Muscle-liver-adipose immunometabolic crosstalk in diabetic sarcopenia: implications for amino acid–targeted nutrition

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Running title: Immunometabolic crosstalk in diabetic sarcopenia

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ABSTRACT

Background and Objectives: Sarcopenia is a frequent complication of type 2 diabetes mellitus, yet a paradox remains unexplained: increasing protein or amino acid supply has repeatedly failed in diabetes whereas exercise and glycemic control succeed. This narrative review addresses that gap by proposing that impaired metabolic permissiveness arises from maladaptive nutrient partitioning across muscle, liver, and adipose tissue, with anabolic resistance representing its muscle-level functional manifestation. **Methods and Study Design:** Evidence identified through a structured search of PubMed/MEDLINE, Web of Science, and Scopus from inception to August 2026, supplemented by reference-list hand-searching, was synthesized thematically around a proposed framework of compromised metabolic permissiveness. **Results:** Within muscle, lipid overload and inflammatory signaling blunt insulin-dependent protein synthesis and accelerate proteasomal degradation, while leucine sensing is preserved but operates at a raised anabolic threshold. Beyond muscle, inflamed adipose tissue supplies lipotoxic and inflammatory input, and upregulated hepatic alanine aminotransferase diverts muscle-derived amino acids toward gluconeogenesis, a mechanism causal in rodents and correlative in humans, redirecting substrate to defend glycemia rather than build protein. This proposed link would explain why amino acid supplementation alone has failed in diabetes. **Conclusions:** The framework attributes the failure of supplementation not to inadequate supply but to a raised threshold and competing hepatic demand. Effective nutrition must deliver a leucine-rich stimulus large enough to cross that threshold, appropriately dosed and distributed, and coupled to measures that reduce inflammation and hepatic substrate demand. Whether relieving that demand improves muscle outcomes remains untested.

Key Words: diabetic sarcopenia, type 2 diabetes mellitus, anabolic resistance, inter-organ crosstalk, metabolic permissiveness

INTRODUCTION

Diabetic sarcopenia is increasingly recognized as a clinically important phenotype in older adults with type 2 diabetes mellitus (T2DM), characterized by concurrent impairments in muscle mass, muscle strength, and physical performance within a background of chronic metabolic dysfunction.[1,2] This condition should not be reduced to a simple loss of lean tissue. Rather, current evidence supports a bidirectional relationship in which diabetes accelerates muscle deterioration, while skeletal muscle impairment worsens glucose disposal and

contributes to poorer systemic metabolic control.[3] Importantly, older adults with diabetes may exhibit reduced muscle strength and poorer muscle quality even when absolute muscle mass is not proportionately lower, indicating that diabetic muscle dysfunction cannot be understood solely in quantitative terms.[4] Together, these observations justify viewing diabetic sarcopenia as a distinct metabolic-musculoskeletal phenotype rather than as age-related sarcopenia occurring coincidentally in people with diabetes.

The pathophysiology of diabetic sarcopenia is now understood to be multi-organ and immunometabolic rather than confined to skeletal muscle alone. Insulin resistance, chronic low-grade inflammation and pro-inflammatory cytokine release, and mitochondrial dysfunction have been consistently identified as shared mechanisms linking T2DM and sarcopenia.[2,5] At the same time, adipose tissue, liver, and skeletal muscle act as endocrine organs that communicate through adipokines, hepatokines, and myokines, thereby shaping whole-body metabolic homeostasis through reciprocal inter-organ signaling.[6] This network is particularly relevant in diabetes, where disturbed lipid handling, ectopic fat deposition, and intramuscular fat accumulation alter muscle structure, impair intracellular signaling, and promote further insulin resistance and mitochondrial dysfunction, ultimately contributing to reduced muscle mass and strength.[7] Viewed in this way, diabetic sarcopenia reflects not merely defective muscle protein turnover, but a broader failure of metabolic coordination across adipose, hepatic, and muscular tissues.

This immunometabolic disruption has direct implications for the capacity of nutritional interventions to engage skeletal muscle. When inter-organ signaling is distorted, the tissue environment in which amino acid-sensitive pathways must operate is itself compromised: chronic inflammatory mediators and lipid-derived intermediates impair insulin signaling within myocytes, while mitochondrial dysfunction limits the energy availability required to sustain protein synthesis.[2,5] Human studies confirm that protein anabolism is abnormal in T2DM and that if such anabolic defects remain uncorrected, especially in the setting of aging, they may compromise muscle function and mass over time.[8–10] The limitations of an exclusively anabolic approach are illustrated by the finding that six months of leucine supplementation in elderly men with T2DM did not improve body composition, muscle mass, strength, glycemic control, or lipid profile.[11] Notably, those participants were non-sarcopenic and habitually consumed adequate dietary protein, a limitation later emphasized by Bassil and Gougeon,[8] which means that these null results cannot be attributed solely to a metabolically hostile environment. This finding is at least consistent with the possibility that anabolic

stimulation alone, delivered into a metabolically disrupted context, may not produce predictable muscle gains.

Although recent reviews have addressed components of its pathophysiology, comorbid management,[1] shared mechanisms,[2] mitochondrial dysfunction,[5] and adipose–muscle lipid effects,[7] none has positioned inter-organ substrate partitioning as the proposed proximate link between immunometabolic dysfunction and the failed anabolic response to nutrition. The present review addresses this gap by conceptualizing diabetic sarcopenia as a disorder of nutrient partitioning across the adipose–liver–muscle axis. We define metabolic permissiveness as the state of the systemic and intramuscular environment that allows skeletal muscle to convert a nutritional stimulus into net protein accretion. It is set by insulin signaling competence, inflammatory tone, bioenergetic capacity, and the amino acid supply remaining after competing organ demands, and is indexed operationally by the amino acid dose required to reach a given synthetic rate. Anabolic resistance is the functional readout of impaired permissiveness rather than a synonym for it. The central argument is that nutritional strategies should be judged by their capacity to restore permissiveness, not only to stimulate muscle protein synthesis (MPS). The principal novelty is the mechanistic prioritization of substrate partitioning, specifically the hepatic pull on muscle-derived amino acids, as a proposed proximate link between immunometabolic dysfunction and anabolic resistance. This prioritization is a hypothesis rather than an established finding: its component lesions are individually documented, but their integration is untested, and we distinguish throughout between what is demonstrated in humans, what is inferred from animal models, and what is proposed here (Figure 1). Validation of this inference awaits dedicated human tracer studies.

LITERATURE SEARCH AND SYNTHESIS APPROACH

This narrative review synthesizes mechanistic, translational, and clinical evidence linking inter-organ immunometabolic dysfunction to anabolic resistance in diabetic sarcopenia. A structured literature search was performed in PubMed/MEDLINE, Web of Science, and Scopus from database inception to August 2026, supplemented by targeted hand-searching of reference lists from identified reviews and seminal primary studies. Search terms combined the following keywords: "diabetic sarcopenia", "type 2 diabetes mellitus", "anabolic resistance", "skeletal muscle protein metabolism", "muscle protein synthesis", "leucine", "branched-chain amino acids", "mechanistic target of rapamycin complex 1 (mTORC1)", "metabolic inflexibility", "myosteatosis", "inter-organ crosstalk", "alanine aminotransferase", and "glucose–alanine cycle". Inclusion was restricted to English-language publications.

Priority was given to randomized controlled trials, meta-analyses, mechanistic human studies, and high-impact preclinical work directly relevant to the inter-organ framework. Foundational older publications were retained where they established conceptual or mechanistic precedent. Consistent with the narrative format, evidence was synthesized thematically around the proposed framework of compromised metabolic permissiveness rather than through formal systematic appraisal. No formal quality assessment or risk-of-bias scoring was performed, and quantitative meta-analysis was not feasible given the heterogeneous study designs. The full search strategy, including database-specific syntax, MeSH terms and limits, is provided as Supplementary Material 1.

DIABETIC SARCOPENIA AS A MULTI-ORGAN IMMUNOMETABOLIC PHENOTYPE

Insulin resistance and metabolic inflexibility across the adipose–liver–muscle axis

In diabetic sarcopenia, insulin resistance is best understood not as a defect of skeletal muscle alone but as a tissue-specific yet interconnected disturbance distributed across adipose tissue, liver, and muscle, with each compartment communicating through endocrine and metabolic signals that amplify systemic dysfunction.[12,13] Layered onto this is metabolic inflexibility—the impaired capacity to switch between glucose and lipid oxidation in response to changing nutrient and hormonal cues.[14] In human skeletal muscle, this manifests as a paradoxical pattern of elevated glucose oxidation in the basal state and reduced insulin-stimulated glucose oxidation, the original demonstration of muscular metabolic inflexibility in T2DM.[15] The defining metabolic feature of diabetic sarcopenia, therefore, is not nutrient scarcity but nutrient mismanagement: substrate is abundant, yet the tissues that should sense, route, and oxidize it have lost their coordinated capacity to do so.

