Review

Pyroptosis and HMGB1 Signaling in T2DM-Related Sarcopenia: Current Evidence, Mechanistic Framework, and Exercise Implications

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Abstract: The pathological mechanisms of type 2 diabetes mellitus (T2DM)-related sarcopenia are complex. Classical explanations based on insulin resistance, mitochondrial dysfunction and impaired protein turnover do not fully explain the chronic inflammatory microenvironment observed in diabetic skeletal muscle. Inflammatory cell death and damage-associated molecular pattern responses have attracted increasing attention in metabolic disease research. Evidence from diabetic muscle models, insulin resistance models and other diabetic complications suggests that pyroptosis-related signaling and high mobility group box 1 (HMGB1)-associated inflammatory responses may participate in the metabolic-inflammatory environment associated with T2DM-related sarcopenia. Direct evidence from human skeletal muscle remains limited, and the relationship between these processes has not been clearly defined in this condition. This narrative review summarizes current evidence for inflammasome- and gasdermin-related pyroptotic signaling, HMGB1-associated damage signaling and their potential relevance to diabetic skeletal muscle. It also discusses exercise as a modulator of upstream metabolic and inflammatory stress, including mitochondrial dysfunction, oxidative stress, autophagic flux and selected inflammasome-related markers. Finally, given the current lack of direct skeletal muscle evidence, future research directions are proposed to inform future mechanistic studies and the rational design of exercise interventions for T2DM-related sarcopenia.

Keywords: type 2 diabetes; sarcopenia; pyroptosis; HMGB1; exercise intervention

1. Introduction

Currently, the global aging population is accelerating, and type 2 diabetes mellitus (T2DM) has become one of the most prevalent chronic metabolic disorders among the elderly [1]. The International Diabetes Federation projects that the number of elderly diabetes patients will continue to rise over the coming decades [2]. Clinical practice reveals that T2DM patients frequently experience progressive skeletal muscle mass loss and functional decline, a phenomenon termed 'T2DM-related sarcopenia' [3]. Research indicates that T2DM patients face a significantly heightened risk of developing sarcopenia compared to non-diabetic individuals. This comorbid condition not only exacerbates the risk of falls, fractures, and physical disability but also serves as a major contributor to deteriorating quality of life and increased mortality among elderly patients [4,5]. Clinical and longitudinal evidence indicates that older adults with T2DM may experience accelerated loss of skeletal muscle mass, muscle strength and muscle quality, a phenotype increasingly described as T2DM-related sarcopenia [4,6]. T2DM-specific systematic reviews and meta-analyses further show that individuals with T2DM have a higher risk of sarcopenia than non-diabetic individuals [3]. Clinically, sarcopenia is associated with adverse outcomes such as falls, fractures, physical disability and mortality in older adults [7,8], while diabetic sarcopenia has been reported to impair function and quality of life in people with T2DM [4]. Cohort evidence also links sarcopenia in T2DM with increased mortality [9]. However, the metabolic disorder hypothesis alone struggles to fully account for the specific 'inflammaging' and persistent microenvironmental immune dysregulation observed in T2DM skeletal muscle. Recent advances in immunometabolism have introduced novel perspectives. Accumulating evidence from

metabolic disease models suggests that pyroptosis-related signaling, particularly that involving NOD-like receptor family pyrin domain-containing 3 (NLRP3) inflammasome activation, may represent one potential mechanistic link between metabolic stress and inflammatory tissue injury. In the setting of T2DM-related sarcopenia, however, the extent to which this process is engaged within skeletal muscle remains insufficiently defined [10]. Alongside inflammasome-related signaling, high mobility group box 1 (HMGB1) is a nuclear protein that can function as a damage-associated molecular pattern (DAMP) after extracellular release. Under cellular stress, HMGB1 may enter the extracellular compartment through passive release from pyroptotic, necrotic, or late apoptotic cells, as well as through stress-induced secretion by immune cells, thereby linking cellular injury to downstream innate immune activation [11,12]. Evidence from diabetic complications such as nephropathy, cardiomyopathy and retinopathy further indicates that inflammasome activation, gasdermin-mediated pyroptotic signaling and HMGB1-associated inflammatory responses can occur under sustained metabolic stress. These findings provide useful biological context for considering related processes in diabetic skeletal muscle. However, the extent to which pyroptosis-related signaling and HMGB1-associated responses are coordinated within skeletal muscle in T2DM-related sarcopenia remains insufficiently defined [10,13–15]. In light of these considerations, the present article provides a narrative review of current evidence on pyroptosis-related signaling and HMGB1-associated inflammatory responses in T2DM-related sarcopenia, with emphasis on their possible convergence in diabetic skeletal muscle, the limitations of existing evidence, and the potential relevance of exercise-responsive regulatory nodes.

