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Perspective Article

Osteosarcopenia School

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Abstract

Osteosarcopenia has been proposed as a syndrome in a subset of frail individuals at higher risk of falls, fractures and institutionalization. In this paper, we will go over the translational aspects of sarcopenia and osteoporosis research and highlight outcomes from different interventions. In addition, preventative measures and therapeutic interventions that can benefit both muscle and bone simultaneously will be analysed also. A new holistic concept called Osteosarcopenia School will be presented. This new concept is based on counselling and education of patients as part of a rehabilitation program, aiming to reduce the risk of social isolation, falls and fractures, and subsequent disability through muscle strengthening and balance training. In this patient group, the combination of pharmaceutical treatments and specific exercise programmes are essential to counteract the consequences of osteosarcopenia. Finally, educational programmes targeting patient functionality through social reintegration may have a substantial impact on their daily living activities and overall quality of life.

Keywords: Elderly, Fractures, Falls, Osteosarcopenia, Rehabilitation

Introduction

Osteopenia/Osteoporosis and Sarcopenia are increasing the incidence of fractures and falls, respectively. Considering that the majority of fractures are occuring due to falls a connection between osteoporosis and sarcopenia is established. The term osteosarcopenia has been recently emerged as a syndrome, combining the biological and clinical features of osteoporosis and sarcopenia[6,7]. Osteosarcopenia is associated with higher side effect risks in vulnerable older individuals, predisposing them to frailty and disability enhancing mortality risk[8]. Eventually, age-dependent loss of bone and muscle mass quality and strength gradually leads to osteopenia/osteoporosis and sarcopenia, respectively[9].

Definition of Osteosarcopenia

Although osteoporosis and osteopenia are defined through the T-/Z-scores for bone mineral density comparisons among populations, the definition of sarcopenia is still a work in progress[10-12]. Therefore, in the future the definition of osteosarcopenia may be modified due to potential changes of sarcopenia representation. The use of several criteria from various organizations and societies regarding sarcopenia may make its definition more complex[13,14]. In the latest definition of sarcopenia from the European Working Group of Sarcopenia Older People II (EWGSOP II), sarcopenia is commenced solely in the presence of concomitantly low muscle strength and muscle mass, while low physical performance is considered a surrogate of severe sarcopenia[12].

Furthermore, values intended to measure low muscle mass estimate appendicular skeletal mass (ASM) levels whereas the assessment of muscle strength is performed through handgrip strength and physical performance (gait speed, chair-to-stand, timed up and go) testing. Although,

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these outcomes may represent similar definitions, they are not identical, and consequently, the application of different interpretations and cut off points in experimental research worldwide may lead to altered outcomes and results of sarcopenia prevalence[11-15]. Using the EWGSOP II definition for osteosarcopenia, the percentages, which corresponded to osteosarcopenia and osteosarcopenia with a severe sarcopenia component (low physical performance) in patients with osteopenia (BMD <-1) or osteoporosis (BMD <-2.5) were relatively the same. On the contrary, EWGSOP I and Foundation of the National Institute of Health FNIH definitions underestimated the percentages of osteosarcopenia and severe sarcopenia[16]. These identical percentages suggest that osteosarcopenia and osteosarcopenia with a severe sarcopenia component may occur in both osteoporotic and osteopenic individuals, increasing symmetrically fracture risk[17].