Adipose tissue insulin resistance represents a major upstream contributor to this axis-level dysfunction. When adipocytes lose insulin-mediated suppression of lipolysis, free fatty acids are released into the circulation in excess of the storage and oxidative capacity of non-adipose tissues, a phenomenon described as lipid spillover.[13,16] In parallel, dysfunctional adipose tissue adopts an altered secretory profile, with diminished release of insulin-sensitizing adipokines such as adiponectin and increased output of pro-inflammatory mediators including tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6).[12] This combination of lipid surplus and aberrant endocrine signaling propagates outward across the axis: in the liver, sustained free fatty acid (FFA) delivery and inflammatory cues are associated with ectopic lipid accumulation, impaired suppression of hepatic glucose production, and altered hepatokine

output.16 In skeletal muscle, the same circulating signals impair insulin signaling and reduce substrate disposal capacity.[13] What begins as an adipose-driven disturbance thus becomes a coordinated metabolic dysfunction in which the liver and muscle do not merely participate but progressively amplify the original signal.

Skeletal muscle, as the largest site of postprandial glucose disposal, is the eventual integrator of these upstream perturbations. Insulin resistance reduces glucose uptake and glycogen synthesis, while the loss of metabolic flexibility constrains the muscle's ability to alternate efficiently between glucose and fatty acid oxidation in response to feeding, fasting, and physical demand.[14,15] The result is a tissue under chronic substrate and energy stress, in which neither fuel is optimally utilized and excess substrate is diverted toward ectopic lipid pools and inflammatory pathways. This persistent metabolic strain shapes the cellular environment in which the further disturbances of diabetic sarcopenia take root: chronic low-grade inflammation propagating from adipose and hepatic sources into muscle, progressive mitochondrial deterioration under sustained substrate overload and oxidative stress, and ectopic intramuscular lipid accumulation as the visible tissue-level manifestation of axis-wide metabolic failure. Insulin resistance and metabolic inflexibility provide an important systemic backdrop against which inflammation, mitochondrial dysfunction, and myosteatosis emerge, and within which the metabolic permissiveness of skeletal muscle's environment is progressively eroded.

Chronic low-grade inflammation

Type 2 diabetes mellitus is now recognized as a state of chronic low-grade inflammation, defined by sustained, low-amplitude elevations in circulating pro-inflammatory mediators, most notably IL-6, TNF-α, and C-reactive protein (CRP), that persist in the absence of overt infection.[3] Unlike acute inflammatory responses, this meta-inflammatory state functions as a continuous biological signal that progressively erodes tissue homeostasis in metabolically active organs. In older adults with T2DM, persistently elevated IL-6, TNF-α, and CRP are mechanistically linked to accelerated declines in muscle mass, reductions in muscle strength, and impaired physical performance, identifying inflammation as a central determinant of muscle deterioration in this population.[3,17] At the cellular level, these cytokines disrupt the balance between muscle protein synthesis and degradation, suppress regenerative capacity, and amplify intramuscular oxidative stress, thereby providing a pathophysiological feature that may accelerate muscle deterioration in diabetic sarcopenia.

The origins of this systemic inflammatory milieu can be traced upstream to adipose tissue dysfunction. In obesity and T2DM, hypertrophic, hypoxic, and macrophage-infiltrated adipose tissue exhibits sustained activation of the c-Jun N-terminal kinase (JNK) and nuclear factor-κB (NF-κB) signaling pathways, leading to transcriptional upregulation and secretion of TNF-α, IL-6, and interleukin-1β (IL-1β) into the systemic circulation.[18] Concurrently, the failure of dysfunctional adipocytes to buffer lipid surplus drives lipotoxic spillover of free fatty acids into the liver and skeletal muscle, where ectopic lipid intermediates further amplify inflammatory signaling and reinforce the circulating cytokine load.[19] When these adipose-derived inflammatory signals reach skeletal muscle, elevated TNF-α and IL-1β activate the ubiquitin-proteasome system, suppress insulin-like growth factor-1/protein kinase B (IGF-1/Akt)-mediated anabolic signaling, and accelerate myofibrillar protein degradation, ultimately tipping the protein turnover balance toward atrophy.[18] Adipose tissue therefore functions not merely as a coincident inflammatory compartment in T2DM but as the principal upstream initiator linking metabolic dysfunction to skeletal muscle deterioration.

The liver constitutes a critical amplifier of this cascade and a key inter-organ mediator linking adipose dysfunction to muscle decline. Hepatic insulin resistance and ectopic lipid accumulation—manifesting clinically as metabolic dysfunction-associated steatotic liver disease (MASLD), formerly non-alcoholic fatty liver disease (NAFLD)—develop in response to adipose-derived free fatty acid flux and inflammatory cytokine exposure, and the steatotic liver in turn becomes a secondary source of pro-inflammatory cytokines and dysregulated hepatokines.[19,20] Altered hepatokine signaling propagates insulin resistance and inflammatory tone to skeletal muscle, while concurrent hepatic dyslipidemia further entrenches intramyocellular lipotoxicity and impairs anabolic responsiveness.[20] The clinical relevance of this hepatic contribution is reflected in the high co-prevalence of MASLD and sarcopenia, in which each condition accelerates the progression of the other through shared mechanisms of insulin resistance, chronic inflammation, and disordered protein metabolism.[21] Taken together, these observations establish that chronic low-grade inflammation in diabetic sarcopenia is not a muscle-local phenomenon but an axis-level disturbance, in which interconnected adipose, hepatic, and muscular inflammatory signals collectively shape the trajectory of muscle deterioration in T2DM by progressively constraining the metabolic permissiveness on which anabolic responsiveness depends.

Mitochondrial dysfunction and energetic stress

Mitochondrial dysfunction is now recognized as a shared pathophysiological mechanism underlying both T2DM and sarcopenia and is increasingly considered an important contributing factor in diabetic sarcopenia.[2,5] In skeletal muscle of individuals with T2DM, mitochondrial impairment is characterized by reduced oxidative capacity, diminished adenosine triphosphate (ATP) production, and elevated generation of reactive oxygen species (ROS) that exceeds endogenous oxidant defenses.[5] These disturbances compromise muscle bioenergetics and have been associated with the inability to appropriately switch between glucose and lipid oxidation in response to changing nutrient and hormonal cues, a defining feature of metabolic inflexibility.[14] Because skeletal muscle is among the most metabolically demanding tissues in the body, even modest reductions in oxidative efficiency may compromise contractile performance, fatigue resistance, and the energy-dependent processes that sustain muscle remodeling, thereby suggesting a mechanistic link between cellular bioenergetic failure and impaired anabolic competence.

Importantly, the mitochondrial impairment observed in diabetic sarcopenia cannot be attributed solely to intrinsic muscle defects but is shaped by upstream disturbances across the adipose–liver–muscle axis. Adipose tissue dysfunction in obesity and T2DM promotes excessive free fatty acid release and intramyocellular lipid accumulation, which may contribute to mitochondrial substrate overload and oxidative stress within muscle.[19] Concurrently, hepatic dysfunction in the form of MASLD alters systemic substrate availability and hepatokine signaling, further influencing muscle oxidative metabolism and insulin responsiveness.[19,20] These adipose- and liver-derived perturbations propagate energetic stress into skeletal muscle through endocrine and metabolic routes. Importantly, these mechanisms are conceptually distinct from the inflammatory pathways described earlier, illustrating that mitochondrial impairment in diabetic sarcopenia is sustained by inter-organ disturbances rather than confined to muscle tissue.

The functional consequences of this axis-level mitochondrial impairment extend directly to the muscle's capacity to respond to nutritional stimuli. Reduced oxidative capacity and impaired substrate switching limit the metabolic flexibility required for efficient nutrient utilization,[14] while diminished ATP availability constrains the energetically demanding processes of MPS.[5] Although a direct causal link to anabolic resistance has not been definitively established, mitochondrial dysfunction may plausibly contribute to it by limiting the bioenergetic capacity required to sustain anabolic signaling and translation under nutrient stimulation.[2,5] Viewed together with adipose- and liver-derived mitochondrial stressors, this

evidence supports the concept that even when amino acids and other nutrients are sufficiently available, skeletal muscle in diabetic sarcopenia may be unable to mount an effective anabolic response because its energetic capacity is constrained by systemic metabolic disturbance. In this context, mitochondrial dysfunction may represent an important mechanistic link between multi-organ metabolic dysregulation and diminished metabolic permissiveness.

