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The Interplay Between Muscle Mass Decline, Obesity, and Type 2 Diabetes

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Abstract: The world’s population is progressively becoming older, and age-related conditions are a major public health concern. A worrying phenomenon worldwide is increasing obesity among ageing societies, which is occurring in parallel with a higher prevalence of sarcopenia in older populations. As a result of the combination of these two states, new medical conditions, such as sarcopenic obesity, have recently become a public health concern. Data from the literature indicate a higher risk of metabolic syndrome, type 2 diabetes (T2DM), and atherosclerosis among patients with sarcopenic obesity than the risks associated with simple obesity or sarcopenia alone. The mechanisms underlying sarcopenic obesity are multifactorial. There is interplay between low-grade inflammation, insulin resistance, hormonal changes, a sedentary lifestyle, eating habits, and ageing. The aim of this review is to summarize the available data regarding the definition, epidemiology, and pathways that lead to sarcopenic obesity, as well as treatment strategies.

Keywords: insulin resistance; muscle mass decline; sarcopenic obesity; type 2 diabetes

1. Introduction

Sarcopenia refers to age-associated muscle mass decline. Various medical societies define sarcopenia in different ways [1]. The most well-known and frequently used criteria were published in 2010 by the European Working Group on Sarcopenia in Older People (EWGSOP) and define sarcopenia as the presence of both the loss of muscle mass and low muscle function (strength or performance) [2]. After 8 years, the European Working Group on Sarcopenia in Older People 2 (EWGSOP2) published a revised European consensus on the definition and diagnosis of sarcopenia based on the scientific and clinical evidence that has accumulated over the last decade [3]. According to the updated consensus, the EWGSOP2 uses low muscle strength as the primary parameter of sarcopenia since it reflects muscle
function in the most reliable way. Moreover, in these revised guidelines, it is acknowledged that strength is better than mass for predicting adverse outcomes. As stated by the EWGSOP2, sarcopenia could be suspected when low muscle strength is detected. To make a diagnosis of sarcopenia, the additional presence of low muscle quantity or quality is necessary in the presence of low muscle strength. When the three criteria (low muscle strength, low quantity or quality, low physical performance) are fulfilled, sarcopenia is considered severe. Of note is the selection of measuring tools by which muscle mass is assessed. Computerized tomography (CT) scans and magnetic resonance imaging (MRI) are considered the gold standards for muscle mass evaluation [2,3]. The cut-off points for low muscle mass are not yet well defined for these measurements. Due to the limited access and high cost of the abovementioned imaging studies, the EWGSOP recommends dual-energy X-ray absorptiometry (DXA) as a reference method [2,3]. Bioelectrical impedance (BIA) methods correlate with DXA, but BIA assessments seem to be less reliable because they are also dependent on hydration status [4].

The EWGSOP2 updates its algorithm for sarcopenia case findings, diagnosis and severity determination. The EWGSOP2 advises using the SARC-F questionnaire to identify individuals with probable sarcopenia. In the next step of the algorithm, they recommend performing grip strength and chair stand measures to identify low muscle strength. To confirm low muscle quality or quantity, the DXA or BIA methods are advised for use in usual clinical care (Fig. 1). EWGSOP2 provided cut-off points relevant to clinical practice (Table 1). The prevalence rates of sarcopenia vary significantly because of different definitions, measurement tools and patient populations. The recently published data from a meta-analysis, based on thirty-five articles, estimate the prevalence of sarcopenia to be 10% in men and 10% in women [5]. A higher prevalence of sarcopenia has been identified among non-Asian populations than among Asian populations in both sexes (11 vs. 10% in men and 12 vs. 9% in women, respectively) [5]. However, the results from different studies regarding the
association between gender and reduced muscle mass are inconsistent [6-7]. Sarcopenia and central obesity are both age-related body compositional changes and often coexist in older patients. Obesity with sarcopenia is known as sarcopenic obesity, a new medical condition that is associated with a higher incidence of metabolic syndrome and type 2 diabetes (T2DM) [8]. Sarcopenic obesity is generally defined as the combination of low lean body mass and high fat mass [9]. There is no universally accepted definition of sarcopenic obesity; currently, the definition based on the individual definitions of sarcopenia and obesity. Different criteria used in diagnosing sarcopenic obesity affect the prevalence rates of sarcopenic obesity, which vary from 4% to 94% [10].

