frontiers in Endocrinology

TYPE Mini Review
PUBLISHED 04 May 2026
DOI 10.3389/fendo.2026.1805067

OPEN ACCESS

EDITED BY
Siraphat Taesuwan,
Chiang Mai University, Thailand

REVIEWED BY
Chris Kargl,
University of Pittsburgh, United States

*CORRESPONDENCE
Qingrong Xu
✉ xuqingro@139.com
Peipei Han
✉ 670087821@qq.com
Ji Sun
✉ samsunmedicine@gmail.com

†These authors have contributed equally to this work

RECEIVED 05 February 2026
REVISED 05 April 2026
ACCEPTED 20 April 2026
PUBLISHED 04 May 2026

CITATION
Zhang W, Wu Q, Chen Q, Qin W, Zhang D, Xu Q, Han P and Sun J (2026) Adipose–muscle crosstalk during the menopausal transition: mechanistic links to sarcopenic obesity in midlife women. *Front. Endocrinol.* 17:1805067. doi: 10.3389/fendo.2026.1805067

Adipose–muscle crosstalk during the menopausal transition: mechanistic links to sarcopenic obesity in midlife women

Weixin Zhang[1†], Qianhao Wu[2†], Qianyuan Chen[2], Wenxing Qin[3], Dongfang Zhang[1], Qingrong Xu[1*], Peipei Han[1*] and Ji Sun[1*]

[1]Jiangwan Hospital of Hongkou District, Shanghai University of Medicine and Health Sciences, Shanghai, China, [2]Collaborative Innovation Center for Biomedicines, Shanghai University of Medicine and Health Sciences, Shanghai, China, [3]Department of Medical Oncology, Fudan University Shanghai Cancer Center, Shanghai, China

Midlife represents a biological “phenotype transition” for women, during which sarcopenic obesity risk can rise despite stable BMI. Evidence anchored to the STRAW + 10 framework suggests that the interval surrounding the final menstrual period is an acceleration window for fat gain and centripetal/ectopic redistribution, creating an “invisible remodeling” trajectory that may increase the risk of developing sarcopenic obesity, which is not captured by routine anthropometrics. We synthesize mechanisms linking menopausal biology to increased risk of sarcopenic obesity: obesity-driven inflammation, adipokine dysregulation, and lipotoxic flux that impair insulin–AKT signaling and metabolic flexibility, coupled with reduced contractile/endocrine muscle output that worsens adipose phenotype. A key mediator is myosteatosis, comprising intramyocellular lipid and intermuscular adipose tissue, which can reduce specific force and manifest as dynapenia even when muscle size is preserved. Scalable monitoring of muscle quality using ultrasound echo intensity may complement CT/MRI in midlife practice. Estrogen withdrawal may further amplify energetic and regenerative vulnerability via ERα-related mitochondrial quality control and satellite-cell support, although menopause-stage human longitudinal data remain limited. In the GLP-1 era, lean mass loss during weight reduction and rapid regain after withdrawal strengthen the case for a function-first strategy integrating progressive resistance training and per-meal protein dosing/distribution. Standardized, menopause-calibrated sarcopenic obesity definitions and cohorts integrating strength, muscle quality, and ectopic fat are key priorities for prevention.

KEYWORDS
mechanism, menopausal transition, midlife women, rehabilitation, sarcopenic obesity

1 Introduction

Sarcopenic obesity (SO) refers to a condition where there is excessive body fat and impaired skeletal muscle mass or function (1). Various criteria have been used to define SO in previous studies (Table 1). The consensus of the European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) defines SO as the presence of both obesity and sarcopenia (2). This phenotype is increasingly

TABLE 1 **Current research on sarcopenic obesity in middle-aged women.**

Participants	Definition of SO	Study design	Body composition measurement methods	Key findings	Ref.
4,766 Korean females (42–52 years), median follow-up duration of 9.1 years	ASM index < 5.7 kg/m^2 combined with PBF ≥ 35%	Longitudinal study	BIA	SO increases across the menopausal stages and becomes more pronounced from the late transition.	(20) 2025
Postmenopausal Thai women (n = 248; age 45–80 years)	Weight-adjusted skeletal muscle mass (SMM/W) < 35.6% with fat mass > 41%	comprehensive cross-sectional study	BIA	Nutritional factors and menopausal hormone therapy represent modifiable influences on SO development, which in turn is linked to a higher risk of osteoporosis in postmenopausal women.	(21) 2025
Postmenopausal Turkish women (n=300; 59.71 ± 9.9 years)	Muscle mass < 0.823 kg/(kg/m^2), Handgrip strength < 22 kg, and Body fat > 60th percentile (population-specific threshold > 41%)	cross-sectional study	BIA	Among the patients evaluated, 15.4% had SO.	(22) 2025
Postmenopausal Korean women (n = 4,150;mean age: 62.41 years)	ASM index<23.0% and BMI≥25.0 kg/m^2	cross-sectional study	DXA	Compared to simple obesity, SO has a greater impact on knee osteoarthritis.	(23) 2022

ASM, Appendicular skeletal muscle mass; BIA, Bioelectrical impedance analysis; BMI, Body mass index; DXA, Dual-energy X-ray absorptiometry; PBF, Percent body fat; SO, Sarcopenic obesity.

closely associated with adverse cardiovascular metabolic and functional outcomes (3). Especially during the middle-aged stage of women, as they experience a decrease in lean mass and an increase in fat mass, their body composition and metabolic risks may still undergo significant changes (4–7). It is worth noting that screening approaches based on an increase in body mass index (BMI) or an expansion of the waist circumference may not detect women in the middle-aged period who have a normal weight range but high fat content or poor fat distribution (6, 8). These phenotypes have a great correlation during the menopausal transition period (6, 9). We define middle-aged women as those between the late reproductive stage and the early menopause stage, using the STRAW + 10 framework for definition (late reproductive period, early/late menopausal transition period, and early menopause), typically corresponding to women in their mid-40s to mid-50s, and the time period before and after the final menstrual period (FMP) as the key turning point for body composition (10).

Midlife represents not merely a chronological midpoint but a biological "phenotype transition" for many women (4, 11). Longitudinal evidence indicates that the interval around the FMP constitutes an acceleration window for body composition remodeling, with fat mass increasing more rapidly and lean mass decreasing beginning roughly two years before the FMP (annual increase rate of fat mass: 1.7%; annual decrease rate of lean mass: 0.2%) and continuing into early postmenopause—patterns that are more clearly reflected than those of body weight or BMI trajectories (5, 6). In this context, relying on body weight or BMI alone can mask clinically meaningful repartitioning of fat and lean tissues—an "invisible remodeling" trajectory that may represent an early phase increasing the risk of SO earlier than traditionally appreciated (5, 12).

