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Sarcopenic obesity and hypertension in elderly patients: a narrative review of pathophysiology and management strategies

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Abstract

Introduction. Sarcopenic obesity and hypertension are a public health problem that is increasing worldwide due to the progressive aging of the population and the increasing prevalence of obesity and physical inactivity. Sarcopenic obesity is characterized by the simultaneous presence of sarcopenia (loss of muscle mass) and adiposity (increase in fat mass). Because symptoms are not specific, sarcopenic obesity remains largely undiagnosed. This review explores the latest research on sarcopenic obesity and its association with hypertension, with a focus on arterial stiffness.

Methods. A comprehensive narrative review was conducted by systematically searching PubMed and Scopus databases for relevant scientific literature.

Results. Sarcopenic obesity and hypertension are closely linked, sharing common factors such as inflammation, insulin resistance, and oxidative stress, with arterial stiffness playing a crucial role.

Discussion. Given the lack of specific symptoms for sarcopenic obesity, early diagnosis and management are crucial. Treatment strategies should prioritize weight loss, adequate protein intake, and regular physical activity. Further investigation is warranted for pharmacological interventions.

Conclusion. Sarcopenic obesity and hypertension present significant challenges to global public health. Addressing arterial stiffness is paramount in managing these conditions effectively. Lifestyle modifications, including weight management and physical activity, remain central to the treatment of sarcopenic obesity, while additional research is needed to explore potential pharmacological options.

Key words

- sarcopenia
- obesity
- hypertension
- aging

INTRODUCTION

Sarcopenic obesity is an emerging public health problem related to the accelerated global ageing of the world population, which has increased rapidly over the past three decades [1]. Baumgartner was the first to propose the term sarcopenic obesity [2] as a clinical and functional condition characterized by the coexistence of sarcopenia (low skeletal muscle mass and function) and obesity (excessive fat mass). Sarcopenic obesity is considered a unique clinical condition, distinct from obesity and sarcopenia alone.

Loss of skeletal muscle mass and function usually occurs with advancing age and is accompanied by a relative or absolute increase in body fat. This process favors the development and occurrence of sarcopenic obesity and leads to many negative clinical complications such as frailty, falls, disability, immobility, fractures, cardiometabolic and respiratory diseases, cancer, and increased mortality [3-5]. Furthermore, obesity, particularly abdominal obesity, can independently lead to loss of muscle mass and function due to the negative effects of oxidative stress, inflammation, insulin resistance, and the presence of chronic non-communicable diseases, all of which negatively impact muscle mass [6].

The decline in physical activity and loss of skeletal muscle mass and function that accompanies ageing is well documented and appears to occur even in relatively weight-stable healthy individuals. Physical inactivity is both a major cause and consequence of sarcopenia and obesity, which can lead to sarcopenic obesity that can be exacerbated by concomitant diseases [7]. Importantly, therapeutic weight loss targeting excess fat

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inevitably leads to greater loss of skeletal muscle mass, which may be more pronounced in individuals with predisposing catabolic conditions (ageing, chronic diseases) or with persistent inadequate diet (especially low protein intake) and weight fluctuations [8, 9].

However, the lack of universally accepted diagnostic criteria for sarcopenic obesity affects patient identification and has strong negative implications for prevention and treatment strategies for sarcopenic obesity. The diagnosis requires the presence of both altered (i.) skeletal muscle function and (ii.) body composition [7].

Assessment of skeletal muscle functional parameters is critical to treatment protocols for sarcopenic obesity because it affects patients' quality of life. Muscle strength (e.g., handgrip strength, HGS) and knee extensor strength (adjusted for body mass in the population for which data are available) should be the functional parameters of choice for the diagnosis of sarcopenic obesity [10, 11]. In addition, the chair-stand test (5 times sit-stand; 30 s chair-stand test) is used to measure physical performance and muscle strength. When low skeletal muscle function is detected, the diagnosis is followed up by body composition determination.