Intramuscular lipid accumulation and myosteatosis in diabetic sarcopenia

If mitochondrial impairment is the bioenergetic face of axis-level metabolic dysfunction, myosteatosis is its tissue-level morphological expression. Myosteatosis, the pathological accumulation of fat within and around skeletal muscle, has emerged as a prominent feature of impaired muscle quality in diabetic sarcopenia, distinct from changes in muscle mass alone. It encompasses three anatomically distinct depots: intermuscular adipose tissue between fascicles, intramuscular adipose tissue between fibers, and intramyocellular lipid within myocytes.[19] The clinical relevance of this distinction lies in the recognition that quantity and function dissociate in T2DM. In the Health, Aging, and Body Composition Study, older adults with T2DM had greater appendicular muscle mass than non-diabetic peers yet showed lower muscle strength and lower muscle quality, with further deterioration in those with longer disease duration or poorer glycemic control.[4] Reduced computed tomography (CT)-derived muscle attenuation, indicative of greater intramuscular lipid content, was similarly associated with lower knee extensor strength in the broader Health ABC cohort,[22] reinforcing the principle that fat-laden muscle performs less effectively than its mass alone would predict.

Mechanistically, myosteatosis can be understood as the muscular consequence of disordered lipid handling across the adipose–liver–muscle axis. When adipose tissue exceeds its expandable storage capacity, free fatty acids spill over into the liver and skeletal muscle, where ectopic accumulation occurs.[19] Within muscle, this excess lipid is associated with the generation of bioactive intermediates, including diacylglycerols and ceramides, that interfere with insulin signaling and contribute to local lipotoxicity.[19] Importantly, the metabolic impact of intramuscular lipid is not determined by quantity alone: trained athletes carry substantial muscle fat while remaining insulin sensitive, indicating that the metabolic characteristics and handling of lipid droplets may be as important as their absolute quantity.[7] In T2DM, by contrast, ectopic muscle lipids are metabolically and functionally consequential. Higher thigh intermuscular adipose tissue is associated with insulin resistance,[23] and patients with T2DM display reduced lower-limb muscle strength alongside increased intramuscular non-contractile tissue compared with matched controls.[24] These alterations occur within a muscle

environment already characterized by impaired oxidative capacity in diabetic sarcopenia,[5] potentially driving further lipid accumulation and metabolic dysfunction.

The downstream consequences of this lipid-laden state extend across the principal determinants of muscle quality. Intramuscular lipid accumulation has been associated with inflammation, oxidative stress, insulin resistance, and mitochondrial dysfunction, and ultimately with reduced muscle mass and strength.[7] Excess lipid deposition has likewise been linked to myocellular apoptosis and altered myokine secretion, perturbing the inter-organ signaling that defines the adipose–liver–muscle axis.[19] A direct causal relationship between myosteatosis and anabolic resistance has not yet been established. Nonetheless, impaired insulin responsiveness, compromised mitochondrial capacity, chronic inflammatory stress, and reduced metabolic flexibility collectively create a biological environment that may compromise the muscle's anabolic response to nutritional stimuli. Viewed in this light, myosteatosis is not a passive deposit but a tissue-level expression of systemic metabolic dysfunction—one in which the intramuscular environment that permits an anabolic response is constrained by the very lipid burden it accumulates.

WHY ANABOLIC RESISTANCE PERSISTS IN A DISTURBED METABOLIC MILIEU

The functional endpoint of the metabolic disturbances outlined above is anabolic resistance. Originally characterized in aging muscle as a blunted muscle protein synthetic response to dietary amino acids despite preserved basal synthesis,[25] the term denotes a state in which stimuli that should drive net protein accretion—feeding, amino acids, insulin, and contractile activity—produce a diminished response. In diabetic muscle, however, this resistance is not uniform across stimuli, and the distinction is mechanistically informative. The most directly demonstrated lesion is an insulin resistance of protein metabolism: under euglycemic, isoaminoacidemic, hyperinsulinemic clamp conditions, the normal insulin-mediated improvement in net protein balance is markedly attenuated in obese men with type 2 diabetes compared with non-diabetic controls.[26] Responsiveness to amino acids, by contrast, appears comparatively preserved: clamping circulating amino acids at postprandial concentrations restores the anabolic response and effectively overcomes this insulin resistance of protein metabolism,[27] and resistance exercise has been reported to elicit muscle protein synthetic responses that are broadly comparable to those of non-diabetic individuals.[8] This dissociation is the conceptual hinge of the present section: diabetic muscle largely retains the intrinsic capacity to respond to amino acids and exercise yet operates at a raised anabolic threshold

imposed by its metabolic surroundings—an environment that simultaneously blunts insulin-dependent anabolism and, as developed below, competes for the substrates that protein synthesis requires. Anabolic resistance, in this framing, is less a fixed property of the myocyte than the muscle-level manifestation of a disordered whole-body metabolic state: the failure of metabolic permissiveness defined earlier in this review (Figure 2). The cell-autonomous signaling lesion is examined first; its inter-organ drivers follow.

This dissociation directs attention to the proximal signaling lesion, which falls specifically on the insulin/IGF-1–phosphoinositide 3-kinase (PI3K)–Akt arm rather than on amino acid sensing. In human skeletal muscle, the fatty-acid surplus that accompanies adipose insulin resistance drives intramyocellular accumulation of diacylglycerol, which activates protein kinase C-θ (PKC-θ). PKC-θ in turn phosphorylates insulin receptor substrate-1 at serine 1101, impairing tyrosine phosphorylation and the downstream activation of Akt2.[28] A parallel sphingolipid route operates through ceramide, generated preferentially from saturated fatty acids, which inhibits Akt directly; in rodents, genetic or pharmacological blockade of ceramide synthesis is sufficient to restore insulin sensitivity and prevent diabetes, establishing ceramide as a causal intermediate rather than a bystander.[29] The inflammatory mediators that propagate from adipose tissue and liver act on the same node: TNF-α induces inhibitory serine phosphorylation of insulin receptor substrate-1 (IRS-1), converting it into an antagonist of insulin-receptor tyrosine kinase activity,[30] and the stress kinase JNK is a necessary mediator of obesity-associated insulin resistance in vivo.[31] Akt therefore becomes the principal metabolic convergence node through which lipid and inflammatory stress blunt insulin-dependent anabolism.

Because Akt sits at the point where insulin and IGF-1 signaling bifurcate into the promotion of synthesis and the restraint of degradation, its suppression carries a dual penalty. Diminished Akt activity lowers mTORC1 signaling and translational drive, while simultaneously failing to phosphorylate and exclude forkhead box O (FoxO) transcription factors from the nucleus, thereby de-repressing the atrophy-associated ubiquitin ligase Atrogin-1/MAFbx and muscle RING-finger protein-1 (MuRF1).[32,33] Inflammatory signaling reinforces these catabolic shifts along a partly Akt-independent route, as inhibitor of κB kinase β (IKKβ)/NF-κB activation induces MuRF1 and accelerates ubiquitin–proteasome proteolysis sufficiently to cause severe muscle wasting.[34] That precisely this configuration—reduced Akt and mTORC1 activity together with FoxO dephosphorylation and elevated Atrogin-1 and MuRF1—is observed in the skeletal muscle of diabetic db/db mice indicates that the convergence is not merely plausible but demonstrable in a diabetic mouse model.[35]

Anabolic signaling in diabetic muscle is therefore not simply weakened: the lipid- and inflammation-derived inputs that blunt synthesis are the same signals that actively drive degradation, so that anabolism is continuously antagonized rather than passively diminished.

This apparent dissociation can be understood through the architecture of nutrient sensing. Leucine signals to mTORC1 through a dedicated route, binding the sensor Sestrin2 and releasing it from GATOR2 to activate the Rag GTPases, an input that operates partly independently of the insulin–Akt–Rheb axis yet normally cooperates with it for full mTORC1 activation.[36] Diabetic muscle therefore retains leucine sensing but cannot reach full activation while Akt input is suppressed, so the response is blunted rather than absent, and the effective anabolic threshold rises. Chronic hyperinsulinemia and nutrient surplus compound this by keeping mTORC1 and its effector ribosomal protein S6 kinase 1 (S6K1) tonically engaged; activated S6K1 phosphorylates IRS-1 at Ser1101, throttling IRS-1 and Akt through a homeostatic negative feedback loop.[37] A pathway already near its ceiling retains little dynamic range to respond sharply to a meal. The branched-chain amino acids that should report nutrient sufficiency are themselves characteristically elevated in type 2 diabetes, reflecting impaired oxidative catabolism, and they reinforce this same feedback while contributing to insulin resistance.[38] The evidence here is discordant: in longitudinal diabetic cohorts, higher circulating BCAAs track with preserved rather than diminished muscle mass.[39] These apparently discordant findings may be reconciled by differences in study design and biological construct: the former derives largely from cross-sectional metabolomic studies of non-diabetic obesity, whereas the latter concerns longitudinal muscle trajectories in diabetes; moreover, circulating BCAA concentration is a poor proxy for intramuscular availability. The discordance nonetheless cautions against reading elevated BCAAs as simply harmful or simply protective, and locates the defect in the transduction of nutrient signaling rather than in its supply.

