Aging Pathobiology and Therapeutics 2026; 8(3): 283-292 ***283***
DOI: 10.31491/APT.2026.09.233

REVIEW

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Unveiling the gut–muscle–adipose axis in sarcopenic obesity: mechanisms of inter-organ crosstalk and perspectives on GLP-1-based therapeutics

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This article belongs to the Special Issue: Sarcopenia: unveiling mechanisms and perspectives

Abstract

Sarcopenia, an age-related loss of muscle mass, strength, and function, reflects failing inter-organ communication. Using sarcopenic obesity (SO) as a model, this review details multi-organ breakdown across three channels: hormonal (declining gut microbial metabolites weakening muscle TGR5/FXR signaling), neural (altered vagal afferent and sympathetic outflow), and immune/cytokine (visceral fat inflammation impairing insulin signaling, while ectopic myocyte lipids trigger MuRF1-mediated muscle breakdown). GLP-1 receptor agonists highlight network fragility, as aggressive therapy strips 20–40% of weight loss from lean tissue. Synthesizing evidence published from January 2000 to July 2026, including clinical and preclinical studies, clinical trials, and trial-derived analyses, and the 2022 ESPEN/EASO consensus criteria, we argue that models of inter-organ communication must reshape SO diagnosis and combination therapeutics.

Keywords: Sarcopenic obesity, gut–muscle axis, GLP-1 receptor agonists, inter-organ crosstalk, vagal afferent signaling, skeletal muscle atrophy

Introduction

Age-related alterations in glucose homeostasis have traditionally been described from an organ-specific perspective, with impaired pancreatic insulin secretion, inadequate hepatic suppression of glucose production, and reduced skeletal muscle glucose uptake viewed as largely independent abnormalities. Sarcopenic obesity (SO) challenges this conventional framework, as its metabolic and functional manifestations may arise from dysregulated signaling among the gut, visceral adipose tissue, skeletal muscle, and brain. This inter-organ crosstalk provides a broader framework for understanding the interconnected mechanisms underlying SO. Nutrient-sensing pathways connecting the gut, vagal afferents, and brainstem contribute to the regulation of feeding, glucose metabolism,

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Received: 30 July 2026 / Revised: 27 August 2026
Accepted:11 September 2026/Published:30 September 2026

and systemic energy homeostasis. In parallel, SO is an emerging public health problem in aging populations, characterized by the coexistence of excess adiposity and reduced muscle mass and function. Together, these perspectives provide a framework for considering how age-related changes in metabolic regulation may intersect with alterations in gut–brain signaling and systemic energy homeostasis [1, 2]. Accordingly, this review asks whether SO can be more appropriately understood as an interconnected disturbance of gut-derived biochemical, neural, and inflammatory signaling rather than simply as the coexistence of obesity and sarcopenia [1, 2]. We advance the conceptual hypothesis that dysfunction across these interacting signaling domains may jointly contribute to impaired muscle metabolism and that interventions targeting more than one node of this network may better preserve muscle during weight loss. This narrative review reframes SO as a problem of inter-organ communication, structured around the three signaling modalities central to this discussion: hormonal/biochemical, neural, and cytokine-mediated. It then examines a translational paradox: glucagon-like peptide-1 (GLP-1) receptor agonists influence hormonal, neural, and indirect inflammatory pathways while producing substantial weight loss that may include reductions in lean mass, raising the question of whether effects at one node of an inter-organ network may have consequences across other components [1-3].

Methodology

Information sources and search strategy

PubMed/MEDLINE, Scopus, and Web of Science were searched for literature published from January 2000 to July 2026. The search combined free-text terms, Boolean operators, and relevant Medical Subject Headings terms. The core search strategy was: ("sarcopenia" OR "sarcopenic obesity" OR "muscle wasting" OR "skeletal muscle") AND ("gut–brain axis" OR "gut–muscle axis" OR "visceral adipose tissue" OR "short-chain fatty acids" OR "SCFA" OR "*Akkermansia muciniphila*" OR "GLP-1" OR "GLP-1 receptor agonist") AND ("inter-organ communication" OR "inflammation" OR "proteostasis" OR "neural signaling" OR "biochemical signaling").

Study selection

Retrieved records were imported into reference management software and duplicates were removed. Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible articles. Reference lists of key mechanistic studies, reviews, and consensus papers were also examined to identify additional publications using related terms such as "cross-talk," "signaling axis," and "endocrine signaling." Selection was based on relevance and scientific quality as judged by the authors; record counts and a PRISMA-style flow diagram are not reported because this was a narrative review and was not conducted as a systematic review.