Various definitional and diagnostic criteria for body composition have been used to estimate the prevalence of sarcopenic obesity. Several studies have detected sarcopenic obesity using dual-energy x-ray absorptiometry (DEXA), which is appropriate for laboratory practice but requires expensive equipment that may not always be available [4]. In clinical practice, sarcopenic obesity is defined by higher fat mass (FM) relative to fat-free mass (FFM). The ratio of FM to FFM (FM /FFM) >0.8 has been established as an index of sarcopenic obesity [12]. FM and FFM are determined clinically using bioelectrical impedance analysis (BIA), a technique widely used in clinical practice [5, 12-17].

Our study aims are to investigate the relationship between sarcopenic obesity and hypertension and explore potential therapeutic strategies. This is motivated by the known association between sarcopenic obesity and hypertension and the higher prevalence of sarcopenic obesity in hypertensive patients.

PATHOPHYSIOLOGICAL PATHWAY OF SARCOPENIC OBESITY

Several mechanisms underlie age-related muscle loss, including hormonal and neuronal changes, poor nutrition, physical inactivity, inflammation, and chronic diseases [18]. In addition, the quality of muscle mass decreases due to a decrease in fiber size and the number of fast-type II muscle fibers, a decrease in muscle protein synthesis, and mitochondrial function [4]. The increasing prevalence of obesity in the elderly independently leads to a loss of muscle mass and function, as adipose tissue negatively affects skeletal muscle mass [4].

In a large sample of men and women, the degree of obesity and waist circumference has been shown to directly influence inflammation, which in turn contributes to the development of sarcopenia [19]. Catabolic pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor α (TNF-α), and hormones such as leptin and resistin are preferentially released from abdominal adipose tissue and can stimulate protein catabolism in skeletal muscle, which promotes the occurrence of sarcopenic obesity [16]. In addition, muscle unloading and physical inactivity in older adults increase abdominal fat accumulation and associated systemic inflammation, oxidative stress, and consequently muscle wasting [16, 20].

On the other hand, sarcopenia can directly increase fat accumulation by decreasing overall energy expenditure. Obesity and sarcopenia can therefore synergistically reinforce each other, with a vicious cycle of fat accumulation and loss of skeletal muscle mass leading to immobility, independence, and disability [2, 3, 7]. In addition, further increases in hormone levels of leptin, which are at least partially dependent on age-related increases in fat mass, may lead to leptin resistance and consequently to a reduction in fatty acid oxidation in muscle. Subsequently, fat deposition in skeletal muscle and other organs such as the heart and liver contributes to loss of muscle quality in obese older adults and negatively affects sarcopenia [4, 21]. Deposition of intramuscular fat promotes lipotoxicity and inflammation, leading to impaired muscle recovery, which in turn can promote fibrosis, and thus insulin resistance.

Contractile skeletal muscle produces and releases anti-inflammatory myokines and plays an important role in counteracting pro-inflammatory effects [22]. Anti-inflammatory myokines, including muscle-derived interleukin 6 (IL-6), interleukin 8 (IL-8), interleukin 15 (IL-15), and interleukin-1 receptor antagonist (IL-1ra), act as antagonists of the overall pro-inflammatory burden [23]. Muscle IL-6 was the first myokine identified and the most-studied myokine exerting extensive anti-inflammatory effects [24]. Interestingly, IL-6 from adipose tissue has a pro-inflammatory effect, whereas IL-6 from skeletal muscle has an anti-inflammatory effect [25]. Therefore, the release of IL -6 during physical activity leads to an increase in the anti-inflammatory IL -1ra and IL-10. In most studies dealing with exercise, TNF-α does not change and is likely suppressed by muscle-derived IL-6, as shown by a modest decrease in TNF-α after exercise [21]. This confirms that the anti-inflammatory effects of regular exercise may protect against systemic inflammation [25]. Furthermore, intracellular fat deposition in skeletal muscle is characterized by a decrease in anti-inflammatory myokines (IL-15, IL-8, IL-6), leading to sarcopenia [18]. A vicious cycle between skeletal muscle loss and fat gain can lead to more sarcopenia and further weight gain. The negative clinical consequences of sarcopenic obesity are of paramount importance. A progressive increase in fat mass is a strong risk factor for poor health status and has significant implications for the development of hypertension and other cardio-metabolic risk factors [10, 6]. These risks may increase with additional loss of muscle mass [26]. Consequently, lower muscle mass has been repeatedly associated with cardiovascular risk factors, including arterial stiffness, suggesting the additive effects of low muscle mass on blood pressure [26]. Thus, sarcopenic obesity and hypertension share common etiologic mechanisms *(Figure 1)*.