Crucially, early deterioration in midlife women may be functionally and qualitatively driven rather than solely quantified by muscle mass. Contemporary muscle health frameworks emphasize that functional impairment (e.g., strength) and tissue composition are not interchangeable with muscle quantity (13). Fat infiltration into skeletal muscle (myosteatosis) is increasingly recognized as an ectopic fat depot that correlates negatively with strength and mobility and is linked to metabolic dysfunction, including insulin resistance and diabetes (14, 15). Thus, the risk of SO in midlife women is plausibly shaped by a combination of increasing adiposity and early declines in muscle quality and performance—changes that may occur without dramatic losses in scale weight (1, 6).

Mechanistically, the menopausal transition provides a compelling biological backdrop for SO (4, 11). Beyond systemic fat redistribution, estrogen signaling supports skeletal muscle mitochondrial function and metabolic homeostasis, and reduced estrogen action can compromise these pathways (11, 16). Experimental and translational evidence further suggests that estrogen deficiency can impair the maintenance and regenerative capacity of satellite cells, providing a cellular rationale for reduced repair and recovery potential as estrogen declines (17). These changes intersect with a broader inflammatory–metabolic axis: inflamed adipose tissue promotes lipotoxicity and the release of pro-inflammatory mediators that impair insulin action, while declining muscle metabolic activity lowers resting energy expenditure and physical capacity, further facilitating fat gain—together establishing a self-reinforcing cycle (18, 19). In this mini-review, we therefore focus on SO as a midlife women's health issue, highlighting how menopausal biology, muscle quality (including myosteatosis), and adipose–muscle crosstalk may jointly accelerate cardiometabolic risk, and we outline key gaps that limit prevention and intervention strategies.

2 Obesity-driven pathways that compromise skeletal muscle in midlife women: inflammation, anabolic sensitivity shifts, and myosteatosis

Midlife women frequently experience a phenotype shift in which body composition reorganizes, while total body weight or BMI do not accurately reflect these changes, with progressive visceral/ectopic fat expansion and concurrent deterioration in muscle performance. In this context, the development of SO is increasingly viewed not as a simple "sum" of fat gain plus muscle loss, but as a pathophysiologic synergy in which adiposity-derived signals accelerate muscle dysfunction and metabolic risk (5, 20, 24–26). Contemporary consensus frameworks provide an essential reference point for defining and staging SO, yet the midlife female phenotype exposes where population-level tools may under-capture early decline dominated by muscle quality and function (2).

2.1 Low-grade inflammation and adipokine imbalance as early drivers of muscle vulnerability

Obesity is characterized by chronic, low-grade inflammation that impairs skeletal muscle metabolic homeostasis (27). In midlife women, this inflammatory load is clinically relevant because adipose-derived endocrine signals can track functional vulnerability beyond BMI. Mechanistically, pro-inflammatory signaling and lipid oversupply may impair glucose disposal and promote ectopic lipid deposition, creating a milieu that may reduce the efficiency of anabolic remodeling and contribute to early declines in muscle quality (28). In parallel, adipokine dysregulation—particularly reduced adiponectin activity and increased leptin tone/leptin resistance—has been implicated in skeletal muscle insulin resistance, oxidative stress, and reduced metabolic flexibility in obesity-related settings, although direct menopause-stage evidence in midlife women remains limited (29, 30). Together, these processes may increase vulnerability to early muscle quality decline and ectopic fat infiltration before overt mass loss becomes apparent.

2.2 Anabolic responsiveness in midlife women: dose dependence, context dependence, and meal distribution

In obesity and metabolic dysfunction, "anabolic resistance" is used to describe an attenuated skeletal muscle protein synthetic response to anabolic stimuli such as dietary amino acids, insulin/IGF-1 signaling, and resistance exercise (31). Mechanistically, nutrient- and growth factor–dependent regulation of muscle protein synthesis converges on the PI3K–AKT–mTORC1 pathway, and obesity-related inflammation and lipid oversupply are consistently associated with impaired insulin signaling and reduced downstream activation of anabolic signaling nodes in skeletal muscle, which can limit the magnitude of postprandial and post-exercise remodeling (32–34). However, direct evidence in midlife women does not support a uniformly blunted anabolic response. Controlled feeding studies indicate that ingestion of an adequate high-quality protein bolus (e.g., ~25 g whey) can elicit a robust postprandial increase in myofibrillar protein synthesis in middle-aged women, suggesting that anabolic capacity may be preserved when the stimulus is sufficiently large and protein quality is high (35). Therefore, rather than describing midlife women as having an intrinsic anabolic resistance phenotype, the current evidence is better interpreted as supporting dose dependence and context dependence. A relative reduction in anabolic efficiency may be more plausible in subgroups such as women with obesity, metabolic dysfunction, or during energy restriction (34, 36, 37). This has practical implications for habitual dietary patterns, because protein intake is commonly skewed toward the evening meal (38); controlled comparisons of isonitrogenous diets demonstrate that a more even distribution pattern approximating ~30 g protein at breakfast, lunch, and dinner yields a higher 24-hour myofibrillar protein synthesis rate (≈25% higher) than a skewed pattern concentrating most protein at dinner (39). Collectively, these data support focusing the discussion in midlife women on modifiable determinants of anabolic outcomes—per-meal protein amount, protein quality (including essential amino acid/leucine content), and meal distribution—rather than presuming a uniform anabolic defect across this population (39–41).