Pathophysiology of Osteosarcopenia

Pathophysiologically, osteoporosis and sarcopenia share common characteristics: a) bones (osteoblasts) and muscles (muscle cells), origin from mesenchymal cells, b) their mass is determined by genetics, cytokines, sex steroids, growth hormone, Wnt proteins, fibroblast growth factors, and myostatin, c) during embryogenesis, they are predetermined by genetic factors and cytokines, while in adolescence under the command of sex steroid hormones, and d) throughout lifespan, mechanical loads and forces exert a generic control[18-20]. Furthermore, muscle to bone cross-talk is a crucial parameter in osteosarcopenia. Muscles interact with bones through myokines (e.g. IGF-1, myostatin, osteoglycine, irisin, osteonectin), while bones interact with muscles via osteokines (IGF-1, sclerostin, osteocalcin)[20]. There is a strong and complex interaction of mechanical and biochemical issues in both conditions. For instance, factors that regulate the damage between muscle and bone are linked to detrimental components of bone and muscle loss regulation (i.e. autophagy, glucocorticoids, myostatin), whereas those that may benefit both tissues are exercise, dietary protein, adequate energy intake, and medications[21,22].

Moreover, the Frost mechanostat theory is the basis of muscle-bone interaction, which describes the variable reaction of bone to the rate of deformation. Interestingly, bone is remodelled based on the strains forced on it, while deformations in the area between 800 and 1500 micro-strain may promote a remodelling balance. However, in case of extreme loss of loading (i.e. immobility-induced paraplegia) or extra force application (i.e. due to physical exercise), bone remodelling may occur and may be balanced in a lower or higher strain threshold[23]. In addition, lipotoxicity is associated with fat deposition in bones and muscles through secretion of free fatty acids and adipokines, affecting cell function and structure[6,21,24]. The infiltration process between the muscle and bone may differ, given that fat is infiltrated intramuscularly and between muscle fibres, and into the bone marrow, respectively[25-27]. The mechanisms that trigger bone and muscle fat infiltration and the characteristics of adipocytes and secretory agents are similar in both tissues (bones and muscles), predominantly via aging, immobility, and neuromuscular and metabolic diseases. Increased levels of free fatty acids and adipokines in muscles and bones may lead to autophagy, resulting in increased osteoclasts and decreased osteoblasts and muscle fibres type II[25,26]. Other factors that increase fat deposition in-between muscles and bones are glucocorticoid therapy, immobilization and leptin deficiency, whereas statin therapy, resistance training and whole-body vibration therapy may be effective strategies that may reduce fat accumulation[27]. Accordingly, vitamin D is crucial in the muscle-bone crosstalk, affecting both muscle cells and osteoblasts through osteoglycine, myostatin, and IGF-1 secretion[20]. Vitamin D and parathyroid hormone (PTH) are main regulators of bone and muscle biology[28,29]. Vitamin D via VDR receptors in muscle and bone acts either through long-acting (classic genomic action) or through short-acting action[30]. These two pathways affect common muscle-bone characteristics, but among others, vitamin D has anabolic properties for bone and muscle mass[28]. Regarding the risk factors of osteosarcopenia, it may be imperative to exclude those not in common in osteoporosis or sarcopenia[7,31,32].