2. Pathogenesis

The mechanisms underlying sarcopenic obesity are multifactorial. There is an interplay between ageing, hormonal changes, a sedentary lifestyle, eating habits, and low-grade inflammation combined with insulin resistance [11] (Table 2). A summary of the role of all mentioned factors is presented below.

2.1. Ageing as the Physiological Process Contributing to Sarcopenic Obesity

The peak muscle mass in humans is estimated to occur at the age of 30 years, and from this moment, a gradual loss of muscle mass begins, as well as parallel weight increase, mainly in the form of gained as fat mass [12]. During ageing, we observed an ectopic accumulation of fat, mostly in the liver (non-alcoholic fatty liver disease, NAFLD) [13], in the muscles [14], and in the pancreas (non-alcoholic pancreatic disease) [15]. The result of skeletal mass decline is a decrease in the basal metabolic rate, which can fall by approximately 30% between 20 and 70 years of age [16], while the caloric intake does not necessarily decrease over the lifespan [17]; these changes together may lead to increased fat accumulation. Fat tissue accumulation, insufficient physical activity and a decrease in protein intake are
considered to be the most important factors contributing to muscle mass loss and obesity, leading to sarcopenic obesity [18]. Muscle fibres are divided into two main types: slow twitch (type I) muscle fibres and fast twitch (type II) muscle fibres. The slow twitch muscle fibres are more efficient at using oxygen as fuel for continuous, extended muscle contractions over a long period of time. Fast twitch fibres use anaerobic metabolism to create fuel, and they are better at generating short bursts of strength or speed than slow muscles. However, fast twitch fibres fatigue more quickly. A greater loss in the number and area of type II versus type I motor units with age has been observed [19]. The loss of type II muscle fibre is mainly responsible for the reduced power of muscles, which is reflected by slower functional performance, such as slower gait speed and reduced muscle power [20]. Loss of muscle power may appear earlier than loss of muscle strength associated with sarcopenia [21].

Muscles have the ability to regenerate through the proliferation and differentiation of satellite cells [22]. A number of local transcription factors, cytokines and hormones (testosterone, insulin, IGF-1) stimulate this process [23]. On the other hand, myostatin inhibits the proliferation and differentiation of satellite cells. The ability of satellite cells to proliferate decreases with age [24]; moreover, obesity reduces the ability to repair skeletal muscle [25].

2.2. Hormonal Changes Related to Sex and Ageing

Changes in estrogen and testosterone occurring during the lifetime induce changes in body composition. In menopausal women, visceral fat mass and waist circumference increase, while fat-free mass has a tendency to decrease [26]. Estrogen deficiency enhances the age related decline of skeletal muscle mass, its strength, and regenerative capacity. In menopause, a decrease in skeletal muscle stem cells is observed because the ovarian hormones are necessary for satellite cell maintenance, self-renewal, and protection from apoptosis, thereby promoting optimal muscle regeneration [27]. It has been shown that estrogen protects skeletal muscle against apoptosis via its effects on HSPs (heat shock proteins) and mitochondria.
Thus, the estrogen deficiency contribute to the loss of muscle mass through apoptotic pathways [28]. Moreover, decreased endogenous estrogen levels lead to disruptions of insulin secretion and insulin sensitivity, what predispose to the T2DM development, independently of aging, but also additively to aging [29]. Menopausal hormone therapy containing oestrogens can alter these changes and influence the repair of skeletal muscle mass [30,31]. In men, during the natural process of ageing, testosterone declines by approximately 1% per year, which negatively affects muscle mass and fat distribution [32]. Under physiological conditions, testosterone promotes muscle protein synthesis by increasing amino acid metabolism in skeletal muscle and alters androgen receptor expression [33]. Moreover, testosterone enhances the regeneration of muscle tissue through satellite cell activation [34]. Moreover, it has been shown that also physiological decline of dehydroepiandrosterone, GH, and IGF-1 have been implicated in the sarcopenia process [35].

