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COPD: osteoporosis and sarcopenia

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Abstract

Systemic involvement and comorbidities are common in chronic obstructive pulmonary disease (COPD). They add to the burden of disease and are associated with significant disability and mortality. These include cardiovascular disease, mood disorders, anemia, cachexia, skeletal muscle dysfunction and bone pathology. In this article, we review the pathophysiology, diagnosis and treatment of two such comorbidities, osteoporosis and sarcopenia, as they relate to patients with COPD.

Introduction

Chronic obstructive pulmonary disease (COPD) is a multisystem disorder, characterized by involvement of multiple organs in addition to the lungs [1]. The inflammatory state inherent to the lung pathology in COPD is thought to be the root cause of this multi-organ dysfunction. Furthermore, it is likely that this state contributes to the development and acceleration of comorbid conditions seen in COPD patients at higher frequencies when compared to the general population.

Currently, the delineation between a systemic feature and comorbidity of COPD is not well defined. Skeletal muscle dysfunction, cachexia, osteoporosis, coronary artery disease, congestive heart failure, anemia, metabolic syndrome, depression and anxiety are all frequently encountered in COPD patients. What is clear, however, is that all of the above lead to morbidity and mortality and need to be identified and addressed by the physician taking care of a COPD sufferer.

In this chapter, we will review osteoporosis and sarcopenia in patients with COPD.

Review

Osteoporosis in COPD

Osteoporosis is a silent "skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features: bone density (in turn determined by peak bone mass and amount of bone loss) and bone quality (a function of bone architecture, turnover, damage accumulation and mineralization)" [2].

At present, except for markers for bone turnover, few indicators exist to concretely describe measures of bone quality. Hence, bone density remains the principal method to define osteoporosis. As per the World Health Organization criteria, a bone mineral density (BMD) score, measured by a dual energy X-ray absorptiometry (DXA) scan, that is 2.5 times or more below the standard deviation (T score of −2.5 on the DXA bone scan) for a young normal population is used to define osteoporosis; a BMD score between −1 and −2.5 is indicative of osteopenia (low bone mass) [3].

Epidemiology

Osteoporosis is the commonest bone disorder to afflict humans [4]. Roughly 10 million Americans have osteoporosis and a staggering 43 million have osteopenia, placing them at risk for fractures [5, 6]. Worldwide, the number of people with osteoporosis is estimated at 200 million [7]. With aging populations, the incidence and burden of osteoporosis and fractures are projected to get significantly worse [8].

Caucasian women constitute the largest at-risk group for osteoporosis; by age sixty, half of them suffer from osteopenia and one in two have an osteoporosis related fracture in their lifetime [4, 9]. However, both genders and all races are affected by the disease.

Despite the preponderance of men in the COPD population, osteoporosis is more common in COPD patients when compared to age matched controls without airflow limitation [10]. Roughly one-third of patients with COPD have osteoporosis (range 9–69% - the wide interval reflecting differences in methodology and demographics

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of the study population, as well as the severity of disease in the various studies) and about 38% have osteopenia (range 27–67%) [10, 11]. The increased prevalence of bone loss and osteoporosis places COPD patients at a significant risk of developing fractures, especially vertebral compression fractures [12, 13] and hip fractures [14].

Pathophysiology

Normal bone homeostasis The skeletal system is in a constant state of flux. Bone remodeling and resorption occur continuously to preserve the integrity of bone structure [15]. Osteoclasts, osteoblasts, and osteocytes, under the control of vitamin D, parathyroid (PTH) and gonadal hormones, are responsible for this process (Fig. 1). It is estimated that up to 25% of trabecular bone (the spongy bone located at the ends of long-bones and in vertebrae) and 3% of cortical bone (located in the shaft) are replaced every year [16, 17].

Osteocytes are cells that are embedded in the bone matrix. They detect microdamage, caused by mechanical fatigue, in the bones and initiate bone remodeling by interacting with osteoclasts and osteoblasts.

Damaged bone is resorbed by osteoclasts. These are multi-nucleate giant cells, from the monocyte/macrophage cell line, that secrete hydrolytic enzymes, including cathepsins and matrix metalloproteinases. Osteoclasts also secrete hydrogen and chloride ions. The resultant acidic environment aids bone resorption; it also activates the proteolytic enzymes, leading to breakdown of collagen/matrix of the compromised bone. Osteoblasts, derivatives of mesenchymal stem cells, then complete the remodeling process by making new bone –both the organic matrix and mineral– at the damaged site.

Two signaling pathways, osteoprotegerin (OPG)/receptor activator of nuclear-factor kappa B(RANK)/ receptor activator of nuclear-factor kappa B ligand (RANKL), and Wnt/β-catenin system, are important in regulating bone metabolism. RANKL, expressed on the surfaces of osteoblasts, bone stromal cells and activated T cells, binds with RANK present in osteoclast progenitor cells' cellular membranes and promotes maturation to osteoclasts; it also inhibits osteoclast apoptosis [18]. Bone resorption is thereby enhanced. OPG, also made by osteoblasts and bone stromal cells, inhibits these processes by binding to RANKL and preventing it from adhering to RANK [19, 20].

