Ageing Research Reviews 101 (2024) 102460

Contents lists available at ScienceDirect

Ageing Research Reviews

journal homepage: www.elsevier.com/locate/arr

Sarcobesity: New paradigms for healthy aging related to taurine supplementation, gut microbiota and exercise

Gabriela Batitucci [a], Gabriela Ferreira Abud [b], Gabriela Ueta Ortiz [b], Lucas Fernandes Belisário [c], Sofia Germano Travieso [b], Marcela Coffacci de Lima Viliod [c], Ana Cláudia Rossini Venturini [c], Ellen Cristini de Freitas [b,c,*,1]

[a] School of Medical Sciences, Obesity and Comorbidities Research Center, University of Campinas - UNICAMP, Campinas, Sao Paulo, Brazil
[b] Department of Health Sciences, Ribeirao Preto Medical School, University of São Paulo - FMRP/USP, Ribeirao Preto, Sao Paulo, Brazil
[c] Laboratory of Exercise Physiology and Metabolism, School of Physical Education and Sports of Ribeirao Preto, University of Sao Paulo - EEFERP/USP, Ribeirao Preto, Brazil

ARTICLE INFO

Keywords:
Sarcobesity
Aging
Taurine
Gut microbiota
Physical exercise
Therapeutic targets

ABSTRACT

Enigmatic sarcopenic obesity is still a challenge for science and adds to the global public health burden. The progressive accumulation of body fat combined with a dysfunctional skeletal muscle structure and composition, oxidative stress, mitochondrial dysfunction, and anabolic resistance, among other aggravating factors, together represent the seriousness and complexity of treating the metabolic disorder of sarcobesity in aging. For this reason, further studies are needed that encourage the support of therapeutic management. It is along these lines that we direct the reader to therapeutic approaches that demonstrate important, but still obscure, outcomes in the physiological conditions of sarcobesity, such as the role of taurine in modulating inflammatory and antioxidant mechanisms in muscle and adipose tissue, as well as the management of gut microbiota, able to systemically re-establish the structure and function of the gut-muscle axis, in addition to the merits of physical exercise as an instrument to improve muscular health and lifestyle quality.

1. Introduction

Understanding the pathophysiology of sarcopenic obesity, also known as sarcobesity (SO), still challenges science, as this condition can aggravate changes in the demographic distribution and emerging global public health problem of a progressively aging population (Batsis and

Abbreviations: 8-OHdG, 8-hydroxy-2′-deoxyguanosine; AKT, Protein Kinase B; AMPK, Adenosine Monophosphate Activated Protein Kinase; APC, Adipocyte Progenitor Cells; AR, Anabolic Resistance; ASM, Appendicular Skeletal Muscle Mass; BAT, Brown Adipose Tissue; BMI, Body Mass Index; CAT, Catalase; CRP, C-reactive protein; CT, Computed Tomography; DXA, Dual-energy X-ray Absorptiometry; EASO, European Association for the Study of Obesity; ESPEN, European Society for Clinical Nutrition and Metabolism; EWSGOP, European Working Group on Sarcopenia in Older People; EWSGOP2, European Working Group on Sarcopenia in Older People 2; FM%, Fat Mass Percentage; FNIH, Foundation National Institute of Health; GLP-1, Glucagon-like peptide 1; GPR41, G-protein coupled receptor 41; GPR43, G-protein coupled receptor 43; GPx, Glutathione Peroxidase; HIIT, High Intensity Interval Training; HRmax, maximum heart rate; IGF-1, Insulin-like growth factor 1; IL-10, Interleukin 10; IL-6, Interleukin 6; IR, Insulin Resistance; LPS, Lipopolysaccharides; M1, Type 1 macrophages; M2, Type 2 macrophages; MAPK, Mitogen Activated Protein Kinases; MDA, Malondialdehyde; MEF2, Myocyte Enhancer Factor-2; MPD, Muscle Protein Degradation; MPS, Muscle Protein Synthesis; MR, Magnetic Resonance; MTauT, taurine mitochondrial transporter; MTOR, mammalian target of rapamycin; MuRF-1, Muscle Ring Finger 1; MyoD, Myogenic Regulatory Factor; NADPH, Nicotinamide Adenine Dinucleotide Phosphate; NF-kB, Nuclear Factor kappa Beta; Nrf2, Nuclear Factor Erythroid 2-Related Factor 2; PGC1-alpha, Peroxisome Proliferator Activated Receptor Gamma Coactivator 1-alpha; PI3K, Phosphoinositide 3-Kinase; PPAR, Peroxisome Proliferator Activated Receptors; PPARγ, Peroxisome Proliferator-Activated Receptor Gamma; PYY, Peptide YY; RM, maximum repetition; RNS, Reactive Nitrogen Species; ROS, Reactive Oxygen Species; RyR, Ryanodine Receptor; SCFA, Short Chain Fatty Acids; SIRT-1, Sirtuin 1; SO, Sarcobesity; SOD, Superoxide Dismutase; TAK1, Serine/threonine protein kinase; TGF-β, Transforming Growth Factor beta; TLR-4, Toll Like Receiver-4; TNF-α, Tumor Necrosis Factor alpha; UCP-1, Uncoupling Protein 1; VO2max, maximum oxygen volume; WAT, White Adipose Tissue.

* Correspondence to: School of Physical Education and Sports of Ribeirao Preto, University of Sao Paulo – EEFERP/USP, Bandeirantes Avenue, Ribeirão Preto, SP 3900, Brazil.
E-mail address: ellenfreitas@usp.br (E.C. de Freitas).
[1] ORCID 0000–0002-7343–2002

https://doi.org/10.1016/j.arr.2024.102460
Received 6 April 2024; Received in revised form 16 July 2024; Accepted 15 August 2024
Available online 22 August 2024

Villareal, 2018). The subset of individuals over 65 years of age with SO, a prevalent geriatric combination between excessive weight gain and loss of muscle mass and strength, has advanced considerably. In this sense, SO may be a risk factor for other chronic inflammatory-based complications, such as Anabolic Resistance (AR), Insulin Resistance (IR), cardiovascular diseases and diabetes (Heymsfield and Wadden, 2017; Batsis and Villareal, 2018; Wagenaar et al., 2021).

Estimates indicate that the prevalence of older adults may reach 2.1 billion by 2050 and science has shown concerns in the search for effective therapies for healthy aging in this population. Aging promotes numerous metabolic alterations that can worsen due to a sedentary lifestyle and a diet with poor nutritional content. In this sense, non-drug therapies are interesting strategies to alleviate these changes (Batsis and Villareal, 2018; Wagenaar et al., 2021).

In this context, despite the existing limitations for a consensual definition of SO, which is still an obstacle to the advancement of science in this regard (Batsis and Villareal, 2018), the population aged 65 years or older presents important aging related changes in body composition, involving the progressive decline in muscle mass and increase in body fat, characterizing sarcopenia linked to obesity (Stenholm et al., 2008; Parr et al., 2013).

When these conditions coexist, called sarcobesity, they further drive the inflammatory process and metabolic dysfunction in aging. This is accompanied by changes in the gut microbiota of these individuals, since both age progression and obesity itself are closely related to potentially pathogenic taxonomic signatures, loss of microbial diversity, and even more exacerbated gut permeability (Biagi et al., 2010; Bana and Cabreiro, 2019). In addition, recently, studies have reported that taurine concentrations naturally decline with age in some organs, raising the possibility that falling taurine may contribute to aging-related physiological decline (Singh et al., 2023).

Taurine deficiency is known to be related to a myriad of adverse health conditions, including diabetes, hypertension, liver disease, inflammation, and obesity, as well as diverse immunological phenotypes (Schaffer and Kim, 2018). However, there is still a gap in the knowledge on the regulatory mechanisms that operate endogenous taurine levels throughout development (Izquierdo, 2023). In mice, a study showed that taurine levels are inversely correlated with age-associated diseases (Mkrtchyan et al., 2020; Singh et al., 2023). The authors found that taurine supplementation increased life expectancy by an average of 12 % in women and 10 % in men, and life expectancy at 28 months increased by 18–25 %, three to four months of life (equivalent to approximately seven to eight human years). These results showed that taurine deficiency is a determining factor in aging, at least in mice, because its reversal increased life expectancy.

Taurine was shown to reduce the number of senescent cells. A decline in circulating taurine is a feature of aging in multiple species, including humans, with levels falling by around 80 % over the human lifespan. It was also found that mice lacking the main taurine transporter had shorter adult lives. Supplementing middle-aged wild-type mice with taurine increased average lifespan by 10–12 % (Schaffer and Kim, 2018; Singh et al., 2023). Studies have noted a decrease in circulating taurine in people with obesity and diabetes, as well as its elevation through exercise, strengthening its correlation with general health.

Adipose and muscle tissue actively interact in the development of SO, because the inflammatory process in obesity signals the secretion of Tumor Necrosis Factor alpha (TNF-α) and other cytokines with pro-inflammatory potential, that drive IR exacerbated by muscle catabolism, with preferential mobilization of muscle and not fat (Schrager et al., 2007; Zamboni et al., 2008; Srikanthan et al., 2010). Furthermore, sarcobesity is accompanied by atrophy of type II muscle fibers (Nilwik et al., 2013), and a reduction in postprandial amino acid availability and digestive capacity, resulting from splenic sequestration of amino acids and changes in glucose metabolism, aspects that result in and increase the risk of AR (Bauer et al., 2013). Additionally, the low-grade inflammatory process becomes even more evident when lipotoxicity mechanisms are activated, since aging can stimulate the infiltration and deposit of fat in the muscle, favoring sarcopenia (Visser et al., 2005).

