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Insights into Sarcopenic Obesity Mechanisms: A Focus on Bidirectional Adipose-Muscle Interactions

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Abstract: Sarcopenic obesity (SO) is a major health issue in aging societies, and its prevalence continues to rise with the global aging process. Compared with sarcopenia or obesity alone, SO is associated with aggravated metabolic disorders and a significantly elevated risk of adverse outcomes. Traditional studies have mostly investigated sarcopenia and obesity as independent pathological conditions; however, recent evidence has revealed a close bidirectional regulatory network between adipose tissue and skeletal muscle, and the imbalance in their crosstalk constitutes the core pathological basis for the occurrence and progression of SO. From the perspective of adipose-skeletal muscle crosstalk, this paper systematically reviews the conceptual framework and bidirectional signaling network in this field, aiming to break through traditional research paradigms and provide an integrated theoretical framework for optimizing diagnostic criteria, identifying biomarkers, and developing precise intervention strategies.

Keywords: sarcopenic obesity, adipo-muscular axis, adipokines, myokines

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1. Introduction

The global population is aging at an unprecedented rate. Population aging has become a major global social transformation in the 21st century, profoundly affecting the economic structures, social security systems and public health policies of countries around the world[1]. The core characteristic of this phenomenon is the continuous increase in the proportion of the elderly population (generally defined as those aged 60 or 65 years and above) in the total population, accompanied by declining fertility rates and prolonged life expectancy[2]. Countries around the globe, from China to Greece and from Japan to Poland, are undergoing this structural shift and facing multiple challenges and opportunities brought about by it[3-6]. Taking Asia as an example, China, the world's most populous country, is experiencing an unprecedented process of population aging. From 2015 to 2050, China has undergone remarkable demographic structural changes, including increased life expectancy and declining fertility rates, which have directly led to population aging[2]. China's population aged 60 and over is projected to account for 40% of the total population by the middle of this century, marking its entry into a "super-aged society"[7]. Similarly, 27.4% of Japan's total population is aged 65 and above, and its overall population has been declining continuously since 2006[6].

With the accelerating process of global population aging, age-related changes in body composition have become an

important issue in public health. Relevant data indicate that population aging and the rising prevalence of obesity show a synchronized increasing trend[8]. As a global noncommunicable disease, obesity has reached pandemic proportions, affecting more than 890 million people, with an additional 2.5 billion adults being overweight[9]. Meanwhile, sarcopenia, an aging syndrome characterized by progressive and widespread loss of skeletal muscle mass and function, has gained increasing clinical significance over the past two decades[10]. When sarcopenia and obesity coexist in the same individual, the condition is defined as sarcopenic obesity (SO), a concept first proposed by Heber in 1996[11].

Diagnosis of SO requires the simultaneous fulfillment of criteria for both obesity and sarcopenia. However, diagnosis remains challenging, as traditional body mass index (BMI) cannot accurately distinguish between adipose and muscle tissue. Among older adults, severe muscle depletion and excess fat mass may occur even with a normal or high BMI[12]. Thus, in 2000, Baumgartner provided the first operational definition of SO, defining the sarcopenic component as appendicular skeletal muscle mass divided by height squared falling more than two standard deviations below the mean of a young healthy reference population[13]. In the subsequent more than two decades, the definition of SO has undergone continuous evolution and debate. In 2022, the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) jointly issued the first international consensus on the definition and diagnostic criteria for SO[14]. The consensus recommends a stepwise "screening–diagnosis–staging" workflow: first, obesity is screened using body mass index (BMI) or waist circumference, and sarcopenia is screened based on risk factors or questionnaires; those with positive screening results undergo further assessment of muscle strength. After confirmed low muscle strength, body composition is evaluated by dual-energy X-ray absorptiometry (DXA) or bioelectrical impedance analysis (BIA), with weight-adjusted skeletal muscle mass and body fat percentage used to define sarcopenia and obesity, respectively. The publication of this consensus marks a critical step toward standardization and comparability in the field of SO research.