Inter-organ immunometabolic competition redirects nutrients away from muscle

These cell-autonomous lesions are sustained and amplified by signals from other organs, which is what makes anabolic resistance in diabetes systemic rather than muscle-intrinsic (Figure 2). Upstream, expanded and insulin-resistant adipose tissue exports excess fatty acids and inflammatory adipokines to muscle and liver, so that the ectopic lipid reaching myofibers continuously supplies the diacylglycerol and ceramide pools that drive the signaling lesion described above rather than constituting a separate problem.[13] Downstream, the liver competes directly for amino acid substrate. Hepatic gluconeogenic demand is chronically

elevated in type 2 diabetes despite nutrient abundance, with increased gluconeogenesis accounting for the bulk of the elevated glucose production characteristic of the disease.[40] Because skeletal muscle is the principal source of alanine, the dominant amino acid extracted by the liver for gluconeogenesis through the glucose-alanine cycle,[41,42] this demand places muscle protein in direct competition with glycemic maintenance. In T2DM, that competition is amplified: the hepatic alanine aminotransferase isoenzymes GPT and GPT2 are upregulated at the transcript, protein, and activity levels in both mice and humans, in proportion to homeostatic model assessment of insulin resistance (HOMA-IR) and glycemic severity, and under chronic glucagon and glucocorticoid drive.[43] The resulting catabolic pull accelerates transamination of muscle BCAAs to generate alanine for hepatic export, lowering muscle BCAA content and mTORC1 activity and depressing protein synthesis, all of which are reversed when hepatic alanine catabolism is silenced in mice.43 Amino acids that support protein accretion are thereby redirected to sustain glucose production, establishing a nutrient-allocation hierarchy in which muscle-derived amino acids are consequently recruited to support glycemic maintenance.

Taken together, the intracellular signaling lesion, the raised sensing threshold and the inter-organ substrate competition converge on a single state in which nutrient availability and nutrient utilization are decoupled. Diabetic muscle is not starved of amino acids; it is embedded in a metabolic and inflammatory environment that simultaneously antagonizes its anabolic machinery and diverts amino acid substrate toward hepatic glucose production. Anabolic resistance is therefore best understood not as a local failure of the myocyte but as the muscle-level readout of a maladaptive nutrient-partitioning state driven by inter-organ immunometabolic competition, in which the priorities of glycemic defense override those of muscle protein accretion. This reframing carries a direct therapeutic corollary: because the limiting step is the utilization and partitioning of amino acids rather than their supply, increasing provision alone may therefore be insufficient. Restoring anabolic responsiveness therefore requires acting on the environment that governs amino acid fate, a premise that motivates the nutritional strategies considered next.

IMPLICATIONS FOR AMINO ACID–TARGETED NUTRITION

The first corollary of a raised anabolic threshold is quantitative: each meal may need to deliver a sufficient amino acid stimulus to cross it. In healthy older men, maximal myofibrillar synthesis is reached only at about 0.40 g protein/kg per meal versus about 0.24 g/kg in the young, the shallower dose-response slope being the signature of anabolic

resistance.[44] Accordingly, intakes near 1.0 to 1.5 g/kg/day delivered as 25 to 30 g per meal are recommended for older adults.[45] Quality is as decisive as quantity. Because leucine is a key driver of the response, leucine enrichment allowed a 10 g protein dose to match 25 g of whey isolate for myofibrillar synthesis in older women,[46] and rapidly digested whey, which raises leucinemia more quickly, stimulated greater postprandial protein accretion than slower casein in older men.[47] Distribution matters independently: spreading protein evenly across meals rather than skewing it toward the evening increased 24-hour synthesis by roughly 25% in healthy adults.[48] These supply-side principles align with the one direct demonstration in diabetes, where raising amino acids to postprandial concentrations overcame the insulin resistance of protein anabolism.[27] Yet the response is finite: beyond the breakpoint surplus amino acids are oxidized rather than incorporated,[44] and six months of leucine supplementation in protein-replete, non-sarcopenic men with T2DM did not improve muscle mass or strength.[11] Optimizing dose, quality and timing is therefore necessary but not sufficient, directing attention to the metabolic environment in which these amino acids are used. Because the anabolic threshold in diabetic muscle remains unquantified, future dose-finding studies could evaluate stepwise protein doses of 0.4, 0.6, and 0.8 g/kg/meal, with appropriate renal and metabolic safety monitoring, to determine the dose at which the muscle protein synthetic response plateaus rather than assuming that the threshold established in healthy older adults applies to T2DM.

Because the supply-side response saturates, the more decisive lever is to lower the threshold itself, and two interventions do so by acting on the muscle and its environment rather than on substrate alone. The first is exercise. A single bout of resistance exercise raised the myofibrillar response to ingested whey at every dose in older men and extended their responsiveness to larger boluses, partially restoring the sensitivity that aging erodes,[49] and across trials protein supplementation augments the gains in muscle mass and strength achieved with resistance training, so the two are most effective in combination.[50] In T2DM the benefit is dual: sixteen weeks of progressive resistance training reduced glycated hemoglobin (HbA1c) from 8.7 to 7.6%, increased lean mass and muscle glycogen, and lowered medication requirements, acting at once on the anabolic deficit and on the glycemic and metabolic environment that sustains it.[51] The milieu can also be remodeled nutritionally: omega-3 fatty acids, which lower inflammatory tone and alter muscle membrane composition, augmented the mixed muscle protein synthetic response to a hyperinsulinemic-hyperaminoacidemic clamp in older adults without changing basal synthesis.[52] That endpoint was a synthetic rate under clamp rather than muscle mass or strength, and the participants

were non-diabetic, so its extension to diabetic sarcopenia remains inferential. These measures share a logic distinct from adding protein: they reduce the metabolic and inflammatory antagonism and raise the gain of the anabolic machinery, so that a given amino acid stimulus is converted more efficiently into muscle protein.

Clinical implications

The logic developed above imposes a caveat on the most supply-side intervention, the loading of branched-chain amino acids or leucine. The same BCAAs that participate in anabolic signaling, when chronically elevated in insulin-resistant states, have also been associated with and may contribute to metabolic dysfunction: circulating BCAAs are characteristically raised in obesity and T2DM and contribute to insulin resistance,[38] and in obese, insulin-resistant rats dietary BCAA restriction normalized skeletal muscle lipid handling and improved muscle insulin sensitivity.[53] In mechanistic terms, omega-3 supplementation and branched-chain amino acid restriction converge on improved metabolic efficiency from opposite directions, the former by lowering inflammatory antagonism to anabolic signaling, the latter by relieving the oxidative burden of amino acid disposal. Within the framework developed here, a BCAA surplus also reinforces the S6K1 negative feedback that throttles insulin signaling,[37] and could supply additional substrate to the hepatic alanine pull that redirects amino acids toward gluconeogenesis.[43] Indiscriminate loading therefore risks aggravating the environment that blunts anabolism rather than overcoming it. A third lever follows from the framework itself and remains almost untested: reducing the hepatic demand that competes for amino acids. Carbohydrate restriction is the intuitive candidate and improves glycemia modestly in type 2 diabetes, with a pooled HbA1c reduction of 0.29% that attenuates beyond three months.54 Its mechanistic premise, however, is only partly sound. Across eucaloric diets in healthy men, postabsorptive glucose production fell principally through suppression of glycogenolysis, whereas gluconeogenesis was minimally affected and was approximately 14% higher after severe carbohydrate restriction.[55] Improving glycemia should therefore not be assumed to relieve the gluconeogenic pull on muscle protein. The clearer route acts through hepatic lipids: in eleven people with T2DM, eight weeks of energy restriction lowered hepatic triacylglycerol from 12.8% to 2.9% and restored insulin suppression of hepatic glucose output from 43% to 74%,[56] although that study was uncontrolled, did not measure amino acid flux, and carries its own risk of lean mass loss. Alternative fuels are similarly unproven: in postabsorptive volunteers, long-chain but not medium-chain triglycerides reduced leucine oxidation, and infused D-β-hydroxybutyrate was similarly without effect,[57] so the amino-

acid–sparing rationale for medium-chain triglycerides is not supported by human tracer data. No strategy directed at hepatic substrate demand has been evaluated with amino acid flux as an outcome or tested in diabetic sarcopenia. Table 1 summarizes this evidence, pairing each mechanistic defect with the intervention that counteracts it, its dose, and the open question in diabetic sarcopenia. Pharmacological options are not considered here in detail but are not negligible. Pioglitazone halved hepatic fat and improved insulin suppression of endogenous glucose production in type 2 diabetes,[68] and sodium-glucose cotransporter-2 inhibitors reduce liver fat.[69] Whether either lowers the alanine pull is unknown, and glucagon-like peptide-1 receptor agonists carry the countervailing risk of lean-mass loss discussed below.[70]

In practice the framework implies three requirements. First, for future clinical trials, protein doses established in healthy older adults may be treated as starting points rather than assumed optimal targets in diabetic muscle, because the anabolic threshold in T2DM remains unquantified. Second, supply should be prescribed with resistance exercise rather than instead of it, because added protein has not improved muscle outcomes in T2DM where intake was already adequate or training was already present. Third, hepatic substrate demand is best addressed by lowering ectopic liver fat by means compatible with muscle preservation, rather than by carbohydrate restriction alone or by medium-chain triglyceride supplementation, neither of which has been shown to redirect amino acids toward muscle. High-dose branched-chain amino acid or leucine supplements should not be given to patients with poorly controlled diabetes unless accompanied by concurrent glycemic and anti-inflammatory improvement; in that setting they may reinforce insulin resistance and feed the hepatic alanine pull rather than overcome the anabolic threshold.