2.3 Adipose–muscle crosstalk as a bidirectional amplifier: adipokines meet myokines

Adipose–muscle crosstalk relevant to SO is bidirectional in the literal sense that adipose tissue actively alters skeletal muscle metabolism and remodeling (adipose → muscle), and skeletal muscle—through contractile activity and secreted factors—also actively regulates adipose tissue phenotype and energy handling (muscle → adipose) (42). On the adipose → muscle side, obesity-related adipose expansion is accompanied by immune cell infiltration and endocrine dysregulation, characterized by higher circulating and local pro-inflammatory mediators (e.g., TNF-α, IL-6–linked signaling, MCP-1–related pathways), adipokine imbalance (relative reduction in adiponectin activity and increased leptin tone/leptin resistance), and increased delivery of lipid substrates and lipotoxic intermediates (e.g., elevated NEFA flux and bioactive lipids such as ceramides/diacylglycerols) (43, 44). These signals converge in skeletal muscle on impaired insulin signaling (reduced IRS-1/AKT pathway efficiency), mitochondrial overload and oxidative stress, and reduced metabolic flexibility, thereby promoting ectopic lipid accumulation within and around muscle and attenuating anabolic remodeling capacity (45, 46). On the muscle → adipose side, skeletal muscle functions as an endocrine organ whose secretome is strongly activity-dependent: contraction-associated myokines (e.g., IL-6 in its acute exercise-associated pattern) can influence adipose lipolysis and substrate utilization, IL-15 has been linked to regulation of adipose mass and oxidative phenotype, and myostatin is a negative regulator of muscle anabolism that is also associated with a more adverse body-fat profile (47, 48); irisin (FNDC5-derived) has been shown in experimental settings to promote thermogenic gene programs (including UCP1-related pathways), although the magnitude and consistency of this mechanism in humans remains variable across studies (49). When muscle mass, strength, and habitual contractile activity decline—as can occur during midlife weight gain and reduced activity—total substrate disposal and resting energy expenditure decrease, and the activity-dependent myokine profile shifts in a direction that is less supportive of adipose oxidative/thermogenic remodeling and more permissive of adipose expansion and inflammation (50). Taken together, “bidirectional” crosstalk in SO refers to two coupled processes: obesity-driven adipose endocrine/lipotoxic signaling that impairs muscle metabolism and function, and reduced muscle contractile/endocrine output that worsens adipose tissue phenotype, jointly amplifying fat accumulation, metabolic dysfunction, and functional decline (42).

2.4 Myosteatosis: IMCL vs IMAT, dynapenia, and scalable assessment using ultrasound

Beyond total muscle mass, muscle quality is strongly shaped by ectopic fat infiltration (14, 51). Myosteatosis includes at least two biologically distinct compartments. Intramyocellular lipids (IMCL) are lipid droplets within muscle fibers; they can reflect adaptive fuel storage in trained states but become maladaptive when coupled with mitochondrial stress, oxidative imbalance, and impaired lipid oxidation (52). Intermuscular adipose tissue (IMAT) refers to fat between muscle groups and fascial planes; it can act as a local inflammatory depot, promoting paracrine immune signaling and impairing contractile performance (53).

Myosteatosis provides a biologically plausible explanation for “hidden” deterioration in BMI-stable midlife women: even when muscle cross-sectional area appears preserved, fat infiltration may be accompanied by deterioration in muscle quality, suggesting early tissue-level decline that may precede overt strength loss (54). Much of the strongest imaging–function evidence linking lower muscle density/attenuation to reduced strength comes from older cohorts, supporting biological plausibility that infiltration depresses functional output beyond what muscle size predicts; nevertheless, this should be treated as mechanistic anchoring rather than direct midlife-specific effect estimation (55).

In the past, ultrasound, bioimpedance analysis (BIA), CT, MRI, and dual-energy X-ray absorptiometry (DXA) have all been used clinically to assess muscle quality (56). To strengthen clinical relevance for midlife practice, muscle quality assessment should not rely exclusively on CT/MRI. Ultrasound echo intensity (EI) is a feasible, scalable surrogate for muscle quality that can support repeated monitoring across the menopausal transition in settings where advanced imaging is impractical. Emerging longitudinal work in women across menopausal stages suggests that muscle size can remain relatively stable while EI increases, consistent with progressive intramuscular fat/connective tissue infiltration and supporting the “invisible remodeling” concept (54). Because EI is influenced by device settings and subcutaneous fat thickness, longitudinal applications should emphasize standardized acquisition and, where feasible, corrected EI (or clearly specified normalization procedures) to improve comparability across time and individuals (57). In addition, DXA offers the advantages of high accuracy, wide availability, and low radiation exposure (56). It is widely reported to be more acceptable and comfortable for patients, and it can provide multiple body composition indices within minutes (58). In DXA, X-rays pass through the human body at two different energy levels and undergo attenuation (58, 59). Depending on the intensity of the emitted energy, as well as the density and thickness of anatomical structures and tissues, the radiation energy is attenuated to varying degrees (58). This allows for the analysis of muscle quality. In a study by Greendale et al. (5) on changes in body composition and weight during the menopause transition, DXA provided accurate measurements of fat mass and lean body mass. The study revealed that an accelerated increase in fat mass and a decrease in lean body mass are phenomena associated with the menopause transition (5).

3 The menopausal transition as an amplifier: estrogen loss, mitochondrial stress, and impaired regeneration

3.1 ERα and mitochondrial quality control: preclinical mechanisms and translational relevance

Skeletal muscle estrogen receptor signaling, particularly via ERα, is implicated in maintaining mitochondrial function and metabolic homeostasis (60). Strong causal support for ERα-related mitochondrial mechanisms comes primarily from preclinical models, including skeletal muscle–specific ERα disruption, which is associated with impaired mitochondrial metabolism and reduced metabolic flexibility (11). These data provide mechanistic plausibility for menopause-associated energetic vulnerability but do not, by themselves, establish that identical fission–fusion or mitophagy defects occur in midlife women (61).

Mitochondrial quality control is best conceptualized as a coordinated system involving mitochondrial dynamics (fission/fusion) that segregate damaged components and preserve network function, and mitophagy that clears dysfunctional organelles. In a midlife SO context, these control nodes plausibly intersect with lipid overload: if mitochondrial remodeling and clearance are less efficient during estrogen withdrawal, lipid oxidation may lag behind lipid delivery, predisposing to IMCL accumulation, oxidative stress, and reduced metabolic flexibility (62). Direct menopause-stage–anchored biopsy studies in midlife women that quantify these pathways remain limited, defining a key translational gap (63).

3.2 The ROS–FoxO–atrogene axis

A key downstream consequence of impaired mitochondrial maintenance is increased oxidative stress. Elevated ROS can shift muscle toward catabolism by enabling transcriptional programs that upregulate ubiquitin–proteasome and autophagy-related degradation (64, 65). Canonically, reduced PI3K/AKT tone permits FoxO activation, which induces atrophy-related ubiquitin ligases such as atrogin-1/MAFbx and MuRF1 (66, 67). This axis provides a mechanistic bridge between energetic stress and functional decline, and it underscores how obesity-linked metabolic stressors may synergize with menopause-linked shifts in cellular homeostasis (68).