In recent years, large-scale population-based meta-analyses have shown that the global prevalence of SO in the elderly population is approximately 7%. However, the reported prevalence varies from 2.1% to 12% due to differences in diagnostic criteria and population characteristics[15]. Of note, SO is not a simple coexistence of sarcopenia and obesity. A growing body of evidence indicates that the combination of these two conditions exerts synergistic adverse health effects. A meta-analysis including nearly 580,000 participants demonstrated that SO was significantly associated with a 2.06-fold increased risk of cardiovascular and cerebrovascular diseases[16]. In the field of oncology, SO has also been confirmed to be closely associated with shortened overall survival (HR = 1.52) and an increased risk of postoperative complications (OR = 2.23) in patients with non-metastatic colorectal cancer[17]. These findings suggest that the health threat posed by SO is far greater than that of sarcopenia or obesity alone. Traditionally, adipose tissue and skeletal muscle have been regarded as functionally relatively independent organs. However, recent studies have revealed that a close bidirectional regulatory network exists between them, forming the so-called " Adipo-Muscular Axis "[9]. Adipose tissue and skeletal muscle are not only organs for energy storage and expenditure, but also active endocrine organs. The adipokines and myokines they secrete form the chemical language for inter-tissue communication, regulating metabolic homeostasis through autocrine, paracrine, and endocrine pathways[18, 19]. Dysregulation of this interactive axis constitutes the core pathological basis of SO: dysfunctional adipose tissue in obesity leads to increased secretion of pro-inflammatory adipokines, free fatty acid spillover, and ectopic lipid deposition, which in turn trigger insulin resistance and mitochondrial damage in skeletal muscle. Conversely, reduced muscle mass and diminished muscle strength lower resting energy expenditure, further exacerbating fat accumulation and forming a vicious cycle[20, 21]. This article aims to systematically review the central role of bidirectional crosstalk between adipose tissue and skeletal muscle in the development and progression of SO, with a focus on the molecular mechanisms mediated by intermuscular adipose tissue, intramuscular adipose tissue, adipokines and myokines, and to discuss the implications of this novel conceptual framework for the identification of SO biomarkers and the development of precise intervention strategies.

2. Anatomical and Functional Basis of Adipose-Skeletal Muscle Crosstalk

Adipose tissue and skeletal muscle are closely adjacent in anatomical structure, and this spatial proximity provides a structural basis for their functional crosstalk. According to anatomical location, adipose tissue is distributed in multiple functionally and metabolically heterogeneous fat depots throughout the body. Among them, those directly associated with skeletal muscle are intermuscular adipose tissue (IMAT) and intramyocellular lipid (IMCL).

IMAT refers to adipose tissue located beneath the muscle fascia and between muscle bundles, constituting a unique anatomical fat depot within the musculoskeletal system[22]. Unlike subcutaneous and visceral adipose tissue, IMAT is adjacent to the epimysium, with adipocytes accumulating in the connective tissue septa between muscle groups. Although IMAT is separated from muscle fibers by fascia, the adipokines and bioactive molecules it secretes can still act on adjacent muscle tissue through paracrine pathways, regulating the local metabolic microenvironment[23]. Several studies have suggested that IMAT may negatively regulate insulin sensitivity and promote insulin resistance by secreting free fatty acids (FFA), inflammatory factors (such as PAI1 and MCP1), and other bioactive molecules[24]. From the perspective of cellular origin, the formation of IMAT is closely associated with the aberrant differentiation of fibro/adipogenic progenitors (FAPs). FAPs are a highly plastic cell population residing in the skeletal muscle interstitium. Under physiological conditions, they interact with muscle satellite cells and immune cells via paracrine signaling, providing a supportive microenvironment for muscle regeneration[25]. However, in the context of aging, obesity and metabolic diseases, the fate of FAPs is regulated by a complex network of multiple factors including the Wnt signaling pathway and PPARγ, thereby leading to the abnormal expansion and accumulation of intermuscular adipose tissue[26].

IMCL is located within muscle fibers and serves as an intramyocellular lipid storage depot. It directly infiltrates the muscle microenvironment and represents the main component of muscular fatty infiltration[27]. Adipocytes within IMCL are in close proximity to muscle fibers without separation by fascia. This high spatial proximity allows IMCL to directly regulate muscle fiber function through dual pathways: physical compression and paracrine signaling. On the one hand, abnormal accumulation of IMCL can disrupt the normal arrangement of muscle fibers and impair the mechanical efficiency of muscle contraction[28, 29]. On the other hand, as an active endocrine tissue, IMCL can secrete a variety of pro-inflammatory adipokines (such as TNF-α and IL-6) and chemokines, which act on adjacent muscle fibers through paracrine pathways, inducing local inflammatory responses and insulin resistance[30, 31]. From the perspective of vascular-muscle crosstalk, abnormal expansion of IMCL can exert mechanical compression on blood vessels running intermuscularly or intramuscularly, increasing vascular resistance and reducing microcirculatory perfusion[32]. This process directly limits the supply of oxygen and metabolic substrates to myocytes, constituting an important vascular mechanism underlying the decline in muscle function. Similar to IMAT, FAPs are also a major source of IMCL. Under pathological conditions, FAPs shift from a functional state that supports muscle regeneration to an adipogenic phenotype, resulting in the accumulation of adipocytes within muscle fibers. Studies by Biltz et al. have confirmed that intramuscular adipose tissue infiltration impairs skeletal muscle contractile function, reduces muscle strength, and exacerbates muscle fibrosis[33].