In this sense, studies have demonstrated the importance of knowing and clarifying the key role of the use of possible non-pharmacological strategies in the context of sarcobesity (Xu et al., 2019), such as taurine supplementation (Mkrtchyan et al., 2020; Singh et al., 2023), the management of gut microbiota (Xu et al., 2019), and physical exercise incorporated into a non-sedentary lifestyle.

This is the first review to connect three potential therapeutic axes from the perspective of sarcobesity. Here, we dedicate our interest to understanding three possible therapeutic targets with the potential to mitigate sarcobesity in aging. The interest is in taurine supplementation, the interface between the microbiota and the distinct axes that shape the host's metabolism, such as the gut-muscle-axis, with implications even for chromosomes and cellular senescence, as well as classic physical exercise therapy that is poorly adhered to in the long term and still lacks in-depth understanding about the best prescription. In general, these aspects are carefully discussed, as this therapeutic triad is directly or indirectly connected, still requiring clarification of the deleterious impact that inflammation in sarcobesity has on peripheral tissues, such as adipose, muscle, and gut, among others, and the crosstalk that these tissues have with microbiota, exercise, and taurine.

Thus, the current review aims to elucidate a general and current approach to sarcobesity, highlighting three potential therapeutic targets involving taurine supplementation, modulation of the intestinal microbiota, and physical exercise as important perspectives on sarcobesity and its challenging clinical implications.

2. Diagnosis of sarcobesity and its challenges

The accentuated and progressive decline in muscle mass and strength, characterized as sarcopenia, is a prevalent condition in people aged 65 years or older. This condition increases the risks for physical disabilities, falls, fractures, and hospitalization (Cruz-Jentoft et al., 2019) and it is a limiting factor for the quality of life of older adults. This prognosis worsens when it is linked to increased body fat, characterizing the clinical and distinct picture of sarcobesity (Donini et al., 2020). Although it is commonly observed in older adults, sarcobesity can also be diagnosed in young people with obesity. This occurs due to behavioral factors, such as a sedentary lifestyle, or hormonal and metabolic alterations, cancer, or after bariatric surgery when there is a lack of proper nutritional care (Donini et al., 2020).

Due to the lack of universally recognized diagnostic criteria, different definitions and methods have been used for the clinical diagnosis of sarcobesity. The absence of diagnostic criteria can underestimate or overestimate sarcobesity, making it a complex, challenging, and unreliable reality (Stenholm et al., 2008; Prado et al., 2012). The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) carried out a systematic review to analyze the definitions and criteria used to diagnose sarcobesity in the scientific literature (Donini et al., 2020). The authors found several definitions and diagnostic approaches, arising from the different definitions of obesity and sarcopenia, as well as differences in methodologies for assessing body composition and function.

The combination of methods that assess muscle mass, strength and functionality, and body fat are useful for the diagnosis of sarcobesity (Cruz-Jentoft et al., 2010; Choi, 2016). In this sense, the use of Computed Tomography (CT) and Magnetic Resonance (MR) to evaluate body composition results in high definition and accurate measurements, however, these are high-cost, have limited access, and involve a high radioactive charge. An alternative widely explored in clinical trials is Dual-energy X-ray Absorptiometry (DEXA) (Choi, 2016).

Table 1 provides a summary of different definitions and methods used in the clinical diagnosis of sarcobesity. Previous evidence used the assessment of appendicular skeletal muscle mass (ASM) exclusively to diagnose sarcopenia, considering cutoff points of < 19.75 kg and $<$

Table 1
Different definitions and methods used in the clinical diagnosis of sarcobesity.

Authors, Year	Sample group, Age range (years)	Sample size	Sarcobesity definition	Body composition assessment
Park et at., 2017	Women (74.1 ±6.1 years)	50	ASM/body weight < 25.1 %; BMI for obesity ≥ 25.0 kg/m^2 (Lim et al., 2010).	BIA
Dieli-Conwright et al., 2018	Women (53±10.4 years)	100	ASM/height^2 < 5.45 kg/m^2 for sarcopenia (Baumgartner, 2000); BMI for obesity ≥ 30.0 kg/m^2	DEXA
Kemmler et al., 2018	Older men (≥70 years)	965	ASM/BMI < 0.789 for sarcopenia (FNIH definition, (Studenski et al., 2014); body fat > 27 % for obesity (Baumgartner, 2000).	DEXA
Zhou et al., 2018	Older men (≥60 years)	48	ASM/height^2 ≤ 7.0 kg/m^2 for sarcopenia (AWGS definition, (Chen et al., 2014); body fat ≥ 25 % for obesity (WHO, 1999).	BIA
Nabuco et al., 2019	Older women (≥60 years)	26	ASM < 15.02 kg for sarcopenia (FNIH definition, (Studenski et al., 2014); body fat ≥ 35 % for obesity (Batsis et al., 2015).	DEXA
Himoto et al., 2020	Women and men (≥ 50 years)	46	ASM/height^2 ≤ 5.7 kg/m^2 women; ≤ 7.0 kg/m^2 men, and Handgrip strength ≤18 women; ≤ 26 kg man for sarcopenia (JSH definition, (Nishikawa et al., 2016); BMI less than 25 for the definition of hidden obesity and body fat > 30 % women; > 25 % men for obesity.	BIA

Note: ASM, appendicular skeletal muscle mass; AWGS, Asian Working Group for Sarcopenia; BIA, Bioelectric Impedance Analysis; BMI, Body mass index; DEXA, Dual-energy X-ray Absorptiometry. FNIH, The Foundation for the National Institutes of Health; JSH, Japan Society of Hepatology; WHO, World Health Organization.

15.02 kg for men and women, respectively (Nabuco et al., 2019). Furthermore, ASM adjusted by the body mass index (ASM/BMI), considering cutoff points of < 0.789 for men and < 0.512 for women (Batsis et al., 2015; Kemmler et al., 2018; Kemmler et al., 2020), and ASM adjusted for height (ASM/h^2) have been a diagnostic target for sarcopenia (Dieli-Conwright et al., 2018; Zhou et al., 2018). These definitions were previously recommended by the Foundation National Institute of Health (FNIH) (Studenski et al., 2014). The diagnostic parameters portrayed by the ASM/h^2 combined with the variable muscle strength (Himoto et al., 2020) or the ASM adjusted for the percentage of body weight (ASM/body weight%) (Park et al., 2017), complement diagnostic strategies using ASM.

Grip strength and the chair stand test are tools for assessing muscle strength and functionality that can be used in the diagnosis of sarcopenia, according to the European Working Group on Sarcopenia in Older People 2 (EWSGOP2) consensus (Cruz-Jentoft et al., 2019). However, the diagnosis of SO has encountered divergences as it does not consider the factors muscular strength and physical performance, but only the reduction in skeletal muscle mass (El Hajj et al., 2018). Corroborating this context, the lack of methodological standardization for the classification of body weight gain and degrees of obesity still persists, challenging the reliable diagnosis of sarcobesity.

Despite being inaccurate and highly controversial, BMI has been used in conjunction with sarcopenia classifications to diagnose sarcobesity (WHO, 1999; Prado et al., 2012; Dieli-Conwright et al., 2018; El Hajj et al., 2018). In addition to BMI, body fat mass percentage (FM%) (Kemmler et al., 2018; Nabuco et al., 2019; Kemmler et al., 2020), sex-adjusted FM% (Batsis et al., 2015; Zhou et al., 2018), and BMI in conjunction with FM%, have also been proposed to aid in the diagnosis of SO (Himoto et al., 2020).

Considering the complexity of defining SO, due to the scarcity of precise and well-established diagnoses (Himoto et al., 2020), previously used tools, such as anthropometric parameters, encompass the changes in body composition intrinsically observed with the progression of the disease, which include a significant loss of muscle mass accompanied by a gain in body fat (Cruz-Jentoft et al., 2010). In this sense, the epidemiological panorama portrays inconsistencies in the global prevalence of sarcobesity (Prado et al., 2012; Johnson Stoklossa et al., 2017). Using the DXA method and the ASM/h^2 definition, a prevalence of 15 % was observed in individuals aged between 60 and 69 years and 40 % in individuals aged 80 years or over (Baumgartner, 2000). In contrast, Batsis et al. (2015) showed that the prevalence of sarcobesity reached 27.3 % in men and 33.5 % in women aged 60 or over, when using the ASM and ASM/BMI methods.

Additionally, Donini et al. (2020) found that the majority of studies used methods that assessed ASM, regardless of muscle functionality. However, this assessment impacts the accuracy of the diagnosis, since sarcopenia is not limited only to the decline in muscle mass, but also to the reduction in the physical and functional capacity of the muscle mass. Therefore, as EWGSOP2 takes into account variables of muscular strength and physical performance to diagnose SO, a more precise and accurate diagnosis is suggested in older adults (Cruz-Jentoft et al., 2010).