2. Pathological Characteristics of T2DM-Related Sarcopenia

Whereas primary sarcopenia is largely driven by age-related hormonal decline, reduced physical activity and nutritional deficiencies, T2DM-related sarcopenia is increasingly discussed as a metabolically modified form of muscle loss with distinct histological and metabolic features [16]. Epidemiological observations and muscle biopsy studies suggest that the progression of muscle deterioration in individuals with T2DM cannot be fully explained by chronological aging alone [17]. Its main features include: (1) muscle fibre-type and metabolic remodeling, with human skeletal-muscle biopsy studies reporting reduced oxidative type I fibre proportion or oxidative function and, in some cohorts, a relative shift toward fast glycolytic type II fibres, including type IIx-classified fibres in adult human limb muscle, accompanied by reduced oxidative capacity and impaired insulin-stimulated glucose handling [18–21]; (2) pronounced intramuscular and perimysial fat infiltration, with substantial lipid accumulation between muscle bundles and within myofibres; (3) mitochondrial dysfunction, including reduced mitochondrial content, disrupted cristae architecture, impaired oxidative phosphorylation and defective fatty-acid β-oxidation [13]; (4) impaired insulin/insulin-like growth factor 1 (IGF-1) signaling and imbalance of protein metabolism, reflected by reduced phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt)/mechanistic target of rapamycin (mTOR) activity, enhanced forkhead box O (FOXO)-dependent proteolytic pathways, and overactivation of the ubiquitin–proteasome system (UPS) and autophagy-lysosome dysfunction; (5) systemic and local chronic inflammation, with persistently elevated concentrations of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6) and other mediators, consistent with inflammaging. Collectively, these alterations furnish both anatomical and molecular substrates for the loss of muscle mass and strength observed in patients with T2DM, and imply that the underlying mechanisms reflect the combined action of multiple metabolic and inflammatory networks rather than a single pathway. These characteristic alterations are summarized in Figure 1.

The relationship between T2DM and sarcopenia appears to be complex and potentially bidirectional, although the precise causal sequence remains incompletely defined. Metabolic disturbances associated with T2DM, including impaired insulin and IGF-1 signaling, may influence skeletal-muscle protein turnover and metabolic regulation [22]. Insulin and IGF-1 are key regulators of muscle anabolism and can promote protein synthesis while limiting proteolysis through activation of the PI3K/Akt pathway [23]. When this signaling is impaired, FOXO-dependent transcriptional programs that regulate proteolytic systems may become more active, thereby favoring muscle protein degradation [24]. Hyperglycemia has also been reported to influence muscle metabolism through transcriptional regulators such as Kruppel-like factor 15 (KLF15), which may enhance ubiquitin-proteasome activity in certain contexts [25]. Chronic inflammation represents another important feature of the diabetic metabolic milieu. Elevated levels of cytokines such as TNF-α and IL-6 have been associated with enhanced proteolytic signaling and activation of inflammatory transcription factors including nuclear factor-κB (NF-κB) [14]. NF-κB signaling has also been linked to oxidative stress responses and may influence the expression of inflammasome-related molecules, including NLRP3, in several tissues [26]. In parallel, activation of stress-related kinases such as c-Jun N-terminal kinase (JNK) has been reported to suppress anabolic signaling in skeletal muscle [27]. Nutritional and lifestyle factors may further modulate these processes. Diets rich in saturated lipids or reduced availability of short-chain fatty acids have been associated with enhanced inflammatory responses,

which could potentially aggravate muscle metabolic dysfunction [28]. In addition, alterations in transforming growth factor-β (TGF-β) superfamily signaling have been implicated in muscle-mass regulation. An imbalance between catabolic myostatin/activin–Smad2/3 signaling and anabolic BMP-Smad1/5/8 signaling may shift skeletal-muscle homeostasis toward reduced muscle growth and increased wasting [29–31]. Lifestyle-related factors may further contribute to this pathological environment. Reduced physical activity can diminish the activity of metabolic regulators such as AMP-activated protein kinase (AMPK) and peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α), which are important for mitochondrial function and energy metabolism [32]. Excessive lipid exposure has also been linked to mitochondrial stress and altered dynamics, including increased activity of dynamin-related protein 1 (DRP1), which may contribute to impaired muscle metabolism [33]. Epidemiological studies further indicate that individuals with T2DM have an increased risk of muscle weakness and functional limitation, while low muscle mass itself is associated with a higher likelihood of impaired glucose tolerance or future T2DM. These observations support the possibility of a self-reinforcing interaction between metabolic dysfunction and muscle loss [34,35].