Traditionally, adipose tissue has been regarded as a passive energy storage organ, and skeletal muscle as an active contractile organ. In recent years, a growing body of research has confirmed that adipose tissue and skeletal muscle are not only central organs for energy storage and expenditure, but also active endocrine organs. Through the secretion of various bioactive factors, they engage in extensive and complex crosstalk, jointly regulating systemic energy metabolism, insulin sensitivity, inflammatory status, and tissue remodeling[34-36]. On this basis, researchers have proposed the conceptual framework of the “Adipo-Muscular Axis” to characterize the bidirectional regulatory network between the two tissues[37]. The core connotations of this axis include: (1) Adipose tissue regulates skeletal muscle protein homeostasis, mitochondrial function, and insulin sensitivity via adipokines, extracellular vesicles, and lipid metabolites; (2) Skeletal muscle reciprocally modulates adipocyte differentiation, thermogenic function, and lipid metabolism through myokines; (3) The integrated effect of their crosstalk maintains systemic energy metabolic homeostasis.

Under physiological conditions, the adipo-muscular axis maintains a dynamic balance: adipose tissue secretes appropriate regulatory signals to ensure energy supply and functional maintenance of skeletal muscle; skeletal muscle

reciprocally modulates the metabolic adaptation of adipose tissue through contractile activity and myokine secretion. However, in the context of obesity, aging and metabolic diseases, this balance is disrupted, leading to a vicious pathological cycle. In obesity, adipose tissue dysfunction results in increased secretion of pro-inflammatory adipokines, free fatty acid spillover, and ectopic lipid deposition[38, 39]. Accumulation of lipid metabolic intermediates (such as ceramides and diacylglycerols) in myocytes disrupts insulin signaling pathways and induces mitochondrial dysfunction, leading to skeletal muscle insulin resistance and enhanced catabolism[40, 41]. Meanwhile, the loss of skeletal muscle mass and decline in muscle strength reduce resting energy expenditure, further exacerbating fat accumulation[42]. The vicious cycle in which fat accumulation and muscle function decline reinforce each other as cause and effect constitutes the core pathological basis of SO.

3. Mechanisms of Adipose Tissue Action on Skeletal Muscle

Adipose tissue is composed of multiple cell types, including adipocytes, fibroblasts, endothelial cells, immune cells, and so on. These cells collectively secrete a diverse array of bioactive molecules that constitute the adipose secretome[43]. Adipokines represent the most extensively studied group, including leptin, adiponectin, resistin and others. They can act on distant organs through the endocrine pathway, and also regulate the function of adjacent tissues via paracrine signaling[44]. In obesity, the secretory profile of adipose tissue undergoes a significant shift from an anti-inflammatory to a pro-inflammatory phenotype, with increased secretion of pro-inflammatory adipokines and decreased levels of protective adipokines.

According to their functional characteristics, adipokines can be categorized into two major groups: proinflammatory adipokines and protective adipokines. The imbalanced expression of these two groups in obesity is a key feature of adipomuscular axis dysfunction: (1) Proinflammatory adipokines: TNFα and IL6 are the most extensively studied proinflammatory adipokines. In obesity, adipose tissue exhibits increased macrophage infiltration, resulting in markedly upregulated secretion of TNFα and IL6[45]. TNF-α can induce the expression of the E3 ubiquitin ligases atrogin-1 and MuRF1 in skeletal muscle cells by activating the NF-κB and p38 MAPK signaling pathways, thereby promoting protein degradation in muscle fibers[46]. Meanwhile, TNF-α can also interfere with insulin signal transduction by inhibiting tyrosine phosphorylation of insulin receptor substrate1 (IRS1), leading to insulin resistance in skeletal muscle[47]. IL6 inhibits the critical muscle anabolic pathway of IGF1/PI3K/Akt/mTOR by activating the SOCS3 signaling pathway[48, 49]. IL-6 also impairs glucose uptake in skeletal muscle, leading to metabolic dysfunction[50]. Existing studies have shown that IL-6 levels are significantly elevated in patients with SO and are positively correlated with disease severity[51]. In addition, leptin is also one of the most representative adipokines secreted by adipose tissue. Under physiological conditions, leptin exerts its core effects of regulating appetite, increasing energy expenditure, and maintaining energy homeostasis by binding to its hypothalamic receptors and activating the JAK2/STAT3 signaling pathway[52]. However, in obesity, despite markedly elevated circulating leptin levels (hyperleptinemia), leptin resistance often occurs[53]. In the resistant state, hyperleptinemia not only fails to effectively suppress appetite, but also promotes the production of pro-inflammatory cytokines such as TNF-α and IL-6 by activating immune cells including T cells and macrophages, thereby inducing systemic low-grade inflammation[54]. Studies have confirmed that serum leptin levels are significantly associated with SO. Even after adjustment for multiple confounding factors, leptin levels remain independently positively correlated with BMI and independently negatively correlated with skeletal muscle index (SMI)[55]. (2) Protective adipokines: Unlike most adipokines, adiponectin is an adipokine with anti-inflammatory, insulin-sensitizing, and metabolic regulatory effects, whose levels are conversely decreased in obese individuals[56]. Adiponectin promotes fatty acid oxidation, inhibits hepatic gluconeogenesis, and improves insulin sensitivity in skeletal muscle by activating the AMPK and PPAR-α pathways[57, 58]. Adiponectin also inhibits the release of pro-inflammatory cytokines such as TNF-α and IL-6, thereby alleviating chronic low-grade inflammation[59]. A cross-sectional study showed that low adiponectin levels are associated with poorer muscle function and physical performance in patients with sarcopenia[60]. Extracellular vesicles (EVs), as novel mediators of