3.3 Impaired regeneration: satellite cell biology and transcriptomic signals

The menopausal transition may influence skeletal muscle regenerative capacity through effects on the satellite cell compartment, which is required for myofiber repair and remodeling after injury, disuse, and training (69). The strongest causal evidence comes from preclinical models: estradiol signaling acting through ERα in satellite cells maintains satellite cell number by limiting apoptosis, and loss of estrogen–ERα signaling reduces satellite cell content and impairs strength recovery following muscle injury (70). Human evidence is more limited but directionally consistent: biopsy observations in women transitioning from peri- to postmenopause have reported reductions in satellite cell indices coincident with declining estradiol (17), and a double-blind randomized trial in early postmenopausal women undergoing resistance training found that satellite cell measures declined in the placebo group but were counteracted when resistance training was combined with transdermal estrogen therapy (with divergent changes in satellite cells per fiber across fiber types) (71). These data support the interpretation that estrogen status can modulate satellite-cell–related remodeling *in vivo*, but they also highlight key constraints for midlife inference: satellite-cell readouts in human studies can be influenced by participant age, training status, exercise mode, and follow-up time after exercise; therefore, comparisons across studies and menopause-stage sampling protocols require careful standardization (72). Complementing these cellular measures, longitudinal transcriptomic studies across the menopausal transition have begun to identify coordinated shifts in gene programs relevant to tissue maintenance and repair (e.g., cell-cycle control, extracellular matrix remodeling, and myogenesis-related signaling), but these signatures should be interpreted as molecular associations rather than direct evidence of altered satellite cell kinetics. Collectively, the current evidence supports a biologically plausible menopause-linked reduction in regenerative support, while underscoring the need for menopause-stage–anchored longitudinal studies in midlife women that jointly quantify satellite cell indices, muscle quality, and strength outcomes under standardized sampling conditions (64).

4 Rehabilitation and intervention strategies: breaking the adipose–muscle vicious cycle in midlife women

4.1 Exercise as the cornerstone: metabolic unloading and strength preservation

In obese midlife women, exercise should be framed not only as "calorie expenditure," but as a targeted strategy to attenuate obesity-driven inflammatory signaling, restore metabolic flexibility, and protect cardiac function (73–76). Aerobic exercise can be positioned as metabolic unloading—reducing ectopic lipid burden, improving insulin sensitivity, and lowering systemic inflammation—while progressive resistance training (RT) directly targets dynapenia and supports muscle quality (77, 78). Because obesity-related inflammation and lipotoxic stress can blunt the normal rise in muscle protein synthesis after amino acids and exercise, RT prescriptions should be progressive, adequately loaded, and sustained, with individualized safety considerations including symptom burden, joint health, bone health risk, and training history (79, 80).

4.2 Nutrition to overcome anabolic sensitivity shifts: per-meal thresholds and targeted distribution

Because anabolic responsiveness in midlife women appears to be context-dependent rather than uniformly impaired, and may be less efficient in subgroups such as women with obesity, metabolic dysfunction, or during energy restriction, nutrition should be framed as a precision strategy to repeatedly deliver a meaningful anabolic stimulus rather than a generic healthy-eating add-on (31, 34, 37). Practically, an evidence-informed scaffold is to ensure adequate total daily protein when the goal is lean-tissue preservation during weight management or functional decline, with explicit individualization to renal function, comorbidity burden, and energy sufficiency (81–83). Within this context, distribution becomes mechanistically relevant because muscle protein synthesis is saturable per eating occasion; therefore, recommendations should move beyond "even spacing" toward per-meal boluses that reliably reach an essential amino acid/leucine trigger, particularly in sensitivity-reduced states where sub-threshold meals may fail to stimulate synthesis meaningfully (84). Importantly, this practical emphasis on adequate per-meal dosing does not imply that midlife women are uniformly "resistant" (37); rather, it acknowledges that robust responses are often preserved when the stimulus is sufficient, while everyday meal patterns frequently do not reach the trigger required to generate repeated daily anabolic pulses (85). These dietary tactics are most defensible when paired with progressive RT, because combined mechanical and amino-acid signaling offers the most plausible route to preserve strength and muscle quality during the midlife transition (86, 87).

4.3 Weight-loss interventions in the GLP-1 era: implications for muscle preservation

Substantial weight loss—whether achieved pharmacologically, surgically, or through caloric restriction—typically reduces both fat mass and lean mass, and the composition of weight loss is clinically relevant when the goal is to prevent sarcopenic obesity in midlife women. Recent evidence from GLP-1 receptor agonists and GLP-1/GIP co-agonists indicates that lean mass decreases alongside fat mass during treatment, highlighting that scale-based success does not necessarily equate to preservation of muscle-related reserve (88, 89). In addition, randomized withdrawal studies show that discontinuation is commonly followed by substantial weight regain and partial reversal of cardiometabolic benefit (90, 91). In midlife women, this pattern is particularly relevant because menopause-related shifts in fat distribution and muscle vulnerability may make long-term outcomes more dependent on preservation of strength and muscle quality than on body weight alone. Therefore, GLP-1-based weight management should be implemented within a function-first framework, in which progressive resistance training, adequate protein intake, and monitoring of strength and body composition are treated as core co-therapies rather than optional adjuncts (88–91).

5 Conclusion

In midlife women, the development of SO is best conceptualized as arising from an invisible remodeling trajectory in which menopause-linked centripetal fat redistribution and ectopic deposition can progress even when changes in body weight or BMI do not fully reflect the underlying body composition remodeling, uncoupling routine anthropometric measures from true metabolic and functional risk. While consensus definitions are essential for standardization, midlife women expose a remaining gap: early decline may be dominated by deteriorating muscle quality and strength and may therefore be under-recognized by BMI/WC-anchored screening in the absence of menopause-calibrated thresholds. Mechanistically, obesity-related inflammation and context-dependent shifts in anabolic sensitivity intersect with estrogen-withdrawal–linked energetic and regenerative vulnerabilities supported strongly by preclinical and translational evidence but incompletely mapped in menopause-stage–anchored human cohorts. In the GLP-1 era, the long-term risk is shaped less by drug-specific muscle harm than by weight cycling after withdrawal and potential asymmetric regain, underscoring a function-first paradigm that tracks strength and muscle quality alongside adiposity and prioritizes resistance training plus per-meal protein strategies that reliably reach an essential amino acid/leucine trigger, individualized to comorbidity and feasibility, during this last major window before later-life disability trajectories consolidate.

Author contributions

WZ: Writing – original draft. QW: Writing – original draft. QC: Writing – review & editing. WQ: Writing – review & editing. DZ: Writing – review & editing. QX: Writing – review & editing. PH: Writing – original draft, Writing – review & editing. JS: Conceptualization, Writing – review & editing.

Funding

The author(s) declared that financial support was received for this work and/or its publication. This work was supported by the Scientific Research and Cultivation Fund of Jiangwan Hospital, Hongkou District, Shanghai (JWKY2026-20), Special Research Fund Project of Community Medicine and Health Management, Shanghai Society of Integrated Traditional Chinese and Western Medicine (2025-SQ-33), and The Third-Round Three-Year Action Plan (2026–2028) for Strengthening and Optimizing Traditional Chinese Medicine in Hongkou District, Shanghai (HKGYQYXM-2026-76).