TRANSLATIONAL GAPS AND FUTURE DIRECTIONS

The clearest gap to emerge from this synthesis is conceptual. Every intervention with evidence in sarcopenic or diabetic muscle acts on the supply or on the myocyte; none has been evaluated against the inter-organ substrate diversion proposed here to contribute to diabetic sarcopenia, and the dietary strategies directed at hepatic demand discussed above have never been tested with amino acid flux as an outcome. That this diversion is modifiable is established in rodents: silencing the hepatic alanine aminotransferase in diabetic mice reverses both hyperglycemia and muscle wasting and restores protein synthesis,[43] whereas human evidence so far extends only to correlative GPT/GPT2 upregulation. The priority is to test whether the alanine pull can be relieved in humans, and whether doing so redirects amino acids toward muscle, ideally with tracer measurements of inter-tissue flux. This reframing

also predicts that part of the muscle benefit of glycemic control and of exercise derives from reduced hepatic amino acid demand rather than from anabolic stimulation alone.

Resolving these questions requires future trials, since almost all evidence comes from general sarcopenia; the few studies in T2DM are small and show that added protein confers little benefit once intake is adequate or exercise is present. Two design priorities follow. First, the anabolic threshold of diabetic muscle is unquantified: healthy older muscle plateaus near 0.4 g protein/kg/meal,[71] and the threshold in insulin-resistant muscle is hypothesized to be higher, so the repeated nulls may reflect sub-threshold dosing rather than true refractoriness, which dose-finding studies could resolve. Second, endpoints must move from mass and strength to mechanism, because body composition cannot distinguish insufficient supply from failed transduction; stable-isotope synthesis rates and biopsy signaling can. Since single-agent supply has consistently failed, the most informative trials will be factorial, combining threshold-crossing protein with exercise and glycemic or anti-inflammatory control. Two hypotheses follow directly and are testable with existing methods. Hepatic demand: in adults with type 2 diabetes and elevated HOMA-IR and hepatic fat, a 4-week low-energy diet sufficient to lower hepatic triacylglycerol augments the myofibrillar synthetic response to a standard 25 g whey bolus, measured by stable-isotope tracer, compared with eucaloric control. Raised threshold: the protein dose at which myofibrillar synthesis plateaus is higher in diabetic than in non-diabetic older muscle, testable by a dose–response design spanning 0.2 to 0.8 g protein/kg/meal with synthesis rate as the endpoint.

A final priority is set by the pace of the therapeutic change. Incretin-based therapies now central to diabetes and obesity care produce large weight loss, roughly a quarter of it lean mass,[70] risking accelerated muscle loss in the very population this review concerns; although that loss is proportional to total weight lost and muscle quality may improve, the absolute decrement matters in patients who are already sarcopenic. Whether threshold-crossing protein and resistance exercise can preserve muscle during pharmacological weight loss is untested in diabetic sarcopenia, while preclinical blockade of the activin and myostatin axis, endogenous brakes on muscle growth signaling through SMAD2/3, preserves muscle during glucagon-like peptide-1 (GLP-1) agonism,[72] showing that the inter-organ perspective extends to pharmacology. The broader implication is to treat diabetic sarcopenia not as a muscle disease to be corrected with more protein, but as a disorder of nutrient partitioning sustained by immunometabolic competition among muscle, liver, and adipose tissue. The task ahead is not to supply amino acids but to govern their fate: lowering the anabolic threshold, quieting the

inflammatory and lipotoxic signals that oppose synthesis, and relieving the hepatic demand that diverts substrate from muscle.

CONCLUSION

The evidence reviewed here supports the view that diabetic sarcopenia is not age-related sarcopenia occurring in diabetes: muscle mass is often preserved while strength and quality fall, insulin-dependent anabolic signaling is impaired while leucine sensing and contractile responsiveness are retained, and adding amino acid supply on top of adequate intake or exercise has not improved muscle outcomes, whereas exercise and glycemic control reliably do. What is strongly supported but not established in humans is the mechanism linking these observations. The framework proposes that hepatic gluconeogenic demand may compete for muscle-derived amino acids through glucagon- and corticosteroid-driven alanine aminotransferase upregulation, demonstrated causally in rodents and so far correlative in people. The hypothesis that this competition contributes to the limited response to amino acid supplementation awaits validation by dedicated human tracer studies; it organizes the existing evidence rather than following from it. Three gaps remain: no trial has measured amino acid flux as an outcome in diabetic sarcopenia, no dietary strategy directed at hepatic substrate demand has been tested for muscle outcomes, and the leucine dose needed to cross the threshold in insulin-resistant muscle is unknown. Testing whether relieving hepatic demand improves the muscle response to a fixed amino acid load would be the most direct test of the framework. Positioning diabetic sarcopenia within an inter-organ immunometabolic framework, rather than as an isolated muscle deficit, reorients both how the condition is studied and how it is treated.

SUPPLEMENTARY MATERIALS

All supplementary tables and figures are available upon request from the editorial office, and are also accessible on the journal's webpage (apjcn.qdu.edu.cn).

DISCLOSURE ON THE USE OF AI AND AI-ASSISTED TECHNOLOGIES

During the preparation of this manuscript, the authors used Claude Sonnet 4.5 (Anthropic, August 2026) for language refinement. Claude was not used to generate the study objectives, methodology, data, interpretations, or scientific conclusions. All scientific content, arguments, interpretations, and conclusions presented in this manuscript were developed by the authors.

The authors have reviewed and verified the output and take full responsibility for the content of this publication.

CONFLICT OF INTEREST AND FUNDING DISCLOSURE

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Table 1. Evidence and translational gaps for mechanism-targeted interventions in diabetic sarcopenia

Pathophysiological defect	Intervention (dose, duration)	Study design	Population	Muscle outcome†	Functional and metabolic outcome†	Open question in diabetic sarcopenia‡
Raised leucine–mTORC1 threshold [58]	Vitamin D and leucine-enriched whey protein supplement (per serving: 20 g whey, 3 g leucine, 800 IU vit D), 2×/day vs iso-caloric control, 13 wk; no exercise	Multicenter, double-blind RCT, n=380	Sarcopenic older adults (SPPB 4–9, low skeletal muscle mass index); diabetes status not specified	↑ appendicular muscle mass (secondary) +0.17 kg (95% CI 0.004–0.338), p=0.045	↑ chair-stand (secondary) −1.01 s (95% CI −1.77 to −0.19), p=0.018; ↔ handgrip strength (p=0.44) and SPPB (p=0.51), co-primary	Untested in T2DM; does insulin-resistant, higher-threshold muscle need a larger leucine bolus?
Inadequate protein intake (T2DM) [59]	Protein 1.2–1.5 vs 0.8–1.0 g/kg/day, 12 wk	Single-blind pilot RCT, n=26	T2DM, middle-aged and older adults (50–75 y) with low muscle mass, strength or performance	Controls ↓ appendicular lean mass (p=0.014), ↓ SMI (p=0.011)	Higher protein ↑ HGS (p<0.001), TUG (p<0.001), GS (p=0.011), SB (p=0.022); controls ↓ HGS (p=0.011); ↔ glucose, insulin, HOMA-IR, lipids and CRP in both groups	Prevented mass more than built mass; optimal target and renal/glycemic safety at higher intakes unresolved
Added supply along with exercise (T2DM) [60]	20 g whey protein isolate vs isocaloric 20 g maltodextrin, with resistance training 2×/wk, 12 wk	Triple-blind RCT, n=26	T2DM, older men (mean age 68 y)	↔ lean and fat mass, no between-group difference	↔ strength, functional tasks and glycemic control, no between-group difference; exercise load rose in both groups (p<0.001); Renal function unaffected	Was 20 g insufficient to cross the raised threshold, or is added supply ineffective once resistance training is present?
Added supply without exercise [61]	Dietary protein 1.3 vs 0.8 g/kg/day ± testosterone enanthate 100 mg weekly (2×2 factorial), controlled feeding, no exercise intervention, 6 mo	RCT, n=92	Functionally limited older men ≥65 y; 15% with diabetes (randomization stratified by diabetes status)	↔ whole-body lean mass (primary) +0.31 kg (95% CI −0.46 to 1.08), p=0.43; ↔ appendicular lean mass (p=0.89)	↔ strength, power, walking speed and stair-climbing power; ↓ fat mass −1.12 kg (95% CI −2.04 to −0.21), p=0.02	Confirms supply alone is insufficient; mandates concurrent exercise or environmental modification

