals given the high prevalence of sensory and cognitive deficits which may limit history taking from the older adult being assessed.
- Person-centered approaches to interventions which are in line with the individual's values and preferences.

Numerous risk assessment and screening tools are available for osteoporosis and sarcopenia, but none are presently available for osteosarcopenia. We recommend the application of the following risk assessment tools in the clinical work up for older adults:

- SARC-F is a 5-item patient reported sarcopenia measure [41].
- FRAX is a validated international tool for fracture risk, inclusive or not of BMD [42].

A comprehensive falls assessment involves a thorough history and physical examination, aimed at addressing modifiable falls risk factors. Such risk factors found on clinical assessment may be further explored by the allied health team, particularly when considering functional and or physical factors. A referral to an occupational therapist or physiotherapist may support further assessment to guide recommendations. Therapists may adopt validated risk factor screening within their discipline-specific competencies. Some of these include static and dynamic balance and self-reported falls questionnaires.

As part of the physical examination, the clinician should undertake assessments of muscle strength and physical performance. The chosen

definition of sarcopenia may guide the clinician's preference. However, the most well-studied physical assessments are:

- Muscle strength: Hand grip strength (kg) using a hand-held dynamometer [43].
- Physical performance: Walking speed (m/s) over 4 m (using 6 m with 1 m lead in and out) [43].

Other measures that may be considered include 5 sit to stands, Short Physical Performance Battery (SPPB), Timed Up and Go test (TUG), and or 400 m walk test [43]. While the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) definition of sarcopenia advocates for interchangeability of these measures, doing so has been shown to result in vastly different prevalence estimates within the same population group [44]. The Sarcopenia Definition and Outcomes Consortium (SDOC) recently published a data-driven definition of sarcopenia which did not include measures of muscle quality or quantity [45], only handgrip strength and walking speed. Thus, the application of the SDOC definition does not require additional imaging methods to confirm the diagnosis of sarcopenia. Given the variability between definitions and cut-points for "normal" and "low," clinicians should take a discerning approach when selecting measures of muscle strength, physical performance and respective cut-points in their assessment.

There are multiple tools that can be utilized when assessing older adults for osteosarcopenia, each with various levels of accuracy and application. Dual-energy X-ray Absorptiometry (DXA) is the most commonly used investigation as it can accurately determine BMD and body composition (fat and lean mass). DXA-determined appendicular lean mass (ALM) approximates muscle mass and is a component of the most recent sarcopenia definitions [43], with the exception of the SDOC definition [45]. However, ALM overestimates true muscle mass, and low ALM is not associated with negative functional or mobility outcomes [46]. BMD predicts fracture risk and can be used to monitor response to antiresorptive and anabolic therapies. The FRAX tool is non-inferior to DXA BMD alone in predicting fracture risk, and thus has great application in resource-poor settings where DXA is not available [42]. Coupled with low handgrip strength, low walking speed and a low trauma fracture (meeting the definition of osteoporosis), a diagnosis of osteosarcopenia may be made in settings where DXA is not available. Fig. 2 represents a clinical algorithm to diagnose and manage older persons with osteosarcopenia where DXA is available.

Indications for further BMD investigation include:

- Age: women ≥ 65 years, and men ≥ 70 years.
- Women: younger in postmenopausal and in menopausal transition.
- Men: aged 50–69 years with risk factors for fracture.
- Fracture history: adults who have a fracture at, or after the age of 50 years.
- Low bone mass or risk: condition (e.g., rheumatoid arthritis) or medication (e.g., glucocorticoids ≥ 5 mg per day for longer than 3 months).

Other diagnostic tools such as peripheral DXA (pDXA), quantitative computed tomography (QCT), quantitative ultrasound (QUS), and radiographic absorptiometry can also be used to assess BMD and fracture risk. Given that an absolute majority of fractures in older adults occur in persons with BMD in the normal or osteopenic range, these techniques all have high specificity but low sensitivity for fracture prediction [47].