The Wnt/β-catenin signaling system promotes bone formation. It does this by a number of mechanisms: by promoting preferential differentiation of mesenchymal stem cells to osteoblasts rather than adipocytes, by inhibiting osteoblast apoptosis, and by increasing the levels of OPG.

Osteoporosis in COPD An imbalance in the processes of bone resorption and formation, either excessive resorption or decreased bone formation, leads to osteoporosis. A number of changes, leading to this imbalance, have been observed in COPD patients with osteoporosis:

- Elevated levels of RANK and RANK/OPG ratio [21]
- Upregulation of RANKL [21]
- Lower levels of OPG [22]
- Decreased activity of Wnt/β-catenin signaling [23]
- Elevated levels of matrix metalloproteinases [24]

The inflammatory milieu observed in COPD patients, especially the emphysema phenotype, is thought to

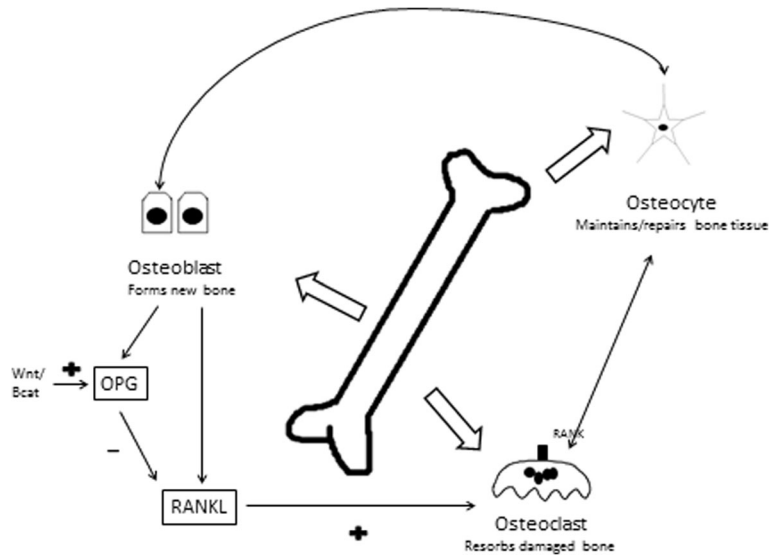

Fig. 1 Simplified diagram representing normal bone homeostasis. OPG = osteoprotegerin, RANK = receptor activator of nuclear-factor kappa-B, RANKL = receptor activator of nuclear-factor kappa-B ligand, Wnt/Bcat = Wnt/β-catenin

contribute to these changes, particularly the OPG/RANK/RANKL axis. Interleukin-1 (IL-1) and tumor necrosis factor-α (TNF α), levels of which are significantly increased in COPD (along with IL-6), favor RANKL activity and promote osteoclastogenesis and, ultimately, osteoporosis [25, 26]. The degree of radiolographically evident emphysema is directly correlated to lower levels of BMD in COPD patients [21].

In addition to the above, various other factors promote osteoporosis in COPD patients. These are described below.

Use of corticosteroids

Corticosteroids, inhaled and systemic, affect all three major cells involved in bone homeostasis, tilting the balance in favor of bone resorption and increasing the risk of fractures. They decrease levels of OPG and enhance expression of RANKL and monocyte/macrophage-colony stimulating factor (M-CSF) – M-CSF, similar to RANKL, stimulates osteoclastogenesis [27–29]. By inhibiting the Wnt/β-catenin pathway, they also decrease the proliferation, differentiation and maturation of osteoblasts; bone formation is decreased resultantly [30, 31]. Lastly, corticosteroids adversely affect the ability of osteocytes to detect microdamages and make bones more susceptible to fractures [32]. Osteocyte apoptosis is promoted, making the bones harder, less vascular and more brittle [33–35].

Steroids, in inhaled or systemic form, are used for specific indications in COPD patients.. Inhaled corticosteroids (ICSs) decrease the frequency of exacerbations and improve quality of life in moderate-to-severe disease [FEV < 60%] [36–39]. Systemic steroids are the cornerstone of therapy in COPD exacerbations and decrease their duration, improve symptoms and prevent relapse [40–45]. However, use of steroids comes at a cost with significant adverse effects, including osteoporosis and fractures. Systemic steroid usage is a predictor of decreased BMD and fracture occurrence [46–48]. The risk is dose dependent, with the highest risk of fractures in the first three to six months after initiation of therapy, and resolution of the risk within one year of treatment cessation [49].

The correlation between ICSs and reduced BMD and fractures is less clear. One long term follow-up of high dose triamcinolone [50] and a systematic review of ICSs revealed lower BMD and a modest increase in fractures respectively [48], but other studies have not corroborated this evidence with high dose ICSs [51–53]. Interestingly, at low doses, ICSs may prevent osteoporosis in COPD patients by decreasing the systemic inflammatory milieu [54].

Vitamin D deficiency

Low levels of vitamin D cause a drop in serum calcium [55]. A compensatory elevation of PTH occurs leading to production and release of calcitriol from the kidneys; calcium levels are normalized by the actions of calcitriol on the gut and the bones [56]. Calcitriol induces RANKL expression on osteoblasts and hence leads to excess resorption of the bones [and release of calcium]. The resultant normalization of serum calcium suppresses PTH production from the parathyroid gland. With vitamin D deficiency, this homeostatic control is lost; unchecked PTH release and its action lead to osteoporosis.