ASMI, appendicular skeletal muscle mass index; AWGS, Asian Working Group for Sarcopenia; CRP, C-reactive protein; EAAs, essential amino acids; EWGSOP, European Working Group on Sarcopenia in Older People; GLP-1, glucagon-like peptide-1; GS, gait speed; HbA1c, glycated hemoglobin; HGS, handgrip strength; HOMA-IR, homeostatic model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; mTORC1, mechanistic target of rapamycin complex 1; PCr, phosphocreatine; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; RCT, randomized controlled trial; SB, standing balance; SGLT2, sodium-glucose cotransporter 2; SMD, standardized mean difference; SMI, skeletal muscle index; SPPB, Short Physical Performance Battery; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α; TUG, timed-up-and-go; vit D, vitamin D.

†Effect metric: values are standardized mean differences or mean differences with 95% CI from the cited meta-analyses, or absolute between-group changes from the cited individual trials; ↑, ↓ and ↔ denote the direction of effect. "Not assessed" indicates that the outcome domain was not measured in the cited study.

‡Synthesis: interventions with established efficacy in general sarcopenia remain largely untested in T2DM; where tested, adding protein on top of adequate intake or exercise has not improved muscle outcomes, whereas exercise and threshold-crossing or deficit-correcting nutrition have. Strategies directed at hepatic substrate demand alter glycemia and hepatic fat but have never been evaluated with amino acid flux or muscle outcomes as endpoints, and no intervention has been tested against the proposed inter-organ substrate-partitioning mechanism considered here to contribute to diabetic sarcopenia.

Table 1. Evidence and translational gaps for mechanism-targeted interventions in diabetic sarcopenia (cont.)

Pathophysiological defect	Intervention (dose, duration)	Study design	Population	Muscle outcome†	Functional and metabolic outcome†	Open question in diabetic sarcopenia‡
Lean-mass preservation during weight loss (T2DM) [62]	High- (40%) protein with ≥4 weekly servings of lean beef vs normal- (21%) protein excluding red meat, energy-restricted, 52 wk	RCT, n=106	T2DM, adults (75% women; mean BMI 39 kg/m²; users of GLP-1 and SGLT2 agents excluded)	Both groups ↑ fat-free mass as % of body weight (p<0.001; between-group p=0.689); Absolute fat-free mass fell in both (high-protein −1.8 kg, normal-protein −2.9 kg; between-group p=0.056)	↓ weight, fat mass, HbA1c, glucose, insulin and HOMA-IR in both groups; no between-group differences (p≥0.33)	Whether leucine-targeted protein preserves muscle during GLP-1/SGLT2-driven weight loss is untested
Anabolic resistance (pooled evidence) [63]	Whey protein 9.6–40 g/day, with or without resistance training vs isocaloric placebo or routine consultation	Meta-analysis, 10 RCTs, n=1154	Sarcopenic older adults (EWGSOP or AWGS criteria; community and hospital settings); diabetes status not specified	↑ appendicular skeletal muscle mass index (SMD 0.47, 95% CI 0.23–0.71); ↑ appendicular skeletal muscle mass (SMD 0.28, 95% CI 0.11–0.45); ↔ fat mass, weight and BMI	↑ gait speed (SMD 1.13, 95% CI 0.82–1.44); ↔ handgrip strength with whey protein alone; ↑ handgrip strength with added resistance training (SMD 0.67, 95% CI 0.29–1.04); ↓ IL-6; ↑ IGF-1	Few T2DM patients; added value of resistance training vs protein alone not isolated
Anabolic resistance + low-grade inflammation [64]	22 g whey + 10.9 g EAAs (4 g leucine) + 100 IU vit D once daily vs isocaloric placebo, with a controlled physical activity program, 12 wk	Double-blind, placebo-controlled RCT, n=130	Sarcopenic older adults (mean age 80.3 y); diabetes status not specified	↑ fat-free mass +1.7 kg (95% CI 0.9–2.5), p<0.001 (primary endpoint); ↑ relative skeletal muscle mass (p=0.009)	↑ handgrip strength (p=0.001) and activities of daily living (p=0.001); ↑ IGF-1 (p=0.002); ↓ CRP (p=0.038)	Multi-component design prevents attribution to any single nutrient; not tested in T2DM

Pathophysiological defect	Intervention (dose, duration)	Study design	Population	Muscle outcome†	Functional and metabolic outcome†	Open question in diabetic sarcopenia‡
Inflammatory tone and anabolic sensitivity [52]	Omega-3 fatty acids, 4 g/day (1.86 g EPA + 1.50 g DHA) vs corn oil, 8 wk	RCT, n=16	Non-diabetic, healthy older adults (65–84 y)	↔ basal muscle protein synthesis (p=0.80); ↑ clamp-stimulated synthesis, from 0.009 to 0.031 %/h above basal (p<0.01); ↔ no effect of corn oil on either measure	↔ body composition and basic metabolic variables over 8 wk	Effect shown on synthetic rate under clamp, not on mass or strength; participants non-diabetic

ASMI, appendicular skeletal muscle mass index; AWGS, Asian Working Group for Sarcopenia; CRP, C-reactive protein; EAAs, essential amino acids; EWGSOP, European Working Group on Sarcopenia in Older People; GLP-1, glucagon-like peptide-1; GS, gait speed; HbA1c, glycated hemoglobin; HGS, handgrip strength; HOMA-IR, homeostatic model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; mTORC1, mechanistic target of rapamycin complex 1; PCr, phosphocreatine; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; RCT, randomized controlled trial; SB, standing balance; SGLT2, sodium-glucose cotransporter 2; SMD, standardized mean difference; SMI, skeletal muscle index; SPPB, Short Physical Performance Battery; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α; TUG, timed-up-and-go; vit D, vitamin D.

†Effect metric: values are standardized mean differences or mean differences with 95% CI from the cited meta-analyses, or absolute between-group changes from the cited individual trials; ↑, ↓ and ↔ denote the direction of effect. "Not assessed" indicates that the outcome domain was not measured in the cited study.

‡Synthesis: interventions with established efficacy in general sarcopenia remain largely untested in T2DM; where tested, adding protein on top of adequate intake or exercise has not improved muscle outcomes, whereas exercise and threshold-crossing or deficit-correcting nutrition have. Strategies directed at hepatic substrate demand alter glycemia and hepatic fat but have never been evaluated with amino acid flux or muscle outcomes as endpoints, and no intervention has been tested against the proposed inter-organ substrate-partitioning mechanism considered here to contribute to diabetic sarcopenia..

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Pathophysiological defect	Intervention (dose, duration)	Study design	Population	Muscle outcome†	Functional and metabolic outcome†	Open question in diabetic sarcopenia‡
Inflammatory tone and anabolic sensitivity (pooled) [65]	Omega-3 monotherapy, EPA 0.12–4.9 g/day and DHA 0.12–2.1 g/day, various durations	Overview of reviews	Healthy adults and clinical populations; not diabetes-specific	↔ no consistent benefit for lean mass	↔ no consistent benefit for muscle strength or physical function	The acute synthetic effect has not translated into mass or function; no trial in diabetic sarcopenia
Bioenergetic deficit (phosphocreatine, PGC-1α) [66]	Creatine 0.1–0.14 g/kg/day or 5 g/day, no loading phase, + resistance training 2–3×/wk, 8–104 wk	Meta-analysis, 8 RCTs, n=482	Healthy untrained older adults and postmenopausal women (mean age ≥50 y); diabetes status not specified	↑ lean tissue mass (SMD 0.27, 95% CI 0.02–0.53), p=0.03	↑ lower-limb strength (SMD 0.29, 95% CI 0.00–0.57), p=0.05; ↔ upper-limb strength (p=0.08)	Creatine transport and PCr handling in diabetic muscle untested; effects without exercise unclear
Glycemic and inflammatory environment (T2DM) [67]	Resistance training vs non-exercise control; frequency and duration varied across trials (3×/wk, ≤12 wk identified as optimal on subgroup analysis)	Meta-analysis, 43 RCTs, n=2012	T2DM, middle-aged and older adults (≥50 y; mean age 57.8 y)	↑ muscle mass +0.89 kg	↑ upper-body (SMD 2.28) and lower-body (SMD 2.02) strength; ↓ HOMA-IR −1.15; ↓ HbA1c −0.55%; ↓ fasting glucose −6.99 mg/dL; ↓ insulin −1.35 µIU/mL; ↓ BMI −0.37 kg/m²; ↓ CRP (SMD −0.80); ↔ TNF-α and IL-6	CRP fell but TNF-α and IL-6 did not; optimal modality and protein co-prescription in diabetic sarcopenia undefined
Hepatic gluconeogenic demand [54]	Low- to moderate-carbohydrate diets, ≥3 mo (no arm sustained <10% of energy as carbohydrate)	Meta-analysis, 27 RCTs, n=2870	T2DM, adults	↓ weight −1.72 kg (95% CI −2.55 to −0.88); ↓ BMI, waist circumference and body fat percentage, all attenuating beyond 3–6 mo	↓ HbA1c −0.29% (95% CI −0.45 to −0.14), largest at 3 mo and attenuating thereafter; ↓ fasting glucose −7.12 mg/dL	Glycemic benefit without evidence of reduced gluconeogenic flux; muscle outcomes not reported