Diagnosis of Osteosarcopenia

Diagnosis of osteosarcopenia is based on the number of annual falls, fracture history, clinical features of osteoporosis (i.e. kyphosis, loss of height due to fractures), and of sarcopenia (i.e. muscle weakness, physical dysfunction, falls). Algorithms may assist with the classification of individuals, identifying them as sarcopenic[12]. For instance, using the SARC-F questionnaire, individuals may be assessed for sarcopenia screening to examine their diagnosis[33,34]. Muscle strength is evaluated by asking if the patient can lift a light weight; ability to lift equals to 2 points, some difficulty represents 1 point, and inability to lift provides 0 points. The same procedures and scores are established in the following questions (i.e. assistance during walking, standing up from a chair, climbing up the stairs, events of falls). Eventually, in regard to the number of falls in the past year, a point score of 2 is given for incidence of >4 falls, 1 point for 1-3 falls and 0 points for no falls[33,34]. The algorithm continues with questions about declines in muscle mass and strength. According to the most recent definition (EWGSOP II), reduced muscle mass and strength highlight a definitive sarcopenia diagnosis[12]. However, if a person with low grip strength is accompanied with reduced physical performance (i.e. walking speed <0.8 m/sec, low SPPB; Short Physical Performance Battery scores, TUG; timed up and go >10 seconds), it translates to severe sarcopenia[12]. Moreover, in clinical practice, the gold standard for appendicular lean muscle mass measurements is whole body DXA (dual-energy X-ray absorptiometry)[12]. However, other devices, including BIA (bioelectrical impedance analysis), CT (computed tomography), and MRI (magnetic resonance imaging) are additionally valuable assessment tools. In this context MRI may be more valuable in the future due to its ability to assess lipotoxicity[12]. Application of DXA scanning for osteoporosis should highlight markers of sarcopenia to prevent misdiagnosis of osteosarcopenic patients, however, measurement of muscle mass requires extra software for body composition analysis, which is rather often available and may calculate indicators, such as appendicular skeletal muscle mass (ASM)[7,11,35]. ASM refers to muscle mass of the arms and legs and is crucial for Skeletal Muscle Index (SMI) estimation, which is calculated by dividing the ASM (kg) by the square of the height (m^2), categorizing individuals as sarcopenic or non-sarcopenic[12,36]. Low values of ASM and bone mass are indicators of osteosarcopenia. However, the lack of comparative studies among osteosarcopenia, osteoporosis and sarcopenia, addresses the need to approach research data carefully. Additionally, another limitation is the examination of high body fat percentage independent of body mass index (BMI), considering an increase in muscle fat filtration regardless of body weight change or changes in subcutaneous adipose tissue[37].

Follow-up DXA scan measurements for osteoporosis should be performed every 2 years, while sarcopenia assessment should be performed annually due to faster changes that occur in skeletal muscle compared to bones[38]. In the absence of DXA, clinical trials measuring physical performance may be performed instead, and muscle strength measurements may be done using a hand dynamometer or subjectively testing grip strength[12]. However, absence of established biomarkers may limit the estimated prevalence of osteosarcopenia, as opposed to osteoporosis and sarcopenia independently. Diagnostic rate versus cost per diagnosis of alternative screening strategies to identify and treat metabolic contributors of falls and fractures to achieve a diagnostic rate over 90%, most cost-effective way, while obtaining valuable information in terms of treatment decision making is the following: incorporating 25-OH vitamin D, calcium, parathyroid hormone, testosterone (in males), thyroid-stimulating hormone (TSH), and creatinine/estimated glomerular filtration rate (eGFR) in clinical practice, which may be potent markers of enhanced falls and fracture risk assessment in vulnerable groups[39].

Emergence of Osteosarcopenia

Osteosarcopenia emerges with weakness and falls, develops from osteopenia or osteoporosis into a functional disorder with falls, fractures, vulnerability, and disability. However, others believe that osteosarcopenia happens in a person suffering from comorbidities i.e. osteoporosis and sarcopenia, entering the vicious circle of falls and fractures and leading to vulnerability, disability, immobilization, and all other negative effects. Our opinion is that both theories are correct, there is a progressive and dynamic development at the same time. The good news is that we may interfere in this process to retard or stop its progress[21].

Prevention and Treatment of Osteosarcopenia

Following osteosarcopenia diagnosis, investigation and treatment of potential secondary causes, including vitamin D deficiency and secondary hyperparathyroidism are imperative[32]. Relevant treatment strategies include counselling related to smoking cessation, alcohol restriction, and incorporation of resistance training (2-3 times/week for 30 minutes) and endurance exercise programs, focusing on appropriate dose, intensity and frequency protocols. In addition, supplementation with vitamin D (when 25(OH)D <50 nmol/L, aiming to minimally reach 75 nmol/L), calcium (1.2 g/d), and dietary protein intake (1.2-1.6 g/kg/day) with daily protein supplementation (i.e. whey protein) due to age-related anabolic resistance may be recommended to improve skeletal muscle mass and functional parameters[40-43]. Furthermore, although, drugs used for osteoporosis have anti-inflammatory effects, investigation of effective drug treatments for sarcopenia is warranted. Remarkably, denosumab has displayed convenient properties on bone density, peripheral bone mass and strength compared with intravenously bisphosphonates and placebo following a 3-year period[44]. Furthermore, in a longitudinal study of 79 community-dwelling older adults presenting for falls and fracture risk assessment with a history or risk of falls and/or fractures, ability to mobilize independently or with gait aids, and no cognitive impairment denosumab administration reported statistical significance compared to zoledronic acid, in gait speed, while enhancing multidirectional agility, as highlighted by Timed Up and Go (TUG), and Four-Square Step Test (FSST) scores. Beneficial results were observed in terms of walking speed from zoledronic acid, which is probably a paradoxical finding[45].