Conflict of interest

The author(s) declared that this work was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Generative AI statement

The author(s) declared that generative AI was not used in the creation of this manuscript.

Any alternative text (alt text) provided alongside figures in this article has been generated by Frontiers with the support of artificial intelligence and reasonable efforts have been made to ensure accuracy, including review by the authors wherever possible. If you identify any issues, please contact us.

Publisher's note

References

1. Lumsden AL, Mulugeta A, Hypponen E. Milk consumption and risk of twelve cancers: A large-scale observational and mendelian randomisation study. *Clin Nutr.* (2023) 42:1–8. doi: 10.1016/j.clnu.2022.11.006

2. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: Espen and easo consensus statement. *Obes Facts.* (2022) 15:321–35. doi: 10.1159/000521241

3. Veronese N, Ragusa FS, Pegreffi F, Dominguez LJ, Barbagallo M, Zanetti M, et al. Sarcopenic obesity and health outcomes: An umbrella review of systematic reviews with meta-analysis. *J Cachexia Sarcopenia Muscle.* (2024) 15:1264–74. doi: 10.1002/jcsm.13502

4. Nappi RE, Chedraui P, Lambrinoudaki I, Simoncini T. Menopause: A cardiometabolic transition. *Lancet Diabetes Endocrinol.* (2022) 10:442–56. doi: 10.1016/S2213-8587(22)00076-6

5. Greendale GA, Sternfeld B, Huang M, Han W, Karvonen-Gutierrez C, Ruppert K, et al. Changes in body composition and weight during the menopause transition. *JCI Insight*. (2019) 4:e124865. doi: 10.1172/jci.insight.124865

6. Samargandy S, Matthews KA, Brooks MM, Barinas-Mitchell E, Magnani JW, Janssen I, et al. Abdominal visceral adipose tissue over the menopause transition and carotid atherosclerosis: The swan heart study. *Menopause*. (2021) 28:626–33. doi: 10.1097/GME.0000000000001755

7. Shieh A, Karlamangla AS, Karvonen-Guttierez CA, Greendale GA. Menopause-related changes in body composition are associated with subsequent bone mineral density and fractures: Study of women's health across the nation. *J Bone Miner Res*. (2023) 38:395–402. doi: 10.1002/jbmr.4759

8. Wijayatunga NN, Dhurandhar EJ. Normal weight obesity and unaddressed cardiometabolic health risk-a narrative review. *Int J Obes (Lond)*. (2021) 45:2141–55. doi: 10.1038/s41366-021-00858-7

9. Juppi HK, Sipila S, FaChada V, Hyvarinen M, Cronin N, Aukee P, et al. Total and regional body adiposity increases during menopause-evidence from a follow-up study. *Aging Cell*. (2022) 21:e13621. doi: 10.1111/acel.13621

10. Harlow SD, Gass M, Hall JE, Lobo R, Maki P, Rebar RW, et al. Executive summary of the stages of reproductive aging workshop +10: Addressing the unfinished agenda of staging reproductive aging. *Climacteric*. (2012) 15:105–14. doi: 10.3109/13697137.2011.650656

11. Pellegrino A, Tiidus PM, Vandenboom R. Mechanisms of estrogen influence on skeletal muscle: Mass, regeneration, and mitochondrial function. *Sports Med*. (2022) 52:2853–69. doi: 10.1007/s40279-022-01733-9

12. Banack HR, Bea JW, Chen Z, Blew RM, Nicholas S, Stefanick M, et al. Longitudinal patterns of abdominal visceral and subcutaneous adipose tissue, total body composition, and anthropometric measures in postmenopausal women: Results from the women's health initiative. *Int J Obes (Lond)*. (2023) 47:288–96. doi: 10.1038/s41366-023-01266-9

13. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyère O, Cederholm T, et al. Sarcopenia: Revised european consensus on definition and diagnosis. *Age Ageing*. (2018) 48:16–31. doi: 10.1093/ageing/afy169

14. Ahn H, Kim DW, Ko Y, Ha J, Shin YB, Lee J, et al. Updated systematic review and meta-analysis on diagnostic issues and the prognostic impact of myosteatosis: A new paradigm beyond sarcopenia. *Ageing Res Rev*. (2021) 70:101398. doi: 10.1016/j.arr.2021.101398

15. Kim MJ, Cho YK, Jung HN, Kim EH, Lee MJ, Jung CH, et al. Association between insulin resistance and myosteatosis measured by abdominal computed tomography. *J Clin Endocrinol Metab*. (2023) 108:3100–10. doi: 10.1210/clinem/dgad382

16. Ribas V, Drew BG, Zhou Z, Phun J, Kalajian NY, Soleymani T, et al. Skeletal muscle action of estrogen receptor alpha is critical for the maintenance of mitochondrial function and metabolic homeostasis in females. *Sci Transl Med*. (2016) 8:334ra54. doi: 10.1126/scitranslmed.aad3815

17. Collins BC, Arpke RW, Larson AA, Baumann CW, Xie N, Cabelka CA, et al. Estrogen regulates the satellite cell compartment in females. *Cell Rep*. (2019) 28:368–81: e6. doi: 10.1016/j.celrep.2019.06.025

18. Severinsen MCK, Pedersen BK. Muscle-organ crosstalk: The emerging roles of myokines. *Endocr Rev*. (2020) 41:594–609. doi: 10.1210/endrev/bnaa016

19. Hyvarinen M, Juppi HK, Taskinen S, Karppinen JE, Karvinen S, Tammelin TH, et al. Metabolic health, menopause, and physical activity-a 4-year follow-up study. *Int J Obes (Lond)*. (2022) 46:544–54. doi: 10.1038/s41366-021-01022-x

20. Cho Y, Jang Y, Park JH, Chang Y, Ryu S. Risk of sarcopenic obesity across menopausal transition stages in middle-aged korean women. *Nutrients*. (2025) 17:3238. doi: 10.3390/nu17203238

21. Chucherd O, Vallibhakara O, Vallibhakara S-O, Sophonsritsuk A, Chattrakulchai K, Anantaburarana M. Association of sarcopenic obesity and osteoporosis in postmenopausal women: Risk factors and protective effects of hormonal therapy and nutritional status. *Arch Osteoporosis*. (2025) 20:83. doi: 10.1007/s11657-025-01573-w

22. Yılmaz A, Şentürk Durmuş N, Yıldız Y, Beşışık Yılmaz Z, Alkaç Ç, Can B, et al. Sarcopenia and sarcopenic obesity in postmenopausal women: A cross-sectional study in Türkiye. *Climacteric*. (2025) 29:61–6. doi: 10.1080/13697137.2025.2537982