Eligibility criteria

Peer-reviewed English-language studies published between January 2000 and July 2026 were considered, including observational and retrospective studies, clinical trials, animal models, cellular assays, and tissue-explant studies. Studies were selected when they addressed mechanistic links between the gut, brain/brainstem, visceral adipose tissue, and skeletal muscle through metabolic, neural, inflammatory, or proteostatic pathways. Evidence involving short-chain fatty acids (SCFAs), weight-loss interventions, *Akkermansia muciniphila*, and GLP-1 receptor agonists was also considered. Authoritative reviews and consensus guidelines, including the 2022 European Society for Clinical Nutrition and Metabolism (ESPEN)/European Association for the Study of Obesity (EASO) consensus, were used to support definitions and the conceptual framework. Studies without relevance to skeletal muscle biology, sarcopenia, or SO, and those examining individual organs without evidence of inter-organ crosstalk, were excluded. Conference abstracts, editorials, non-peer-reviewed preprints, and articles without accessible full text were not considered.

Evidence synthesis

The selected literature was synthesized according to three major routes of inter-organ communication: biochemical/hormonal, neural, and inflammatory signaling. Human studies were used primarily to examine clinical and phenotypic findings, while animal, cellular, and tissue-based studies were used to clarify underlying molecular, intracellular, and proteostatic mechanisms.

The hormonal/biochemical channel: microbial metabolites and bile acid signaling

The gut functions as the network's initiating node rather than a passive backdrop. Aging shifts the microbiome toward fewer SCFA-producing taxa and a smaller secondary bile acid pool, and recent gut–muscle axis syntheses agree that the SCFAs acetate, propionate, and butyrate act as direct hormonal-biochemical regulators of muscle protein turnover, insulin sensitivity, and mitochondrial function, with sarcopenic cohorts showing measurably lower fecal SCFA-producing taxa and circulating SCFA levels than age-matched non-sarcopenic peers [4]. Secondary bile acids such as lithocholic acid activate Takeda G protein-coupled receptor 5 (TGR5) on muscle, and enteroendocrine L-cell signaling is linked to incretin output [3, 4], while experimental evidence indicates that lithocholic acid promotes skeletal muscle regeneration through TGR5 [5]. Gut-derived metabolite signaling of this kind is not restricted to muscle: comparable microbiome-derived metabolite networks contribute mechanistically to the gut–liver axis in metabolic dysfunction-associated fatty liver disease, indicating that such inter-organ metabolite signaling is a broader feature of gut–organ crosstalk [6]. Figure 1 provides a schematic overview of these three channels linking the gut, brain/brainstem, visceral adipose tissue, and skeletal muscle, and illustrates the multi-node actions of GLP-1 receptor agonists.