Regarding the treatment of osteosarcopenia, only the effect of testosterone administration on bone and skeletal muscle is well established, but its effectiveness against falls and fracture prevention is yet to be tested[46,47]. Although, positive outcomes related to body composition, lean body mass and adipose tissue declines in older adults have been reported, the benefit/harm ratio concerning patient safety issues (i.e. sleep apnea, polycythemia, prostate cancer) due to testosterone administration has been long-confirmed[48]. Furthermore, SARMS (selective androgen receptor modulators), including myostatin and myostatin antibodies, may be a potential treatment for osteosarcopenia. Such hypothesis has emerged from *in vivo* studies, exploring mutations against myostatin, that display a supreme physical development, as myostatin inhibition may lead to muscle hypertrophy[49]. A subcutaneous injection of 315 mg myostatin antibody for 4 weeks has has shown powerful muscle mass improvements, although, it did not provide benefits in relation to falls risk[50].

Figure 1. Warming up exercises; for details see text. Published with permission from [53].

Osteosarcopenia School

i) General information

Osteosarcopenia is a significant disorder in older age that may impact daily activities. Prolonged isolation, following a confirmed osteosarcopenia diagnosis may lead to signs of withdrawal, low self-esteem and self-respect, self-sustaining melancholia, increased stress, (social) isolation, cognitive and physical dysfunction, and dependency[51]. The contribution of rehabilitation medicine may delay the development of this vicious cycle, integrating patients in a newly formed environment with specific limitations and concrete directions through proper education.

ii) Education

The primary intention is patient's education in osteosarcopenia which should focus on: 1) understanding their actual physical abilities, 2) analysis of their activities around the newly formed environment, 3) motor adjustment to the new circumstances, 4) facilitation and increase of physical activity levels, and 5) accessory utilization to achieve daily self-service activities. It is paramount that patients understand their actual abilities kinetically, mechanically, kinaesthetically and functionally. This may be achieved by explaining the new mechanics of the body by admitting the change of body model. Body image modification, provoked by spine deformation has an instant impact on basic mechanism of motor control and proprioception[52]. This may be comprehended even by patients themselves when referring to specific activities, while comparing older circumstances to present ones. An immediate result of osteosarcopenia is the modification of the mechanical sufficiency of the body. The circumstances and the environment in which they perform the tasks are changed, while performing specific activities are modified (lifting, transferring and moving objects), or actions of self-service (cleaning, diet and body care). In addition, the distribution of force and loading is also modified. As a result, the sensory perception and the information provided from the distal receptors during and after the execution of specific tasks may change. The perception of this "new environment", is achieved by understanding the new body mechanisms, facilitated via appropriate training. As a fundamental principle of this new mechanic behaviour, all forces that develop, must be focused near the center of gravity. Turns or any other dangerous movement which may be catastrophic must be avoided. Finally, extreme positions of distal joints and torso's range of motion should be avoided as they may increase fall risk (Figure 6).

iii) Exercise

During the training process, the usual activities of lifting and/or weight transferring may be adopted in the exact same way as previously mentioned, which is crucial for hospitalized patients following a hip fracture (conservative or operative treatment). The appropriate schedule should be organized after hospital discharge and training should be gradual to ensure mobilization and rehabilitation as early as possible. Training should be focused on muscle strengthening and weight bearing exercise programs adjusted around the appropriate dose, intensity, and frequency. Emphasis should be put on clothing (athletic tracksuit, sweats, and socks) and proper footwear to make patients feel more comfortable and be more consistent.