Vitamin D deficiency, defined as serum 25-hydroxyvitamin D levels of < 20 ng/ml [57], is quite prevalent in COPD. There are many reasons for this, including poor dietary intake, decreased 25-OH D production from senescent skin (a result of smoking), poor sunlight exposure due to COPD induced functional and mood impairment, renal dysfunction and steroid use [58]. Up to two-thirds of COPD patients can have a vitamin D deficiency, and the prevalence increases with the severity of airflow limitation (approximately 40% in GOLD stage I, rising to ~80% in GOLD stage IV) [59–61].

Lastly, vitamin D deficiency increases the risk of fractures due to its beneficial effects on balance and muscle strength [62]. Vitamin D supplementation in elderly patients with deficiency, especially in conjunction with calcium, results in a lower risk of falls and fractures [63].

Hypogonadism

The human sex hormones play an important role in maintaining skeletal integrity in the adult, by promoting bone formation and inhibiting resorption [64, 65]. Estradiol, in particular, is clearly implicated, with low levels being strongly associated with bone loss and fractures [66, 67]. Hypogonadism is common in COPD patients, various studies indicating a prevalence rate range of 22–69%, and is associated with osteoporosis and muscle weakness [68].

Reduced body mass index, fat free mass, sarcopenia and reduced physical activity

Mechanical loading plays an important role in maintaining bone mass and integrity [69]. The osteocyte network senses and transduces strain to the effector cells, osteoclasts and osteoblasts, to decrease bone resorption and enhance bone formation at sites where more strength is required to counter stress. Decreased mechanical stress, as occurring in low gravity, disuse and reduced physical activity, lead to bone loss [70–73].

The reduced mechanical load on bones that occurs with decreased body mass index [BMI], fat free mass [FFM] and with sarcopenia, can reduce bone formation. Physiological derangements in body composition are common in patients with COPD, with a high prevalence of low BMI, and low FFM [cachexia], and sarcopenia (reduced muscle strength and mass). Up to a third of

COPD patients suffer from low BMI, low FFM or sarcopenia [74, 75]. A significant correlation with osteoporosis has been observed in patients with COPD and sarcopenia, low BMI or low FFM [76, 77]. Besides a decreased mechanical load, other factors that may link osteoporosis and sarcopenia/low FFM/low BMI are vitamin D deficiency, inflammatory mediators, genetic factors, and the use of corticosteroids.

Sarcopenia is also related to impaired physical mobility, physical ability and falls with a higher risk of fractures [78].

Anemia and hypoxia

Hypoxia, by inhibiting stem cell differentiation into osteoblasts via decreased expression of transcription factor (Cbfa-1/RUNX2), reduces bone formation, while strongly stimulating osteoclast formation and bone resorption [79, 80]. Anemia is also thought to be associated with osteoporosis because of the same mechanism, as a result of anemia induced decreased tissue oxygen delivery. Both conditions are commonly seen in COPD patient, especially with severe disease, and are likely to contribute to COPD associated osteoporosis [81–83].

Others

Hypercapnia: A significant proportion of COPD patients have chronic carbon dioxide retention [84]. As expected, more severe airflow limitation (with reduced FEV1 and high airway resistance) is associated with hypercapnia. Elevated carbon dioxide levels, even in the absence of acidosis, are potent stimulators of osteoclast activity and are associated with low BMD [85].

Smoking: A meta-analysis of over 40,000 subjects indicated that cigarette smoking, the most important risk factor for COPD, has an independent, dose-dependent effect on BMD and risk of fractures, that is partially reversible with cessation of smoking [86]. Smoking contributes to osteoporosis through a variety of mechanisms, including effects on estradiol activity [87], as well the as Vit D/PTH axis [88], increased free radicals and oxidative stress resulting in more bone resorption [89], and modulation of OPG/RANK/RANKL system [90].

COPD exacerbations: These have been shown to be an independent risk factor for progression of osteoporosis [91]. The mechanism involved is likely a combination of factors discussed above: augmentation of the systemic inflammatory state during an exacerbation, worsening hypoxia and hypercapnia, elevated MMP levels, oxidative stress, use of steroids, and physical inactivity [92].

Age and gender: Older age is a common risk factor for both COPD and osteoporosis. After reaching peak bone mass in the middle-to-late twenties, people have gradual, continuous bone loss as they grow older. This bone loss is accelerated in women in the peri- and postmenopausal period [93].

Clinical features and consequences of osteoporosis in COPD

Osteoporosis is asymptomatic unless it is complicated by a fracture, with its accompanying physical, psychosocial and financial sequelae. Unlike people with healthy bones, patients with osteoporosis are susceptible to fractures from minor mechanical stress or trauma [94, 95]. These are termed as fragility fractures.

The commonest site of fracture with osteoporosis is the vertebral column. The thoracolumbar junction (T12-L1) and mid-to-lower thoracic area (T7–T8) are usually affected in patients with COPD [96]; various studies report a vertebral compression fracture (VCF) rate of 24–63% in COPD [13, 97–99]. Other commonly involved areas include the hip and the ribs.