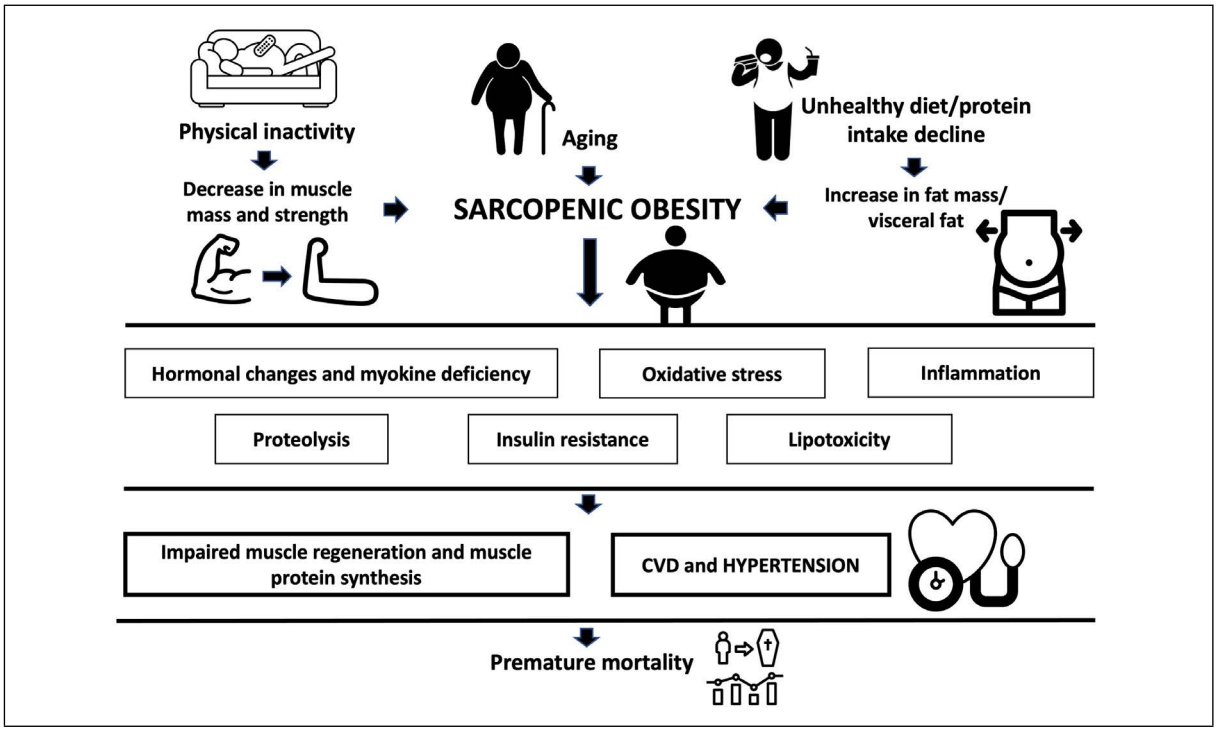

Figure 1
Pathophysiological mechanisms and consequences of sarcopenic obesity.
Schematic biological pathways leading to sarcopenic obesity during ageing. Ageing is associated with physical inactivity and inadequate food intake. These changes contribute to age-related decreases in muscle mass and strength and increases in body fat, as well as unfavorable changes such as increased inflammation, oxidative stress, insulin resistance, and an imbalance of pro- and anti-inflammatory cytokines. In addition, this can impair skeletal muscle mass and function and lead to numerous adverse cardiometabolic effects and hypertension, which in turn contributes to poor health.