Exercise program

1) Warm up

We recommend a slow start with moderate loads and calm breathing. A break after each exercise of sufficient duration and adequate hydration before, during and after exercise is also recommended. Prior to the main exercise program, warm up is essential, and the program should start with "on-site gait" and "lifting legs from a supine position" (Figure 1).

During this exercise, patients are trained to walk through

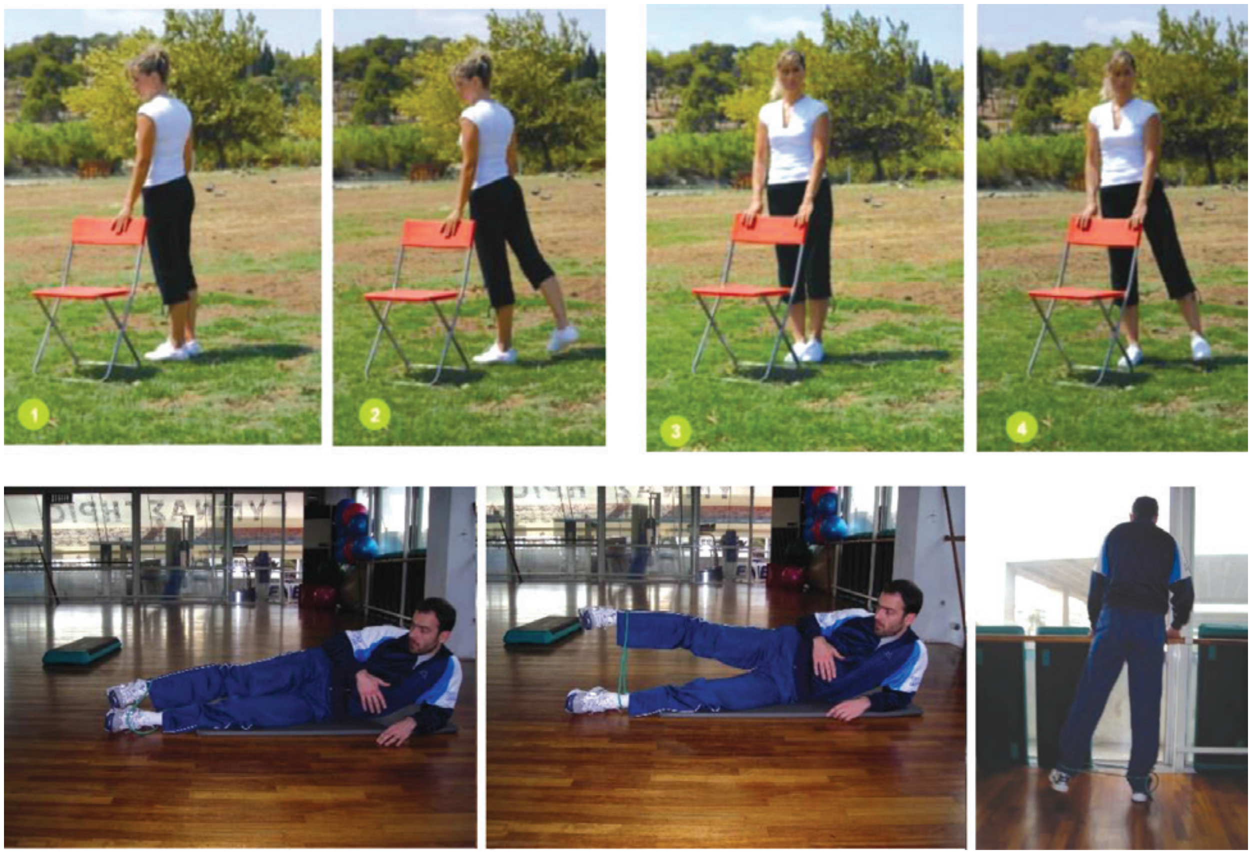

Figure 2. Muscle strengthening of hip abductors; for details see text. Published with permission from [53].