intercellular communication, have attracted extensive attention in the field of adiposeskeletal muscle crosstalk research in recent years. EVs are nano to micrometersized particles with a lipid bilayer membrane structure, which can carry bioactive molecules such as proteins, microRNAs, and lipids to transmit signals between tissues and regulate metabolic homeostasis[61]. EVs derived from adipose tissue (especially white adipose tissue, WAT), termed AdEVs, can reach skeletal muscle through the circulatory system and affect its metabolism and function[62]. Recent studies have shown that miR-146a-5p carried by adipose tissue-derived small extracellular vesicles (sEVs) can target Fbx32 (Atrogin-1) to inhibit excessive activation of mitophagy, reduce apoptosis and reactive oxygen species (ROS) production, and enhance ATP generation, thereby modulating the progression of muscle aging and muscle atrophy[63]. Adipose-derived sEVs also carry various other miRNA molecules, such as miR-27a, which can participate in the regulation of skeletal muscle lipid metabolism by targeting signaling pathways including PPARγ[64]. An animal study found that EVs derived from obese mouse models significantly upregulated the secretion of IL6 (a proinflammatory factor) and inhibited the secretion of IL4 (an antiinflammatory factor) in a coculture system, suggesting that obesityassociated EVs may promote muscle degradation through a proinflammatory microenvironment[65]. These findings suggest that adipose tissue constitutes a novel molecular pathway regulating skeletal muscle function through sEV-mediated miRNA delivery, providing a new perspective for understanding the mechanism of adipose-skeletal muscle crosstalk.

4. Retrograde regulation of adipose tissue by skeletal muscle

Skeletal muscle also possesses active endocrine function and can synthesize and secrete a variety of myokines. Myokines are cytokines or polypeptides secreted by skeletal muscle, which regulate multi-organ function through autocrine, paracrine or endocrine modes[66]. Released after exercise, they mediate the beneficial effects of exercise on metabolism, immunity and energy homeostasis[67]. Several myokines have been identified to date, including irisin, brain-derived neurotrophic factor (BDNF), myostatin (MSTN), and meteorin[68]. These molecules play central roles in regulating the function of adipose tissue. Irisin is produced through the exercise-induced PGC-1α/FNDC5 pathway, promotes the conversion of white adipocytes into beige fat by activating UCP1 expression in these cells, enhances thermogenesis and energy expenditure, and improves glycolipid metabolism in obesity and diabetes[69, 70]. Irisin can significantly inhibit adipogenic differentiation of adipose-derived mesenchymal stromal cells (ASCs), reduce their antioxidant capacity, and simultaneously increase ATP production and the generation of reactive oxygen species (such as superoxide anion), suggesting its dual regulatory role in adipose tissue homeostasis[71]. Studies have confirmed that irisin levels are negatively correlated with BMI and body fat percentage, and may serve as a predictor of adipose dysfunction[72]. Myostatin (also known as GDF8), a member of the transforming growth factorβ superfamily primarily secreted by skeletal muscle, is traditionally regarded as a negative regulator of muscle mass[73]. However, recent studies have revealed that it also plays a similarly complex and critical role in the metabolism and functional remodeling of adipose tissue, as well as in the regulation of systemic energy homeostasis[74]. Studies have found that myostatin is not secreted exclusively by muscle; brown and white adipose tissues themselves can also express and secrete a certain amount of myostatin[75]. Myostatin derived from brown adipose tissue exhibits autocrine and paracrine functions, thereby regulating the thermogenic function of brown adipose tissue itself[76]. For example, specific knockout of the myostatin gene in brown adipose tissue results in increased body weight, hepatic steatosis, and is accompanied by mitochondrial dysfunction and inflammatory characteristics in brown adipose tissue in mice fed a high-fat diet[76].