2.3. The Role of Diet

Additionally, the main problem in older people is inadequate protein intake compared to the overall protein requirements. Inadequate intakes of protein [36] and vitamin D [37] have been shown to promote sarcopenic obesity. Optimal protein intake is considered to be essential for maintaining muscle mass and strength. Therefore, efforts should be made to ensure that elderly patients in particular consume the recommended daily amount of protein [38].

2.4. From Adipose Tissue Inflammation to Sarcopenic Obesity

Age-related weight gain results in fat accumulation [39]. Excess adipose tissue is characterized by an increase in the size and number of adipocytes, which causes the infiltration of macrophages and other immune cells secreting pro-inflammatory cytokines and adipokines [40], leading to local and systemic chronic low-grade inflammation [41]. This
Inflammation induced by obesity has been associated with muscle mass decline [42] but may also result in insulin resistance. Moreover, this unfavourable adipokine/cytokine profile precedes insulin resistance and increases inflammation and oxidative stress, leading to ectopic fat deposition [43]. The interplay between obesity, inflammation, muscle mass decline, and insulin resistance creates a vicious cycle [Fig. 2] resulting in sarcopenic obesity and T2DM development. Additionally, visceral adipose tissue (VAT) accumulation is associated with a future loss of skeletal muscle, providing a novel insight into sarcopenic obesity [44].

In addition to general fat accumulation, as mentioned above, the ectopic storage of lipids between muscle fibres is a significant risk factor for further muscle dysfunction in older adults [45]. Intramyocellular lipids (IMCL) cause a reduction in the number of mitochondria and produce reactive oxygen species (ROS), which may reduce the oxidative capacity of muscle, contributing to impaired muscle function [46].

The main factors contributing to low-grade inflammation are the overexpression of tumour necrosis factor (TNF)-alpha in VAT and the infiltration of adipose tissue with macrophages [47]. This mechanism links obesity and the immune system. During the process of weight gain, anti-inflammatory macrophage M2 switches to pro-inflammatory macrophage M1, triggering the inflammatory process [48]. M1 macrophages secrete pro-inflammatory molecules such as TNF-alpha, IL-1, and IL-6 [49]. TNF-alpha has been shown to directly reduce adiponectin signalling, mitochondrial biogenesis, and myogenesis in primary human myotubes [50].

Adipose tissue is an active endocrine organ, and apart from cytokine secretion, it also produces adipokines (leptin and adiponectin, among others), which are involved in appetite, satiety, and energy expenditure regulation, as well as associated with glucose and insulin levels and lipid metabolism [51]. Adiponectin stimulates fatty acid oxidation and glucose uptake in skeletal muscles and adipose tissue through AMPK-activated signalling [52].
Interestingly, this effect is not observed in obesity [53]. Moreover, the level of adiponectin decreases with age and with weight gain and negatively correlates with the amount of fat tissue [54]. Adiponectin acts through its receptors AdipoR1 and AdipoR2, which are abundantly expressed in human skeletal muscle and primary myotubes [55]. In contrast to adiponectin, the other adipokine, leptin, is positively correlated with overall adipose mass [56]. Leptins exert a pro-inflammatory effect by activating monocytes, leading to the secretion of the pro-inflammatory cytokines TNF-alpha and IL-6 [57]. An increased level of TNF-alpha and IL-6 reduces the anabolic role of IGF-1. Moreover, many of the anabolic effects of leptin on skeletal muscle are likely to be mediated by IGF-1 [57]. Leptin receptors are abundant in skeletal muscles, and their expression is altered by physical activity [58]. The effects of leptin are countered by adiponectin, but monocytes activated by leptin produce TNF-alpha, which inhibits adiponectin, resulting in the decline in muscle mass protein synthesis and the mitochondrial process [59].

2.5. Myocellular Pathway Potentially Mediates the Development of Sarcopenia

Intramuscular fat infiltration in combination with low-grade inflammation can result in an imbalance of myocytes that produce myostatin.