The different criteria for diagnosing sarcobesity reflect the use of methods that are still poorly standardized, resulting in underestimation or overestimation of sarcobesity. This fact deserves caution and public health educational strategies, able to resolve the divergences observed in this diagnosis (Barazzoni et al., 2018; Trouwborst et al., 2018). These obstacles hinder patient treatment, early diagnosis, disease prognosis, and adequate treatment. Furthermore, possible risks of complications associated with high adiposity and a reduction in muscle mass, strength, and functionality can be masked during aging (Barazzoni et al., 2018; Donini et al., 2020).

Thus, well-designed clinical trials covering a large sample size are encouraged, to contribute to knowledge gaps regarding the diagnostic approach to sarcobesity. These findings would make it possible to promote a solid and well-established consensus, as considered by the ESPEN and EASO (Barazzoni et al., 2018).

3. Taurine supplementation as a therapeutic strategy in sarcobesity

3.1. Mechanisms of action in adipose tissue

AR, IR, and obesity, as well as the progressive decline in strength and muscle mass, are metabolic disorders commonly observed in the aging

process. This problem can be partially explained by the morphological and functional changes in White Adipose Tissue (WAT). These alterations may present a structure of hypertrophied fat follicles, infiltration of inflammatory cytokines in adipocytes, and abundant senescent cells, capable of signaling the systemic inflammatory cascade and promoting irreversible interruption of cell proliferation. The fact is that WAT loses its endocrine functionality as a regulator of energy homeostasis via pro-inflammatory adipokine signaling, leading to a reduction in mitochondrial content. This reinforces the impairment in the insulin signaling pathway, with the ability to store lipids and dissipate energy (Von Bank et al., 2021; Smith et al., 2021).

WAT dysfunction is seen in coexisting conditions of obesity and sarcopenia in aging (Longo et al., 2019), and has negative impacts on muscle function and catabolism (Kalinkovich and Livshits, 2017; De Carvalho et al., 2019). Brown Adipose Tissue (BAT) and beige adipose tissue also present anatomical alterations that are accompanied by dysfunctional characteristics in aging. For example, deregulation in the secretion of adipokines, reduced oxidation capacity for substrates (lipids and carbohydrates), and the occurrence of inflammatory processes (Zoico et al., 2019; Y. Liu et al., 2020; Silva and Amato, 2022).

The decline in thermogenic capacity observed in adipocytes during aging seems to be associated with damage induced by the cellular senescence system in brown and beige adipocyte progenitor cells (APC), affecting the ability of these cells to proliferate and differentiate. The intrinsic factors that contribute to this decline involve not only the impact of cellular senescence system on APC, but also encompass aspects associated with mitochondrial dysfunction during aging (Zoico et al., 2019; Z. Liu et al., 2020; Silva and Amato, 2022), for example, a reduction in mitochondrial content and biogenesis, in addition to the decrease in the expression and activity of the thermogenesis of mitochondrial proteins, such as Uncoupling Protein 1 (UCP1) (Zoico et al., 2019; Amorim et al., 2022).

The implications related to the thermogenic activity of adipocytes in aging are not yet fully understood. Previous evidence indicates that the age-related decline in the thermogenic capacity of adipose tissue can negatively affect metabolic homeostasis and consequently contribute to the development of IR (Silva and Amato, 2022). Additionally, the obesogenic condition may act in conjunction with age-related adipose tissue dysfunction, thus increasing the risk of metabolic disorders (Conte et al., 2019; Silva and Amato, 2022). Although most studies focus on animal models, new insights in the scientific literature on the mechanisms underlying the thermogenic capacity of adipose tissue in aging could contribute to the development of strategies that are promising for improving health (Silva and Amato, 2022), in particular for the growing population of older people, which is generating public health concerns. Among the proposed strategies, taurine has been mentioned as an area of interest, standing out as a possible non-pharmacological intervention.

The scientific community has demonstrated the promising effects of taurine supplementation on adipose tissue, in terms of anti-inflammatory, antioxidant, and energy regulation potential (Murakami, 2017). However, the scarcity of studies demonstrating the role of taurine in sarcobesity is still evident. Taurine, 2-aminoethanesulfonic acid, is a quasi-essential nutrient found in all eukaryotic organisms and highly expressed in mammalian tissues. It is synthesized from cysteine through the action of cysteine sulfonic acid decarboxylase (Sharma et al., 2023), although it can also be obtained from the diet (meat, fish, and milk/dairy), and transported into cells by the Slc6a6 transporter (Warskulat et al., 2007). Supplementation with this nutrient improved the inflammatory profile of the obese phenotype in an experimental model. The results indicated greater polarization of type 2 macrophages (M2), with a potentially anti-inflammatory action, to the detriment of type 1 macrophages (M1) (Lin et al., 2013). This mechanism is not fully understood, but taurine appears to act on the activation of Peroxisome Proliferator Receptors Gamma (PPARγ), playing a key role in M2 differentiation (Bouhlel et al., 2007; Gao et al., 2019).

Furthermore, taurine can interact with neutrophils in adipose tissue during the process of taurine chloramine synthesis, which contributes to the suppression of the phosphorylation of Nuclear Factor kappa Beta (NF-kB), closely linked to the activation of low-grade inflammation. However, the processes by which this occurs still remain unclear (Schuller-Levis, 2005). Researchers have also demonstrated that taurine can improve glucose tolerance, and reduce concentrations of triglycerides and total cholesterol, in addition to mitigating the synthesis of pro-inflammatory cytokines, and modulating glucose and lipid metabolism, in order to reduce the risk of comorbidities associated with weight gain (Lin et al., 2013; Murakami, 2017).

Investigations of the few clinical trials already carried out still lack clear and significant results, as taurine has demonstrated limited effects in humans. Rosa et al. (Rosa et al., 2014) in a pioneering clinical trial, investigated the effects of taurine supplementation using 3 g of taurine daily in conjunction with nutritional counseling in women with obesity. The authors observed that taurine showed promising effects on greater production of adiponectin and reduced levels of C-reactive protein (CRP), independent of changes in body weight. The same dose as used by Rosa et al. (Rosa et al., 2014) was tested on new inflammatory parameters, and taurine associated with physical training demonstrated good results in women with obesity. The women showed a reduction in levels of interleukin 6 (IL-6), which has inflammatory potential, and increases in IL-5 and IL-10 levels (De Carvalho et al., 2022). These results provide scientific support for the potential of taurine supplementation as an adjuvant therapy in the treatment of obesity, since it leads to even better metabolic effects when combined with classic and well-documented strategies (i.e., dietary interventions and physical exercise) for the prevention and treatment of metabolic disorders, especially obesity (De Carvalho et al., 2019). Table 2 elucidates the main clinical findings of taurine supplementation, combined or not with physical exercise

Clearly, the interface between the role of taurine supplementation in the confluence of obesity and sarcopenia in aging involves the therapeutic approach of this nutrient, considering the functional changes in adipose tissue and possible risks of comorbidities associated with excessive weight, with emphasis on diabetes, cardiovascular diseases, and cancer (Von Bank et al., 2021; Z. Liu et al., 2020; Murakami, 2017). Another dysfunctionality of adipocytes in the aforementioned conditions is related to the exacerbated accumulation of Reactive Oxygen Species (ROS) (Z. Liu et al., 2020), since the imbalance between antioxidant defenses and the release of ROS converge in oxidative stress, which in turn accelerates the process of cellular senescence (Monickaraj et al., 2013). Taurine appears to modulate and mitigate oxidative stress (Baliou et al., 2021) by acting as an antioxidant, stimulating an increase in the plasmatic enzyme Superoxide Dismutase (SOD) in obese women aged between 55 and 70 years (Abud et al., 2022).

In sarcobesity, this categorically inflamed adipose tissue has even more deleterious outcomes. These hypertrophied adipocytes lead to hypoxia and poor vascularization of the tissue, impacting the loss of mitochondrial function, one of the main hallmarks of aging (Miwa et al., 2022). These damages can compromise the homeostasis of lipid and energy metabolism (Von Bank et al., 2021; Heinonen et al., 2020). Recently, Singh et al. (Singh et al., 2023) found that taurine reduced cellular senescence, suppressed mitochondrial dysfunction, attenuated inflammation, and suppressed DNA damage in a study involving aged animal models and older humans.

Moreover, taurine supplementation can restore mitochondrial function in WAT by elevating gene expression of Peroxisome Proliferator-Activated Receptor Gamma Coactivator 1-alpha (PGC1-alpha), Peroxisome Proliferator-Activated Receptors (PPAR), genes that modulate energy metabolism and thermogenesis, as well as other compounds that modulate lipid metabolism, such as acyl-CoA oxidase, synthase, and dehydrogenase (Murakami, 2015; Tsuboyama-Kasaoka et al., 2006). Taurine supplementation also resulted in greater expression of the mitochondrial respiration UCP-1 in the WAT of mice. Furthermore, the supplementation protected against body weight gain, increased energy expenditure, and improved glucose metabolism (Guo et al., 2019).

Table 2
Effects of taurine in isolation, exercise in isolation, and taurine plus physical exercise.