Fractures are associated with significant morbidity and mortality in osteoporotic, COPD patients. Vertebral compression fractures can cause pain and result in kyphosis, decreased rib cage excursion and lung volumes [100]; an increased frequency of COPD exacerbations secondary to an impaired ability to expectorate can occur with the hypoventilation related to rib fractures [101]. It is estimated that each VCF is associated with a 9% drop in vital capacity [102]. VCFs also increase the rate and duration of hospitalization, and are associated with a worsened health-related quality of life [103, 104]. Worryingly, VCFs often escape detection, especially when they are not painful (which is the case in a massive 60–70% of VCF cases), leading to a missed opportunity to treat osteoporosis and prevent further fractures [105, 106]. Approximately, one in five patients who sustain a VCF suffer another VCF within a year [107].

Hip fractures have the highest impact on health and survival among osteoporosis related fractures, especially in the elderly. They are associated with a significant rate of death (one year mortality rate of 14–36%, including a 4% mortality rate for the corrective surgery itself) [108–110], as well as a loss of mobility and independence, increased need for institutionalization and healthcare utilization, high cost, mood and cognitive impairment, and a higher risk of subsequent fractures [111]. The risk of death after a hip fracture is 60–70% higher in COPD patients when compared to those without COPD [112]. At present, the exact incidence and prevalence of hip fractures in COPD is not well studied. However, in two large cohorts, COPD was found to be associated with a higher risk of hip fractures (23% for women, 30% for men) and a higher rate of occurrence when compared to the general population [113, 114].

Diagnosis

Osteoporosis is commonly missed. Even when resulting in fractures, diagnosis and treatment can be overlooked. Up to a third of VCFs are missed, and even when fragility fractures are picked up, physicians can

fail to look for osteoporosis and place patients on appropriate treatment [115–117].

Every patient with COPD should have a risk evaluation performed by his physician to assess the likelihood of a future fracture risk. FRAX is a useful tool developed by the WHO for predicting a ten-year risk of fractures [118]. It uses ten clinical predictors to calculate this probability. These include gender, age, height, weight, and prior or current history of fragility fracture, smoking, corticosteroids use, alcohol consumption, rheumatoid arthritis and parental fracture. FRAX can be used with or without a BMD score. However, it should be noted that FRAX can underestimate the risk of fracture in COPD [119–121]. To improve the accuracy of its prediction, a modified FRAX with the addition of severity of airflow limitation assessed by FEV1, degree of physical inactivity, and a history of recent fall, has been proposed. This model, however, has not yet been validated [122].

A diagnosis of osteoporosis is confirmed by demonstration of either a low BMD or a fragility fracture of the hip or spine [123]. Laboratory tests to rule out secondary causes of osteoporosis (e.g. type 1 diabetes, hyperthyroidism, chronic malnutrition, chronic liver disease etc.) should be performed if a clinical evaluation is suggestive of such conditions.

The current gold standard for the diagnosis of osteoporosis is the dual-energy X-ray absorptiometry (DXA) test [124]. This assesses bone mass by measuring bone mineral density, generally at the femoral neck or lumbar spine. Areal BMD is calculated by comparing the absorption by a subject's bone of two different energy-level low radiation X-ray beams. It is then compared with either the BMD of a healthy gender-matched early adult cohort to obtain a t-score, or (for premenopausal women, men < 50 years of age, and children) with age-, gender-, and ethnicity-matched reference population to obtain a z-score [3]. T-scores of −2.5 or lower, i.e. a BMD that is 2.5 standard deviations below the reference population, confirm osteoporosis. Scores between −2.5 and −1 indicate osteopenia, while a score above −1 is considered normal [125]. When a z-score is used, a cut-off of −2 is used to differentiate between normal and low BMD "for expected range for age" [126]. A one standard deviation drop in score is associated with a 1.5–3 times higher risk of fracture [127]. DXA scans should be interpreted with caution in individuals with small body frames or with degenerative disease of the spine. DXA may overestimate or underestimate the risk of fractures in these situations respectively [128].

DXA scans are also used for monitoring the progress of osteoporosis and its response to treatment. These should generally be performed at 2 year intervals in otherwise healthy patients with osteoporosis, as DXA is usually unable to detect significant changes in BMD earlier than this period [129]. With corticosteroid therapy, osteoporosis is accelerated. Therefore, consideration should be given to performing DXA scans more frequently, possibly annually, in COPD patients who are currently or have been on steroids [130].

The presence of a VCF, even when BMD results are not available, is sufficient to establish a diagnosis of osteoporosis [123]. VCFs are diagnosed by lateral thoracic and lumbar X-rays or by lateral vertebral fracture assessment on DXA scan [131]. VCFs can often be picked up on chest X-rays, and should actively be looked for when reviewing chest imaging of COPD patients [12, 132]. A decrease in height by more than 4 cm from age 25, should alert the physician to the possibility of a VCF [133].

Other means of assessing bone strength include biochemical markers of bone turnover, CT-based absorptiometry, and quantitative ultrasound densitometry [128, 134]. However, at present, these are not widely available in routine clinical practice and are mostly used for research purposes.

Treatment of osteoporosis in COPD

The osteoporosis literature focuses almost exclusively on post-menopausal women and the elderly for obvious reasons. There is a dearth of studies specific to osteoporosis in the COPD population. Till more data is available for this population, the management of osteoporosis in COPD should follow established guidelines for primary osteoporosis [123].