Materials to use	Target: muscle strengthening	Intensity Frequency Duration	Precautions
Chair, wall, elastic bands, bottle of water, free weights equipment in the gym etc.	Increasing strength, (targets are mostly hip muscles, back muscles, biceps, triceps).	8-10 repetitions 2-3 sets 3-5 times weekly 20-30 minutes	Subjects with kyphosis should avoid bending and turning the spine and perform the exercises seated.

Table 1. Characteristics of Muscle strengthening exercises. Published with permission from [53].

a more appropriate way and get informed on the importance of pertaining a standard walking rate. In addition, walking speed of younger individuals may be significantly faster, and in many cases, they may carry a backpack (5 to 8 kg). An uneven ground is not suggested, because it may increase fatigue and incidence of falls[54].

2) Muscle strengthening of lower limbs

Following warm-up, interventional strategies should move forward with muscle strengthening exercises, focusing on specific regions of the skeleton where fractures are most prevalent, primarily the hip, the spine, and the wrist. The program may include: 1) strengthening of extensor and abductor hip muscles; The participant places the hand on a fixed spot for safety (i.e. chair) and lifts one leg backwards to stimulate extensor muscles. Furthermore, the patient lifts one leg to the side to strengthen the abductor muscles (10 reps/3 sets). Both exercises can be done with pulleys (at home or at the gym), lying sideways on the ground, under the guidance of a qualified instructor (Figure 2 and Table 1).

Figure 3. Muscle strengthening of upper extremity, for details see text, published with permission from [53].

Figure 4. Balance exercises: Tandem walking and balancing on one foot, for details see text [53].

3) Muscle strengthening of upper limbs

Arm Exercises: Exercises for strengthening the biceps and triceps can be done from a standing or seated position. From a standing position, the knees are slightly flexed, using medium load weights (i.e., a bottle of half liter water or pulleys for lower resistance) Perform three sets of 10 repetitions with each arm (Figure 3).

4) Balance exercises

This type of exercise is the most important in falls prevention. Simple exercises for balance are walking heel to toe beside a wall or rail and balancing on one foot. The purpose of the exercises is the development of synchronized movements, resulting in balanced sitting and standing positions. Tandem walking (heel to toe walking) beside a wall or rail for a short time. In alternative balancing on one foot, standing at the side of a chair (for safety) and leaning on the chair with one hand, whereas at the same time the opposite leg is raised with the knee bent as shown in the picture. Subjects perform the exercise, first with open and then with closed eyes and continue by changing side and leg of support (Figure 4). Ten repetitions for each leg are necessary[53].

5) Flexibility exercises

During aging the body becomes more rigid, which results in movement difficulties leading to falls and increasing risk of fracture. Thus, it is crucial to perform exercises to maintain flexibility. Exercises of this category may help to maintain elasticity, muscle length, the range of joint movement, improve posture, and reduce (back) pain.

Stretching muscles of the lumbar spine: The patient is kneeling on the floor with knees slightly apart (photo 1), and carefully bends forward, until the palms touch the floor (photos 2, 3), keeping this position for several seconds and repeats 5 times (Figure 5).

At this point, the patient needs to be encouraged to perform these activities in an energetic way. The use of any device is only supplemental, complementing their active effort. Therefore, the choice of accessories and devices is individualized and defined by the daily requirements of each patient.

6) Follow – up

This is a functioning model in a group level to rehabilitate patients with osteosarcopenia. The program may be performed in a rehabilitation department, an outpatient geriatric clinic etc. Due to the content of the program rehabilitation physicians, physiotherapists, psychologists, nurses, and social workers are important members of the rehabilitation team. Essential areas of this model are the frequent attendance of group patients, up to 3 times per week for 3 months.