In addition to the direct effects of myokines, the overall metabolic status of skeletal muscle affects adipose tissue function through various indirect pathways. As the major consumer of systemic glucose and fatty acids, the metabolic activity of skeletal muscle directly determines the flow of energy substrates. Under insulin-sensitive conditions, skeletal muscle efficiently takes up and oxidizes glucose and fatty acids, reducing lipid overflow into adipose tissue; in contrast, under insulin-resistant conditions, the metabolic load of skeletal muscle decreases, redirecting more energy substrates to adipose tissue for storage and exacerbating obesity[77]. Furthermore, the protein turnover status of skeletal muscle affects

adipose tissue function through amino acid metabolism. Increased muscle protein synthesis enhances the utilization of branched-chain amino acids (BCAAs) and reduces circulating BCAA levels, whereas enhanced muscle breakdown leads to BCAA overflow, which activates mTORC1 signaling in adipocytes and induces insulin resistance in adipose tissue[78].

5. Conclusion

From the perspective of adipose-skeletal muscle crosstalk, this article systematically reviews the bidirectional signaling network underlying SO. Adipose tissue acts on skeletal muscle through multiple pathways, including pro-inflammatory adipokines, extracellular vesicles, and lipid metabolites, disrupting insulin signaling, inducing mitochondrial dysfunction, and promoting protein degradation; in turn, skeletal muscle reciprocally regulates the differentiation and thermogenic function of adipose tissue via myokines. Imbalance in this bidirectional network leads to fat accumulation, impaired muscle function, and reduced energy expenditure, forming the core pathological basis of SO. Future research should further explore the regulatory mechanisms of extracellular vesicles as novel mediators, the functional significance of lipid droplet heterogeneity, multi-omics-based molecular classification strategies, and develop precise interventions targeting the adipose-skeletal muscle axis. The paradigm shift from “dual-organ crosstalk” to a “multi-system network” will open new avenues for the early diagnosis and treatment of SO.

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References

[1] Hua K, Pan Y, Fang J, et al., 2024, Integrating social, climate and environmental changes to confront accelerating global aging. *BMC Public Health*, 24(1): 2838.

[2] Luo Y, Su B, Zheng X, 2021, Trends and challenges for population and health during population aging—China, 2015–2050. *China CDC Weekly*, 3(28): 593.

[3] Fang EF, Fang Y, Chen G, et al., 2025, Adapting health, economic and social policies to address population aging in China. *Nature Aging*, 1-12.

[4] Theodorakis N, Feretzakis G, Kreouzi M, et al., 2025, *Envisioning the Future of Health Informatics and Digital Health*. IOS Press, 473-477.

[5] Czyżewski Ł, Dudziński Ł, Silczuk A, et al., 2026, HEMS and the challenges of an aging population: a nationwide study of interventions. *Frontiers in Public Health*, 14: 1746463.

[6] Matsuda S, 2019, Health policy in Japan – current situation and future challenges. *JMA Journal*, 2(1): 1-10.

[7] Aximu N, Yimingniyazi B, Lin D, et al., 2025, Human resources in long-term care for older adults in China: Challenges amid population aging. *BioScience Trends*, 19(6): 626-640.

[8] Ruperez C, Madeo F, de Cabo R, et al., 2025, Obesity accelerates cardiovascular ageing. *European Heart Journal*, 46(23): 2161-2185.

[9] Barber TM, Kabisch S, Pfeiffer AF, et al., 2025, Optimised skeletal muscle mass as a key strategy for obesity management. *Metabolites*, 15(2): 85.

[10] Zhou Q, Zhu Y, Guo Q, et al., 2025, Association between sarcopenia and falls, fractures, hospital readmission, and all-cause mortality in older adults with endocrine disorders: a longitudinal study of aging in China. *BMC Musculoskeletal Disorders*, 26(1): 842.

[11] Heber D, Ingles S, Ashley JM, et al., 1996, Clinical detection of sarcopenic obesity by bioelectrical impedance analysis. *The American Journal of Clinical Nutrition*, 64(3): 472S-477S.

[12] Wannamethee SG, Atkins JL, 2015, Muscle loss and obesity: the health implications of sarcopenia and sarcopenic obesity. *Proceedings of the Nutrition Society*, 74(4): 405-412.

[13] Baumgartner RN, 2000, Body composition in healthy aging. *Annals of the New York Academy of Sciences*, 904(1): 437-448.

[14] Donini LM, Busetto L, Bischoff SC, et al., 2022, Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Obesity Facts*, 15(3): 321-335.

[15] Şengül Ayçiçek G, Okyar Baş A, Karabulut E, et al., 2025, Prevalence, diagnosis and treatment of sarcopenic obesity in older adults: a systematic review and a meta-analysis. *Acta Clinica Belgica*, 80(6): 226-249.

[16] Luo Y, Shu L, Wang Y, et al., 2025, Sarcopenic obesity and risk of cardio-cerebrovascular disease and mortality: a systematic review and meta-analysis: Epidemiology and Population Health. *International Journal of Obesity*, 49(12): 2406-2414.