SARCOPENIC OBESITY AND HYPERTENSION

The interaction of skeletal muscle and adipose tissue has been found to play a key role in the regulation of blood pressure and the development of hypertension. Few studies have investigated and confirmed the association between sarcopenic obesity and hypertension, as the ratio of fat mass to fat-free mass is an important predictor of hypertension [26, 27]. In addition, low muscle mass has been directly associated with cardiovascular risk factors, including arterial stiffness [26, 28, 29], suggesting the effects of low muscle mass on blood pressure.

Sarcopenic obesity and its association with arterial stiffness suggest that individuals with lower muscle mass and higher fat mass in the general population are more likely to have higher blood pressure and sarcopenic obese individuals tend to consume higher amounts of antihypertensive drugs [30]. There was a significant difference in the prevalence of hypertension in older adults with sarcopenic obesity compared with individuals without sarcopenic obesity [31]. In women, a strong association was found between sarcopenic obesity and hypertension [32]. In postmenopausal women with sarcopenic obesity, hypertension was the most prevalent chronic morbidity [33]. These findings are consistent with other cross-sectional studies showing that individuals with sarcopenic obesity have higher cardio-metabolic risk [34].

The KNHANES series of cross-sectional studies by Park [26] found a 6.5-fold higher risk of hypertension in sarcopenic obese participants, who had higher systolic and diastolic blood pressure than participants with normal body composition. These results confirm the association between sarcopenic obesity and an increased risk of hypertension. In this study, the risk of hypertension associated with sarcopenic obesity was reduced by 30% after controlling for physical activity.

Several studies have previously reported the beneficial effects of physical activity on hypertension, with both systolic and diastolic blood pressure being reduced by 5-7 mmHg in people with hypertension [35]. This suggests that the pathway by which sarcopenic obesity affects hypertension is related in part to physical activity. On the other hand, it is also possible that physical inactivity leads to sarcopenic obesity, which in turn contributes to the risk of hypertension. One possible mechanism by which physical activity affects hypertensive patients is by increasing the quantity or quality of skeletal muscle.

In addition, abdominal obesity and sarcopenia negatively affect hypertension. The inflammatory status of older adults is associated with higher circulating levels of catabolic pro-inflammatory cytokines, even in the absence of chronic disease [36]. The previously described myokine concept suggests that the long-term anti-inflammatory effects of physical activity are mediated via

the effects of exercise leading to a reduction in visceral fat mass [21]. Interestingly, a negative correlation was found between plasma concentrations of muscle IL-15 and visceral fat mass [21]. IL-15 inhibits lipid accumulation in adipose tissue, supporting the idea that IL-15 is involved in reducing visceral fat mass and may play an important role in reducing inflammation. Therefore, physical activity and the resulting release of myokines provide the maintenance of fat stores, muscle mass, and metabolic homeostasis, as well as blood pressure [34, 37]. Based on these findings, abdominal obesity and sarcopenia might potentiate each other to induce hypertension.

TREATMENT STRATEGIES FOR LIFESTYLE MODIFICATIONS

Lifestyle interventions, including physical activity and caloric restriction, are the hallmark of treatment for sarcopenic obesity. Weight loss or physical activity alone has been reported to improve physical function. However, a combination of weight loss and physical activity was the more effective method for improving physical function and frailty [38].

PHYSICAL ACTIVITY

Physical activity is important to maintain skeletal muscle mass. In particular, aerobic exercise and resistance training are the most beneficial types of exercise to reduce fat mass and increase lean mass in overweight and obese individuals of all ages and genders [39]. Aerobic exercise, resistance training, and their combination have been shown to increase muscle protein synthesis in older adults despite age-related decreases in anabolic signaling [40]. In addition, aerobic activity and resistance training counteract inflammation and improve glucose metabolism, and insulin sensitivity, which may attenuate the progression of sarcopenic obesity [40, 41]. Aerobic activity decreases the negative effects of fat deposition in skeletal muscle and promotes lipolysis, leading to an increase in capillary density, which in turn stimulates mitochondrial production [41-45]. Importantly, 24 weeks of aerobic and resistance training in older women with sarcopenic obesity reduced carotid intima-media thickness and improved carotid flow velocity, resulting in a lower risk of cardiovascular disease [46].