23. Kim HI, Ahn SH, Kim Y, Lee JE, Choi E, Seo SK. Effects of sarcopenia and sarcopenic obesity on joint pain and degenerative osteoarthritis in postmenopausal women. *Sci Rep*. (2022) 12:13543. doi: 10.1038/s41598-022-17451-1

24. Hurtado MD, Saadedine M, Kapoor E, Shufelt CL, Faubion SS. Weight gain in midlife women. *Curr Obes Rep*. (2024) 13:352–63. doi: 10.1007/s13679-024-00555-2

25. Moreira MA, Zunzunegui MV, Vafaei A, da Camara SM, Oliveira TS, Maciel AC. Sarcopenic obesity and physical performance in middle aged women: A cross-sectional study in northeast Brazil. *BMC Public Health*. (2016) 16:43. doi: 10.1186/s12889-015-2667-4

26. Kang S-Y, Lim GE, Kim YK, Kim HW, Lee K, Park T-J, et al. Association between sarcopenic obesity and metabolic syndrome in postmenopausal women: A cross-sectional study based on the korean national health and nutritional examination surveys from 2008 to 2011. *J Bone Metab*. (2017) 24:9–14. doi: 10.11005/jbm.2017.24.1.9

27. Karvonen-Gutierrez CA, Zheng H, Mancuso P, Harlow SD. Higher leptin and adiponectin concentrations predict poorer performance-based physical functioning in midlife women: The michigan study of women's health across the nation. *J Gerontol A Biol Sci Med Sci*. (2016) 71:508–14. doi: 10.1093/gerona/glv123

28. Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, et al. Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating amp-activated protein kinase. *Nat Med*. (2002) 8:1288–95. doi: 10.1038/nm788

29. Jortay J, Senou M, Abou-Samra M, Noel L, Robert A, Many M-C, et al. Adiponectin and skeletal muscle: Pathophysiological implications in metabolic stress. *Am J Pathol*. (2012) 181:245–56. doi: 10.1016/j.ajpath.2012.03.035

30. Chen MB, McAinch AJ, Macaulay SL, Castelli LA, O'Brien PE, Dixon JB, et al. Impaired activation of amp-kinase and fatty acid oxidation by globular adiponectin in cultured human skeletal muscle of obese type 2 diabetics. *J Clin Endocrinol Metab*. (2005) 90:3665–72. doi: 10.1210/jc.2004-1980

31. Paulussen KJM, McKenna CF, Beals JW, Wilund KR, Salvador AF, Burd NA. Anabolic resistance of muscle protein turnover comes in various shapes and sizes. *Front Nutr*. (2021) 8:615849. doi: 10.3389/fnut.2021.615849

32. Samuel VT, Shulman GI. The pathogenesis of insulin resistance: Integrating signaling pathways and substrate flux. *J Clin Invest*. (2016) 126:12–22. doi: 10.1172/JCI77812

33. Goul C, Peruzzo R, Zoncu R. The molecular basis of nutrient sensing and signalling by mtorc1 in metabolism regulation and disease. *Nat Rev Mol Cell Biol*. (2023) 24:857–75. doi: 10.1038/s41580-023-00641-8

34. Beals JW, Skinner SK, McKenna CF, Poozhikunnel EG, Farooqi SA, van Vliet S, et al. Altered anabolic signalling and reduced stimulation of myofibrillar protein synthesis after feeding and resistance exercise in people with obesity. *J Physiol*. (2018) 596:5119–33. doi: 10.1113/JP276210

35. Mamerow MM, Mettler JA, English KL, Casperson SL, Arentson-Lantz E, Sheffield-Moore M, et al. Dietary protein distribution positively influences 24-h muscle protein synthesis in healthy adults. *J Nutr*. (2014) 144:876–80. doi: 10.3945/jn.113.185280

36. Beals JW, Sukiennik RA, Nallabelli J, Emmons RS, van Vliet S, Young JR, et al. Anabolic sensitivity of postprandial muscle protein synthesis to the ingestion of a protein-dense food is reduced in overweight and obese young adults. *Am J Clin Nutr*. (2016) 104:1014–22. doi: 10.3945/ajcn.116.130385

37. Larsen MS, Witard OC, Holm L, Scaife P, Hansen R, Smith K, et al. Dose-response of myofibrillar protein synthesis to ingested whey protein during energy restriction in overweight postmenopausal women: A randomized, controlled trial. *J Nutr*. (2023) 153:3173–84. doi: 10.1016/j.tjnut.2023.08.011

38. Hudson JL, Iii REB, Campbell WW. Protein distribution and muscle-related outcomes: Does the evidence support the concept? *Nutrients*. (2020) 12:1441. doi: 10.3390/nu12051441

39. Horstman AMH, Kouw IWK, van Dijk JW, Hamer HM, Groen BBL, van Kranenburg J, et al. The muscle protein synthetic response to whey protein ingestion is greater in middle-aged women compared with men. *J Clin Endocrinol Metab*. (2019) 104:994–1004. doi: 10.1210/jc.2018-01734

40. Witard OC, Jackman SR, Breen L, Smith K, Selby A, Tipton KD. Myofibrillar muscle protein synthesis rates subsequent to a meal in response to increasing doses of whey protein at rest and after resistance exercise. *Am J Clin Nutr*. (2014) 99:86–95. doi: 10.3945/ajcn.112.055517

41. Areta JL, Burke LM, Ross ML, Camera DM, West DW, Broad EM, et al. Timing and distribution of protein ingestion during prolonged recovery from resistance exercise alters myofibrillar protein synthesis. *J Physiol*. (2013) 591:2319–31. doi: 10.1113/jphysiol.2012.244897

42. Guo L, Quan M, Pang W, Yin Y, Li F. Cytokines and exosomal mirnas in skeletal muscle-adipose crosstalk. *Trends Endocrinol Metab*. (2023) 34:666–81. doi: 10.1016/j.tem.2023.07.006

43. Chakarov S, Bleriot C, Ginhoux F. Role of adipose tissue macrophages in obesity-related disorders. *J Exp Med*. (2022) 219:e20211948. doi: 10.1084/jem.20211948

44. Chavakis T, Alexaki VI, Ferrante AW. Macrophage function in adipose tissue homeostasis and metabolic inflammation. *Nat Immunol*. (2023) 24:757–66. doi: 10.1038/s41590-023-01479-0

45. Chaurasia B, Summers SA. Ceramides in metabolism: Key lipotoxic players. *Annu Rev Physiol*. (2021) 83:303–30. doi: 10.1146/annurev-physiol-031620-093815