[17] Wang W, Fang F, Wang T, et al., 2025, The impact of sarcopenic obesity on the prevalence and prognosis of non-metastatic colorectal cancer: a systematic review and meta-analysis. *Clinical Nutrition ESPEN*.

[18] Park MJ, Choi KM, 2023, Interplay of skeletal muscle and adipose tissue: sarcopenic obesity. *Metabolism*, 144: 155577.

[19] Jang SY, Choi KM, 2025, Impact of adipose tissue and lipids on skeletal muscle in sarcopenia. *Journal of Cachexia, Sarcopenia and Muscle*, 16(4): e70000.

[20] Axelrod CL, Dantas WS, Kirwan JP, 2023, Sarcopenic obesity: emerging mechanisms and therapeutic potential. *Metabolism*, 146: 155639.

[21] Fan S, Yu Y, Wei Y, et al., 2025, Targeting the mTOR-mitochondrial function axis: Calcitriol attenuates sarcopenic obesity with lipid dysregulation etiology. *Free Radical Biology and Medicine*.

[22] Jones HG, Kopinke D, Meyer GA, 2025, Intramuscular adipose tissue: from progenitor to pathology. *American Journal of Physiology-Cell Physiology*, 329(4): C1268-C1282.

[23] Zhang T, Li J, Li X, et al., 2023, Intermuscular adipose tissue in obesity and related disorders: cellular origins, biological characteristics and regulatory mechanisms. *Frontiers in Endocrinology*, 14: 1280853.

[24] Sachs S, Zarini S, Kahn DE, et al., 2019, Intermuscular adipose tissue directly modulates skeletal muscle insulin sensitivity in humans. *American Journal of Physiology-Endocrinology and Metabolism*.

[25] Zhan P, Yan SB, Liu Y, et al., 2026, The Role of Fibro/adipogenic Progenitors (FAPs) in Sarcopenia: Mechanisms and Potential Therapeutic Strategies. *Stem Cell Reviews and Reports*, 1-29.

[26] Li CW, Yu K, Shyh-Chang N, et al., 2022, Pathogenesis of sarcopenia and the relationship with fat mass: descriptive review. *Journal of Cachexia, Sarcopenia and Muscle*, 13(2): 781-794.

[27] Goodpaster BH, Bergman BC, Brennan AM, et al., 2023, Intermuscular adipose tissue in metabolic disease. *Nature Reviews Endocrinology*, 19(5): 285-298.

[28] Shen KC, Collins KH, Ferey JL, et al., 2024, Excess intramyocellular lipid does not affect muscle fiber biophysical properties in mice or people with metabolically abnormal obesity. *Diabetes*, 73(8): 1266-1277.

[29] Yoshiko A, Maeda H, Takahashi H, et al., 2022, Importance of skeletal muscle lipid levels for muscle function and physical

function in older individuals. *Applied Physiology, Nutrition, and Metabolism*, 47(6): 649-658.

[30] Wu H, Ballantyne CM, 2017, Skeletal muscle inflammation and insulin resistance in obesity. *The Journal of Clinical Investigation*, 127(1): 43-54.

[31] Komiya H, Mori Y, Yokose T, et al., 2006, Effect of intramuscular fat difference on glucose and insulin reaction in oral glucose tolerance test. *Journal of Atherosclerosis and Thrombosis*, 13(3): 136-142.

[32] Reiter DA, Bellissimo MP, Zhou L, et al., 2023, Increased adiposity is associated with altered skeletal muscle energetics. *Journal of Applied Physiology*, 134(5): 1083-1092.

[33] Biltz NK, Collins KH, Shen KC, et al., 2020, Infiltration of intramuscular adipose tissue impairs skeletal muscle contraction. *The Journal of Physiology*, 598(13): 2669-2683.

[34] Kong X, Yao T, Zhou P, et al., 2018, Brown adipose tissue controls skeletal muscle function via the secretion of myostatin. *Cell Metabolism*, 28(4): 631-643.e633.

[35] Montgomery MK, De Nardo W, Watt MJ, 2023, Exercise training induces depot-specific remodeling of protein secretion in skeletal muscle and adipose tissue of obese male mice. *American Journal of Physiology-Endocrinology and Metabolism*, 325(3): E227-E238.

[36] Sakaguchi M, 2025, Aging-Induced Dysfunction of Adipose Tissue and Skeletal Muscle and its link to Insulin Resistance. *The Journal of Biochemistry*, mvaf081.

[37] Pollak N, Janežič EG, Šink Ž, et al., 2025, Crosstalk Between Skeletal Muscle and Proximal Connective Tissues in Lipid Dysregulation in Obesity and Type 2 Diabetes. *Metabolites*, 15(9): 581.