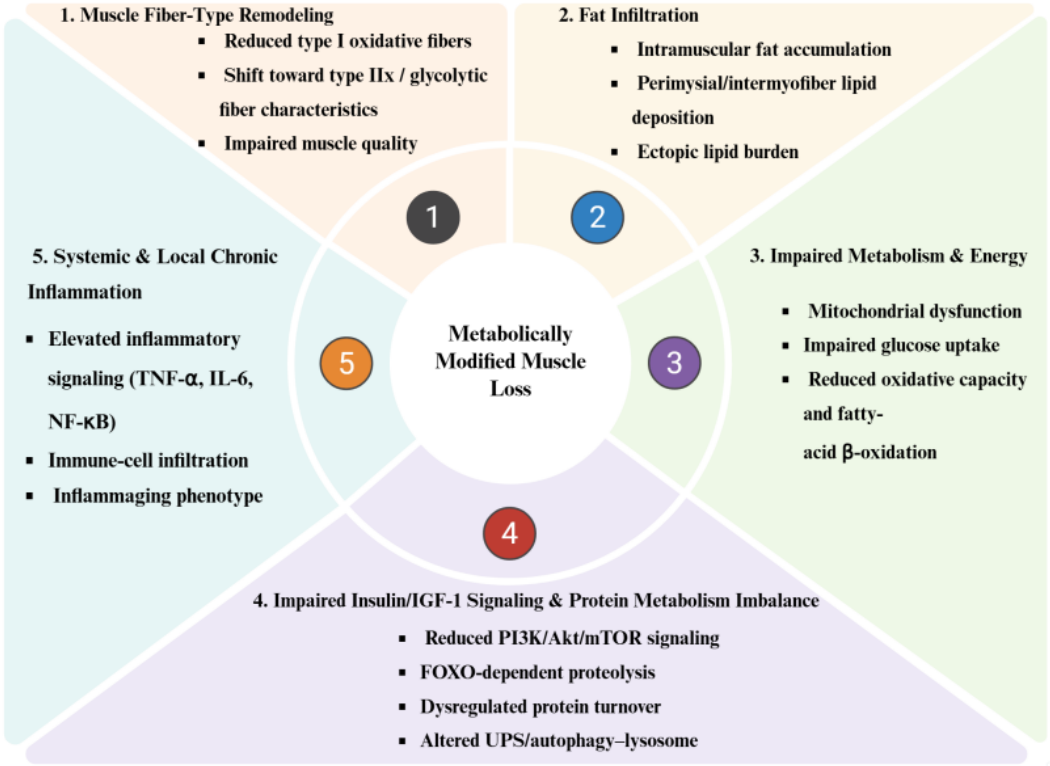

Figure 1. Pathological characteristics of T2DM-related sarcopenia.

3. Pyroptosis Signaling in Metabolic Inflammation

Pyroptosis is defined as a distinct form of regulated cell death, fundamentally differing from apoptosis and necrosis in both morphology and molecular mechanisms [36,37]. The process is initiated by the activation of inflammatory caspases within inflammasome complexes and is subsequently executed by members of the gasdermin (GSDM) family. Cleaved gasdermins migrate to the plasma membrane, forming pores that trigger cell swelling, membrane rupture, and the release of cytoplasmic contents—including potent pro-inflammatory mediators [38]. Although pyroptosis has been extensively studied in immune cells and various inflammatory diseases, its precise role in skeletal muscle pathology remains incompletely defined.

3.1. Fundamental Pathways of Pyroptosis

Among the various inflammasome complexes, the NLRP3 inflammasome is the most extensively investigated in metabolic disorders. It is commonly described as a cytosolic multiprotein platform composed of NLRP3, apoptosis-associated speck-like protein containing a CARD (ASC), and pro-caspase-1. Its activation usually involves two functional steps: a priming signal that increases the transcription of NLRP3 and pro-interleukin-1β (IL-1β), and an activation signal that promotes assembly of the NLRP3-ASC-pro-caspase-1 complex and caspase-1 cleavage [39]. In metabolic disorders such as T2DM, various metabolic stressors—including hyperglycemia, saturated fatty acids,

cholesterol crystals, islet amyloid polypeptide and reactive oxygen species (ROS)—have been reported to influence NLRP3 inflammasome activation [40,41]. Current evidence indicates that pyroptotic signaling can be activated through both canonical and non-canonical pathways.

3.1.1. Classical Pathway

Under conditions of metabolic stress such as glycotoxicity, lipotoxicity or stimulation by DAMPs, pattern-recognition receptors including NLRP3 may recruit ASC and pro-caspase-1 to assemble the inflammasome complex. This process can result in autocatalytic activation of caspase-1 [14]. Activated caspase-1 subsequently cleaves gasdermin D (GSDMD), generating the N-terminal fragment (GSDMD-N), which inserts into the plasma membrane to form pores [42]. These pores facilitate ionic imbalance and cellular swelling and allow the release of IL-1β and interleukin-18 (IL-18), thereby promoting inflammatory signaling [15].

3.1.2. Non-Canonical Pathway

In the non-canonical pathway, intracellular lipopolysaccharide (LPS) can be sensed directly by caspase-4/5 in humans or caspase-11 in mice, leading to GSDMD cleavage and membrane pore formation. This process may also indirectly activate the NLRP3 inflammasome through potassium efflux [14]. In addition to NLRP3, several other inflammasomes—including absent in melanoma 2 (AIM2) and NLR family CARD domain-containing protein 4 (NLRC4)—have been reported to trigger pyroptotic signaling. Furthermore, members of the gasdermin family beyond GSDMD, such as gasdermin E (GSDME), may also participate in inflammatory cell death under specific conditions. These findings indicate that pyroptosis is not restricted to a single NLRP3-GSDMD pathway but rather represents a broader regulatory network involving multiple inflammasome sensors and gasdermin proteins [15,43].

Evidence from skeletal muscle-related disease models further supports this pathway diversity. In a sarcopenia model, TNF-α was reported to induce caspase-8/caspase-3/GSDME-mediated pyroptosis in myotubes, accompanied by reduced myosin heavy chain expression and myotube loss [44]. In dermatomyositis, caspase-3- and GSDME-dependent mitochondrial pyroptosis has been implicated in perifascicular atrophy, suggesting that GSDME-mediated inflammatory cell death may participate in inflammatory muscle remodeling [45]. Conversely, NLRP3/GSDMD-mediated pyroptosis has also been reported in dexamethasone-induced muscle atrophy in C2C12 myotubes and mouse skeletal muscle [46]. Together, these studies suggest that pyroptosis in skeletal muscle can arise through different gasdermin-dependent routes according to the inflammatory stimulus and disease context.