Physicians should avoid excessive glucocorticoid use, inhaled and systemic, as a general principle when managing COPD, due to their significant side effects. Inhaled corticosteroids, in low to medium doses if possible, should be restricted to patients with FEV1 < 60% with a history of recurrent COPD exacerbations [37]. High dose inhaled corticosteroids are associated with a higher risk of pneumonia [36]. Short duration of systemic corticosteroids in medium doses are the preferable treatment for most patients with an acute exacerbation as outcomes with such a regimen are similar to doses given for longer duration [135].

Non-pharmacological interventions

Lifestyle modifications conducive to maintaining bone strength should be encouraged. Excessive alcohol intake – daily consumption of more than two drinks for women, and three for men– can lead to deleterious effects on bone health and increased risk of fall, and should be discouraged; individuals should be assessed for the possibility of alcoholism and managed appropriately [136]. Fall risk should be assessed for individual patients and interventions that decrease their risk should be implemented; strategies include withdrawal of psychotropic medications, exercise programs [including Tai Chi], and home

safety assessment and modification by an occupational therapist [123].

Other lifestyle changes have a positive impact on both osteoporosis and COPD (Fig. 2). These include quitting tobacco, improving diet [especially calcium and vitamin D], and engaging in exercise programs. Smokers should be enrolled in smoking cessation programs; tobacco cessation leads to improved respiratory function [137] and modest improvements in BMD [138]. Exercise programs, especially when performed in a multi-disciplinary setting, confer significant health benefits to COPD sufferers, improve bone density and decrease the risk of falls and fractures [139–142].

Pharmacological interventions

Indications for pharmacological treatment for osteoporosis in COPD

Treatment for osteoporosis should be considered if patients with COPD have a history of a fragility fracture or have been using systemic corticosteroids for three months/year. Other criteria include low BMI (<21 kg/m^2, active smoking, significant alcohol use, age above 65, rib fracture, physical inactivity, menopause, FEV1 < 50% and parental hip fracture) [143]. Initial therapy should focus on ensuring adequate intake of calcium and vitamin D with or without additional medications.

Calcium and vitamin D

Calcium and vitamin D play an important part in preventing and treating osteoporosis. As mentioned before, vitamin D, in conjunction with calcium supplementation, decreases the risk of falls by improving stability and strength. Adequate dietary intake of both should be advised. A combination of supplemental calcium and vitamin D can decrease the risk of osteoporotic fractures [144]. The recommended dietary allowance [RDA] for calcium is 1,000 mg/day for men aged 51–70 and 1,200 mg/day for women above 50 and men above 70 [145]. The RDA for vitamin D is 600 international units/day for adults aged 51–70 and 800 IU/day for older individuals. Patients should be encouraged to meet their RDA through dietary intake (fruits, vegetable, dairy products fortified with vitamin D, fish, liver); if this proves inadequate, supplements should be prescribed. Caution should be exercised with using excessive doses of both, as there is a risk of toxicity with high doses of vitamin D [146] and a possible, controversial, link with renal stones and cardiovascular events with calcium intake above 1200–1500 mg/day [147–149]. Daily intake of up to 4,000 IU/day of vitamin D is generally considered as a safer upper limit.

Teriparatide

Teriparatide is a biosynthetic form of human PTH. It is the only FDA approved anabolic treatment of osteoporosis

