OSTEOSARCOPENIA

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Abstract:

Osteoporosis, a state of decreased bone mineral density, is a well-known entity. Similarly sarcopenia a condition where there is significant loss of muscle associated with ageing is also well documented. Osteosarcopenia[1] where there is co-existence of the above two mentioned chronic musculoskeletal conditions, associated with ageing is a recently described clinical entity. Both these conditions share common risk factors and biological pathways. They lead to greater risk of falls, fractures, institutionalisation and significant socioeconomic costs. With an increasing elderly population, osteosarcopenia is a community healthy issue that will become increasingly relevant in the future.

Epidemiology

The true prevalence of osteosarcopenia is unknown since it is a recently described syndrome. However, a large study conducted by Huo et al., including 680 frail individuals with history of falls found that the prevalence of osteosarcopenia was 37%. They also noticed that these patients had a higher incidence of other co-morbidities, impaired mobility and depression[2].

Osteosarcopenia is also associated with significantly increased incidence of fragility fractures, hospitalisation and even mortality. A study by Yoo et al., of 324 elderly Korean patients with hip fractures found that 1-year mortality rate was 15.1% in osteosarcopenic patients, which was significantly higher as compared to osteoporotic (5.1%) or sarcopenic (10.3%) patients alone[3]. Another study by Wang et al., included 316 Chinese patients ≥65 years old found that 10.4% of men and 15.1% of women had osteosarcopenia, with the odds of frailty being significantly higher in the osteosarcopenic patients as compared to osteoporosis or sarcopenia patients alone[4].

Etio-pathogenesis

Apart from age, there are multiple other factors contributing to the development of osteosarcopenia.

1. Genetic polymorphisms of certain genes like Glycine-N-acyltransferase (GLYAT), methyltransferase-like 21C (METTL21C), myostatin, α-actinin 3, proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and myocyte enhancer factor 2C (MEF-2C) leads to bone and muscle loss[5].

Fig1: Etiopathogenesis of Osteosarcopenia

2. Endocrine and paracrine disorders mainly diabetes, abnormal thyroid function and low levels of vitamin D, sex steroids, growth hormone and IGF-1 leads to osteosarcopenia. Malnutrition, obesity and the use of corticosteroids are also associated with osteosarcopenia[5].

3. Microsomal damage – It is due to the process called as “lipotoxicity” where inflammatory cytokines like IL-6 and TNF-α (secreted by fat and bone marrow) cause microsomal damage which in turn leads to acceleration of apoptosis, ultimately leading to fat replacing the bone or muscle tissue7.

4. Physical activity - Lack of physical activity in old age and immobility due to chronic illnesses like malignancy, chronic heart failure, chronic kidney disease, COPD etc., ultimately leads to disuse atrophy of the skeletal muscles.

5. Diet has a major role in maintaining the muscle-bone balance. Between the ages of 40 and 70 years, the average intake of calories reduces by 25%. Vitamin D and protein deficiency increases the risk of falls, by multiple damaging pathways against muscles and bones[8].

6. Cigarette smoking is a significant risk factor for both osteoporosis and sarcopenia. Also, alcohol intake of ≥ 3 units/day increases fracture risk in a dose-dependent manner. In a recent Korean study, high-risk alcohol drinking was associated with a higher risk of sarcopenia in postmenopausal women[9].

Diagnosis

The diagnosis of both osteoporosis and sarcopenia is needed to make a diagnosis of osteosarcopenia

Osteoporosis

In 1994, the World Health Organisation developed specific criteria to define osteoporosis in postmenopausal women, based on bone mineral density of femoral neck as the T-score of less than -2.5[10]. DEXA is known as the gold standard for diagnosis of osteoporosis and has a high degree of validity[11].

Sarcopenia

The muscle mass reaches its maximum by approximately twenty five years of age. By the age of fifty, there is a 5% decrease in the number of muscle fibres. At the end of second decade of life, the muscle mass begins to decrease and its rate increases in the fifth decade of life. The annual loss of muscle mass is between 1% and 2% per year, resulting in a 30% reduction in muscle mass by the age of eighty. The European Union Geriatric Medicine Society (EWGSOP) proposed an algorithm for the diagnosis of sarcopenia.