Upstream metabolic stress signals may influence these pathways. For example, excessive production of ROS has been shown to promote dissociation of thioredoxin-interacting protein (TXNIP) from the thioredoxin (Trx) complex, allowing TXNIP to interact with NLRP3 and potentially enhance inflammasome activation. In parallel, NF-κB-dependent priming can increase the transcription of inflammasome components such as NLRP3 and pro-IL-1β, thereby lowering the threshold for inflammasome activation [47]. Experimental studies have also suggested that certain anti-inflammatory compounds, including the diterpenoid triptolide, may attenuate inflammatory signaling and muscle atrophy in animal models by modulating NF-κB-related pathways.

3.2. Potential Role of Pyroptosis in T2DM-Related Sarcopenia

Direct evidence demonstrating activation of pyroptosis in skeletal muscle from patients with confirmed T2DM-related sarcopenia remains limited. Only a small number of studies have attempted to quantify inflammasome or pyroptosis markers in diabetic skeletal muscle, and most mechanistic insights discussed in the current literature are derived from experimental models or other diabetic complications rather than from human muscle tissue. This limitation should be considered when interpreting the proposed involvement of pyroptosis in T2DM-related muscle wasting. At the same time, the distinct metabolic-inflammatory milieu of diabetic muscle provides a biological context in which inflammasome-related processes remain of particular interest.

Available data suggest that muscle loss in T2DM is accompanied by a more pronounced metabolic–inflammatory environment than that observed in primary age-related sarcopenia or simple disuse atrophy [38,48]. Chronic exposure of skeletal muscle to elevated glucose and lipid levels, together with intramuscular fat accumulation, has been associated with increased ROS production, TXNIP upregulation, mitochondrial stress and calcium dysregulation. These changes are biologically compatible with NLRP3 priming and activation, although whether the complete NLRP3-caspase-1-GSDMD cascade is consistently engaged in diabetic skeletal muscle remains to be clarified.

Persistent low-grade inflammation may also contribute to this environment. Activation of inflammatory transcription factors such as NF-κB can increase the expression of inflammasome components, including NLRP3

and pro-IL-1β, thereby potentially lowering the threshold for inflammasome activation [49,50]. In parallel, human biopsy studies and experimental models suggest that diabetic skeletal muscle may exhibit reduced oxidative capacity, altered type I/type II fibre composition or fibre-specific metabolism, and mitochondrial impairment, although these findings vary across cohorts, muscle groups, diabetes severity and model systems [29–31]. Mitochondrial dysfunction combined with excess glucose and lipid exposure may enhance oxidative stress and disturb calcium homeostasis, processes that can influence cellular homeostasis and inflammatory signaling [51,52]. Together, these changes may create conditions permissive for inflammasome-related inflammatory signaling in diabetic skeletal muscle.

Metabolic signaling pathways that regulate protein turnover may further interact with these inflammatory processes. Impaired IGF-1–PI3K/Akt/mTOR signaling together with activation of FOXO-dependent proteolytic pathways can enhance UPS-mediated protein degradation and disturb autophagy-lysosome-dependent quality control, thereby shifting muscle protein balance toward net degradation [53]. In such contexts, inflammasome activation could contribute to the release of inflammatory cytokines such as IL-1β and IL-18, which may further reinforce catabolic signaling pathways including NF-κB and JNK [54]. Taken together, current evidence suggests that pyroptosis may act as a potential amplifying mechanism within a broader metabolic-inflammatory network, rather than serving as a primary initiating event in T2DM-related muscle loss. Given the involvement of TNF-α and other inflammatory cytokines in diabetic skeletal muscle dysfunction, future studies should also evaluate whether caspase-8/caspase-3/GSDME-related signaling contributes to inflammatory cell death or muscle remodeling in T2DM-related sarcopenia.

3.3. The Role of the NLRP3 Inflammasome in T2DM and Its Complications

Accumulating evidence suggests that NLRP3-mediated inflammatory signaling may contribute to the development of T2DM and several of its complications [14,39,41]. Activation of the NLRP3 inflammasome has been associated with increased production of IL-1β and other inflammatory mediators, which can influence insulin signaling and β-cell function. Experimental studies in diabetic models have reported increased expression of inflammasome-related molecules, including NLRP3, CASP1, GSDMD, IL-1β and IL-18, in tissues such as the kidney, vascular endothelium, retina and myocardium. These alterations have been linked to inflammatory injury and tissue remodeling in diabetic complications [42,55,56]. Importantly, most of these findings originate from experimental models or non-muscle tissues, and their direct relevance to skeletal muscle pathology in T2DM-related sarcopenia remains to be clarified. Nevertheless, pharmacological or genetic inhibition of NLRP3 signaling has been reported to attenuate inflammatory injury in several diabetic disease models, suggesting that this pathway may represent a potential therapeutic target. In this context, emerging pharmacological approaches, including selective NLRP3 inhibitors such as dapansutrile, are currently being explored as possible anti-inflammatory strategies for metabolic diseases [57,58].

4. HMGB1 Signaling in Metabolic Inflammation

HMGB1 is a highly conserved non-histone chromatin-binding protein that predominantly resides in the nucleus under physiological conditions [59]. Under cellular stress conditions such as infection, ischemia, oxidative stress, or metabolic disturbance, HMGB1 can be released into the extracellular space through two principal mechanisms: passive release from damaged or dying cells (including necrosis, late apoptosis, or pyroptosis) and active secretion from immune cells following nuclear-cytoplasmic translocation [60]. Once released extracellularly, HMGB1 can function as a DAMP that participates in innate immune signaling.