Myostatin, a member of the TGFβ superfamily, is a negative regulator of the growth of skeletal muscles [60]. Myostatin contributes to muscle mass decline by inducing oxidative stress and producing ROS in skeletal muscle cells through the TNF-alpha pathway [61]. Interestingly, myostatin is also enhanced in aged skeletal muscle [62].

Another factor involved in the crosstalk between muscle mass and obesity is irisin, a myokine that is mainly secreted from skeletal muscles during exercise and that may mediate some beneficial effects of exercise in humans, such as weight loss and an increase in thermoregulation. An increase in irisin causes the browning of human white adipose tissues. Irisin reduces pro-inflammatory cytokines and induces M2 macrophage polarization, resulting
in the anti-inflammatory action of irisin on fat cells [63]. Irisin promotes oxidative metabolism and mitochondrial biogenesis and reduces metabolic risk [64]. Irisin positively correlates with muscle mass strength and metabolism [65]. In several studies, it was reported that myostatin is upregulated and irisin is downregulated in sarcopenia [66,67]. The opposite profile of myostatin/irisin has been proposed as promoting the browning of white adipose tissue with a beneficial effect on weight and insulin sensitivity [68].

Other molecules are bone morphogenetic proteins (BMPs), which enhance muscle growth by diminishing the negative effects of the TGFβ/myostatin/activin signalling pathway [69]. BMPs promote the browning of white adipose tissue and inhibit insulin resistance and adipose fat tissue inflammation [70].

The molecules mentioned above, secreted by myocytes, participate in crosstalk between skeletal muscles and adipose tissue, exerting negative effects.

3. Metabolic Consequences of Sarcopenic Obesity

The interplay between reduced muscle mass and obesity can lead to insulin resistance, metabolic syndrome, and T2DM. It has been shown that sarcopenic obesity increases the risk of metabolic syndrome and insulin resistance development more than obesity or sarcopenia alone [71]. Similar findings have been noticed in the Caucasian population, where sarcopenic obesity was also associated with metabolic syndrome [72]. The results of the study by Srikanthan P et al. [73] supported the data mentioned, showing that relative muscle mass is inversely associated with prediabetes status. The same author showed that sarcopenia in subjects under 60 years old significantly correlates with a higher prevalence of T2DM among obese populations [74]. The findings listed above indicate that a one-time measurement of muscle mass is associated with T2DM and that a gradual decline in muscle mass observed over a few years correlates with glucose dysmetabolism and the development of T2DM [11]. In our study, we observed that a reduction in muscle mass over a five-year time span is a risk
factor for T2DM susceptibility, independent of insulin resistance among adult subjects [75]. Furthermore, the Korean Genome Epidemiology Study showed that low muscle mass was strongly associated with an increased risk of T2DM, independent of obesity, in middle-aged Korean adults during a nine-year follow-up period [76]. This is all the more important in the light of the fact that diabetes increases the risk of cardiovascular disease, through various mechanisms, which have been recently well described and discussed by Gajos G. [77].

Muscle mass in primary tissue contributes to whole-body insulin-mediated glucose disposal, accounting for almost 40–50% of lean body mass [78]. Insulin is a powerful anabolic hormone that simulates muscle protein synthesis in young people but not older people [79]. An adequate supply of essential amino acids stimulates protein synthesis [80]. Under physiological conditions, insulin acts through the mammalian target of rapamycin (mTOR) pathway that inhibits the degradation of protein. The impaired insulin signalling associated with insulin resistance may contribute to muscle loss in diabetes [81]. Moreover, in aged muscle, the supply of amino acids and the perfusion of muscle are impaired [82], which may provide an additional explanation for the reduced protein synthesis. Moreover, in elderly individuals, impaired insulin-mediated suppression of proteolysis is observed [83]. Another important consequence of sarcopenic obesity is a higher risk of disability than that of healthy subjects [84]. Sarcopenic obesity results in an increased risk of falls and fractures and leads to mobility disorders. Moreover, sarcopenic obesity is associated with cardiac disease, respiratory disease, and cognitive impairment and contributes to a reduced quality of life. Obese patients with reduced muscle mass are more prone to knee osteoarthritis and depression and have worse psychological health than individuals with normal muscle mass and a normal waist circumference [85]. Data relating to sarcopenic obesity and mortality are conflicting [86]. In financial terms, the presence of sarcopenia increases the risk for hospitalization and increases the cost of care during hospitalization.
4. Management of Sarcopenic Obesity