SMOKING AND PSYCHOLOGICAL DISTRESS

Cigarette smoking contributes to the development of sarcopenia [47], obesity [48], and hypertension [49]. Therefore, smoking cessation is an important intervention step for this specific patient population.

Psychological distress leads to elevated cortisol levels and promotes adipogenic processes, as well as excessive consumption of high-calorie, high-fat, and high-sugar foods [50]. Recently, several interventions that combined cognitive behavioral therapy with mindfulness reported successful weight loss during the 18-month follow-up period [51].

NUTRITION-RELATED INTERVENTIONS

Strategies that optimize protein anabolism during weight loss, such as consumption before exercise or distribution of protein intake throughout the day, can prevent weight loss-induced sarcopenia [52, 38]. An adequate protein intake of 1.0-1.2 g/kg body weight per day should be provided for healthy non-geriatric individuals, while a higher intake of 1.2-1.5 g/kg body weight per day is recommended for high-risk patients with acute or chronic diseases [53, 54]. Higher doses of up to 2.2 g/kg/day are used only in obese patients under acute metabolic stress in the intensive care unit [54]. The general approach to nutrition in sarcopenic obese patients is to decrease caloric intake (hypocaloric diet) while increasing protein intake to prevent further loss of muscle mass [55]. The use of protein supplements is recommended when adequate food intake is not possible [56, 57].

Omega-3 long chain polyunsaturated fatty acids supplementation has been shown to enhance lower-body strength and functionality in older adults, without impacting lean mass, walking performance, or upper body strenght [58, 59]. Additionally, the inclusion of creatine supplementation in resistance training for older adults has resulted in increased lean tissue mass and significant improvements in both upper and lower body muscular strength [60]. On the other hand, there is insufficient evidence to support the use of β-hydroxy-β-methyl butyrate (HMB) supplementation for increasing or retaining skeletal muscle mass, enhancing muscle strength, or improving physical function in patients with sarcopenia or older individuals [61]. Similarly, vitamin D supplementation has not been shown to improve lower extremity function [62]. The use of coenzyme Q10, which has potential muscle-specific antioxidant and anti-inflammatory effects, in patients with sarcopenia is subject to an ongoing debate, as there is currently a lack of clinical trials confirming these effects [63].

In addition, some studies have shown that increased consumption of vegetables and fruits [64], dietary fiber [65], carotenes, and vitamins C and E [66] may also lead to a lower risk of sarcopenia. Interestingly, regular coffee consumption has been associated with a lower prevalence of sarcopenia [67]. Moreover, chronic coffee consumption has not been associated with an increased risk of hypertension [68], and several studies have shown no significant increase in systolic and diastolic blood pressure among hypertensive patients [69].

POTENTIAL PHARMACOLOGICAL APPROACHES

Currently, there is no specific pharmacological treatment for sarcopenic obesity. However, several potential pharmacological approaches have been proposed and discussed for patients with sarcopenic obesity and hypertension.

The drugs most commonly used in hypertension therapy are inhibitors of angiotensin converting enzyme (ACE), which converts angiotensin I to angiotensin II. Angiotensin II binds to AT1 receptors and leads to generalized vasoconstriction, increased noradrenaline release, secretion of aldosterone from the adrenal cortex, tubular reabsorption of Na^+ ions, and growth of cardiac and vascular cells [70]. Thus, ACE inhibitors reduce

arterial pressure in hypertensive patients by affecting capacitance and resistance vessels and reducing cardiac workload. Interestingly, the common isoform of ACE is found on the surface of endothelial cells, thus particularly abundant in lungs due to the large endothelial surface area. However, ACE is also found in other vascular tissues, including striated muscle, and is not restricted to endothelial cells. Moreover, angiotensin receptors are not only bound to cell membranes but have also been identified on mitochondrial membranes [71]. Altered mitochondrial angiotensin signaling leads to changes in angiotensin receptor expression, mitochondrial nitric oxide production, and altered cellular respiration associated with age-related mitochondrial dysfunction [71].