The biological activity of HMGB1 is highly context-dependent and influenced by factors including its redox state, subcellular localization, and interacting ligands [61]. Among the best-characterized receptors for extracellular HMGB1 are Toll-like receptor 4 (TLR4) and the receptor for advanced glycation end products (RAGE) [62,63]. Distinct redox forms of HMGB1 may engage different receptor complexes and trigger diverse downstream responses [61]. For example, disulfide HMGB1 can interact with the myeloid differentiation factor 2 (MD-2) component of the TLR4 complex to promote inflammatory signaling, whereas HMGB1 bound to nucleic acids or lipopolysaccharide may undergo RAGE-mediated endocytosis and subsequently activate intracellular pattern-recognition pathways [64,65]. In studies of diabetes and its vascular complications, Nogueira-Machado and colleagues proposed the concept of an "HMGB1-TLR-RAGE functional tripod," suggesting that hyperglycemia-induced accumulation of advanced glycation end products (AGEs) and increased oxidative stress may enhance the expression of HMGB1 and its receptors [62]. Engagement of these receptors can activate signaling pathways converging on NF-κB, thereby sustaining inflammatory cytokine production and contributing to chronic metabolic inflammation [63]. Recent studies have also highlighted interactions between HMGB1 signaling and autophagy [66]. Experimental evidence suggests that HMGB1 may influence autophagic processes

through several pathways, including the Akt/mTOR axis, mitogen-activated protein kinase (MAPK) signaling, and NF-κB activation [67,68]. Conversely, autophagy has been reported to regulate HMGB1 synthesis, secretion, and turnover through ROS-dependent mechanisms and feedback pathways involving proteins such as heat shock protein 90 alpha family class A member 1 (HSP90AA1) [69]. These findings suggest the existence of a bidirectional regulatory relationship between HMGB1 signaling and cellular autophagy.

In the context of metabolic diseases, elevated circulating HMGB1 and inflammatory mediators have been reported in patients with diabetes and related complications [70,71]. Hyperglycemia and lipotoxicity are associated with skeletal-muscle inflammatory responses and macrophage-related cytokine signaling in obesity and insulin-resistant states [72,73]. In skeletal-muscle-related experimental contexts, HMGB1 has been implicated in muscle inflammation, impaired regeneration and atrophy-related signaling [74–76]. However, these findings are mainly derived from inflammatory myopathy, ischemic muscle injury, cachexia or experimental atrophy models rather than from skeletal muscle of patients with T2DM-related sarcopenia. Therefore, direct evidence demonstrating macrophage-derived HMGB1 or HMGB1-mediated skeletal-muscle catabolism in T2DM-related sarcopenia remains limited [77].

5. Proposed Interaction Between Pyroptosis and HMGB1 Signaling in T2DM-Related Sarcopenia

The preceding sections suggest that pyroptosis and HMGB1 signaling may be connected within the inflammatory component of metabolic disease. Activation of the NLRP3-caspase-GSDMD pathway can promote IL-1β/IL-18 maturation, membrane pore formation and the release of intracellular danger signals, including HMGB1 [78,79]. After extracellular release, HMGB1 may participate in inflammatory signal amplification in diabetes-related inflammatory and vascular contexts [80–83]. Together, these findings suggest that pyroptosis-related cell stress and HMGB1-associated DAMP signaling may converge within the inflammatory environment of T2DM-related sarcopenia.

This inflammatory context is relevant to T2DM-related sarcopenia because diabetic skeletal muscle is exposed to several stressors that may influence both inflammasome-related signaling and HMGB1 release. Chronic hyperglycemia, lipid overload, AGEs accumulation, mitochondrial dysfunction, oxidative stress and low-grade inflammation are characteristic features of the diabetic muscle microenvironment [53,84,85]. These factors may facilitate inflammasome priming and activation, while also increasing cellular stress and DAMP release. Therefore, inflammasome-related signaling and HMGB1-associated inflammatory responses may help explain how metabolic disturbance is accompanied by persistent local inflammation, complementing the classical mechanisms of insulin resistance, mitochondrial dysfunction and protein metabolism imbalance.

In diabetic skeletal muscle, metabolic stress may create conditions that favor inflammasome–caspase–gasdermin activation, accompanied by IL-1β/IL-18 maturation and possible HMGB1 release [78,79]. Once present in the extracellular space, HMGB1 may act together with AGEs accumulation, oxidative stress and cytokine signaling to sustain a local inflammatory environment [80–83]. This inflammatory milieu may further interfere with insulin signaling, mitochondrial homeostasis and protein turnover, thereby contributing to muscle mass loss, reduced muscle quality and functional decline in T2DM-related sarcopenia [84,85].

Current evidence supports several relevant components, but the temporal and functional relationship among inflammasome-caspase-gasdermin activation, HMGB1 release and muscle catabolic remodeling has not been fully established in T2DM-related skeletal muscle. Accordingly, HMGB1 should be viewed as a candidate DAMP-related contributor to diabetic muscle inflammation, while its direct role in muscle catabolism and functional decline remains to be defined. These evidence-supported components and unresolved links are summarized in Figure 2, with exercise positioned primarily as a modifier of upstream metabolic, mitochondrial and quality-control stress.