Authors, year	Sample group	Groups	Sample size	Taurine Dose	Type of exercise	Outcomes found		
						Taurine isolate	Exercise isolate	Taurine + physical exercise
(De Carvalho et al., 2021a)	Obese women (32.3 ± 6.9 years)	Taurine supplementation (n=8) Taurine supplementation + exercise (n=8)	16	3.0 g	8-Weeks combined exercise training 3 times/week, for 55 min/day.	Decreased interleukin−6; Reduction in adipocyte size; Increased connective tissue and multilocular droplets in scWAT.	-	Increased anti-inflammatory interleukins (IL−15 and IL−10); Reduced IL−1β gene expression in the scWAT; Reduction in adipocyte size; Increased amount of connective tissue and multilocular droplets in scWAT.
(Chupel et al., 2018)	Older women (83.6 ± 6.9 years)	Combined exercise training (n=13) Taurine supplementation (n=12) Exercise training/ taurine (n=11) Group control (n = 12)	48	1.5 g	14-weeks combined exercise training 2 times/week.	Increased neuron specific enolase levels Decreased the IL−1β/ IL−1 ratio.	-Reduced TNF-α, IL−6, and IL−1β/ IL−1ra, IL−6/ IL10, and TNF-α/IL−10 ratios	Increased the mini mental state examination score.
(Masouleh et al., 2021)	Women with Type 2 Diabetes (53 ± 5 years)	TRX suspension training + placebo (n=10) TRX suspension training + taurine supplementation (n=10) Taurine supplementation (n=10) Group control (n=10).	40	2.5 g	8-weeks resistance exercise suspension training, 3 times/week, for 60 min/day.	-	-	Decreased HbA1c, HOMA-IR, insulin, TG, and TC; - Increased HDL; - Declined BFP.
(De Carvalho et al., 2021b)	Obese women (32.9 ± 6.3 years)	Taurine supplementation group (n=8) Exercise group (n=8) Taurine supplementation + exercise group (n=8)	24	3 g	8-weeks combined exercise training 3 times/week, for 55 min/day.	Increased expression of fat oxidation genes (*ACO2 and ACOX1*)	Increased resting energy expenditure rate; Decreased respiratory quotient; Increased lipid oxidation and improved scWAT mitochondrial respiratory capacity. Increased expression of fat oxidation genes (*ACO2 and ACOX1*)	Increased resting energy expenditure rate; Decreased respiratory quotient; Incresead of fat oxidation genes (*PPARa, PPARγ, LPL, ACO1, ACO2, HSL, ACOX1, and CD36*); Higher expression of mitochondrial activity genes (*CIDEA, PGC1a, PRDM16, UCP1, and UCP2*); Improved scWAT mitochondrial respiratory capacity.
(Batitucci et al., 2019)	Obese women (36.6 ± 6.4 years)	Exercised and supplemented with placebo (n=14) Exercised and supplemented with taurine (n=8)	22	3 g	8-weeks of high intensity physical training, Deep water running, 3 times/week, for 50 min/day.	-	Increased resting metabolic rate	Increased Resting metabolic rate; Higher plasma concentrations of irisin.
(Chupel et al., 2021)	Older women (83.6 ± 6.9 years)	Exercise training (n=13) Taurine supplementation (n=12) Exercise training and taurine (n=11) Group control (n=12)	48	1.5 g	14-weeks combined exercise training 2 times/week.	Decreased MPO and MMP 9; Decreased lymphocytes.	-	Improvements in physical fitness (better agility and anaerobic capacity)

Note: Subcutaneous white adipose tissue (scWAT); Interleukin-15 (IL-15); Interleukin-10 (IL-10); Interleukin-1β (IL-1beta); Interleukin-1β / Interleukin-1 ratio (IL-1β/ IL-1 ratio); Tumor necrosis factor (TNF-α); Interleukin-6 (IL-6); Interleukin-1β / Antagonist of receptor of interleukin 1 ratio (IL-1β/IL-1ra); Interleukin-6 / Interleukin-10 ratio (IL-6/IL10); Tumor necrosis fator / Interleukin-10 ratio (TNF-α/IL-10). Total body resistance exercise (TRX); Hemoglobin A1c (HbA1c); Insulin resistance (HOMA-IR); Triglyceride (TG); Total cholesterol (TC); High-density lipoprotein (HDL); Body fat percentage (BFP); Myeloperoxidase (MPO); matrix metalloproteinase-9 (MMP-9).

However, it is important to highlight that these outcomes do not reflect aging conditions and were only observed in animal models. In humans, promising effects of taurine supplementation were only reported when combined with physical exercise. Our group of researchers observed that this combination improves energy metabolism, mitochondrial activity, and lipid oxidation in adult women with obesity (De Carvalho et al., 2021b).

It is known that there are still many gaps in the knowledge regarding the role of taurine in adipose tissue, especially in the aging population with sarcobesity, however there is scientific support to encourage and

strengthen future hypotheses regarding the relevance of taurine as a possible target with therapeutic potential.

3.2. Mechanisms of action in skeletal muscle

Muscle loss commonly seen in aging and sarcopenia is a multifactorial process that involves distinct metabolic pathways. AR is a result of low intestinal protein absorption, splenic sequestration of amino acids, reduced responsiveness to anabolic stimuli, and reduced Muscle Protein Synthesis (MPS), depicting the different metabolic signaling recruited (Ahmed et al., 2021; Baliou et al., 2021). There are several factors that contribute to the functional imbalance of skeletal muscle in sarcobesity. Among them, unbridled driving catabolic processes throughout aging (i.e., exacerbated production of ROS), muscle mitochondrial dysfunction, systemic inflammation, and a reduction in anabolic hormones, such as Insulin-like Growth Factor 1 (IGF-1), testosterone, and estrogen. This process is similar to that of adipose tissue due to the cross-talk between the changes in metabolism of sarcobesity and peripheral tissues in older adults (Kalyani et al., 2014).

Studies investigating taurine supplementation have demonstrated the potential benefit of this substance in various metabolic pathways involved in SO in animals (Barbiera et al., 2022) and in vitro (Barbiera et al., 2020). Taurine can reduce muscle catabolism (Li et al., 2012; Doss et al., 2022) and directly and indirectly help in reducing muscle loss, which is strongly associated with SO in advanced age. Thus, taurine may represent a potential non-pharmacological therapeutic target in promoting muscular health (Surai et al., 2021).

SO in aging aggravates oxidative stress and can lead to cellular damage, further contributing to impairments in muscle function. It is in this context that taurine supplementation appears to be a potential antioxidant agent in the biological progression of aging (Abud et al., 2022), as it has the potential to improve redox balance by acting on the body's antioxidant system (Surai et al., 2021). Directly, taurine can donate electrons and act as a chelator of transition metals such as copper and iron, which are responsible for the heightened production of free radicals. Therefore, taurine prevents the excessive production of ROS and neutralizes Reactive Nitrogen Species (RNS), preserving natural antioxidant defenses (Seidel et al., 2019). Indirectly, taurine modulates antioxidant enzymes, including SOD, Catalase (CAT), and Glutathione Peroxidase (GPx), by increasing the expression and plasma concentration of these enzymes (Abud et al., 2022; Seidel et al., 2019). On the other hand, taurine can modulate the activity of oxidant enzymes, such as Malondialdehyde (MDA) and 8-hydroxy-2′-deoxyguanosine (8-OHdG), by regulating the body's antioxidant pathways (Surai et al., 2021; Seidel et al., 2019). In this sense, taurine presents antioxidant properties that are important in protecting muscles against oxidative damage, preventing mitochondrial dysfunction, catabolism, and muscle weakness (Seidel et al., 2019).

The pivotal role that taurine plays in maintaining mitochondrial function, crucial for energy production and tissue functionality, is clearly elucidated. The linked mechanisms in these processes are associated with regulating mitochondrial membrane potential, and mitochondrial fission and fusion, and increased oxidative phosphorylation, biogenesis, and mitochondrial morphology (Jong et al., 2021). These signaling pathways align with increased expression of genes involved in energy metabolism and mitochondrial biogenesis, such as PGC1-alpha, which is modulated by taurine's action (Jong et al., 2021). In this context, ensuring the structural and functional maintenance of mitochondria is essential in conditions of sarcobesity, and taurine supplementation has been shown to participate in these processes (Jong et al., 2021). Previous review studies demonstrated that taurine has intracellular actions through transporters, facilitating its entry into the mitochondria, such as the taurine mitochondrial transporter (mTauT) (Jong et al., 2021; Wen et al., 2019).

The cellular damage inherent in the coexisting conditions of sarcopenia and obesity in aging is also closely linked to the subclinical inflammatory process that can exacerbate harmful catabolic mechanisms. In this sense, taurine can modulate systemic inflammation through the Nuclear Factor Erythroid 2-Related Factor 2 (Nrf2) and Serine/threonine protein kinase (TAK1) / Mitogen activated protein kinases (MAPK) pathways, reducing pro-inflammatory cytokines, including IL-6, CRP, TNF-α, and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) oxidase. In addition, taurine supplementation increases anti-inflammatory cytokines, including IL-10 and Transforming Growth Factor beta (TGF-β) (Li et al., 2022) and can suppress the NF-kB signaling pathway. The NF-kB is a nuclear transcription factor that regulates the expression of various pro-inflammatory genes and is involved in muscular catabolism by stimulating the expression of Atrogin-1 and Muscle Ring Finger 1 (MuRF-1) (Qaradakhi et al., 2020; Doss et al., 2022). In animal models, taurine was also able to inhibit the MAPK-dependent pathway, involved in the production of pro-inflammatory cytokines and the inflammasome (Doss et al., 2022).