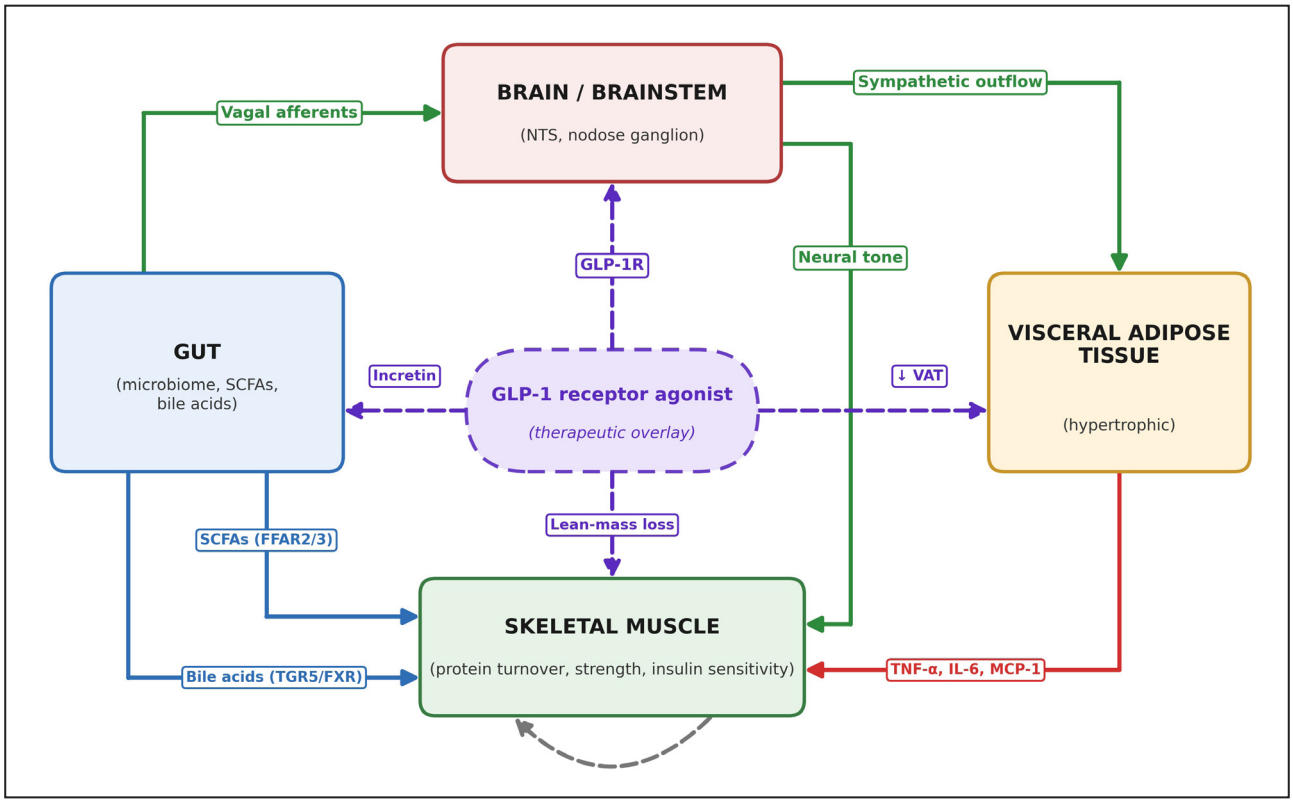

Figure 1. Inter-organ signaling between the gut, brain/brainstem, visceral adipose tissue (VAT), and skeletal muscle in sarcopenic obesity. Three routes of communication connect the four organs: biochemical/hormonal signaling (blue), in which bile acids act through TGR5/FXR and short-chain fatty acids (SCFAs) act through FFAR2/3; neural signaling (green), through vagal afferents, sympathetic outflow, and neural tone (neuromuscular output); and inflammatory signaling (red), involving TNF-α, IL-6, and MCP-1 released from hypertrophic VAT. GLP-1 receptor agonists (GLP-1 RA) are shown as a therapeutic overlay (dashed purple pill and arrows) rather than as a fifth organ. All purple arrows point away from the GLP-1 RA, indicating its actions at each site: incretin mimicry in the gut, neural GLP-1R signaling in the brain/brainstem, reduced visceral fat and inflammatory tone in VAT, and lean-mass loss in skeletal muscle. The grey dashed self-loop on skeletal muscle denotes the degraded signal associated with MuRF1/atrogin-1-mediated proteolysis. NTS, nucleus tractus solitarius.

Gut microbial alterations: an early associated disturbance

In older adults with low muscle mass and impaired physical performance, shotgun metagenomic analysis identified lower abundances of *Faecalibacterium prausnitzii*, *Roseburia inulinivorans*, and *Alistipes shahii*, taxa with relevant metabolic and SCFA-producing functions [7]. A separate study of sarcopenia or possible sarcopenia found lower abundances of several putative butyrate-producing genera, including *Roseburia*, *Eubacterium*, *Lachnospira*, *Fusicatenibacter*, and *Lachnoclostridium* [8]. A systematic review of seven human and five animal studies found that gut–microbiota alterations are associated with skeletal-muscle wasting across sarcopenia and other muscle-wasting conditions. In age-related sarcopenia, reductions in several SCFA-associated taxa, including *Lachnospira*, *Fusicatenibacter*, *Roseburia*, *Eubacterium*, and *Lachnoclostridium*, have been reported. These findings suggest that microbiome changes may contribute to the hormonal and biochemical disturbances linked to SO; however, the predominantly observational evidence does not establish whether such alterations precede, contribute to, or result from muscle decline [9]. Gut–microbiota dysbiosis has similarly been implicated in other hormonally driven metabolic conditions, such as polycystic ovary syndrome, where altered microbial composition is associated with insulin resistance and endocrine dysfunction, reinforcing the broader relevance of gut–hormone signaling disruption to metabolic disease [10].