Initially, discussion and information take place about the patients' condition, and afterwards, the everyday activity training process, and the application of exercise programs. In the meantime, the discussion and psychological support should be maintained (i.e. on personal problems of the group members).

Figure 5. Stretching muscles of the lumbar spine, for details see text. Published with permission from [53].

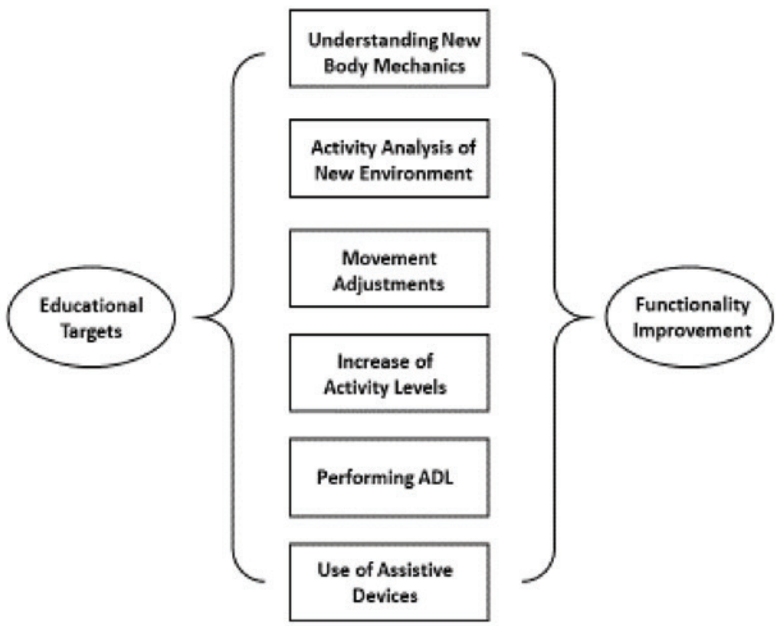

Figure 6. Educational targets applied in Osteosarcopenia school lead to improved functionality.

iv) Targets in Osteosarcopenia school

By "Osteosarcopenia School", we characterize a holistic therapeutic process-program, which involves patient informing-counselling, training, and entertainment, by applying specific programs and activities on a group basis. This concept is introduced to substantially cover the actions that may take place individually and attempt a therapeutic intervention, emphasizing on each of the above procedures (counselling, training). The intention is to improve the functionality, independence, and self-care of elderly patients that suffer from osteosarcopenia, and promote an active social engagement.

In the beginning, counselling may aid to identify the problem. Considering that osteosarcopenia increases the risk of falls and fractures, patients must acknowledge and understand their condition, which may prove beneficial on handling this detrimental disorder.

Patients should be encouraged to continue with their daily activities and interests, to participate in social activities and if possible, to broaden their function cycle by pertaining new interests and taking part in social groups (e.g. entertainment, dance, excursions, handcrafting, art, theatre, sport activities).

These lifestyle modifications may offer significant support and increase functionality levels, while providing a safe environment.

The basic targets of the "Osteosarcopenia School" program are shown in the chart (Figure 7).