Taking into consideration all of the possible consequences of sarcopenic obesity, we should develop treatment strategies for obese patients with reduced muscle mass. The main points of treating sarcopenic obesity are based on weight loss together with an increase in physical activity. Intentional weight loss in older adults reduces morbidity and improves physical function [87]. Anti-obesity medications (liraglutide, orlistat, naltrexon/bupropion) are approved for use in obese patients younger than 65 years old, but they have not been evaluated for use among obese sarcopenic patients [88]. In nine older adults taking GLP-1, a weight decrease (2 kg) was observed with a marginal improvement in the skeletal muscle index [89]. The available data suggest that weight loss without exercise, while reducing fat mass, also inevitably decreases lean mass, thus worsening sarcopenia [90]. The combination of a well-balanced diet with exercise (aerobic plus resistance programme) has been proposed as the best choice for the management of sarcopenic obesity [91]. Aerobic training improves cardiometabolic health by reducing oxidative stress and inflammation; it also increases insulin sensitivity, decreases blood pressure and improves the blood lipid profile. Notably, during aerobic training, energy expenditure is two- to three- times higher than during resistance training. During resistance training, the preferential reduction in visceral fat compared to peripheral fat is observed. Moreover, resistance training prevents the regaining of fat, especially visceral fat. Resistance training may be more useful to counteract sarcopenia, and aerobic training may be more useful to address obesity. The results from intervention studies (a six-month randomized controlled trial (RCT) and a three-month RCT) revealed that subjects who performed resistance and aerobic exercise experienced more benefits, such as an improved physical performance test, a better quality of life (QoL), and greater strength compared to the same parameters in the aerobic group or resistance group alone [92]. The
A combination of aerobic and resistance training could reduce the development of sarcopenia, decrease fat accumulation and minimize the risk of developing metabolic disease.

Apart from physical activity, dietary intervention is the main goal of treatment strategies. A suggested approach is calorie restriction to 500–1000 kcal per day to achieve a 0.5-kg weight loss per week [93]. Reduction in weight should be enhanced by adequate protein consumption to avoid protein anabolism during weight loss. The source of protein, the timing of protein intake, and specific amino acid consumption stimulate muscle synthesis [94]. The recommended protein intake is 1.0–1.2 g/kg per day in healthy patients without renal failure [95]. It has been shown that protein supplementation and resistance training increase lean mass, upper body strength, and leg strength more than resistance training alone [96]. There are no available data in terms of vitamin D supplementation as a monotherapy for sarcopenic obesity. One intervention study in a Japanese population showed that vitamin D together with amino acid supplementation, tea catechins, and a combination of exercise reduced fat mass and improved physical function but not muscle mass in individuals with sarcopenic obesity [97]. In summary, the right combination of exercise, a moderate-weight-loss-inducing diet with adequate protein supplementation seems to be the most effective strategy in terms of sarcopenic obesity treatment. Studies based on animal models have indicated that calorie restriction prevents age-associated diseases and extends longevity by modulating mitochondrial activity and decreasing oxidative stress [98]. Weight loss should be gradual to avoid a rapid loss of muscle mass. To the best of our knowledge, in terms of pharmacological management, there are no trials evaluating the effects of the available anti-obesity medications in obese sarcopenic subjects. Recently, a paper was published that showed the beneficial effect of myostatin antibodies among the elderly, demonstrating a decrease in body fat, an increase in skeletal muscle mass, and physical capacity improvement [99], but these findings should be confirmed in individuals with sarcopenic obesity. Only one study
evaluating the impact of bariatric surgeries in sarcopenic obese and non-sarcopenic obese subjects showed similar weight loss and similar improvements in comorbidities in both the sarcopenic and non-sarcopenic morbidly obese groups [100].