Biochemical signals do not act only on muscle

SCFAs function as signaling molecules with effects extending beyond skeletal muscle to gut endocrine, immune, adipose, and neural/autonomic systems; for example, acetate and propionate stimulate GLP-1 secretion from enteroendocrine L-cells through FFAR2/GPR43-dependent mechanisms in murine cell and animal models [11]. Evidence for SCFA involvement in peptide YY (PYY) regulation includes reduced PYY expression in colonized *Gpr41*-deficient mice [12], while colonic infusion of SCFA mixtures increased fasting and postprandial plasma PYY in overweight or obese men [13]. SCFAs also regulate immune activity: butyrate inhibited pro-inflammatory mediator production in murine intestinal macrophages, and separately promoted differentiation of colonic regulatory T cells in mice [14]. In human adipose-tissue explants, propionate increased leptin expression and secretion while reducing resistin expression [15]. In the randomized crossover trial, colonic SCFA infusion also increased fat oxidation, increased energy expenditure with acetate- and propionate-rich mixtures, and reduced plasma

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glycerol, a marker of lipolysis [13]. Thus, SCFAs represent an upstream biochemical signal capable of influencing endocrine, immune, adipose, and metabolic processes, although their effects vary according to the individual SCFA, dose, tissue examined, host metabolic state, and experimental model. Diet-derived compounds can also modulate this axis: lutein supplementation has been shown to improve gut microbiota composition, hepatic oxidative metabolism, and growth performance in high-fat-diet-fed mice, indicating that nutritional strategies targeting the gut microbiome can influence metabolic organ function under obesogenic conditions [16].

Cross-talk with neural and immune signaling

Experimental evidence indicates that SCFAs, particularly propionate, can directly regulate sympathetic nervous-system activity through GPR41-mediated signaling at the level of sympathetic ganglia in mice [17]. Recent human evidence also supports an association between SCFA availability and sympathetic activity. In a study of 21 patients with resistant hypertension and 28 healthy controls, higher serum acetate concentrations were inversely associated with muscle sympathetic nerve activity (MSNA) burst frequency, providing preliminary human support for a link between SCFA signaling and sympathetic regulation; however, this association has not been established specifically in SO [18]. This potential autonomic pathway is relevant because sympathetic regulation influences adipose-tissue lipolysis, thermogenesis, energy expenditure, and neuroimmune signaling within adipose tissue [19]. Consequently, reduced SCFA availability in aging could plausibly affect metabolic and inflammatory regulation through concurrent endocrine, adipose, immune, and autonomic mechanisms; however, direct evidence establishing this specific SCFA → sympathetic → SO pathway in humans remains limited.

The neural channel: vagal afferents and sympathetic outflow

The neural channel represents an emerging and comparatively understudied component of the gut–brain–adipose network, linking gut-derived signals with vagal afferent and sympathetic pathways. GLP-1 receptors are expressed on vagal afferent neurons (VANs), whose cell bodies lie in the nodose ganglia; GLP-1 can activate gastric vagal afferents [20], while intraportal GLP-1 is detected through hepatic vagal pathways [21]. These findings support distinct gastric and hepatic vagal routes through which GLP-1-related signals may contribute to gut–brain communication. This gut–brain pathway has also been demonstrated directly in humans: a randomized, sham-controlled crossover study combining transcutaneous auricular vagus nerve stimulation with functional magnetic resonance imaging (fMRI) showed that stimulating the vagal afferent pathway increases stomach-brain coupling in the brainstem, midbrain, and transmodal cortex of healthy volunteers, with signal changes tracking changes in hunger ratings, providing direct human neuroimaging evidence for the gastric-afferent-to-brainstem relay described above [22]. Human evidence for GLP-1-related autonomic effects specifically is more recent but remains limited and indirect: a 2022 systematic review and meta-analysis found that GLP-1 receptor agonists increase heart rate in people with diabetes, based on heart-rate variability indices and cardiac autonomic reflex testing, without clear evidence of an altered sympatho-vagal balance [23]. However, available human studies generally use indirect autonomic measures, do not isolate vagal afferent function, and have not specifically examined people with SO; therefore, extrapolating these findings to muscle-related outcomes should be done with caution. This gut–brain neural circuitry is functionally connected with autonomic pathways that regulate adipose tissue lipolysis and lipogenesis: in rodent models, local lipolysis in white adipose tissue activates sensory afferent nerve fibers, and this afferent signal is relayed centrally to drive sympathetic outflow to a distant adipose depot [24]. Whether an analogous relay contributes to visceral fat expansion and the inflammatory arm of SO in humans has not been tested. Seen this way, GLP-1 receptor agonism may influence a neuro-hormonal circuit, with potential neural contributions to skeletal-muscle outcomes alongside direct metabolic effects; however, the relevance of these mechanisms to sarcopenic obesity remains poorly defined. At the adipose level, neural communication includes both afferent and efferent components: sensory projections from adipose tissue signal toward the brain, while sympathetic efferents independently regulate outflow to adipose depots, though whether these form a true closed feedback loop, rather than largely separate afferent (neural/hormonal) and efferent (sympathetic) channels, remains an active area of investigation [25]. Norepinephrine released from sympathetic nerve endings activates β-adrenergic signaling in adipocytes and regulates lipolysis, adipogenesis, browning, and thermogenesis; altered autonomic tone may therefore modify lipid flux, fat storage, and exposure of non-adipose tissues to circulating lipid substrates [26]. The neural adipose interface is also immunologically relevant: in lean male mice, sympathetic signaling through the β2-adrenergic receptor–protein kinase A pathway helped maintain an anti-inflammatory adipose-macrophage state by suppressing TNF-α expression [27]. Accordingly, the neural channel can be viewed as a bridge through which gut-derived hormonal signals may influence not only appetite and glucose regulation, but also adipose metabolic handling and inflammatory tone. However, most direct evidence for these neural–adipose–immune interactions comes from experimental models and obesity research rather than from studies specifically involving people with SO.