Except for whole-body magnetic resonance imaging (MRI), which is not feasible in practice, all currently available techniques to assess muscle are approximations. Terminology in this regard is important, as some historical studies assumed ALM and muscle mass were equivalent which led to the false belief that low muscle mass may not be clinically significant. The investigations and terminology used are described below [48]:

- Muscle mass:
  1 Lean mass (or ALM) when derived from DXA.
  2 Fat-free mass when derived from DXA or BIA (bioimpedance analysis).
  3 Cross-sectional area (CSA) when derived from peripheral CT.
  4 Muscle volume when derived from MRI.
- Muscle quality

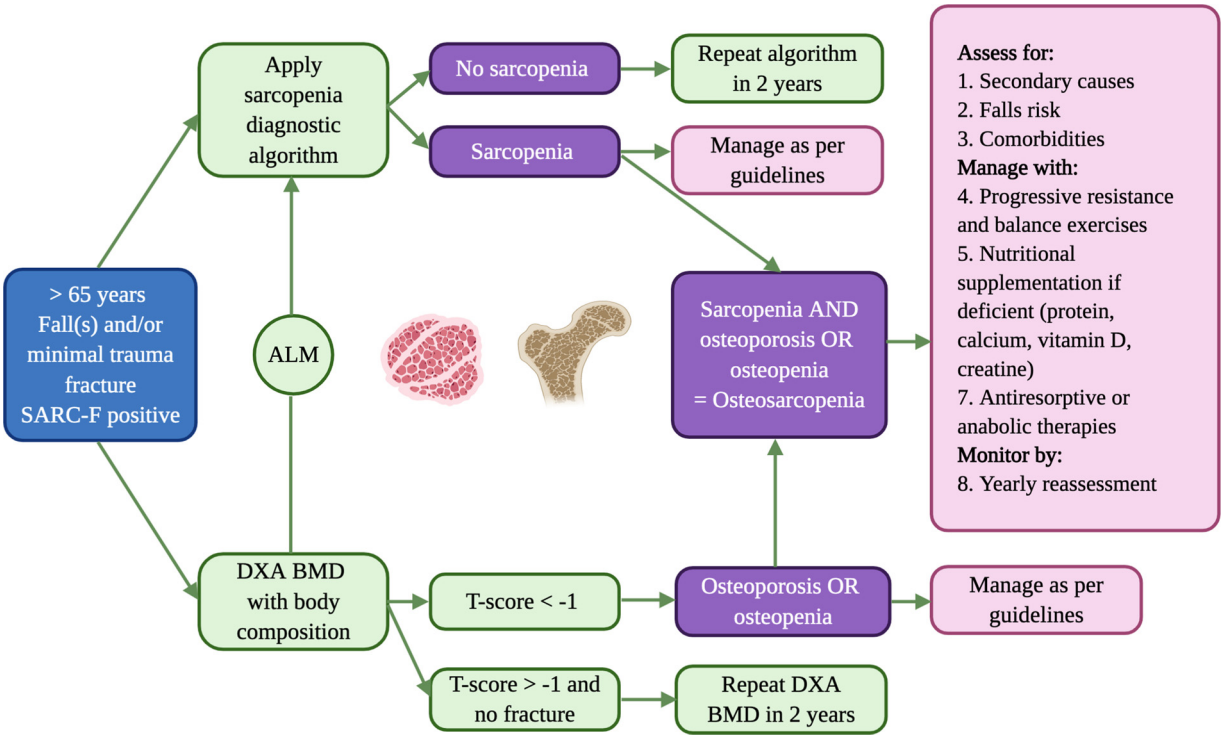

Fig. 2. A clinical algorithm to diagnose and manage osteosarcopenia.

1 Intramuscular adipose tissue (IMAT) derived from peripheral CT [30].
2 Echogenicity derived from ultrasound.

5. Preventative and treatments options for osteosarcopenia

Regular participation in physical activity, especially resistance exercise (RE), offers benefits to the whole body [49]. Cross-sectional studies also demonstrate the benefits of RE on attenuating age-related losses of muscle and bone mass [27] and increases in adiposity [50]. Clinical trials in osteopenic/sarcopenic individuals offer further evidence that RE can improve multiple musculoskeletal health outcomes as well as quality of life [25,26], while others show a positive association between physical activity and reductions in falls and fractures [51,52]. A recent Cochrane review also found that a combination of resistance, balance and functional exercise was the most effective at combatting falls in community-dwelling older adults [52]; however, strategies to improve adherence rates are still needed.

Regarding nutritional intake, increasing protein intake above 1.2 g/kg/day is safe [53] and recommended to regain/maintain muscle mass with or without RE in healthy older adults or in those with acute or chronic diseases [54]. However, according to the PROT-AGE expert group, the exception is in patients with severe chronic kidney disease who are advised to limit protein intake [54]. The benefits of increasing protein intake on bone are also well established [23].