5. Conclusions

Sarcopenic obesity is a new challenging condition in ageing populations, especially in the context of the current obesity epidemic. Sarcopenic obesity is a chronic state resulting in metabolic consequences, impairment of physical capacity, and likely an increased risk of mortality. The question regarding sarcopenic obesity is associated with an agreement on a uniform definition and the use of DXA rather than other measurement tools. It would be helpful to systematize the results from research and trials to create recommendations. Clarifying the mechanism that contributes to sarcopenic obesity may be useful for developing novel therapies. It is worth remembering that weight loss, together with adequate protein intake and exercise, is essential for the management of sarcopenic obesity.

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<table>
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<th></th>
<th>Cut-off points for men</th>
<th>Cut-off points for women</th>
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<tr>
<td><strong>EWGSOP2 sarcopenia cut-off points for low strength by chair stand and grip strength</strong></td>
<td></td>
<td></td>
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<tr>
<td>Grip strength</td>
<td>&lt;27 kg</td>
<td>&lt;16 kg</td>
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<tr>
<td>Chair stand</td>
<td>&gt;15 s for five rises</td>
<td></td>
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<tr>
<td><strong>EWGSOP2 sarcopenia cut-off for low muscle mass</strong></td>
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<tr>
<td>ASM&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&lt;20 kg&lt;sup&gt;b&lt;/sup&gt;</td>
<td>&lt;15 kg&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
<td>ASM/height&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;7,0 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
<td>&lt;5,5 kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
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<tr>
<td><strong>EWGSOP2 sarcopenia cut-off points for low performance</strong></td>
<td></td>
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<tr>
<td>Gait speed</td>
<td>≤ 0,8 m/s</td>
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<tr>
<td>SPPB&lt;sup&gt;c&lt;/sup&gt;</td>
<td>≤ 8 points score</td>
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<tr>
<td>TUG&lt;sup&gt;d&lt;/sup&gt;</td>
<td>≥ 20 s</td>
<td></td>
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<tr>
<td>400 m walk test</td>
<td>Non-completion or ≥ 6 min for completion</td>
<td></td>
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**Table 1. EWGSOP2 (European Working Group on Sarcopenia in Older People) sarcopenia cut-off points**

<sup>a</sup>appendicular skeletal muscle mass  
<sup>b</sup>cut-off point for DXA (dual-energy X-ray absorptiometry)  
<sup>c</sup>Short physical performance battery  
<sup>d</sup>Timed-up-and-go test
<table>
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<tr>
<th>Sarcopenia</th>
<th>Primary sarcopenia</th>
<th>Age-related sarcopenia</th>
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<tr>
<td>Secondary sarcopenia</td>
<td>Activity-related sarcopenia</td>
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<td></td>
<td>Sedentary lifestyle, limited mobility</td>
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<td></td>
<td>Disease-related sarcopenia</td>
<td>Advanced organ failure, inflammatory, malignancy or endocrine diseases</td>
</tr>
<tr>
<td></td>
<td>Nutrition-related sarcopenia</td>
<td>Inadequate dietary intake, malabsorption, gastrointestinal disorders (diarrhea, inflammatory bowel disease) or use of medication</td>
</tr>
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</table>

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<tr>
<th>Obesity</th>
<th>Family inheritance</th>
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<tr>
<td></td>
<td>Behavioral causes</td>
<td>poor eating habits, excessive calorie intake sedentary life style</td>
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<tr>
<td></td>
<td>Hormonal and metabolic influences</td>
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<td></td>
<td>Increase fat mass, mainly visceral obesity</td>
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<td>Low grade inflammation</td>
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<td>Insulin resistance</td>
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Table 2  The causes of sarcopenic obesity
Figure 1. EWGSOP 2 algorithm for case finding, making a diagnosis and quantifying severity in practice.
Figure 2. Pathomechanism of sarcopenic obesity. The interplay between muscle mass decline, obesity, inflammation and insulin resistance.