Hyperglycemia, lipotoxicity, AGE accumulation, mitochondrial dysfunction and oxidative stress may create conditions permissive for NLRP3 inflammasome priming and activation in diabetic skeletal muscle. Canonical inflammasome activation can promote caspase-1 activation, GSDMD cleavage and IL-1β/IL-18 maturation, whereas stressed or dying cells may release HMGB1, which can contribute to receptor-associated inflammatory signaling. In this framework, exercise is positioned upstream, where it may reduce metabolic and mitochondrial stress through AMPK/PGC-1α-mediated mitochondrial adaptation, improved redox balance and autophagy/mitophagy-related quality control. Current exercise evidence is stronger for metabolic improvement, mitochondrial adaptation, systemic inflammatory markers and selected NLRP3/canonical pyroptosis-related proteins than for HMGB1-specific signaling within diabetic skeletal muscle.

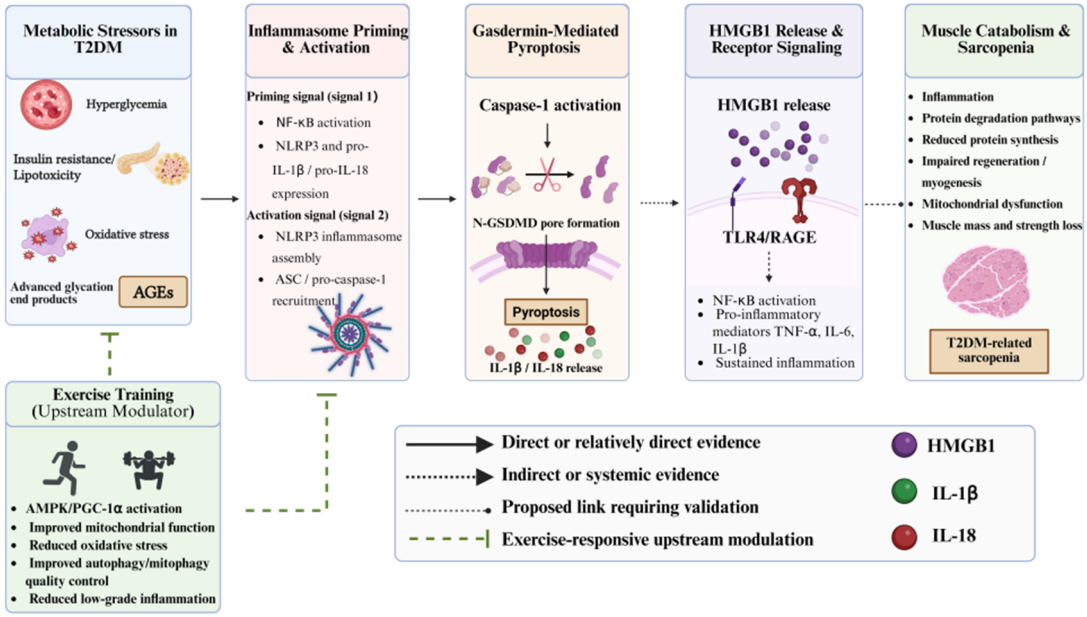

Figure 2. Proposed links among metabolic stress, pyroptosis-related signaling, HMGB1-associated inflammation and exercise-responsive upstream regulation in T2DM-related sarcopenia.

6. Exercise as a Modulator of Immunometabolic Pathways

6.1. AMPK/PGC-1α Signaling and Reduction of NLRP3-Permissive Stress

Exercise-induced AMPK activation may influence the pyroptosis-HMGB1 framework mainly by reducing upstream stress signals that favor NLRP3 inflammasome activation. In diabetic skeletal muscle, mitochondrial dysfunction, excessive ROS production, disturbed redox balance, TXNIP-related stress and NF-κB-dependent inflammatory priming may collectively lower the threshold for NLRP3 activation [49,50,86,87]. AMPK activation, together with downstream PGC-1α signaling, can improve mitochondrial biogenesis, oxidative metabolism and antioxidant defense in skeletal muscle [88–90]. These adaptations may reduce mitochondrial stress-derived signals that contribute to inflammasome activation.

AMPK may also influence the priming phase of inflammasome activation. In diabetic db/db mice, moderate exercise activated the sirtuin 1 (SIRT1)-AMPK-PGC-1α axis and suppressed NF-κB signaling while attenuating muscle loss [88]. This suggests that exercise-responsive AMPK signaling may reduce inflammatory priming in diabetic skeletal muscle. However, AMPK should be positioned as an upstream metabolic regulator rather than as a direct inhibitor of the entire pyroptosis-HMGB1 pathway.

Therefore, in the present framework, exercise-induced AMPK/PGC-1α activation may reduce NLRP3-permissive stress by improving mitochondrial function, limiting oxidative stress and attenuating inflammatory priming. This provides a more direct mechanistic link between exercise-responsive energy sensing and inflammasome-related signaling in T2DM-related sarcopenia.

6.2. Autophagic Flux and Mitochondrial Quality Control

Autophagy and mitophagy are major quality-control processes that remove damaged organelles and protein aggregates through lysosome-dependent degradation. In diabetic skeletal muscle, disruption of this quality-control system may allow dysfunctional mitochondria to accumulate, thereby increasing mitochondrial ROS and other danger signals that can facilitate NLRP3 inflammasome activation [87,91,92]. Because changes in autophagy-related proteins do not necessarily indicate efficient completion of autophagic degradation, autophagic flux is used here to emphasize the degradative capacity of the pathway rather than the abundance of individual autophagy markers. Exercise-induced improvement of autophagy–mitophagy function may therefore reduce inflammasome-permissive signals mainly by improving mitochondrial quality control.