The cytokine/immune channel: adipo-myokine crosstalk and proteostatic failure

As visceral adipose tissue expands and becomes hypertrophic, its secretory profile shifts toward increased pro-inflammatory mediators, including TNF-α and IL-6. In obese elderly women, sarcopenic obesity was as-

sociated with higher IL-6 and lower muscle strength and lean body mass compared with non-sarcopenic obesity [28]. TNF-α can impair skeletal-muscle insulin signaling through IKKβ-dependent inflammatory pathways, with downstream effects on Akt/AS160 signaling and insulin-stimulated glucose uptake [29]. MCP-1, in contrast, primarily promotes monocyte recruitment and macrophage accumulation within adipose tissue and contributes to obesity-associated insulin resistance [30]. Within the muscle, ectopic lipid accumulation (myosteatosis) may further promote oxidative stress, insulin resistance, and muscle dysfunction, contributing to the progression of SO [31]. The inflammatory response should therefore not be regarded as an isolated third pathway. Rather, it represents a downstream tissue-level effector stage at which altered endocrine/metabolic signaling and dysregulated autonomic control may converge with adipocyte stress, immune-cell activation, lipid spill-over, and impaired muscle insulin action.

This process is also bidirectional, with adipose–muscle crosstalk potentially reinforcing inflammatory and metabolic dysfunction in sarcopenic obesity [31]. The resulting feedback loop links the three channels: microbiome-associated biochemical changes may influence incretin, metabolic, and immune signals; neural dysregulation may alter adipose lipid handling and inflammatory regulation; and the cytokine-rich adipose–muscle environment may subsequently worsen anabolic resistance, proteostatic failure, and metabolic dysfunction. Longitudinal evidence in older adults indicates that higher baseline inflammatory marker levels, particularly TNF-α, were associated with subsequent declines in muscle mass and strength over 5 years, although many associations were attenuated after adjustment for weight change [32]. While longitudinal human evidence links inflammatory markers with subsequent muscle decline, much of the mechanistic evidence for cytokine-mediated insulin resistance and inflammatory signaling derives from obesity or insulin-resistance models rather than SO-specific longitudinal studies. Although this integrated model is biologically plausible, further longitudinal studies are needed to determine the temporal order and relative contribution of each component in SO.

The GLP-1 paradox as a network-level failure

GLP-1 receptor agonists may influence all three channels through overlapping hormonal (incretin mimicry), neural (vagal afferent glucagon-like peptide-1 receptor [GLP-1R] engagement) [33, 34], and, indirectly, cytokine (reduced visceral fat lowers TNF-α/IL-6 tone). The vagal afferent mechanism is well described in neuroscience reviews of central GLP-1 signaling [33, 34]. Studies of weight loss and inflammation support the link between visceral fat loss and reduced adipose IL-6/TNF-α expression [35, 36]. However, lean-mass loss during GLP-1-associated weight reduction should not by itself be interpreted as proof that the network fails to rebalance, because some loss of lean tissue can accompany weight reduction achieved through diet, exercise, bariatric surgery, or pharmacotherapy alike, and is not unique to incretin-based mechanisms. Pharmacological reviews of obesity treatment confirm consistent reductions in visceral fat and improved glycemic control with GLP-1 therapy, but with lean tissue mobilized alongside fat, and mechanistic/clinical syntheses report that lean mass typically accounts for roughly one-fifth to two-fifths of total weight loss with these agents, a proportion that carries added risk for a patient already close to a frailty threshold, though not one that is necessarily specific to GLP-1 pharmacology itself [37]. Strength data add a further, more specific signal: short-to-mid-term trials in younger cohorts show handgrip strength relatively preserved despite falling lean mass [38], while a longitudinal cohort of older adults with type 2 diabetes showed measurable grip-strength decline with prolonged semaglutide exposure [39]. This indicates that strength (a neuromuscular-function output) and mass (a structural output) can move separately, and that monitoring one cannot substitute for the other. However, this dissociation is descriptive rather than proof of a network-specific failure mode.