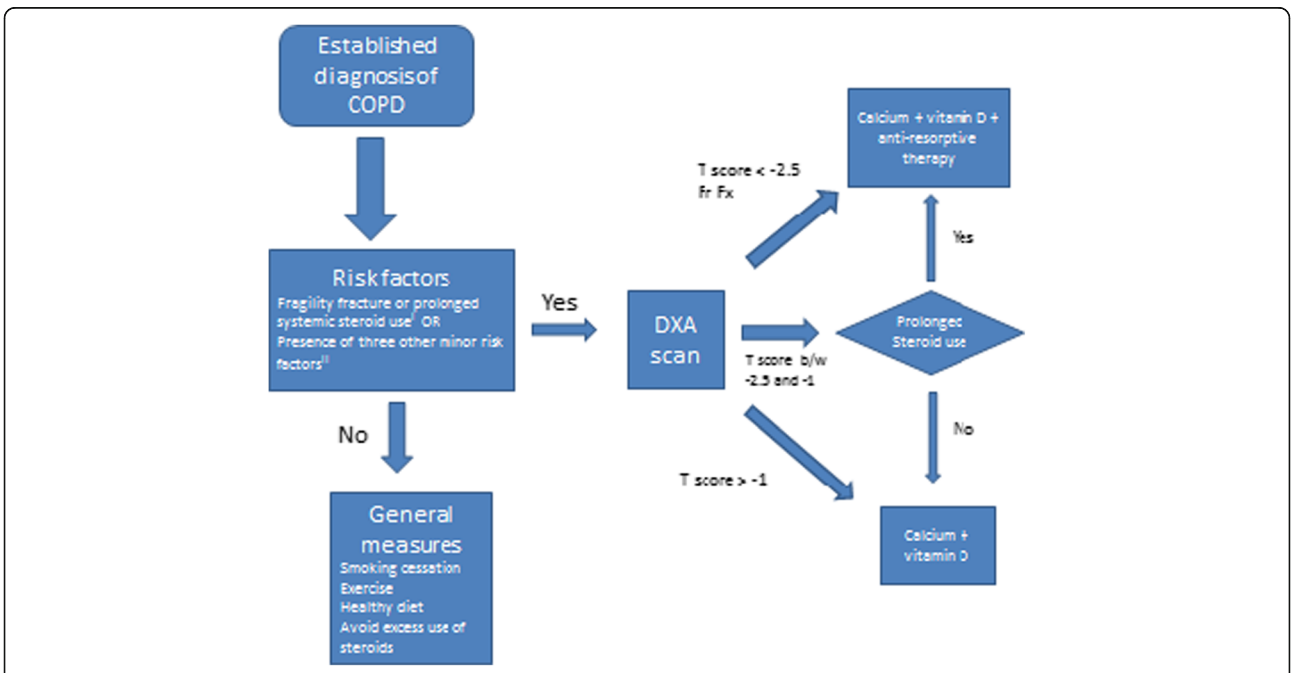

Fig. 2 Schematic diagram summarizing risk factor assessment, diagnosis and treatment for osteoporosis in COPD. [I]Fragility fracture is defined as a fracture of the hip or spine; prolonged systemic steroid use duration is defined as 3 months. [II]Risk factors include: BMI < 21, active smoking, daily significant alcohol intake, age > 65 years, menopause, rib fracture, inactivity, FEV1 < 50%, parental hip fracture. Fr Fx = Fragility fracture

available so far [150]. When used intermittently, teriparatide stimulates bone formation by promoting differentiation of osteoblasts from mesenchymal stem cells, activating preexisting osteoblasts and inhibiting their apoptosis.

Teriparatide decreases the risk of VCF by two-thirds and non-VCFs by half in patients with osteoporosis when given for an average of 18 months [151]. It is superior to alendronate in preventing osteoporosis in patients on glucocorticoid therapy [152, 153]. Treatment duration should generally not exceed two years when using the medication. Unlike bisphosphonates, its effect wears off quickly; alternate therapy should be initiated when stopping teriparatide.

In high doses for prolonged duration, teriparatide increases the incidence of osteosarcoma in animal models. Its use is hence contraindicated in patients at a high risk of osteosarcoma, i.e. those with a history of skeletal malignancy, bone metastases, radiation treatment of bones, and Paget's disease.

Anti-resorptive treatment

Bisphosphonates

The most commonly used medications for osteoporosis treatment, bisphosphonates are synthetic analogues of pyrophosphates, a naturally occurring substance, with high affinity for hydroxyapatite in the bone [154]. Bisphosphonates inhibit osteoclast activity by blocking a key enzyme, farnesyl pyrophosphate synthase, and promote osteoclast apoptosis, ultimately decreasing bone resorption [155].

Bisphosphonates have a well-established role in treating osteoporosis and decreasing the risk of fractures, particularly VCFs, in post-menopausal women and those on glucocorticoids [156, 157]. Most bisphosphonates decrease VCF incidence by 40–50% and non-VCF by around 20–30%. They also improve lumbar spine bone density scores in patients with airway disease [158]. Bisphosphonates are generally well tolerated. Gastrointestinal disturbance is the most common side effect with oral formulations. Oral medications should be avoided in patients who are unable to sit up straight for half an hour after ingesting the medication, in those with severe upper gastrointestinal symptoms or with significant esophageal pathology (e.g. dysmotility, stricture, achalasia). Uncommon side effects include atypical fracures, atrial fibrillation and osteonecrosis of the jaw [159].

Calcitonin

Calcitonin transiently decreases osteoclastic activity without affecting collagen synthesis by osteoblasts [160]. Salmon-calcitoinin is available in oral and nasal forms and decreases the risk of VCFs by about a third with no significant impact on the incidence of non-vertebral fractures [161]. It is very much a second line medication, used for those unable to take bisphosphonates, due to a small increase in risk of malignancies associated with the drug [162], and better efficacy of other medications. Calcitonin may have some use in the setting of acute osteoporotic fractures due to its adjunctive effect of pain relief which helps in earlier mobilization [163].

Denosumab

This monoclonal antibody against RANKL inhibits osteoblast differentiation, activation and survival, thereby decreasing osteoclastogenesis [164]. It decreases the risk of VCFs by two-thirds, hip fracture by 40% and non-VCFs by 20% [165] and improves BMD in post-menopausal women [166]. It is superior to most bisphosphonates in its effect on BMD [167, 168]. Efficacy is greater with combination therapy of both denosumab and teriparatide [169]. Denosumab is injected subcutaneously every 6 months by a health professional. Side effects include risk of hypocalcemia, cellulitis and skin rash.

Estrogen agonist/antagonist compounds (previously known as Selective Estrogen Receptor Modulators)

This group of medications binds to intracellular estrogen receptors, acting as either agonists or antagonists in different tissues [170]. In bones, these compounds improve BMD and decrease the risk of osteoporosis associated VCFs [171]. They are approved for use in post-menopausal women.