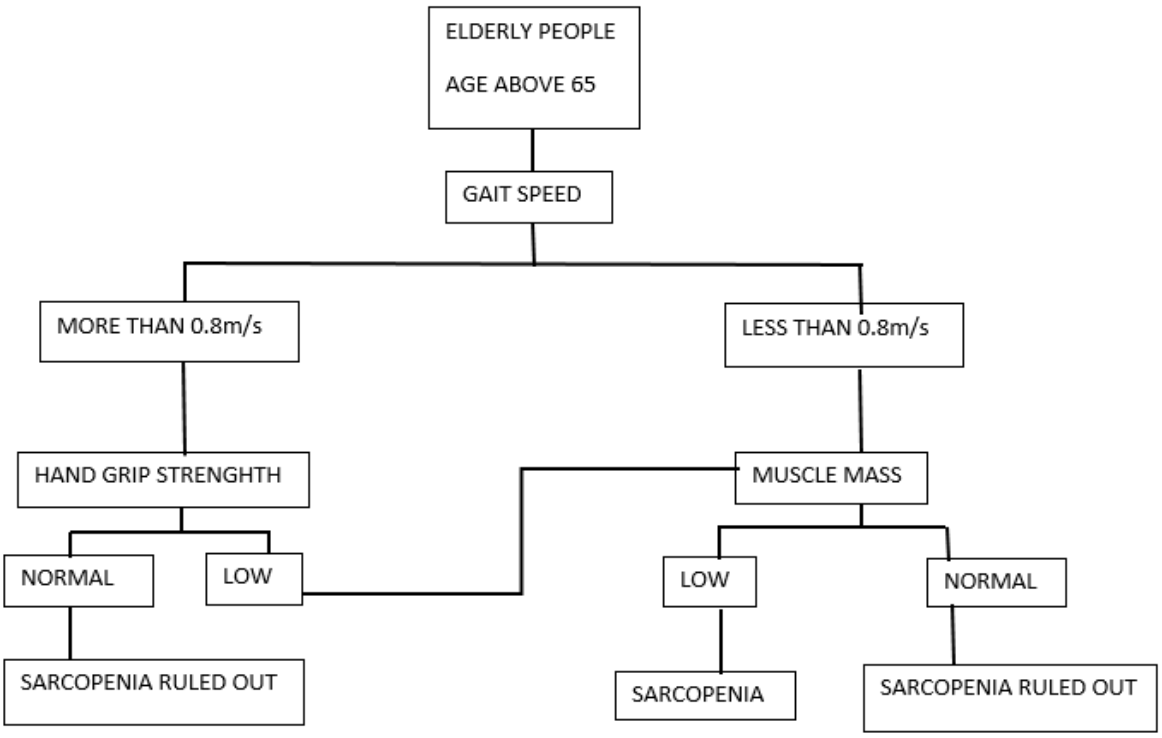

Fig 2; EWGSOP[6] – suggested algorithm for sarcopenia case finding in older individuals.

There are many modalities to assess muscle mass like DEXA, bioimpedence analysis[6] and CT scan. DEXA is the modality of choice as it is quantitative, inexpensive, minimises radiation exposure and is widely available with its current role in osteoporosis[1].

Management

Multifactorial approach should be considered to prevent osteosarcopenia. Changes in lifestyle and behavior that include elimination of modifiable risk factors, such as smoking, excessive

alcohol consumption are helpful. Similarly environmental factors which increases risk of falls should be eliminated. Osteosarcopenic individuals benefit from comprehensive physical activity programme, nutritional intervention and pharmacological treatment.