The fact is that the inflammatory signaling cascade, when activated, triggers impairments in MPS, and studies have demonstrated the mechanistic and metabolic relevance of taurine in mitigating these deleterious responses. Taurine accomplishes this by modulating intracellular muscle signaling pathways, including mammalian target of rapamycin (mTOR), Phosphoinositide 3-Kinase (PI3K)/ Protein Kinase B (AKT), MAPK, Myogenic Regulatory Factor (MyoD), and Myocyte Enhancer Factor-2 (MEF2), which regulate MPS signaling. Additionally, taurine contributes to the regulation of calcium channels and stabilization of cell membranes, thereby mitigating Muscle Protein Degradation (MPD) and attenuating processes of muscle atrophy (Barbiera et al., 2020). However, these outcomes on the beneficial effects of taurine on muscle restoration were demonstrated in animal in vitro models, while in humans, the results are still limited and poorly understood.

Regarding the role of taurine in regulating intramuscular calcium homeostasis, taurine is involved in activating calcium channel transporters, which are essential for maintaining osmotic balance, muscle contraction, and relaxation. These functions are crucial in protecting the muscle from damage caused by either an excess or a deficiency of intracellular calcium (Seidel et al., 2019). Taurine enhances the activity of the sarcoplasmic reticulum Ca2+ ATPase (SERCA), responsible for calcium reuptake into the sarcoplasmic reticulum during muscle relaxation. Furthermore, it increases the activity of the Ryanodine Receptor (RyR), which releases calcium during muscle contractions (Seidel et al., 2019; Wen et al., 2019). This occurs because taurine modulates muscular chloride and potassium ion channels, guarantees the maintenance of cellular action potential, prevents muscle depolarization, and ensures proper functionality of skeletal muscle (Seidel et al., 2019).

Furthermore, the ubiquitin-proteasome system involved in the degradation of misfolded proteins may play a role in Disuse Muscle Atrophy (DPM). Taurine has been associated with regulating this system by controlling the expression of genes involved in this signaling pathway. This regulation enhances the efficiency of muscle cell homeostasis and safeguards skeletal muscle from degradation processes (Seidel et al., 2019; Barbiera et al., 2022).

Chronic low-grade inflammation negatively impacts the MPS process and also involves impairments in glucose uptake and IR. These are commonly observed in the AR of SO in advanced age (Wang et al., 2020). Therefore, reversing the pathway that leads to muscular AR through avenues capable of blocking IR is fundamental for muscular health. In this sense, taurine supplementation appears to play a leading role in this scenario (Inam-U-Llah et al., 2018). Additionally, activation of Adenosine5'-Monophosphate (AMP)-Activated Protein Kinase (AMPK), an intracellular sensor for energy and mitochondrial homeostasis, largely to activate glucose and fatty acid uptake and oxidation when cellular energy is low, also appears to be mediated by the action of intracellular taurine, contributing to better insulin signaling and glucose uptake (Wen et al., 2019). Borck et al., 2018 demonstrated, in a clinical trial with animals, that supplementation with 5 % taurine diluted in drinking water for 12 months appears to have led to greater activation of

AMPK, with an increase in the AMPK content in the gastrocnemius muscle, while the total content of AMPK reduced compared to the control group. Furthermore, an improvement in insulin sensitivity was demonstrated in the taurine-supplemented group (Borck et al., 2018). However, the magnitude of these effects in humans has not yet been clarified, which strongly reinforces the need for clinical trials in this field of knowledge.

In summary, compromised mitochondrial biogenesis and oxidative capacity lead to the progressive accumulation of ROS and this damage contributes to cellular aging and senescence in skeletal muscle (Kauppila et al., 2017; Singh et al., 2023). In this sense, taurine supplementation can minimize these effects, as evidenced by Singh et al. (Singh et al., 2023), who observed less accumulation of ROS in mitochondria isolated from skeletal muscle after taurine treatment in middle-aged mice.

The present review encourages the importance of exploring the multifactorial capabilities of taurine supplementation in skeletal muscle in well-controlled trials with individuals with SO. In this way, it will be possible to expand scientific contributions regarding the key role that taurine may have in counteracting metabolic alterations resulting from aging. Given the emerging needs of global public health, it is important to investigate the effects by which taurine mechanisms could be considered a potential non-drug therapeutic strategy in the future.

Fig. 1 summarizes the physiological mechanisms through which taurine supplementation could enhance muscle and adipose tissue functionality, contributing to healthy aging.

4. Aging and gut permeability: modulation of gut microbiota as a therapeutic strategy in sarcobesity

The complex processes of age-related diseases are aggravated by sarcobesity, a multifaceted condition, endorsed by crucial changes in the gut microbiota that inevitably occur with aging, and the expected imbalance in general health. The gut microbiota is reciprocally related to age, which means that the factors that determine aging, such as genetics, epigenetics, behavior, and lifestyle, are also conditioned by changes in the gut microbiota (Ghosh et al., 2022). It is in this approach that the gut microbiota has been considered as a potential metabolic biomarker of the host (Nagpal et al., 2018), since chronological age is accompanied by changes in host-microorganism homeostasis. Dysbiosis is an additional hallmark of old age (O'Toole and Jeffery, 2015; Bana and Cabreiro, 2019; Ticinesi et al., 2020), accentuated even more by the coexistence of obesity and other metabolic disorders, as has already been well elucidated (Turnbaugh et al., 2006; Fan and Pedersen, 2021). However, there is still much to be explored and clarified about the metabolic enigma of sarcobesity in aging.

Functional and structural dysregulation of the microbiota due to loss of integrity and increased permeability of the intestinal epithelium are interlinked with the aging process and inflammation, characterizing the gut microbiota of older adults by taxonomic signatures that are potentially inflammatory and inversely related to longevity (Bana and Cabreiro, 2019; Ticinesi et al., 2023). This means that tight-junction proteins can undergo ruptures that signal mechanisms of metabolic endotoxemia, characterized by the activation of Toll Like Receptor-4 (TLR-4) receptors and translocation of lipopolysaccharides (LPS) present in the outer membrane of gram-negative bacteria, favoring systemic inflammation and compromising the host's normal immune response (Cani and Jordan, 2018).

Older individuals have a gut microbiota that differs from young adults without chronic diseases (O'Toole and Jeffery, 2015). Overall, microbial diversity decreases with age, along with a reduction in Short-Chain Fatty Acid (SCFA)-producing species, particularly butyrate (Biagi et al., 2010). SCFAs are one of the main metabolites produced by the gut microbiota and have demonstrated important effects on metabolic health by circulating systemically to peripheral tissues, such as adipose, muscle, liver, and brain tissue, acting as potential signaling molecules by binding to G-protein coupled receptor 41 (GPR41) and G-protein coupled receptor 43 (GPR43), expressed both in the intestinal epithelium and in these peripheral tissues (Tilg and Kaser, 2011; Canfora et al., 2015; Plaza-Diaz et al., 2019).

Additionally, it is also well established that a diet typically rich in fiber increases the SCFA content in the bloodstream and mobilizes groups of intestinal bacteria with symbiotic and anti-inflammatory potential that signal the production of intestinal hormones, such as Peptide YY (PYY) and Glucagon-Like Peptide 1 (GLP-1), which communicate with neurotransmitters that control hunger and satiety mechanisms, which are important for management in conditions of obesity (Canfora et al., 2015; Agus et al., 2021)

Deciphering changes in the gut microbiota in aging is even more complex in conditions of sarcobesity, not merely as a result of chronological aging, but also because the microbiota is intrinsically resilient

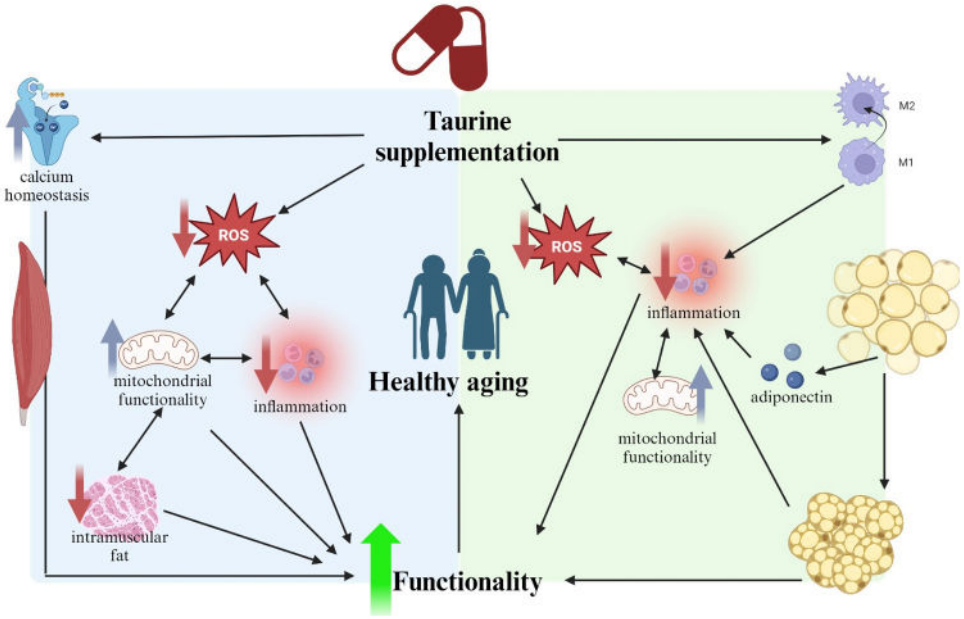

Fig. 1. Summary chart of the effects of taurine supplementation on skeletal muscle (left) and adipose tissue (right), contributing to the recovery of functionality in both tissues and promoting healthy aging. Created with Biorender.

and dynamic, as external conditions such as lifestyle, eating habits, general health status, and medication, can impact the phylogenetic community of bacteria (An et al., 2018; Ghosh et al., 2022). Therefore, advances in metagenomics and metabolomics can provide greater understanding regarding the triggers, or protection against diseases, mediated by the gut microbiota, as well as contributing to understanding of the synthesis of metabolites and metabolic pathways capable of deciphering the intestinal functional, genomic, and taxonomic profile, techniques that assist in the complete mapping of the gut microbiota and, possibly, in the development of personalized therapies (Mainardi et al., 2018; González Olmo et al., 2021).