This interpretation is supported by diabetic muscle studies showing that exercise can modify autophagy-related signaling. In streptozotocin-induced diabetic rats, swimming exercise improved muscle mass and fiber morphology together with changes in autophagy-related protein expression [93]. In db/db mice, exercise improved T2DM-induced muscle atrophy and was accompanied by increased phosphorylated AMPK (p-AMPK)/AMPK, unc-51-like autophagy activating kinase 1 (ULK1) and Beclin1 expression, enhanced autophagosome formation

and improved autophagic degradation [94]. Yang et al. further reported that exercise improved skeletal muscle insulin resistance in diabetic mice partly through autophagy-related mechanisms [95].

Importantly, current evidence does not support a conclusion that exercise-induced autophagy selectively removes GSDMD pores or extracellular HMGB1 in diabetic skeletal muscle. Accordingly, autophagy is discussed here as an upstream quality-control mechanism that may limit mitochondrial stress, DAMP generation and inflammasome activation, rather than as a direct clearance pathway for pyroptotic pores or extracellular HMGB1.

6.3. Exercise-Associated Modulation of Inflammasome and HMGB1 Signaling

Beyond its effects on glucose metabolism, mitochondrial adaptation and autophagy, exercise may influence the inflammatory milieu that accompanies metabolic dysfunction. In T2DM-related sarcopenia, this is relevant because hyperglycemia, lipid overload, mitochondrial stress and low-grade inflammation are also upstream conditions that can facilitate inflammasome priming and activation [96–99].

A previous study from our laboratory reported that aerobic exercise improved grip strength, exercise performance, gastrocnemius wet weight and muscle fiber cross-sectional area in db/db mice, together with reduced cleaved caspase-1 and GSDMD-N in gastrocnemius muscle and lower circulating IL-1β and IL-18 [100]. These findings suggest that exercise can attenuate canonical pyroptosis-related signaling in diabetic skeletal muscle and improve muscle atrophy-related phenotypes.

Human studies provide complementary evidence at the systemic level. In middle-aged and older adults with prediabetes, 12 weeks of Tai Chi reduced serum ROS, NF-κB, NLRP3, ASC, caspase-1, GSDMD, IL-1β and IL-18, while improving glucose and lipid metabolism-related variables [96]. In elderly prediabetic subjects, six months of combined Yijinjing and resistance training improved insulin resistance and liver-related outcomes, accompanied by reduced NLRP3 inflammasome activity in peripheral blood mononuclear cells [97]. Together, these studies indicate that exercise can attenuate inflammasome-related inflammatory activity in metabolically impaired populations. Because the measured outcomes were derived from serum or peripheral blood mononuclear cells, these findings are most informative for the systemic inflammatory milieu that may influence diabetic skeletal muscle.

The relationship between exercise and HMGB1 is more complex because HMGB1 functions as an alarmin released during cellular stress as well as a mediator of inflammatory signaling. During strenuous or prolonged exercise, mechanical loading, metabolic disturbance and tissue turnover may increase extracellular danger signals. A marathon study reported increases in circulating HMGB1, soluble RAGE and nucleosomes immediately after the race, followed by changes during the recovery period [101]. Similarly, high-intensity exercise has been discussed as a physiological stressor capable of mobilizing alarmins, including HMGB1, as part of the exercise-induced immune response [60,102].

By contrast, exercise training in metabolically impaired individuals may reduce basal inflammatory burden. In individuals with insulin resistance, six weeks of bodyweight high-intensity interval training reduced circulating HMGB1, with similar changes observed in an exercise-conditioned mouse model [103]. This finding suggests that HMGB1 may be responsive to exercise-induced metabolic and inflammatory adaptation. Because HMGB1 was measured in circulation, the result primarily reflects systemic HMGB1-associated inflammatory status, while its relationship to intramuscular HMGB1 signaling in T2DM-related sarcopenia requires further clarification. Exercise-related regulation of pyroptosis has also been observed in other metabolically stressed tissues. In a high-fat diet-induced diabetic cardiomyopathy model, exercise training improved cardiac dysfunction and reduced pyroptosis-related signaling [99]. Although cardiac and skeletal muscle differ in cellular composition and disease phenotype, such findings indicate that exercise can regulate pyroptosis-associated pathways in tissues exposed to diabetic metabolic stress.

Because the available evidence is heterogeneous across human systemic studies, diabetic animal models, cell models and non-muscle diabetic complication tissues, the key study types, tissues examined, pyroptosis/HMGB1-related markers, major findings and limitations are summarized in Table 1.

Table 1. Evidence summary for human studies, animal models, cell models, tissues examined, pyroptosis/HMGB1 markers, major findings and limitations.