Duration of treatment and follow-up

The need for continuing therapy should be periodically re-evaluated intervals due to the risk of side effects with medications. The risk of atypical femoral fractures and osteonecrosis of the jaw increases when on treatment beyond five years. The effect of non-bisphosphonate medications is temporary and wanes after cessation of therapy. In contrast, bisphosphonates can have residual treatment effects that last for several years [172].

Patients should be monitored at regular intervals. Compliance with medications, adequacy of calcium and vitamin D intake, level of physical activity and risk of fall should be assessed. Annual accurate height measurements should be performed; a loss of height by 2 cm is an indication for vertebral imaging [123]. Serial DXA scans should be performed to check BMD. Vitamin D levels should be monitored. The decision on the duration of treatment should be made after assessing all of the above in each individual patient separately. For patients with low-to-moderate risk of fall and fractures, medications may possibly be stopped. In case of a high risk for fracture, treatment should be continued [173].

COPD and sarcopenia

Skeletal muscles play a critical part in metabolism and overall functional health. Sarcopenia is a syndrome characterized by progressive decrease of muscle mass and strength. It is estimated that after the age of fifty, healthy adults lose roughly 1–2% of their skeletal muscle each year. Underlying mechanisms for this age-related muscle loss include malnutrition, physical inactivity, hypogonadism and chronic inflammation. Progressive muscle loss can also occur in multiple disease states, such as cancer, heart failure, HIV, end-stage renal disease, end-stage liver disease, COPD and in prolonged illness [174]. Muscle mass loss is prevalent in patients with COPD as a result of both the disease and aging [175].

The prevalence of sarcopenia increases with age. An estimated 15% of people older than 65 years are affected by the condition; in those above the age of 80, the proportion of affected individuals is as high as 50% [176]. Sarcopenia places a significant public health and economic burden, with an estimated $18.5 billion spent on its treatment in 2000 [177].

Sarcopenia is quite common in COPD, with quadriceps weakness being observed in a third of COPD outpatients, even in individuals exhibiting mild to moderate airway obstruction [74, 75, 178]. It contributes significantly to a diminution of exercise capacity, reduced quality of life, increased healthcare utilization, and premature mortality [179, 180]. Given the substantial morbidity and mortality associated with sarcopenia, significant effort is being expended to identify strategies for prevention, early diagnosis and treatment of sarcopenia in high risk individuals. Whether these strategies will improve survival in such individuals is yet to be ascertained [181].

Pathophysiology

Muscle dysfunction in COPD is a consequence of reduction in muscle mass, altered muscle metabolism and a shift in muscle fiber composition.

Muscle strength and endurance are both adversely affected. At the cellular level, this dysfunction is thought to be due to an imbalance favoring protein breakdown over synthesis, apoptosis, sarcomere and sarcolemma damage, reduced myosin heavy chain-I isoform type I [slow twitch/endurance] muscle fibers, and a decreased density of capillaries and mitochondria [182–188]. Abnormalities in essential oxidative enzymes, mitochondrial activity and expression of myogenin and m-cadherin– key molecules required for muscle growth and repair– also contribute to the pathology [189].

At present, the exact reason for these changes in COPD patients is unclear; it is thought that a variety of mechanisms are responsible. These include poor peripheral oxygenation (due to COPD related gas exchange abnormalities and anemia, leading to inflammation, oxidative stress, apoptosis and poor muscle repair) [190–192], systemic inflammatory state particularly during exacerbations (inhibits muscle contractions, activates catabolic systems such as ubiquitin proteasome, leads to oxidative stress and causes apoptosis) [193–195], oxidative stress (linked to systemic inflammation, with an imbalance between reactive oxygen species and antioxidants) [196, 197], hypercapnia (leading to acidosis and impaired muscle proteostasis) [198, 199], diminished effect of anabolic hormones such as growth hormone and testosterone [189], net catabolic state [200], effect of tobacco (through a number of the aforementioned mechanisms) [201], myopathy induced by use of corticosteroids (especially systemic steroids) [202, 203], malnutrition/negative energy balance [200, 204], and decreased physical activity leading to muscle disuse [205–207].

The last putative mechanism, i.e. sedentary behavior due to the breathlessness caused by COPD, might be the most important factor contributing to skeletal muscle dysfunction. Evidence pointing to its central role in sarcopenia pathogenesis includes disproportionate impairment of lower limb musculature in comparison to the upper limbs (that are subjected to a lesser degree of physical inactivity than the legs) [208], similarity in the structural changes seen in the sarcopenia of COPD and atrophy due to muscle disuse [209], partial recovery of strength with muscle training and conditioning [210, 211], and the apparent lack of correlation between the severity of airflow limitation and extent of muscle dysfunction [212].

Clinical features and consequences of sarcopenia in COPD

The loss of muscle strength and function leads to limitation of activity, decrease in mobility, slow gait, poor stamina and, overall, general frailty [213]. Risk of falls and subsequent fractures, due to prevalent comorbid osteoporosis in this population, is increased. The consequences of fractures in COPD patients have been outlined in the osteoporosis section of this article. Lastly, in addition to diminished exercise capacity and health status, presence of sarcopenia is an independent predictor for mortality in patients with COPD [75, 179, 180, 214].