ACE inhibitors and angiotensin receptor blockers (ARBs) are discussed as potential therapies to reduce the development of sarcopenia [72]. In fact, ACE inhibitors are safe, approved, and widely-used drugs and, therefore, are probably the preferred therapeutic option for sarcopenic obesity with hypertension. Indeed, some studies have shown that hypertensive patients treated with ACE inhibitors have a significantly slower decline in muscle strength and higher lower limb muscle mass compared with patients treated with other antihypertensive agents [73]. One study also showed an improvement in physical performance on the 6-minute walk distance test in the elderly [74]. However, ACE inhibitors did not provide additional benefits to physical function when added to a standard exercise training program in functionally impaired older people [75]. A study in sarcopenic elderly patients receiving perindopril, an ACE inhibitor, over a 12-month period showed no improvement in physical performance or muscle mass [76]. Another trial (The ACES Trial, NCT03295734) is currently underway to evaluate the effect of three first-line antihypertensive agents: the ACE inhibitor perindopril, the angiotensin AT1 receptor antagonist losartan, and the thiazide diuretic hydrochlorothiazide on potential improvement in the self-paced gait speed [77]. In summary, the existing evidence does not support the use of ACE inhibitors or angiotensin receptor blockers as a single intervention to improve sarcopenia or exercise capacity in elderly obese patients.

Treatment with anabolic androgenic steroids such as testosterone improved muscle performance in elderly men with sarcopenia, as described by increases in maximal voluntary muscle strength [78], improvement in 6-minute walk test distance, and self-reported walking ability [79, 80]. However, the risk of adverse events associated with testosterone use must be considered, such as increased risk for thrombosis and cardiovascular events, prostatic hyperplasia with related urinary tract symptoms, and prostate cancer, among others [81, 82].

The antidiabetic drug metformin can slow the progression of sarcopenia by inhibiting NFkappaB inflammation, reducing oxidative stress, regulating lipid metabolism, and activating AMPK-dependent signaling, leading to the restoration of muscle size and function [83, 84].

There are also several experimental drugs in the pipeline that may be useful as potential therapeutics in the future. Ghrelin mimetics can reduce muscle loss under catabolic conditions by increasing pulsatile growth hormone secretion and decreasing inflammatory cytokines secretion [85]. Thus, ghrelin mimetics can increase fat-free mass and improve muscle function [86]. Another attractive approach is the inhibition of myostatin signaling pathways, either by monoclonal antibodies targeting myostatin or by antagonists of activin receptors. Myostatin is a negative regulator of muscle mass and transmits its effects by binding to activin receptors on the muscle membrane. Indeed, anti-myostatin antibodies have increased muscle mass and strength in mice [87]. Unfortunately, clinical trials have not been successful to date.

In the context of pharmacotherapy of sarcopenic obesity, we should also consider anti-obesity drugs. However, many appetite suppressants were withdrawn from clinical use due to serious adverse effects, such as dexfenfluramine, fenfluramine, and sibutramine. Their mechanism of action is to inhibit the noradrenaline and serotonin reuptake transporters, thereby increasing the levels of both neurotransmitters in the neuronal synapses of the hypothalamic region that controls food intake [88]. Similarly, lorcaserin acts as a selective agonist of serotonergic receptors $5HT_{2C}$ in the hypothalamus and suppresses appetite. It is used as an adjunctive pharmacotherapy to diet and improved weight loss, but patients regained weight after discontinuation [88, 89]. Another approach is to inhibit pancreatic lipases, which break down dietary fat into fatty acids and glycerol in the gastrointestinal tract. One such drug is orlistat, which is currently the only approved drug for the treatment of obesity. Orlistat inhibits intestinal absorption of 30% of triglycerides, and resulted in 5-10% greater weight loss than in the placebo group [90].

While several potential pharmacological approaches have been proposed and discussed for sarcopenic obesity, none have been fully successful to date.

CONCLUSIONS

One of the main reasons for the growing research interest in sarcopenic obesity is the increasing ageing of the world population associated with chronic diseases that share common pathophysiological aspects. According to the results of the studies included in this review, both sarcopenic obese men and sarcopenic obese women have higher blood pressure than individuals who are only obese or sarcopenic. Further studies are needed to develop an effective treatment for sarcopenic obesity in clinical practice.

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MJ and LŽ equally contributed to this manuscript.

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