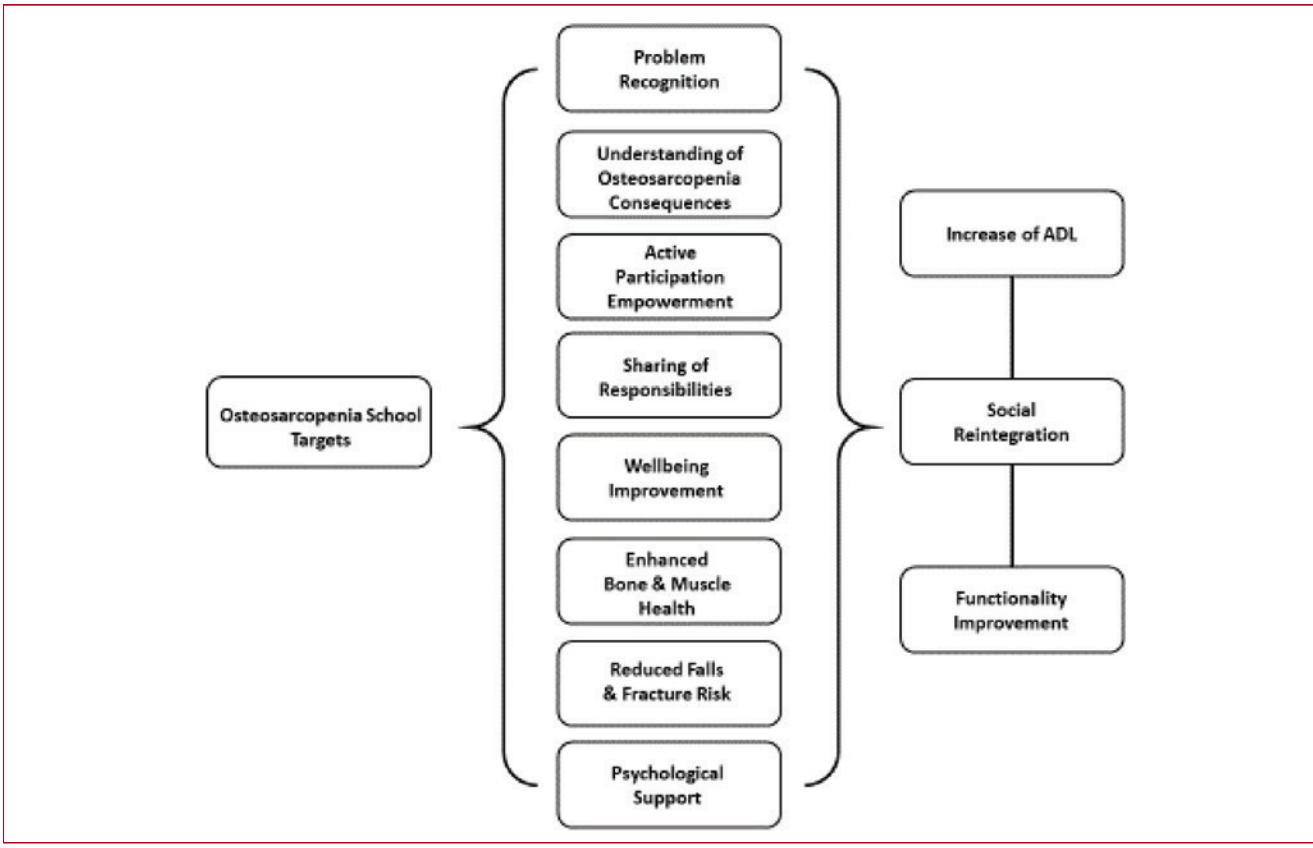

Figure 7. Targets in Osteosarcopenia school and outcome categories.

v) Limitations

Some individuals may not be eligible for this program. Applicability may be limited in small groups of individuals visiting specialised geriatric clinics and further, attendance of participants with systemic comorbidities, cognitive problems, musculoskeletal and neurological disorders may be limited due to more complicated status of these subjects.

Conclusion

It is paramount to be aware of osteosarcopenia, primarily due to its asymptomatic incidence, considering that is usually diagnosed following the repercussions of initial fractures. Additionally, there is a high risk of treating osteoporosis alone, yet osteosarcopenia is a condition requiring multidisciplinary support and assistance through the parallel treatment of both osteoporosis and sarcopenia. Implementation of well-structured exercise protocols, optimal nutrition strategies, and patient-based education programs highlighting their condition may prove pivotal methods of osteosarcopenia treatment and prevention.

Disclaimer

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