A more direct test of whether muscle loss can be dissociated from weight loss itself, rather than assumed to be an unavoidable cost of it, comes from combination pharmacology that intervenes in the cytokine/growth-factor channel alongside the incretin channel. Bimagrumab, a monoclonal antibody targeting type II activin receptors, blocks myostatin/activin A signaling and promotes muscle hypertrophy while independently driving adipose lipolysis [40]. In diet-induced obese mice, combining activin-receptor blockade with GLP-1 agonism produced fat loss at least equal to GLP-1 monotherapy while preserving the lean mass that monotherapy did not [40]. This finding has since moved into phase 2 human obesity research: the randomized, placebo-controlled BELIEVE trial evaluated bimagrumab combined with semaglutide in adults with obesity, excluding participants with diabetes, rather than in a population specifically defined by SO. The combination produced greater total weight loss than semaglutide alone (−17.8 kg *vs.* −14.2 kg at week 48), with approximately 92.3% of weight loss attributable to fat mass versus 71.1% with semaglutide alone, while lean-mass loss was substantially smaller (−0.8% to −2.3% *vs.* −6.9%) [41]. Rather than demonstrating that GLP-1 monotherapy constitutes a network failure, this provides a useful experimental framework for testing whether muscle loss can be mechanistically separated from fat loss when a second node is targeted alongside the incretin pathway. The upstream, gut–microbiome side of the hormonal/biochemical channel remains comparatively unexplored in this context. A randomized, double-blind, placebo-controlled trial tested pasteurized *Akkermansia muciniphila* not during active weight loss but during the maintenance phase that follows it: adults with overweight/obesity who had already lost ≥ 8% of body weight on a low-energy diet were randomized to daily *A. muciniphila* Muc^{T} or placebo for 24 weeks. The *A. muciniphila* group regained significantly less weight (1.2 ± 0.7 kg *vs.* 3.2 ± 0.4 kg, $P = 0.012$), achieved greater net weight loss, and showed adipose-tissue gene-expression changes consistent with a less inflammatory profile

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[42]. The trial did not assess muscle or neural outcomes. However, no published human randomized trial has yet evaluated a gut–microbiome intervention combined with GLP-1 therapy, during treatment or withdrawal, specifically in an older population meeting criteria for sarcopenic obesity. Additional recent evidence on GLP-1-associated body-composition change and SCFA-mediated muscle regulation is summarized in Table 1.

Discussion

What the current evidence means for inter-organ communication models

Taken together, this evidence supports viewing SO as a network-level phenotype expressed through three coupled channels rather than as two co-occurring diseases. As discussed in Section "The GLP-1 paradox as a network-level failure", the BELIEVE trial is informative less for its weight-loss figures than for what it demonstrates structurally: fat loss and muscle preservation can be decoupled by intervening at a second network node, consistent with the possibility that lean-mass loss under GLP-1 monotherapy may reflect intervention at a single dominant network node rather than being an unavoidable cost of weight loss itself, though, as noted in Section "The GLP-1 paradox as a network-level failure", this remains a hypothesis the trial supports rather than one it directly proves. The vagal afferent and sympathetic adipose innervation literature further suggests that some of the variability in muscle outcomes across GLP-1 trials may be neurally, not only hormonally, mediated, a hypothesis current trial designs are not equipped to test, since none measure autonomic or vagal function alongside body composition [53, 54].

Why current practice is inadequate

Clinical and research practice have not kept pace with this network picture in three specific ways. First, glucagon-like peptide-1 receptor agonist (GLP-1 RA) prescribing in older adults is driven almost entirely by glycemic and weight targets, with body composition monitored only afterward, by which point lean tissue may already account for roughly one-quarter of the total weight lost [55]. Second, the dissociation between body weight and body composition demonstrates that scale weight or body mass index (BMI) alone cannot distinguish changes in a patient's fat mass from changes in muscle mass, underscoring the limitations of relying on weight-based metrics alone during obesity treatment [56, 57]. Third, and most specific to an inter-organ-communication framing, the neural chan-

Table 1. Evidence on GLP-1/incretin-associated lean-mass changes and short-chain fatty acid–mediated skeletal-muscle regulation.