ASMI, appendicular skeletal muscle mass index; AWGS, Asian Working Group for Sarcopenia; CRP, C-reactive protein; EAAs, essential amino acids; EWGSOP, European Working Group on Sarcopenia in Older People; GLP-1, glucagon-like peptide-1; GS, gait speed; HbA1c, glycated hemoglobin; HGS, handgrip strength; HOMA-IR, homeostatic model assessment of insulin resistance; IGF-1, insulin-like growth factor 1; IL-6, interleukin-6; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; mTORC1, mechanistic target of rapamycin complex 1; PCr, phosphocreatine; PGC-1α, peroxisome proliferator-activated receptor-γ coactivator-1α; RCT, randomized controlled trial; SB, standing balance; SGLT2, sodium-glucose cotransporter 2; SMD, standardized mean difference; SMI, skeletal muscle index; SPPB, Short Physical Performance Battery; T2DM, type 2 diabetes mellitus; TNF-α, tumor necrosis factor-α; TUG, timed-up-and-go; vit D, vitamin D.

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Pathophysiological defect	Intervention (dose, duration)	Study design	Population	Muscle outcome†	Functional and metabolic outcome†	Open question in diabetic sarcopenia‡
Hepatic gluconeogenic demand (mechanism) [55]	Eucaloric diets varying in carbohydrate (85%, 44%, 2%; 15% of energy as protein), 11 d each	Mechanistic tracer study, n=6	Non-diabetic, healthy men	Not assessed	↓ glucose production 13.0 → 11.4 → 9.7 µmol/kg/min across the three diets, falling principally via glycogenolysis (7.5 → 5.9 → 3.4 µmol/kg/min, $p<0.001$); ↑ gluconeogenesis ~14% on 2% carbohydrate vs control (p=0.001); ↔ high-carbohydrate vs control	Carbohydrate restriction lowers glycemia without relieving the gluconeogenic pull; alanine flux not measured, and not studied in T2DM
Hepatic gluconeogenic demand (ectopic liver fat) [56]	Energy restriction, 600 kcal/day, 8 wk	Single-arm mechanistic study, n=11	T2DM, adults (mean age 49.5 y)	Not assessed	Hepatic triacylglycerol 12.8% → 2.9% at 8 wk (p=0.003); Insulin suppression of hepatic glucose output 43% → 74% after 1 wk (p=0.003; non-diabetic comparators 68%)	Whether lowering hepatic fat redirects amino acids toward muscle is untested; lean-mass cost of severe restriction unquantified
Amino acid sparing by alternative fuels [57]	Infused long-chain triglyceride 0.15 g/kg/h vs 50:50 medium-chain/long-chain mixture 0.15 g/kg/h vs D-β-hydroxybutyrate 540 µmol/kg/h vs saline	Tracer infusion study, n=4–6 per arm	Non-diabetic, healthy postabsorptive volunteers	Leucine oxidation ↓ with LCT (0.31 → 0.24 µmol/kg/min, p<0.01); ↔ with MCT–LCT despite matched free fatty acids; ↔ with D-β-hydroxybutyrate and saline	Not assessed	Single dose only; higher ketone concentrations untested; no MCT trial in sarcopenia or T2DM

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Table 1. Evidence and translational gaps for mechanism-targeted interventions in diabetic sarcopenia (cont.)

Pathophysiological defect	Intervention (dose, duration)	Study design	Population	Muscle outcome†	Functional and metabolic outcome†	Open question in diabetic sarcopenia‡
Inter-organ alanine pull and substrate partitioning (diabetes-specific lesion)	No intervention has been tested against this target	—	—	—	—	No nutritional or pharmacological strategy has been evaluated against the inter-organ alanine pull in a clinical setting. The dietary strategies above address hepatic demand in general, not alanine diversion specifically, and none reports amino acid flux

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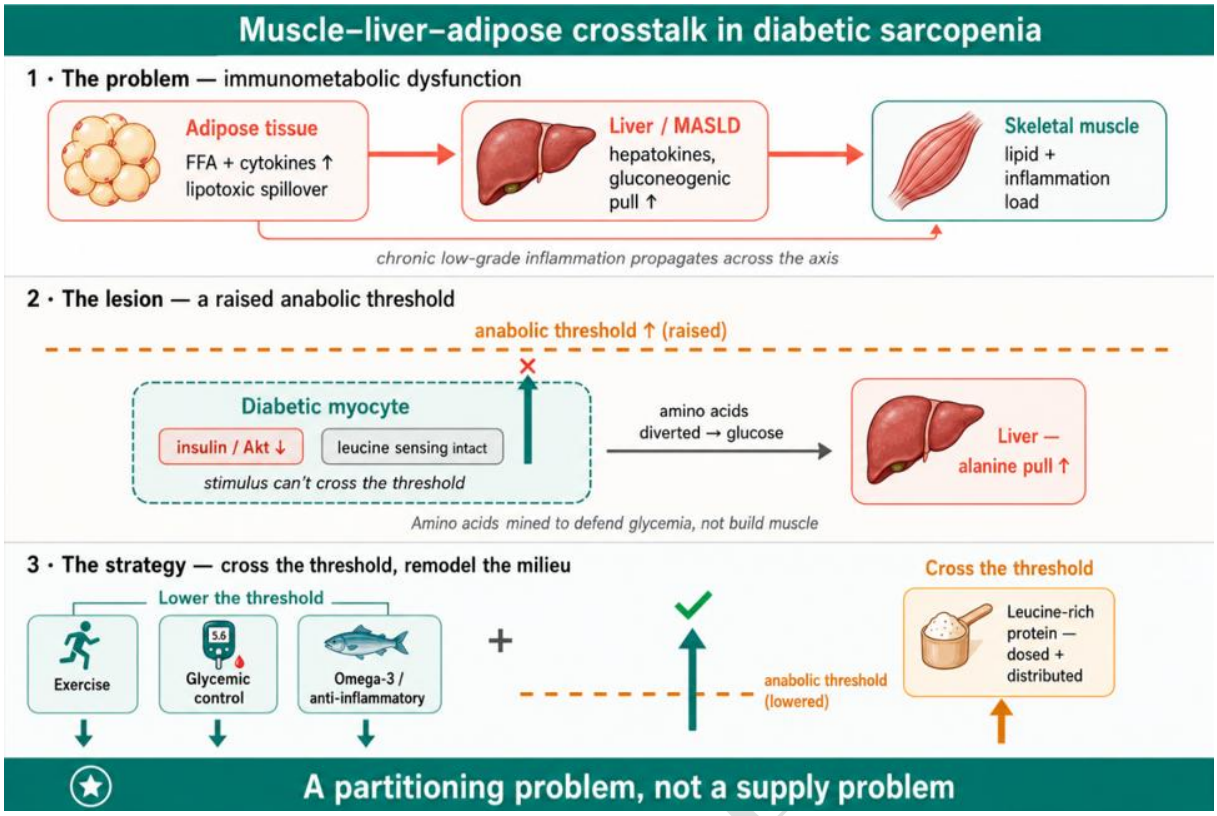