Furthermore, other biomarkers and external factors also strongly influence aging and modulation of the gut microbiota. This can influence the modification of histones, such as Sirtuin-1 (SIRT-1), a protein that plays a role in regulating inflammation of the intestinal epithelium and longevity (Wellman et al., 2017). In addition, telomeres play an important role in genomic maintenance and their length is considered a biomarker of biological aging and DNA damage (Cheng et al., 2021). Telomeres are located at the ends of eukaryotic chromosomes and have sequences of a protein complex that leads to chromosomal stability (Zhang et al., 2016). Telomere length is related to longevity, while shortened telomeres are directly related to cellular senescence and increased inflammation (López-Otín et al., 2013). However, while there is a direct link between telomere attrition and aging, the role of the gut microbiota in mediating these effects has yet to be demonstrated. Evidence suggests that both obesity and a typically Western diet can exacerbate telomere shortening (Valdes et al., 2005) and it is in this sense that the gut microbiota may indirectly influence telomeres and longevity.

The transition from a natural diet to typically industrialized eating patterns has led to drastic changes in the gut microbiota, exacerbating inflammatory mechanisms. So-called "*junk food*" has gained prominence in the scientific community, particularly in the area of microbiota. Longer telomeres were found in participants who had a more anti-inflammatory diet, assessed in a population at a high risk of cardiovascular disease (García-Calzón et al., 2015; Ojeda-Rodríguez et al., 2020), however, the relationship between these outcomes and the gut microbiota is still unknown.

From a therapeutic perspective, physical exercise has been proposed as a strategy capable of positively modulating the gut microbiota, raising species that synthesize SCFA, and through anti-inflammatory effects seems to activate mechanisms that help the integrity of the intestinal epithelium (Bermon et al., 2015; Y. Liu et al., 2020), in addition to providing protection against telomere shortening (Brandao et al., 2020). The trilateral interaction between gut microbiota, telomere shortening, and inflammation in aging is still an obscure field, but it is plausible to think of the crosstalk that exists between a dysbiotic microbiota resulting from aging and obesity, under the strong influence of a categorically inflammatory diet, which may drive telomere shortening through an increase in ROS and dysfunctional mitochondria, increasing the risk of a poor prognosis for sarcobesity with worsening associated complications (Assis et al., 2022).

In sarcobesity in older adults, the composition and functionality of the gut microbiota face complex changes. Increased inter-individual variability in composition, reduced biodiversity, and overgrowth of pathobionts are signatures of the microbiota in these conditions (O'Toole and Jeffery, 2015; Zhang et al., 2023). The gut-muscle interface reinforces the idea that changes in the composition and diversity of the gut microbiota directly influence host physiology, regulating anabolic balance, influencing protein homeostasis (Nay et al., 2019), and the systemic availability of amino acids, as well as mediating age-related AR (Neis et al., 2015; Ticinesi et al., 2019; Mancin et al., 2023).

The use of different amino acids from dietary protein sources or endogenous synthesis relies on the participation of the gut microbiota, which can modulate the processes of muscle protein synthesis and degradation (Neis et al., 2015). In addition, it is also recognized that excess protein from food can alter the bacterial metabolism aimed at the degradation and fermentation of amino acids in a more accentuated way (Picca et al., 2019).

The gut-muscle axis is decisive in understanding the processes involving the loss of microbial diversity in aging, specifically the decrease in butyrate-producing bacteria, accompanied by the prevalence of pathobionts such as Enterobacteriaceae, and the existing dialogue with muscle atrophy and increased fragility in older adults (Jackson et al., 2016; Picca et al., 2019). This means that changes in muscle metabolism, to the detriment of dysbiosis, are influenced by the decline in SCFA-producing bacteria, intimidating anabolic signals and enhancing mitochondrial dysfunction, impairing glucose uptake in skeletal muscle and potentially favoring intramuscular fat deposits (Walsh et al., 2015; Lahiri et al., 2019).

Collectively, the processes outlined so far reinforce the importance of modulating the gut microbiota in order to mitigate metabolic endotoxemia, the production of undesirable metabolites, and susceptible taxonomic alterations in aging and obesity, improving the gut-muscle interface in sarcobesity. However, despite the versatility and resilience of the human gut microbiome, designing microbiome-based interventions in sarcobesity still holds great promise, as the responsiveness of the gut ecosystem to therapeutic modulation is largely unclear, especially in older adults (Ghosh et al., 2022). Personalized therapeutic strategies for rebuilding the microbiome of older adults have been proposed, aimed at identifying the phenotypic interactions of the host, the microbiota, and the overall response to a given intervention (Ghosh et al., 2022).

In this context, interventions have included the use of probiotics, especially *Lactobacillus, Bifidobacterium, and Faecalibacterium*, prebiotics, synbiotics, postbiotics, such as butyrate, and Mediterranean-type dietary modulation, which can culminate in an increase in the abundance of potentially beneficial taxons (Liao et al., 2020; Ghosh et al., 2020; Meslier et al., 2020; Chen et al., 2022; C.C. Lee et al., 2021; M.C. Lee et al., 2021; Ghosh et al., 2022). In addition, phenolic compounds appear to exert protective effects on muscle cells in conditions of sarcopenia, but these effects are dependent on the composition of the gut microbiota and may affect the bioavailability of dietary polyphenols (Cortés-Martín et al., 2020; Bagherniya et al., 2022). Furthermore, the analysis of three independent cohorts revealed that the decline in the *Bacteroides* genus emerged as one of the main characteristics of healthy aging (Wilmanski et al., 2021), as well as the important increased abundance of *Akkermansia muciniphila* (O'Toole and Jeffery, 2015; Ragonnaud and Biragyn, 2021). Considering physical exercise as an important component in the modulation of the gut microbiota, in the therapeutic aid of anabolic resistance and as a behavioral change that aids weight loss in obese conditions, has also been crucial in the management of sarcobesity at the existing interface with the gut microbiota (Burtscher et al., 2022).

Science supports the role of physical exercise as a behavioral component that can drive qualitative and quantitative alterations in the composition and function of the gut microbiota, benefiting the host. However, prudent and cautious choices need to be made regarding the type of exercise, considering that the modulation of the gut microbiota exerted by exercise is dependent on the physiological state of the individual, varying between athletes, lean sedentary subjects, or those with obesity (Mohr et al., 2020). It has already been shown that exhausting exercise promotes a more permeable intestinal epithelium and susceptibility to metabolic endotoxemia (Clark and Mach, 2016), while moderate exercise can protect the intestine from these effects, being less deleterious to the microbiota (Zuhl et al., 2014).

Furthermore, considering that along with advancing age there are changes in intestinal transit time (Harari et al., 1996), which together alter the composition of the microbiota, when not prolonged, moderate intensity exercise seems to confer advantages by speeding up digestive transit (Motiani et al., 2019). The recent review by Mohr et al., 2020

summarizes the advantages and disadvantages of different categories of physical exercise on the gut microbiota of individuals with different nutritional status, elucidating the potential damage that prolonged excessive exercise can have on the composition and function of the microbiota and intestinal permeability, deleterious effects that are much less pronounced in sedentary subjects.

Controlling environmental influences, including diet, exercise, multimorbidity, and excess medication, in aging in sarcobesity conditions, is relevant to designing well-targeted clinical trials and scientifically advancing the possible causal relationships between microbiota and advancing age, so that therapeutic strategies can actually corroborate the management of gut microbiota in aging.

Fig. 2 summarizes the impact of sarcobesity and the associated lifestyle on the gut microbiota, demonstrating the role that the microbiota plays as a potential metabolic biomarker of the host in aging.