1. **Exercise**- Exercise promotes muscle strength, muscle tension and helps in maintaining a good posture and gait. It has many positive effects especially in elderly individuals. Regular exercise reduces bone loss, particularly at the femoral neck. A meta-analysis which included adults over 45 years found that there was an overall reduction of fragility fracture risk by 51% only with implementation of comprehensive exercise programme[12]. Another study by Silva et al., also reported that the risk of falls in those who underwent combined resistance and balance training programmes, reduced by 29%[13]. The WHO recommendation for exercise activity for the elderly includes moderate aerobic activity for 30 minutes for 5 days a-week, muscle strengthening activities 2 days a-week and balance exercise for subjects with poor mobility and consequent increased risk of falls.

2. **Nutrition**- Adequate nutritional intake of vitamin D, calcium and protein are the main goals of nutritional therapy for osteosarcopenia. Vitamin D supplementation can have many beneficial effects, including increased muscle strength, decreased mortality and falls and functional improvement. Recommended daily allowance of vitamin D is 800-2000 IU/day in older adults, aiming for a target serum 25(OH)D of at least 50 nmol/L (20 ng/ml). Adequate calcium intake is also advised in patients with osteosarcopenia, with a recommended daily intake of 700 – 1200 mg. Meta-analyses showed combined supplementation of vitamin D and calcium is safer and effective in reducing risk of fractures in older individuals[14].

   There is sufficient evidence to suggest that formation of complex proteins within the body is markedly reduced with inadequate protein intake[14]. Thus, a higher protein intake of 1.0-1.2g/kg/day is recommended in the elderly, with at least 20-25g of high-quality protein with each meal and post-exercise[15].

3. **Pharmacotherapy-** There are many proven therapeutic drugs for the treatment of osteoporosis. But it is not the same in case of sarcopenia and most drugs are still under research and development[16].

   Bisphosphonates are the first-line treatment for osteoporosis. Alendronate, risedronate and zoledronate are few commonly used bisphosphonates. Other major pharmacological therapies for osteoporosis include denosumab, a RANKL inhibitor that prevents production of osteoclasts, selective oestrogen receptor modulators (SERMs) such as raloxifene (partial oestrogen agonist, selective for bone) and anabolic agents such as teriparatide (a recombinant form of parathyroid hormone). The latter treatment is restricted to high-risk fracture patients refractory to other treatment, due to its high expense[17].

   Several new therapies are being developed which target muscle in addition to bone. Selective androgen receptor modulators (SARMs), such as Andarine have anabolic effects in muscle and bone and due to their high tissue selectivity, limit the androgenic side-effects associated with testosterone therapy[16]. Other promising agents centre on the activin-signalling pathway and include myostatin-neutralising antibodies or propeptide, recombinant follistatin, follistatin derivatives, and soluble activin receptors[16]. Pathways that centrally regulate bone and muscle, such as GH/IGF-1 and androgen signalling, can also be targeted. Possible therapeutic agents include recombinant GH (which increases lean mass and lumbar BMD, but has safety issues), GH secretagogues (which increase GH/IGF-1 levels through more "physiological" means), and testosterone therapy (which has positive effects on muscle mass, strength and BMD, but is limited by androgenic side effects and concerns about cardiovascular events and prostate cancer).

CONCLUSIONS

Sarcopenia leads to muscle imbalance and defective gait which in-turn leads to frequent falls and osteoporosis makes the bone fragile, both these conditions leads to fragility fractures in the elderly. Osteoporosis and sarcopenia co-exist and share common etio-pathogenesis so rather than two separate entities they should be considered as a single clinical syndrome of osteosarcopenia.

Multiple causes that lead to this syndrome like metabolic, cellular, vascular and inflammatory factors, etc., have not been fully understood. Advancements in DEXA and CT scan can be used to diagnose this condition easily. Adequate protein, vitamin D and calcium intake together with an appropriate comprehensive exercise programme may have a beneficial effect in preventing it. Upon diagnosis of this condition appropriate pharmacotherapy can be adopted as a part of the treatment along with physical and nutritional intervention. Management of this syndrome improves functional performance and reduce falls and fracture risk, resulting in benefits for the older patients.

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