[38] Wang D, Zheng X, Yang Z, et al., 2026, High-fat diet exacerbates skeletal muscle mass loss via Nrf2/Prdx6 pathway in sarcopenic obesity mice. *The Journals of Gerontology, Series A: Biological Sciences and Medical Sciences*, 81(3): glaf271.

[39] Dantas WS, Zunica ER, Heintz EC, et al., 2022, Mitochondrial uncoupling attenuates sarcopenic obesity by enhancing skeletal muscle mitophagy and quality control. *Journal of Cachexia, Sarcopenia and Muscle*, 13(3): 1821-1836.

[40] Russ DW, Manickam R, Tipparaju SM, 2025, Targeting intramyocellular lipids to improve aging muscle function. *Lipids in Health and Disease*, 24(1): 197.

[41] Kitessa SM, Abeywardena MY, 2016, Lipid-induced insulin resistance in skeletal muscle: the chase for the culprit goes from total intramuscular fat to lipid intermediates, and finally to species of lipid intermediates. *Nutrients*, 8(8): 466.

[42] Welch AA, Hayhoe RP, Cameron D, 2020, The relationships between sarcopenic skeletal muscle loss during ageing and macronutrient metabolism, obesity and onset of diabetes. *Proceedings of the Nutrition Society*, 79(1): 158-169.

[43] Pogodziński D, Ostrowska L, Smarkusz-Zarzecka J, et al., 2022, Secretome of adipose tissue as the key to understanding the endocrine function of adipose tissue. *International Journal of Molecular Sciences*, 23(4): 2309.

[44] Gu X, Wang L, Liu S, et al., 2023, Adipose tissue adipokines and lipokines: Functions and regulatory mechanism in skeletal muscle development and homeostasis. *Metabolism*, 139: 155379.

[45] Gkrinia EMM, Belančić A, 2025, The mechanisms of chronic inflammation in obesity and potential therapeutic strategies: A narrative review. *Current Issues in Molecular Biology*, 47(5): 357.

[46] Glass DJ, 2005, Skeletal muscle hypertrophy and atrophy signaling pathways. *The International Journal of Biochemistry & Cell Biology*, 37(10): 1974-1984.

[47] Takaguri A, 2018, Elucidation of a new mechanism of onset of insulin resistance: effects of statins and tumor necrosis factor-α on insulin signal transduction. *Yakugaku Zasshi: Journal of the Pharmaceutical Society of Japan*, 138(11): 1329-1334.

[48] Sakuma K, Yamaguchi A, 2013, Sarcopenic obesity and endocrinal adaptation with age. *International Journal of Endocrinology*, 2013(1): 204164.

[49] Kwon EY, Kim JW, Choi JY, et al., 2025, Setaria viridis Ethanol Extract Attenuates Muscle Loss and Body Fat Reduction

in Sarcopenic Obesity by Regulating AMPK in High-Fat Diet-Induced Obese Mice. *Food Science & Nutrition*, 13(7): e70655.

[50] Kob R, Bollheimer LC, Bertsch T, et al., 2015, Sarcopenic obesity: molecular clues to a better understanding of its pathogenesis? *Biogerontology*, 16(1): 15-29.

[51] Dutra MT, Avelar BP, Souza VC, et al., 2017, Relationship between sarcopenic obesity-related phenotypes and inflammatory markers in postmenopausal women. *Clinical Physiology and Functional Imaging*, 37(2): 205-210.

[52] Silveira Pereira S, Alvarez-Leite JI, 2014, Adipokines: biological functions and metabolically healthy obese profile. *Journal of Receptor, Ligand and Channel Research*, 7: 15-25.

[53] Farr OM, Gavrieli A, Mantzoros CS, 2015, Leptin applications in 2015: what have we learned about leptin and obesity? *Current Opinion in Endocrinology, Diabetes and Obesity*, 22(5): 353-359.

[54] Ren Y, Zhao H, Yin C, et al., 2022, Adipokines, hepatokines and myokines: focus on their role and molecular mechanisms in adipose tissue inflammation. *Frontiers in Endocrinology*, 13: 873699.

[55] Yang ZY, Chen WL, 2021, Examining the association between serum leptin and sarcopenic obesity. *Journal of Inflammation Research*, 14: 3481-3487.

[56] Kim Y, Song HJ, Kim DH, et al., 2026, Cross-Sectional and Longitudinal Associations of Irisin and Adiponectin With Obesity, Sarcopenia and Sarcopenic Obesity. *Journal of Cachexia, Sarcopenia and Muscle*, 17(1): e70172.

[57] Tero-Vescan A, Degens H, Matsakas A, et al., 2025, Exercise-induced muscle–fat crosstalk: molecular mediators and their pharmacological modulation for the maintenance of metabolic flexibility in aging. *Pharmaceuticals*, 18(8): 1222.