46. Needham EJ, Hingst JR, Onslev JD, Diaz-Vegas A, Leandersson MR, Huckstep H, et al. Personalized phosphoproteomics of skeletal muscle insulin resistance and exercise links mindy1 to insulin action. *Cell Metab*. (2024) 36:2542–59:e6. doi: 10.1016/j.cmet.2024.10.020

47. Kistner TM, Pedersen BK, Lieberman DE. Interleukin 6 as an energy allocator in muscle tissue. *Nat Metab*. (2022) 4:170–9. doi: 10.1038/s42255-022-00538-4

48. Chen ZT, Weng ZX, Lin JD, Meng ZX. Myokines: Metabolic regulation in obesity and type 2 diabetes. *Life Metab*. (2024) 3:loae006. doi: 10.1093/lifemeta/loae006

49. Wang H, Guo S, Gao H, Ding J, Li H, Kong X, et al. Myostatin regulates energy homeostasis through autocrine- and paracrine-mediated microenvironment communication. *J Clin Invest*. (2024) 134:e178303. doi: 10.1172/JCI178303

50. Yang J, Vamvini M, Nigro P, Ho LL, Galani K, Alvarez M, et al. Single-cell dissection of the obesity-exercise axis in adipose-muscle tissues implies a critical role for mesenchymal stem cells. *Cell Metab*. (2022) 34:1578–93:e6. doi: 10.1016/j.cmet.2022.09.004

51. Henin G, Loumaye A, Leclercq IA, Lanthier N. Myosteatosis: Diagnosis, pathophysiology and consequences in metabolic dysfunction-associated steatotic liver disease. *Jhep Rep*. (2024) 6:100963. doi: 10.1016/j.jhepr.2023.100963

52. Goodpaster BH, Bergman BC, Brennan AM, Sparks LM. Intermuscular adipose tissue in metabolic disease. *Nat Rev Endocrinol*. (2023) 19:285–98. doi: 10.1038/s41574-022-00784-2

53. Gold RS, Unkart JT, Larsen BA, Price CA, Cless M, Araneta MRG, et al. Association of abdominal muscle area and density with glucose regulation: The multi-ethnic study of atherosclerosis (Mesa). *Diabetes Metab Res Rev*. (2022) 38:e3488. doi: 10.1002/dmrr.3488

54. Smith-Ryan AE, Hirsch KR, Cabre HE, Gould LM, Gordon AN, Ferrando AA. Menopause transition: A cross-sectional evaluation on muscle size and quality. *Med Sci Sports Exerc*. (2023) 55:1258–64. doi: 10.1249/MSS.0000000000003150

55. Hori M, Takahashi A, Hosoda K, Ogura M, Harada-Shiba M. A low-frequency Apob p.(Pro955ser) variant contributes to the severity of/variability in familial hypercholesterolemia. *J Clin Endocrinol Metab*. (2023) 108:422–32. doi: 10.1210/clinem/dgac572

56. Heymsfield SB, Gonzalez MC, Lu J, Jia G, Zheng J. Skeletal muscle mass and quality: Evolution of modern measurement concepts in the context of sarcopenia. *Proc Nutr Soc*. (2015) 74:355–66. doi: 10.1017/S0029665115000129

57. Canever JB, Lanferdini FJ, de Moura BM, Diefenthaeler F, Lima K. Influence of subcutaneous adipose thickness and dominance on reliability of quadriceps muscle quality in healthy young individuals. *J Ultrasound*. (2022) 25:513–9. doi: 10.1007/s40477-021-00615-6

58. Messina C, Albano D, Gitto S, Tofanelli L, Bazzocchi A, Ulivieri FM, et al. Body composition with dual energy X-ray absorptiometry: From basics to new tools. *Quant Imaging Med Surg*. (2020) 10:1687–98. doi: 10.21037/qims.2020.03.02

59. Guglielmi G, Ponti F, Agostini M, Amadori M, Battista G, Bazzocchi A. The role of Dxa in sarcopenia. *Aging Clin Exp Res*. (2016) 28:1047–60. doi: 10.1007/s40520-016-0589-3

60. Zhou Z, Moore TM, Strumwasser AR, Ribas V, Iwasaki H, Morrow N, et al. Muscle metabolic resilience and enhanced exercise adaptation by Esr1-induced remodeling of mitochondrial cristae-nucleoid architecture in males. *Cell Rep Med*. (2025) 6:102116. doi: 10.1016/j.xcrm.2025.102116

61. Romanello V, Sandri M. Implications of mitochondrial fusion and fission in skeletal muscle mass and health. *Semin Cell Dev Biol*. (2023) 143:46–53. doi: 10.1016/j.semcdb.2022.02.011

62. Mastrototaro L, Roden M. Insulin resistance and insulin sensitizing agents. *Metabolism*. (2021) 125:154892. doi: 10.1016/j.metabol.2021.154892

63. Hevener AL, Ribas V, Moore TM, Zhou Z. The impact of skeletal muscle Eralpha on mitochondrial function and metabolic health. *Endocrinology*. (2020) 161:bqz017. doi: 10.1210/endocr/bqz017

64. Singh A, Phogat J, Yadav A, Dabur R. The dependency of autophagy and ubiquitin proteasome system during skeletal muscle atrophy. *Biophys Rev*. (2021) 13:203–19. doi: 10.1007/s12551-021-00789-7

65. Zhang H, Qi G, Wang K, Yang J, Shen Y, Yang X, et al. Oxidative stress: Roles in skeletal muscle atrophy. *Biochem Pharmacol*. (2023) 214:115664. doi: 10.1016/j.bcp.2023.115664

66. Grozier C, Keen M, Collins K, Tolzman J, Fajardo R, Slade JM, et al. Rectus femoris ultrasound echo intensity is a valid estimate of percent intramuscular fat in patients following anterior cruciate ligament reconstruction. *Ultrasound Med Biol*. (2023) 49:2590–5. doi: 10.1016/j.ultrasmedbio.2023.08.027

67. Joshi AS, Tomaz da Silva M, Kumar S, Kumar A. Signaling networks governing skeletal muscle growth, atrophy, and cachexia. *Skelet Muscle*. (2025) 15:29. doi: 10.1186/s13395-025-00397-z

68. MacGregor K, Ellefsen S, Pillon NJ, Hammarstrom D, Krook A. Sex differences in skeletal muscle metabolism in exercise and type 2 diabetes mellitus. *Nat Rev Endocrinol*. (2025) 21:166–79. doi: 10.1038/s41574-024-01058-9

69. Sullivan BP, Larson AA, Shams AS, McMillin SL, Ebeling MC, Peng S, et al. Estradiol deficiency as a consequence of aging contributes to the depletion of the satellite cell pool in female mice. *Aging Cell*. (2025) 24:e14441. doi: 10.1111/acel.14441