5. Physical exercise as a therapeutic strategy in sarcobesity

Physical inactivity and sedentary behavior are particularly high in older adults, presenting global public health challenges (Dogra et al., 2022). The causes of physical inactivity and a sedentary lifestyle among older adults are multifaceted, and include environmental, demographic, and socioeconomic factors, and physical and cognitive limitations or health conditions that hinder exercise participation (Evenson et al., 2012; Ding et al., 2012). Furthermore, the reduction in time spent in social interactions and active behavior is also responsible for the increase in sedentary behavior (Perissinotto et al., 2012). Promising strategies, such as physical exercise, have been widely employed as a potentially effective therapy to prevent and treat obesity, as well as to improve muscle mass and functionality, and the literature discusses its applicability as an efficient treatment in the condition of SO

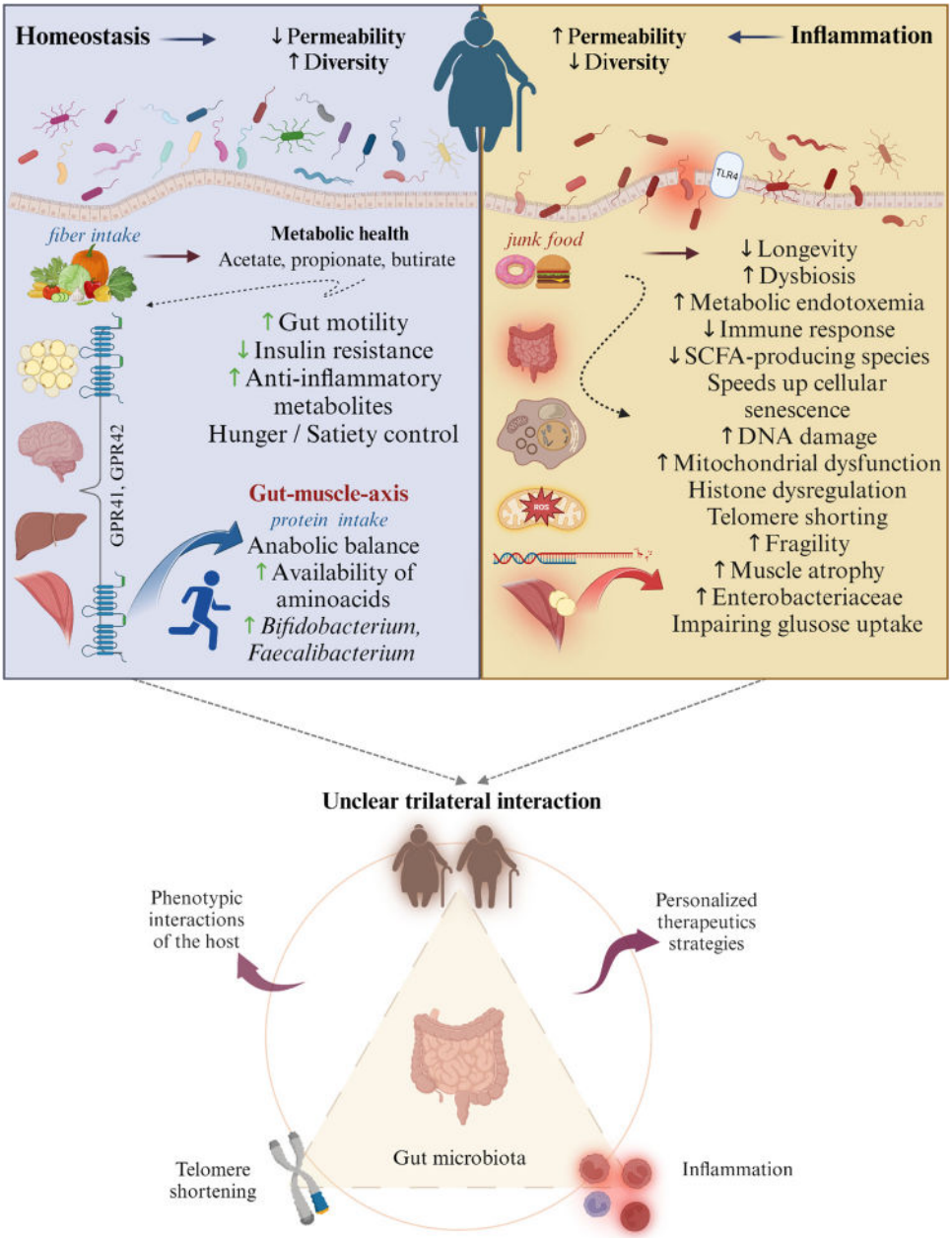

Fig. 2. Impact of sarcobesity on the gut microbiota, strongly influenced by typically western dietary patterns that can have deleterious repercussions on peripheral tissue machinery in a systemic way. In addition, homeostatic conditions of the gut microbiota are characterized by the production of potentially beneficial metabolites, and a preserved gut-muscle axis, conferring metabolic health for healthy aging. Created with Biorender.

(Trouwborst et al., 2018).

According to the American College of Sports Medicine, the recommendation for physical exercise for individuals over 65 years of age should involve different fitness capacities, such as aerobic exercises, muscle strengthening, balance, and flexibility (Chodzko-Zajko et al., 2009), ensuring improvement in physical and aerobic capabilities, and body composition, particularly the increase in lean muscle mass (Distefano and Goodpaster, 2018). This approach contributes to reducing the risk of premature mortality and morbidity, improved quality of life, and better management of chronic disease (Dogra et al., 2022).

Strength exercises with control of variables of intensity, strength, rest time, and correct execution of the movement improve strength and muscle anabolism in individuals with obesity, and long-term aerobic exercise favors improvements in aerobic capacity (Silva and Farinatti, 2007; Aksović et al., 2020; Grgic et al., 2020). Among older adults who meet the guidelines for aerobic activity, participating in any strength training is associated with better balance, mobility, body composition, perceived health, and healthy aging (Copeland et al., 2019).

Strength exercise is highly recommended in the sarcobesity condition, as it promotes mTOR signaling, and thus greater activation of satellite cells. This leads to an increase in protein synthesis and a reduction in muscle catabolism, and, consequently, to an increase in muscle mass, which is directly related to the improvement in functional aspects, such as balance, strength, and a reduced risk of falling (Johnston et al., 2008; de Oliveira Silva et al., 2018). Therefore, the greater the number of muscle groups worked per session at high intensity, the better the observed strength results (Yoo et al., 2018). Furthermore, training promotes improved neural function, with greater activation of motor units and, consequently, greater muscle activation (Aguirre and Villareal, 2015; Consitt et al., 2019; Colleluori and Villareal, 2021).

The training protocol indicated for increasing muscle strength should be performed with a load of between 60 % and 85 % of one maximum repetition (RM), 3–4 sets of 15 repetitions (Mayer et al., 2011; Aguirre and Villareal, 2015; Izquierdo et al., 2021). To increase strength, training must be carried out at high intensity, however it needs to be aligned with the physical, motor, and functional capacity of the individual with SO. This care is important, since strength exercises present greater risks of muscle and joint damage, whether due to excessive load or poor execution. These injuries can cause an acute reduction in strength and function, leading the older adult to abandon physical exercise (Yoo et al., 2018; Peterson et al., 2010; Mayer et al., 2011; Orssatto et al., 2018).

Aerobic training is also highly recommended for older adults with sarcobesity, since it promotes improvement in vascular tone and muscle oxidative capacity, and an anti-inflammatory effect. In addition, aerobic training helps control body composition by reducing body fat, oxidative stress, and insulin resistance (Short et al., 2004; Xiao and Fu, 2015; Erlich et al., 2016; Chen et al., 2017; Batsis and Villareal, 2018; Ramos et al., 2019; Consitt et al., 2019; Aksović et al., 2020; Colleluori and Villareal, 2021; Izquierdo et al., 2021).

In aerobic exercise, both duration and intensity must be controlled to achieve the best results. Lower intensity training is linked to longer duration. Therefore, training sessions of 50' – 60' at 60 % – 90 % of maximum heart rate (HRmax) or 50 % – 85 % maximum oxygen volume (VO2max) are strongly recommended to improve cardiorespiratory function and promote changes in body composition (Sunami et al., 1999; Aksović et al., 2020; Bull et al., 2020). Another aerobic training method widely used to control body composition and improve cardiorespiratory capacity is High-Intensity Interval Training (HIIT). HIIT is characterized by training with intensities ≥90 % VO2max or ≥90–95 % HRmax for 6' to 4' and low-intensity active or passive intervals (Viana et al., 2019; Ballesta-García et al., 2019). Despite the high effectiveness of HIIT for energy expenditure and muscle gain, it is necessary to pay attention to the type of stimulus performed, due to the high risk of muscle and joint damage. Furthermore, additional studies are needed to provide evidence of the safety of the practice for the population with SO (Liu et al., 2022).

Robust evidence has shown the benefits of exercise associated with nutritional interventions, which can play a crucial role in the treatment of SO (Hita-Contreras et al., 2018; Martínez-Amat et al., 2018). Hypocaloric diets may be efficient in reducing body fat (Jensen et al., 2014), but inadequate protein intake can negatively impact protein synthesis, increasing muscle catabolism and impairing the maintenance of lean mass (Schoufour et al., 2021; Prado et al., 2014). Therefore, protein intake of 1.0–1.2 g/kg body weight is strongly recommended in older adults with multimorbidity, to maintain and recover muscle mass and function over the long term, and higher intake (1.2–1.5 g/kg body weight) should be prescribed with caution (Weijs and Wolfe, 2016; Schoufour et al., 2021; Cheah and Cheah, 2023). However, despite evidence demonstrating potentially positive effects regarding the combination of exercise and nutritional interventions, the results remain obscure due to the heterogeneity of the sarcopenia criteria and the characteristics of physical training, which represent some of the limiting factors (Martínez-Amat et al., 2018).