[58] Lv J, Li Y, Shi S, et al., 2022, Skeletal muscle mitochondrial remodeling in heart failure: An update on mechanisms and therapeutic opportunities. *Biomedicine & Pharmacotherapy*, 155: 113833.

[59] Ge Y, Li S, Yao T, et al., 2023, Promotion of healthy adipose tissue remodeling ameliorates muscle inflammation in a mouse model of sarcopenic obesity. *Frontiers in Nutrition*, 10: 1065617.

[60] Udomsinprasert W, Manoy P, Yuktanandana P, et al., 2020, Decreased serum adiponectin reflects low vitamin D, high interleukin 6, and poor physical performance in knee osteoarthritis. *Archivum Immunologiae et Therapiae Experimentalis*, 68(3): 16.

[61] Hendrix A, Lippens L, Pinheiro C, et al., 2023, Extracellular vesicle analysis. *Nature Reviews Methods Primers*, 3(1): 56.

[62] Macleod M, Price J, Tsonou E, et al., 2026, Adipose-Derived Extracellular Vesicles and Intercellular Crosstalk With Skeletal Muscle: Implications for Sarcopenic Obesity and Metabolic Dysregulation. *Obesity Reviews*, 27(1): 1-22.

[63] Qin M, Wang Y, Wang Z, et al., 2025, Adipose-derived small extracellular vesicle miR-146a-5p targets Fbx32 to regulate mitochondrial autophagy and delay aging in skeletal muscle. *Journal of Nanobiotechnology*, 23(1): 287.

[64] Wang D, Zhang X, Li Y, et al., 2022, Exercise-induced browning of white adipose tissue and improving skeletal muscle insulin sensitivity in obese/non-obese growing mice: do not neglect exosomal miR-27a. *Frontiers in Nutrition*, 9: 940673.

[65] Jeong I, Park S, Park J, et al., 2024, Adipose tissue-derived extracellular vesicles from obese mice suppressed splenocyte-mediated pancreatic cancer cell death. *Food & Nutrition Research*, 68: 10.29219/fnr.v29268.10545.

[66] Zhang L, Lv J, Wang C, et al., 2023, Myokine, a key cytokine for physical exercise to alleviate sarcopenic obesity. *Molecular Biology Reports*, 50(3): 2723-2734.

[67] Chen J, Yao X, Zhao Z, et al., 2025, Myokine-mediated muscle-organ interactions: Molecular mechanisms and clinical significance. *Biochemical Pharmacology*, 225: 117326.

[68] Orioli L, Thissen JP, 2025, Myokines as potential mediators of changes in glucose homeostasis and muscle mass after bariatric surgery. *Frontiers in Endocrinology*, 16: 1554617.

[69] Mahajan RD, Patra SK, 2013, Irisin, a novel myokine responsible for exercise induced browning of white adipose tissue. *Indian Journal of Clinical Biochemistry*, 28(1): 102-103.

[70] Boström P, Wu J, Jedrychowski MP, et al., 2012, A PGC1-α-dependent myokine that drives brown-fat-like development of white fat and thermogenesis. *Nature*, 481(7382): 463-468.

[71] Basini G, Bussolati S, Grolli S, et al., 2022, Effects of the myokine irisin on stromal cells from swine adipose tissue. *Biomolecules*, 12(12): 1895.

[72] Mutlu HH, Koç Ada S, Uzunlulu M, et al., 2024, A comparison of brown fat tissue related hormone levels in metabolically healthy and unhealthy individuals with obesity. *Endocrine*, 86(3): 1025-1034.

[73] Knapp M, Supruniuk E, Górski J, 2023, Myostatin and the Heart. *Biomolecules*, 13(12): 1777.

[74] Yang M, Liu C, Jiang N, et al., 2023, Myostatin: a potential therapeutic target for metabolic syndrome. *Frontiers in Endocrinology*, 14: 1181913.

[75] Gavaldà-Navarro A, Villarroya J, Cereijo R, et al., 2022, The endocrine role of brown adipose tissue: An update on actors and actions. *Reviews in Endocrine and Metabolic Disorders*, 23(1): 31-41.

[76] Wang H, Guo S, Gao H, et al., 2024, Myostatin regulates energy homeostasis through autocrine-and paracrine-mediated microenvironment communication. *The Journal of Clinical Investigation*, 134(16).

[77] Sheptulina AF, Antyukh KY, Kiselev AR, et al., 2023, Possible mechanisms linking obesity, steroidogenesis, and skeletal muscle dysfunction. *Life*, 13(6): 1415.

[78] Tabone M, 2025, Muscle Mechanics in Metabolic Health and Longevity: The Biochemistry of Training Adaptations. *BioChem*, 5(4): 37.