70. Larson AA, Shams AS, McMillin SL, Sullivan BP, Vue C, Roloff ZA, et al. Estradiol deficiency reduces the satellite cell pool by impairing cell cycle progression. *Am J Physiol Cell Physiol*. (2022) 322:C1123–37. doi: 10.1152/ajpcell.00429.2021

71. Dam TV, Dalgaard LB, Johansen FT, Bengtsen MB, Mose M, Lauritsen KM, et al. Effects of transdermal estrogen therapy on satellite cell number and molecular markers for muscle hypertrophy in response to resistance training in early postmenopausal women. *Eur J Appl Physiol*. (2023) 123:667–81. doi: 10.1007/s00421-022-05093-0

72. Dewi L, Lin YC, Nicholls A, Condello G, Huang CY, Kuo CH. Pax7(+) satellite cells in human skeletal muscle after exercise: A systematic review and meta-analysis. *Sports Med*. (2023) 53:457–80. doi: 10.1007/s40279-022-01767-z

73. Tan L, Huang D, Liu B, Ossowski Z, Wang N, Yan W. The intensity of exercise and inflammation markers in women with overweight & obesity: A systematic review and network meta-analysis. *Int J Obes*. (2025) 49:1229–39. doi: 10.1038/s41366-025-01777-7

74. Malin SK, Haus JM, Solomon TPJ, Blaszczak A, Kashyap SR, Kirwan JP. Insulin sensitivity and metabolic flexibility following exercise training among different obese insulin-resistant phenotypes. *Am J Physiol Endocrinol Metab*. (2013) 305:E1292–8. doi: 10.1152/ajpendo.00441.2013

75. Ellulu MS, Patimah I, Khaza'ai H, Rahmat A, Abed Y. Obesity and inflammation: The linking mechanism and the complications. *Arch Med Sci*. (2017) 13:851–63. doi: 10.5114/aoms.2016.58928

76. Malandish A, Rahmati-Yamchi M. The effect of moderate intensity aerobic exercise on cardiovascular function, cardiorespiratory fitness and estrogen receptor alpha gene in overweight/obese postmenopausal women: A randomized controlled trial. *J Mol Cell Cardiol Plus*. (2022) 2:100026. doi: 10.1016/j.jmccpl.2022.100026

77. Chang YH, Yang HY, Shun SC. Effect of exercise intervention dosage on reducing visceral adipose tissue: A systematic review and network meta-analysis of randomized controlled trials. *Int J Obes (Lond)*. (2021) 45:982–97. doi: 10.1038/s41366-021-00767-9

78. Jayedi A, Soltani S, Emadi A, Zargar MS, Najafi A. Aerobic exercise and weight loss in adults: A systematic review and dose-response meta-analysis. *JAMA Netw Open*. (2024) 7:e2452185. doi: 10.1001/jamanetworkopen.2024.52185

79. Ji F, Lee HS, Kim JH. Resistance exercise and skeletal muscle: Protein synthesis, degradation, and controversies. *Eur J Appl Physiol*. (2025) 125:2353–82. doi: 10.1007/s00421-025-05832-z

80. Zhao F, Su W, Sun Y, Wang J, Lu B, Yun H. Optimal resistance training parameters for improving bone mineral density in postmenopausal women: A systematic review and meta-analysis. *J Orthop Surg Res*. (2025) 20:523. doi: 10.1186/s13018-025-05890-1

81. Razi O, Zamani N, Saeidi A, Hadjicharalambous M, Ayed K, Hackney AC, et al. Muscle insulin resistance elicits muscle atrophy in obesity. *Curr Obes Rep*. (2025) 14:80. doi: 10.1007/s13679-025-00672-6

82. Castillo IMP, Argiles JM, Rueda R, Ramirez M, Pedrosa JML. Skeletal muscle atrophy and dysfunction in obesity and type-2 diabetes mellitus: Myocellular mechanisms involved. *Rev Endocr Metab Disord*. (2025) 26:815–36. doi: 10.1007/s11154-025-09954-9

83. Allard C, Miralpeix C, Lopez-Gambero AJ, Cota D. Mtorc1 in energy expenditure: Consequences for obesity. *Nat Rev Endocrinol*. (2024) 20:239–51. doi: 10.1038/s41574-023-00934-0

84. Kokura Y, Ueshima J, Saino Y, Maeda K. Enhanced protein intake on maintaining muscle mass, strength, and physical function in adults with overweight/obesity: A systematic review and meta-analysis. *Clin Nutr ESPEN*. (2024) 63:417–26. doi: 10.1016/j.clnesp.2024.06.030

85. Zaromskyte G, Prokopidis K, Ioannidis T, Tipton KD, Witard OC. Evaluating the leucine trigger hypothesis to explain the post-prandial regulation of muscle protein synthesis in young and older adults: A systematic review. *Front Nutr*. (2021) 8:685165. doi: 10.3389/fnut.2021.685165

86. Agergaard J, Justesen TEH, Jespersen SE, Tagmose Thomsen T, Holm L, van Hall G. Even or skewed dietary protein distribution is reflected in the whole-body protein net-balance in healthy older adults: A randomized controlled trial. *Clin Nutr*. (2023) 42:899–908. doi: 10.1016/j.clnu.2023.04.004

87. Justesen TEH, Jespersen SE, Tagmose Thomsen T, Holm L, van Hall G, Agergaard J. Comparing even with skewed dietary protein distribution shows no difference in muscle protein synthesis or amino acid utilization in healthy older individuals: A randomized controlled trial. *Nutrients*. (2022) 14:4442. doi: 10.3390/nu14214442

88. Sanchis-Gomar F, Neeland IJ, Lavie CJ. Balancing weight and muscle loss in Glp1 receptor agonist therapy. *Nat Rev Endocrinol*. (2025) 21:584–5. doi: 10.1038/s41574-025-01160-6

89. Karakasis P, Patoulias D, Fragakis N, Mantzoros CS. Effect of glucagon-like peptide-1 receptor agonists and co-agonists on body composition: Systematic review and network meta-analysis. *Metabolism*. (2025) 164:156113. doi: 10.1016/j.metabol.2024.156113

90. Aronne LJ, Sattar N, Horn DB, Bays HE, Wharton S, Lin WY, et al. Continued treatment with tirzepatide for maintenance of weight reduction in adults with obesity: The Surmount-4 randomized clinical trial. *JAMA*. (2024) 331:38–48. doi: 10.1001/jama.2023.24945

91. Wilding JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, et al. Weight regain and cardiometabolic effects after withdrawal of semaglutide: The Step 1 trial extension. *Diabetes Obes Metab*. (2022) 24:1553–64. doi: 10.1111/dom.14725