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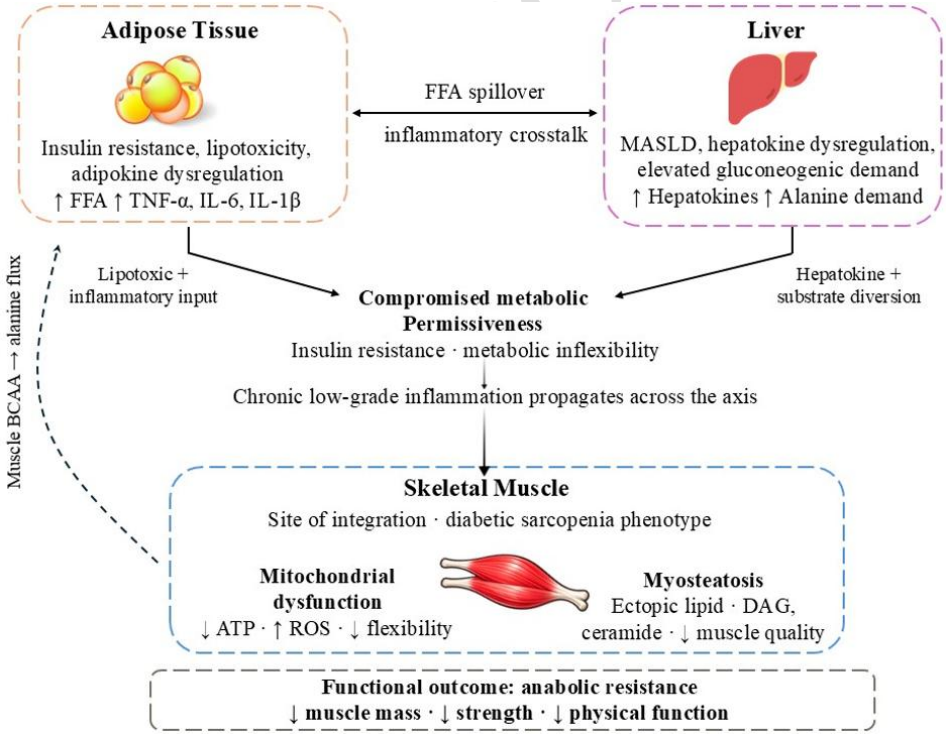

Figure 1. Diabetic sarcopenia arises from coordinated dysfunction across three metabolically active tissues. Insulin-resistant adipose tissue exports free fatty acids and pro-inflammatory adipokines (TNF-α, IL-6, IL-1β) into the systemic circulation, while the steatotic liver, manifesting clinically as metabolic dysfunction-associated steatotic liver disease (MASLD), contributes dysregulated hepatokines and an elevated demand for gluconeogenic substrate. These two tissues are linked by a continuous lipotoxic and

inflammatory crosstalk that propagates across the axis as chronic low-grade inflammation. Both organs converge on a central pathophysiological state, compromised metabolic permissiveness, as defined in the Introduction. Insulin resistance and metabolic inflexibility constitute the systemic backdrop of this state. Skeletal muscle integrates these upstream perturbations, with mitochondrial dysfunction and myosteatosis as the principal tissue-level manifestations. A dashed feedback loop indicates that muscle-derived branched-chain amino acids are diverted toward hepatic alanine production, a diversion driven by glucagon- and corticosteroid-mediated upregulation of hepatic alanine aminotransferase (GPT/GPT2) and previewing the inter-organ substrate-partitioning lesion. The net functional outcome is anabolic resistance, expressed clinically as reduced muscle mass, strength, and physical function.
BCAA, branched-chain amino acid; DAG, diacylglycerol; FFA, free fatty acids; IL, interleukin; MASLD, metabolic dysfunction-associated steatotic liver disease; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α

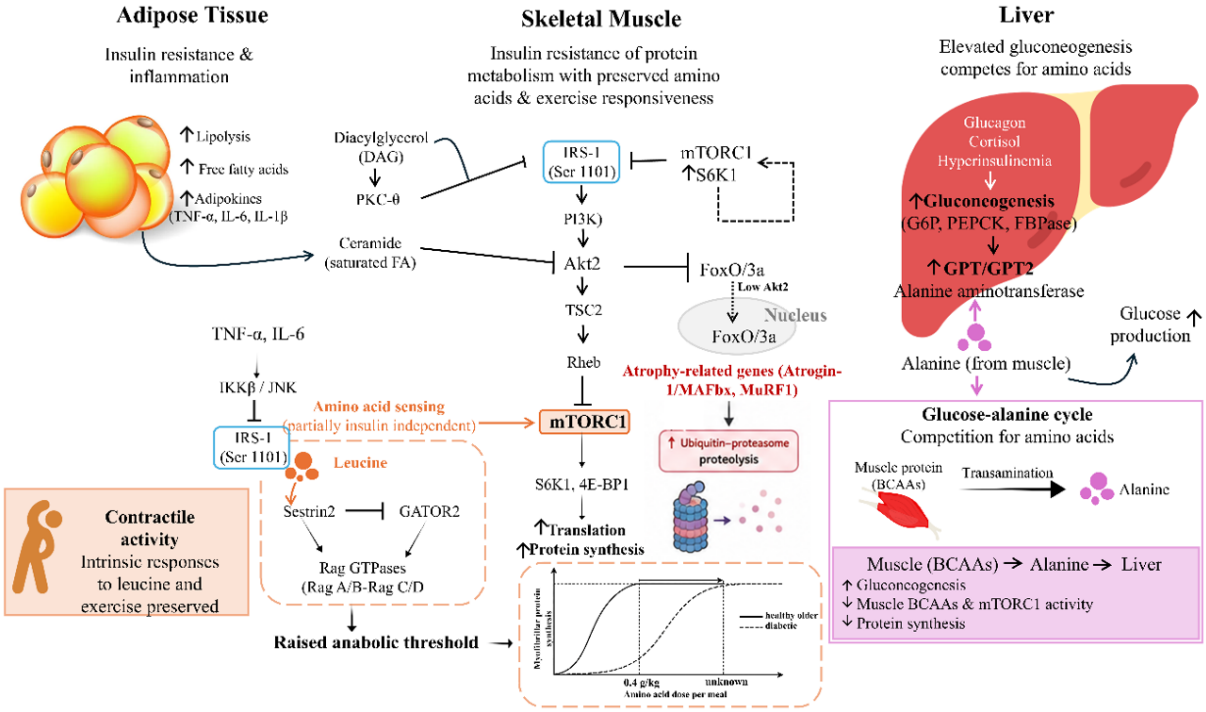

Figure 2. Anabolic resistance in diabetic skeletal muscle as a selective insulin-signaling lesion with inter-organ substrate competition. In type 2 diabetes, adipose tissue insulin resistance supplies free fatty acids and pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) to skeletal muscle. Diacylglycerol activates PKC-θ, which inhibits IRS-1 via Ser1101 phosphorylation; ceramide, generated in parallel from saturated fatty acids, inhibits Akt2 directly and TNF-α/IL-6 activates IKKβ and JNK, which converge on the same inhibitory IRS-1 site. The resulting suppression of Akt2 carries a dual penalty: reduced mTORC1-driven translation and loss of FoxO1/3a inhibition, the latter permitting FoxO nuclear translocation, induction of atrophy-related genes (Atrogin-1/MAFbx and MuRF1), and ubiquitin–proteasome proteolysis. An mTORC1–S6K1 feedback loop further phosphorylates IRS-1 at Ser1101, narrowing the dynamic range of insulin signaling. The leucine-sensing arm (Sestrin2–GATOR2–Rag GTPases) is preserved but cannot fully activate mTORC1 while Akt2 is suppressed, raising the anabolic threshold rather than abolishing the response; resistance exercise and clamped postprandial amino acids similarly retain efficacy, identifying the lesion as insulin-specific. In parallel, the liver competes for muscle-derived amino acids; glucagon, cortisol, and hyperinsulinemia upregulate gluconeogenic enzymes and the alanine aminotransferase GPT/GPT2, accelerating transamination of muscle BCAAs to alanine for hepatic export and depressing muscle BCAA content and mTORC1 activity. The net phenotype is anabolic resistance with blunted insulin/feeding responses, relatively preserved amino acid and exercise responsiveness, and a nutrient-allocation hierarchy favoring glycemic defense over muscle protein accretion. Inset: schematic dose–response of myofibrillar protein synthesis to increasing amino acid availability. The diabetic curve is displaced rightward with a preserved maximal response, illustrating a raised anabolic threshold rather than an abolished one. Curves are illustrative and not drawn to scale; the threshold in diabetic muscle is unquantified.
Abbreviations: 4E-BP1, eukaryotic translation initiation factor 4E-binding protein 1; BCAAs, branched-chain amino acids; DAG, diacylglycerol; FA, fatty acid; FBPase, fructose-1,6-bisphosphatase; GPT/GPT2, glutamic-pyruvic transaminase 1 and 2; IGF-1, insulin-like growth factor 1; IKKβ, inhibitor of NF-κB kinase subunit beta; IL, interleukin; IRS-1, insulin receptor substrate-1; JNK, c-Jun N-terminal kinase; mTORC1, mechanistic target of rapamycin complex 1; PEPCK, phosphoenolpyruvate carboxykinase; PI3K, phosphoinositide 3-kinase; PKC-θ, protein kinase C-θ; Rheb, Ras homolog enriched in brain; S6K1, ribosomal protein S6 kinase 1; TNF-α, tumor necrosis factor-α; TSC2, tuberous sclerosis complex 2