Study (author, year)	Design	Key finding	Reference
Look *et al*., 2025	RCT DXA substudy (SURMOUNT-1)	Tirzepatide at week 72: fat mass−33.9% and lean mass−10.9% from baseline; ~75% of total weight lost was fat, and ~25% was lean tissue, with this proportion consistent across subgroups	[43]
Hidalgo Ramos *et al*., 2025	Systematic review of RCTs	Tirzepatide associated with fat-mass reduction and relative preservation of lean mass; muscle composition indicators stable or improved	[44]
Sattar *et al*., 2025 (SURPASS-3 MRI)	Post-hoc MRI substudy, phase 3 trial, T2D	Tirzepatide shifted body fat distribution favorably (visceral/liver fat loss); thigh muscle volume decline tracked the expected weight-loss relationship	[45]
De Girolamo *et al*., 2026	Narrative review	GLP-1 RAs reduce fat mass more than lean mass; function largely preserved; recommends resistance training and protein intake alongside therapy	[46]
Jensen *et al*., 2024	Secondary analysis, RCT (liraglutide ± exercise)	GLP-1 RA alone reduced hip/spine bone mineral density; combination with exercise preserved BMD despite larger weight loss	[47]
Jensen *et al*., 2026	Secondary analysis, RCT (liraglutide ± exercise)	Combined exercise + liraglutide improved functional performance and relative muscle strength versus liraglutide alone	[48]
Mechanick *et al*., 2025	Clinical review	Outlines strategies (nutrition, resistance exercise, monitoring) for minimizing muscle loss during incretin-mimetic therapy	[49]
Liu *et al*., 2025	Narrative review	Acetate enhances mitochondrial function; butyrate preserves muscle mass by suppressing inflammation/autophagy; propionate has mixed, dose-dependent effects	[50]
Frampton *et al*., 2020	Review	Foundational synthesis of how SCFAs (acetate, propionate, butyrate) regulate skeletal-muscle lipid, carbohydrate, and protein metabolism	[51]
Liu *et al*., 2024	Preclinical, sarcopenic mice	SCFAs enhanced muscle mass and function via mTOR pathway activation	[52]

Note: Lean-mass findings are reported using two different metrics that are not interchangeable: (i) percentage change from baseline in lean mass, and (ii) lean tissue as a percentage of total weight lost. In SURMOUNT-1, for example, lean mass fell by ~10.9% from baseline, whereas ~25% of the weight lost was lean tissue. DXA, dual-energy X-ray absorptiometry; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MRI, magnetic resonance imaging; RCT, randomized controlled trial; SCFA, short-chain fatty acid; T2D, type 2 diabetes.

nel remains essentially invisible in current SO research: a recent scoping review found no clinical study of GLP-1 RAs in older adults meeting SO criteria that included autonomic, vagal, or sympathetic outflow measures [58], despite mechanistic evidence placing this channel directly upstream of both satiety [59] and adipose lipolysis [60]. In other words, practice is still built around single-organ endpoints even though the underlying model is now explicitly a network one.

How diagnosis should change

The 2022 ESPEN/EASO consensus statement already provides part of the necessary infrastructure and should serve as the new baseline: it moves beyond BMI alone to a staged pathway that adds reduced handgrip strength, skeletal muscle mass, and elevated fat mass to initial BMI or waist-circumference screening, because weight-normalised muscle mass is more useful for identifying sarcopenic obesity than height-normalised mass in older adults [61, 62]. Two extensions follow from the network model developed here. First, we suggest that function be recorded at baseline and at regular intervals in individuals initiating GLP-1 receptor agonist therapy after midlife, as an expert-opinion extension of current practice, because changes in muscle strength and muscle mass may not occur in parallel [63]. Beyond this core clinical assessment, the network model suggests a potential role for multi-domain biomarker assessment in research settings. This is not proposed as a validated clinical diagnostic requirement, nor does it assume that biochemical, inflammatory, and neural markers provide interchangeable information. Rather, the purpose of assessing more than one domain is to distinguish potentially different patterns of dysfunction among individuals with otherwise similar fat mass, muscle mass, and functional impairment. For example, one individual may show a predominantly biochemical phenotype, characterized by altered SCFA or bile-acid status; another may show a predominantly inflammatory adipose–muscle phenotype, reflected by elevated IL-6, TNF-α, or selected myokines; and another may show evidence of altered autonomic regulation. Measuring only one marker, such as an SCFA, would identify a possible disturbance in microbial-metabolic signaling but would not indicate whether this disturbance coexists with inflammatory activation or altered neural regulation. The potential value of combining markers is therefore not to replace established diagnosis, but to characterize whether different biological processes converge in the same individual or whether one domain appears to predominate. Such information could help identify research-defined subgroups that are not distinguishable through body composition alone and could subsequently be tested for differences in progression, functional decline, or response to treatment. Accordingly, fat mass, skeletal-muscle mass, and muscle function should remain the basis of clinical diagnosis. Assessment of biochemical, cytokine, and autonomic markers should currently be confined to research settings, where prospective studies can determine whether these multi-domain phenotypes provide clinically meaningful information beyond conventional measures [64].