It should be highlighted that while increasing protein intake is effective at increasing muscle mass [55], the effects on sarcopenia-related measure such as strength and functional capacity are less consistent [56–58] but the effects of RE are overwhelming [59,60].

In regards to other micronutrients, sufficient intake of vitamin D and calcium are recommended to delay osteoporosis, and these micronutrients may play a role in muscle metabolism too [23].

The most recent advancement in the muscle-bone field in regards to dietary-intake is the benefits of creatine which is discussed in depth elsewhere [61]. Fig. 2 outlines current therapeutic interventions for osteosarcopenia, which should be initiated at the earliest stage of diagnosis.

Current pharmacological agents for osteoporosis have been addressed in detail by our team in a recent publication [22]. In short, multiple FDA-approved drug treatments exist; including, antiresorptive (denosumab, bisphosphonates), anabolic (teriparatide, abaloparatide), anti-sclerostin (romosozumab), and hormonal (hormone replacement therapy, selective estrogen receptor modulators) agents [22]. However, there are no approved pharmacological agents for the specific treatment of osteosarcopenia. Nevertheless, two clinical trials have found benefits of denosumab, a receptor activator of nuclear factor-κB ligand inhibitor, on muscle and bone mass, as well as muscle strength and balance in older persons at risk of falls and fractures [62,63]. In this regard, further double-blind trials are needed to confirm the efficacy of denosumab in treating osteosarcopenia.

6. Moving the field forward

Knowledge of the shared pathophysiological mechanisms underpinning osteoporosis and sarcopenia continues to grow. There is a great appeal at the prospect of being able to simultaneously treat muscle and bone dysfunction, with the goal of improving the independence, quality of life and health outcomes of older adults worldwide. However, numerous steps are required to advance the osteosarcopenia field and translate knowledge into clinical practice. These include:

1) Longitudinal, epidemiological studies which determine the temporal order of underlying disease of muscle and bone, coupled with determination of risk of negative outcomes in persons living with osteosarcopenia.
2) Establishment of the mechanism(s) driving the development of osteosarcopenia (particularly the role of systemic and localized growth factors needs further elucidation).
3) Consensus on a definition of sarcopenia for clinical and research applications, including further study on novel techniques for estimating muscle mass (such as the d_3-creatine dilution technique).
4) Randomized controlled trials examining the impact of exercise, nutrition and pharmacological compounds on both the prevention and treatment of osteosarcopenia in older adults.
5) Translation of knowledge of osteosarcopenia into clinical practice on a global scale.

7. Summary

Osteosarcopenia is a progressive musculoskeletal syndrome which associates with falls, fractures and premature death. The pathology of this condition is multidimensional with strong evidence for environmental factors such as physical inactivity, adiposity (including fat infiltration) and poor nutritional status effecting muscle and bone health. Data from animals and humans suggest a combination of genetic polymorphisms, hormonal imbalances and other endocrine factors may also play a contributing role. Assessment of osteosarcopenia should include muscle and bone imaging (i.e., DXA), physical assessment (i.e., grip strength and gait speed) as well as identifying notable risk factors (i.e., glucocorticoid use, physical activity and nutritional status). An evaluation of falls and fracture risk should also be performed. Early identification of this debilitating syndrome is important to intervene with efficacious treatments such as progressive resistance- and balance-exercise and improving nutritional intake for those with deficiencies. Further clinical trials are needed to test the dual effects of environmental and pharmaceutical agents on muscle and bone in older adults. An efficacious biomarker for osteosarcopenia is also currently lacking and would aid early identification. It is anticipated that over the coming years those in the field of aging will develop answers to these questions and in turn, reduce the growing burden of osteosarcopenia.

Contributors

Ben Kirk participated in study conceptualization, data curation, formal analysis, and writing, review, and editing of the manuscript.

Sarah Miller participated in study conceptualization, data curation, formal analysis, and writing, review, and editing of the manuscript.

Jesse Zanker participated in study conceptualization, data curation, formal analysis, and writing, review, and editing of the manuscript.

Gustavo Duque participated in study conceptualization, data curation, formal analysis, and writing, review, and editing of the manuscript.

All authors saw and approved the final version.

Conflict of interest

The authors declare that they have no conflict of interest.

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