Diagnosis

The diagnosis of sarcopenia is confirmed in the presence of low muscle mass in addition to decreased muscle strength and/or reduced physical performance [215]. The most accurate diagnostic tests are generally used in a research setting; constraints due to cost, availability, and ease of use limit their clinical application (e.g. the most precise measurements of muscle mass are obtained with whole body imaging using CT scan or MRI; however, the cost, lack of easy access and concerns about

radiation exposure make it difficult to use these modalities in routine clinical practice). Proposed diagnostic methods to ascertain muscle mass, strength and performance in clinical practice are listed in Table 1.

DXA allows quantification of body components (bone mineral, fat, and bone-mineral-fat-free mass) by detecting the relative attenuation of two different energy X-rays by the body; radiation exposure is minimal and calculated muscle mass is similar to findings obtained on whole body imaging [216]. Bioimpedance analysis can also be used to measure muscle mass, especially when a portable alternative to DXA is required [217]. Anthropometric measures (e.g. calf and mid-upper arm circumference, skin fold thickness) are vulnerable to error and are not recommended for use in clinical practice [218].

Muscle strength is routinely assessed with the use of a handheld dynamometer to measure handgrip strength. It is reliable, easy to perform and inexpensive [219]. Isometric handgrip strength correlates well with power in the lower extremities and is a strong predictor of disability and mortality [219].

Measures of physical performance include gait speed alone or as part of the short physical performance battery test [where an individual is asked to perform a few physical maneuvers including ability to stand with feet in tandem/semi-tandem position, walk 8 ft, and get up from a chair and sit down five times], and the timed get-up and go test (measures the time required for a subject to get up from a chair, walk a short distance, turn around and sit back down) [215]. These tests measure balance, strength, endurance and gait. A cut-off gait speed of 0.8 m/s is a useful screening tool for predicting risk of sarcopenia [220].

Treatment

Exercise is the only modality known, to date, to prevent and improve muscle dysfunction [221, 222]. Resistance training, either through traditional strength training or functional strength training (which mimics activities of daily living), increases muscle mass and power and perception of well-being [223, 224].

Pulmonary rehabilitation significantly improves exercise capacity, severity of dyspnea and health-related quality of life in COPD subjects, including in patients with baseline normal exercise capacity [225, 226]. Sarcopenia does not appear to diminish the impact of pulmonary rehabilitation on these outcomes. Moreover, a small proportion of patients appear to have reversal of their muscle dysfunction with pulmonary rehabilitation [227].

Table 1 Diagnostic testing for sarcopenia

Muscle mass	a. Dual energy X-ray absorptiometry (DXA) b. Bioimpendence analysis (BIA)
Muscle strength	Handheld dynamometer
Physical performance	a. Gait speed b. Timed Up and Go (TUG) c. Short Physical Performance Battery (SPPB)

There is no definite evidence supporting the use of nutritional supplements – antioxidants, creatine, amino acid combinations, for sarcopenia at present [204]. Optimization of vitamin D levels and protein intake [1–1.5 g/kg/day] is recommended for all patients with sarcopenia [228].

A number of medications that could potentially treat sarcopenia associated with disease and aging are being developed. These include medications that work through the growth hormone/insulin-like growth factor 1 pathway (ghrelin mimetics/growth hormone secretagogues) [229, 230], selective androgen receptor modulators (SARMs), and agents that work through the myostatin/acitivin A pathway.

The use of anabolic steroids and testosterone for muscle atrophy has been limited by their associated adverse effects, e.g. worsening of prostatic hyperplasia or cancer in men, virilization in women, and cardiovascular events [231, 232]. Medicines with selective anabolic activity in bones and muscles, with no effect on levels of luteinizing hormone and which are not converted to dihydrotestosterone or estradiol, would have a favorable risk/benefit ratio and would be ideal for the treatment of sarcopenia. Enobosarm, a non-steroidal SARM, appears to have these properties and has shown promising results in phase II trials, with improvement in muscle and bone mass and little effect on other androgen-sensitive tissues [233].

Other medications under development include agents that work through the myostatin/activin pathway. Myostatin is a molecule from the transforming growth factor B (TGF-B) superfamily that is upregulated in diseases associated with cachexia and has been strongly linked to muscle wasting by binding and activation of the activin receptor. Inhibitors of this pathway cause regeneration of muscle mass and improvement in muscle performance in animal models [234, 235]. It remains to be seen whether these therapies will prove to be effective in humans.

Conclusion

Osteoporosis and sarcopenia are common in COPD and are associated with significant disability and mortality. Despite a high prevalence, osteoporosis and sarcopenia are underdiagnosed and undertreated in patients with COPD. Osteoporosis increases the risk of fractures, while sarcopenia contributes to significant functional limitation. Physical activity/exercise, especially in the form of a multi-disciplinary pulmonary rehabilitation program, has a cardinal role in the prevention and treatment of both conditions. Ensuring adequate vitamins'

levels and nutritional intake, and smoking cessation are also important. Pharmacological therapy for osteoporosis consists of anti-resorptive medications and teriparatide; so far, there are no commercially available drugs for the treatment of sarcopenia, although many promising agents are in the process of being developed. There remains a pressing need for further research related to both conditions and formulation of guidelines for their management, specifically in COPD subjects.

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