Perspectives: modeling the network and translational priorities

Three directions follow directly from this. Pharmacologically, activin-pathway co-therapy has progressed from a preclinical hypothesis to phase 2 human data within roughly two years, findings that, like the Akkermansia result described above, currently rest on a single trial and would benefit from independent replication and the logical next step is to test multinode combination regimens specifically in patients who already meet ESPEN/EASO SO criteria at baseline, rather than in general obesity cohorts where muscle preservation is only a secondary endpoint. Mechanistically, the vagal afferent and adipose-innervation literature makes the case for explicit systems modeling of this network, using quantitative frameworks treating gut hormonal output, vagal afferent firing, sympathetic adipose tone, and myokine/adipokine flux as coupled variables rather than separate research literatures, so that a GLP-1 RA's effect can be predicted as a network perturbation rather than measured only through a downstream weight-loss number [65-67]. This is as much a methodological gap as a conceptual one: continuous glucose and body-composition sensors are now routine, but comparable continuous or repeated measures of autonomic/vagal tone and circulating myokine/adipokine panels are not yet standard in metabolic trials, and closing that gap is a precondition for the network models this field increasingly requires. Microbially, the preclinical Akkermansia–GLP-1 RA combination study raises the translational question of whether restoring gut–axis signaling can be layered onto GLP-1 therapy to influence lean-mass preservation through the hormonal/biochemical channel rather than the activin/growth-factor channel; this hypothesis now requires testing in human, particularly sarcopenic-obese, populations. None of this argues against GLP-1 therapy in older adults; it argues against relying on a single-node hormonal tool for what is demonstrably a multi-channel communication network [68, 69].

Conclusions

SO reflects a systemic breakdown across interconnected biochemical, neural, and inflammatory channels rather than isolated multi-organ failures. While GLP-1 receptor agonists deliver substantial metabolic benefits, their use in vulnerable populations can be accompanied by clinically important lean-mass loss. Emerging multi-target strategies such as activin receptor blockade and gut microbiome modulation provide early proof-of-concept that fat reduction can be mechanistically decoupled from muscle erosion. Advancing SO management requires shifting from single-organ metrics to multi-domain network profiling, pairing ESPEN/EASO diagnostic criteria with multi-node therapeutic approaches to preserve skeletal muscle integrity while effectively reducing adiposity.

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Declarations

Acknowledgments: The authors would like to thank their university for the technical support.

Author contributions: Made substantial contributions to conception and design of the work, data curation and formal analysis, and drafted the manuscript: Krishnan A; developed the methodology and supervised and administered the project: Ranganathan V; performed the investigation, validation, and visualization: Sabarathinam S, Varadhan P; provided resources and software and performed formal analysis: Ganamurali N; substantively revised the manuscript: Ranganathan V, Sabarathinam S, Ganamurali N, Varadhan P.

Availability of data and materials: Not applicable.

Financial support and sponsorship: None.

Conflicts of interest: All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

AI and AI-assisted tools statement: AI tools were used only for grammar and language editing. The authors reviewed and approved all changes and take full responsibility for the final manuscript.

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Cite this article as: Krishnan A, Ranganathan V, Sabarathinam S, Ganamurali N, & Varadhan P. Unveiling the gut-muscle-adipose axis in sarcopenic obesity: mechanisms of inter-organ crosstalk and perspectives on GLP-1-based therapeutics. *Aging Pathobiol Ther*, 2026, 8(3): 283-292. doi: 10.31491/APT.2026.09.233