In view of the above, the need to practice physical exercise becomes evident, both strength exercise with adequate intensities for muscle gain, and strength and aerobic exercise with adequate duration and intensity, in order to guarantee improvement in cardiorespiratory capacity and body composition. In this sense, both exercise protocols must be performed safely. It is important to highlight that physical exercise needs to be associated with nutritional strategies for clinical improvement in SO, since adequate protein intake favors the gain and maintenance of muscle, triggering a reduction in the losses caused by SO.

Aging promotes alterations in body composition, such as the redistribution of muscle mass and fat mass, bone reduction, and increased adiposity, in addition to a greater risk for other chronic diseases (Siervo et al., 2016; Bray et al., 2017; Batsis and Villareal, 2018; Blüher, 2019). In this sense, lifestyle interventions for older individuals with obesity, with or without sarcopenia, that encompass diverse protocols of exercise and nutritional interventions, could contribute to improving quality of life. These interventions may lead to increased muscular functionality, reduced physical frailty, and enhanced autonomy. Such improvements are associated with a greater life expectancy and, consequently, a lower risk for the development of chronic diseases (Mathus-Vliegen, 2012).

Overall, Fig. 3 illustrates the importance of physical, aerobic, and strength exercises in breaking sedentary behavior and the key role that these exercises play in global metabolic health on sarcobesity, particularly in muscle, protein, and glucose metabolism, as well as helping to manage body adiposity and promoting more pronounced physical fitness and quality of life.

Sarcobesity is a concerning and progressive health condition that can impact the older population. Additionally, the lack of consensus on diagnostic criteria is an additional concern, which may result in underestimation or overestimation of sarcobesity. Possible non-pharmacological strategies, such as taurine supplementation, management of gut microbiota, as well as physical exercise incorporated into a non-sedentary lifestyle, appear promising. However, knowledge gaps related to these strategies still remain obscure.

Overall, studies have shown that taurine supplementation appears to reduce the synthesis of pro-inflammatory cytokines, modulate lipid metabolism and adipose tissue morphology, and decrease oxidative stress and mitochondrial dysfunction. These potential benefits interact with the gut microbiota, which is intrinsically affected by aging and aggravated by the coexistence of sarcobesity. However, when modulated, the microbiota seems to provide protection against DNA damage and telomere shortening, as well as improvements in dysbiosis through more diverse microbial enrichment, and a less permeable intestinal epithelium, combinations that can provide a more functional and healthy gut-muscle axis.

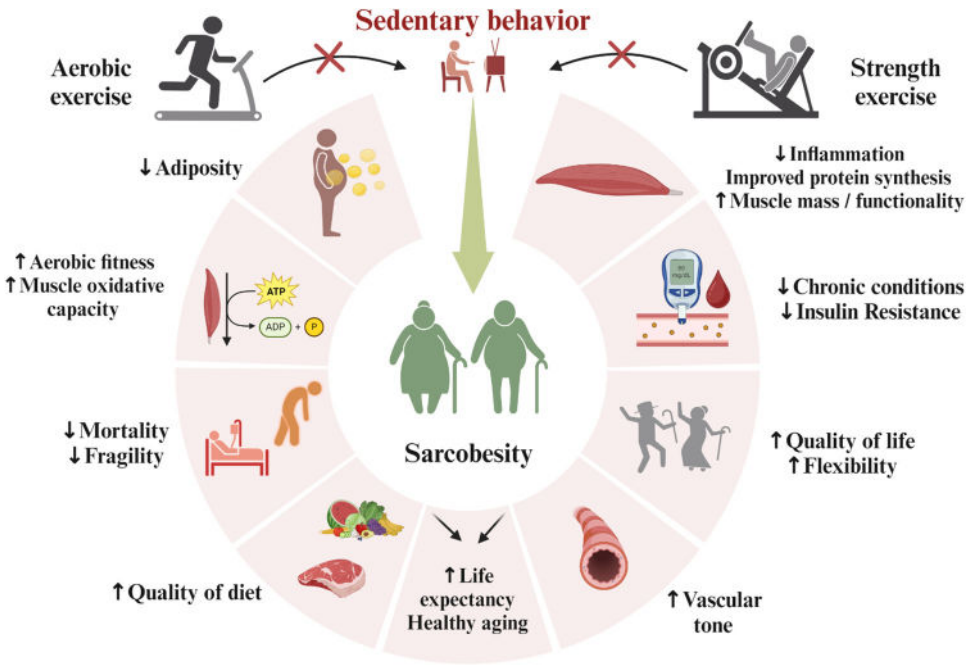

Fig. 3. Breaking the sedentary behavior pattern typically seen in advanced age in sarcobesity, with aerobic and strength physical exercise, demonstrating that physical exercise is a relevant therapy, capable of mitigating the deleterious effects of sarcobesity, opening promising ways for behavioral, metabolic, and global alterations for minimally healthy aging. Created with Biorender.

6. Future perspectives

This review addresses a topical issue that still requires major advances in knowledge in view of the emerging need for truly effective therapeutic perspectives capable of preventing and treating sarcobesity. Herein, we encourage the search for more clinical and experimental trials that can contribute to the lack of understanding of the problem discussed and, in particular, we focus on potential therapeutic approaches, such as taurine supplementation, which acts on adipose and muscle tissue, in the modulation of the intestinal microbiota, intrinsically related to the dietary pattern, longevity, and microbial metabolites that interact systemically with the senescence process in aging, as well as aerobic and resistance exercise, two classics that effectively modulate the individual's lifestyle and offer metabolic and molecular benefits to anabolic resistance, inflammation, and the prevention of chronic metabolic disorders.

Considering that there is still much to be explored and clarified about the metabolic enigma of sarcobesity in aging, it is relevant to value the advances in metagenomics and metabolomics, that can offer important approaches to understanding regarding the triggers or protection against diseases mediated by the gut microbiota. In addition, this knowledge can contribute to the understanding of the synthesis of metabolites and metabolic pathways capable of deciphering the microbial functional, genomic, and taxonomic profile, techniques that assist in the complete mapping of the gut microbiota and in the development of personalized therapies in sarcobesity. Interventions based on the microbiome in sarcobesity remain very promising, since the ability by which the intestinal ecosystem responds to therapeutic modulation, including the use of probiotics, prebiotics, and future components based on the SCFA-producing microbiota, such as butyrate and other potentially beneficial bacteria, for example *Akkermansia muciniphila*, is still largely obscure, with predominantly inconclusive clinical outcomes and scarce studies in older adults. Furthermore, although the mechanisms by which taurine supplementation could be a potential non-pharmacological therapeutic have been widely discussed, it is not yet a strategy with clinical viability, justified by the shortcomings in knowledge of the exact doses, adequate clinical management, well understood and established mechanisms, and the need for well-controlled trials able to clarify the use of taurine supplementation in sarcobesity. In this perspective, we encourage scientific advancement in this field of research, as it appears to be promising within the perspective of personalized therapies in the management of sarcobesity and its complex clinical implications.

The incessant struggle for public policies that are truly interested in mitigating the dramatic reality of public health worldwide in the face of the inability to slow down the advance of obesity in old age, aggravated by sarcopenia, is still an urgent priority. This path will make it possible to; plan educational approaches involving socioeconomic, cultural, social, demographic, and ethnic principles, that can help to reduce sedentary behavior in the long term, understand the deleterious impacts of physical inactivity, make lasting changes towards a non-sedentary lifestyle and more nutritious eating patterns that are less condensed in terms of the palatability junk food, and finally, highlight how necessary and precisely important it is to disseminate scientific information to society in proper and accessible language.

Obesity is known to be one of the world's most serious public health problems, but this scenario is aggravated by the coexistence of sarcopenia and serious future actions are needed to encourage and motivate the elderly population to exercise regularly. The perspectives discussed here could pave the way for more effective and personalized therapeutic interventions, for a promising scientific advance in this field of knowledge.

7. Conclusions

Finally, we suggest that research and public health initiatives on active aging should focus on the importance of knowing and clarifying the fundamental role of using possible non-pharmacological tools in the context of obesity linked to sarcopenia, with the aim of providing a greater breadth that is less constrained by a focus on the prevention and management of particular chronic diseases. This broader, multidisciplinary approach and its major components should allow for the creation of more inclusive and relevant research outputs and public health messages that facilitate active aging, based on improvements in quality of life and effective management of sarcobesity.

Author contributions

GB: Conceptualization, Writing - Original Draft and Review & Editing final version. **GFA:** Writing - Review & Editing final version. **GUO:** Writing - Review & Editing final version. **LFB:** Writing - Review & Editing. **SGT:** Writing - Review & Editing final version. **MCLV:** Writing - Review & Editing. **ACRV:** Writing - Review & Editing final version. **ECF:** Supervision.

Funding

This research was funded by Fundação de Amparo à Pesquisa do Estado de São Paulo (Fapesp), grant numbers 2019/17947–7, 2019/11820–5, 2022/15078–4, 2022/00221–6, 2022/06638–6, 2023/09554–0, 2023/01611–5, 2024/01271-2 and National Council for Scientific and Technological Development, CNPq number 303766/2022–0.

Declaration of Competing Interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

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