Evidence Type	Study/Model Context	Tissue or Cell Examined	Pyroptosis/HMGB1 Markers	Major Findings	Limitations	References
Human systemic and immune-cell evidence	T2DM, prediabetes, insulin resistance and diabetic complications; exercise-intervention cohorts.	PBMCs, monocyte-derived macrophages, serum or plasma.	NLRP3, ASC, caspase-1, IL-1β, IL-18, GSDMD, HMGB1, RAGE/sRAGE.	Human metabolic-disease cohorts show systemic inflammasome/HMGB1 activation. Exercise studies suggest that systemic NLRP3-related markers and circulating HMGB1 can be modified by training.	Mostly blood-based evidence; not direct skeletal-muscle biopsy evidence; sarcopenia diagnosis is often absent.	[70,96,97,103–106]
Human skeletal-muscle evidence and evidence gap	T2DM-related sarcopenia, insulin resistance and diabetic skeletal-muscle dysfunction literature.	Human skeletal-muscle phenotype and biopsy-related literature.	Direct intramuscular pyroptosis/HMGB1 markers are generally not measured.	Human evidence supports a metabolically stressed, inflammatory and lipid-overloaded skeletal-muscle environment that is compatible with inflammasome activation.	Does not directly prove coordinated pyroptosis-HMGB1 signaling in skeletal muscle from patients with confirmed T2DM-related sarcopenia.	[17,22,33–35,85]
Animal models: diabetic skeletal muscle	STZ-diabetic mice, db/db mice, diabetic myopathy and diabetic nephropathy-associated muscle atrophy; interventions include exercise, MCC950, BMP-7, STING deficiency and dapagliflozin.	Gastrocnemius and other skeletal muscles.	NLRP3, ASC, cleaved caspase-1, GSDMD/GSDMD-N, IL-1β, IL-18, HMGB1, STING.	Diabetic muscle atrophy is accompanied by canonical pyroptosis markers. Inhibition of NLRP3/GSDMD/STING or use of exercise, BMP-7 or dapagliflozin improves muscle phenotype and reduces inflammatory cell-death markers.	Rodent models differ from human sarcopenia; diabetes model, muscle examined and intervention vary; translation to human skeletal muscle remains uncertain.	[100,107–109]
Skeletal-muscle cell models	C2C12/myotube models exposed to TNF-α, dexamethasone, high glucose or palmitate; STING knockdown or pharmacological inhibition.	Myoblasts, differentiated myotubes and skeletal-muscle cells.	Caspase-8/caspase-3/GSDME; NLRP3, caspase-1, GSDMD/GSDMD-N, IL-1β, IL-18.	Inflammatory, glucocorticoid or metabolic stress can induce gasdermin-mediated myotube injury and atrophy. TNF-α activates caspase-8/caspase-3/GSDME signaling in myotubes; dexamethasone activates NLRP3/GSDMD-related pyroptosis in C2C12 myotubes; glucose-induced C2C12 myotube atrophy/pyroptosis is attenuated by STING knockdown; palmitic acid induces GSDME-N and inflammatory factors in C2C12 cells, which are reduced by dapagliflozin.	Simplified in vitro systems cannot reproduce endocrine, immune, vascular and mechanical features of diabetic sarcopenia.	[44,46,108,109]
Diabetic non-muscle tissue evidence	Diabetic kidney disease, diabetic cardiomyopathy, diabetic wounds and islet/adipose metabolic inflammation.	Kidney tubules/podocytes, myocardium, wound macrophages, islets and adipose tissue.	NLRP3, ASC, caspase-1, GSDMD, IL-1β, IL-18, HMGB1/RAGE/TLR4.	Multiple diabetic tissues show pyroptosis or HMGB1-associated inflammatory injury under hyperglycemia, AGEs, lipid stress and oxidative stress. These findings support biological plausibility for diabetic muscle.	Indirect for skeletal muscle; tissue-specific mechanisms may not translate fully to T2DM-related sarcopenia.	[41,42,56,82,99,110–112]
HMGB1-pyroptosis interface	DAMP signaling, macrophage pyroptosis, HMGB1-RAGE/TLR4 inflammatory amplification and diabetic inflammatory complications.	Macrophages, monocytes, diabetic complication tissues and serum/plasma.	HMGB1, TLR4, RAGE, NF-κB, NLRP3, caspase-1, GSDMD, IL-1β.	HMGB1 can amplify innate immune signaling and interact with NLRP3-related inflammatory pathways, providing mechanistic context for a pyroptosis-HMGB1 framework.	HMGB1 release is not specific to pyroptosis and may reflect necrosis, late apoptosis or active secretion depending on cell type and redox context.	[62,78,80–83,106,107]

Overall, exercise appears to act primarily by improving the metabolic and inflammatory environment that favors inflammasome activation. Current evidence is strongest for metabolic improvement, mitochondrial adaptation, systemic inflammatory markers and selected NLRP3/canonical pyroptosis-related proteins. Evidence linking exercise to HMGB1-specific signaling within diabetic skeletal muscle remains limited.

7. Limitations and Evidence Gaps

Direct muscle-specific evidence linking coordinated pyroptosis-related signaling and HMGB1-associated processes to rigorously defined T2DM-related sarcopenia remains limited. Although findings from diabetic skeletal muscle models, insulin resistance models and other diabetic complications support the biological plausibility of this framework, they cannot fully substitute for evidence from human skeletal muscle with confirmed T2DM-related sarcopenia. Exercise-related evidence is also uneven: current studies more consistently support improvements in metabolic regulation, mitochondrial quality control and selected NLRP3/canonical pyroptosis-related markers, whereas HMGB1-specific mechanisms in diabetic skeletal muscle remain less well characterized. In addition, heterogeneity in study populations, sarcopenia diagnostic criteria, diabetes severity and exercise protocols limits direct comparison across studies. Future research should integrate standardized sarcopenia diagnosis, muscle-specific molecular assessment and functional outcomes to clarify the relevance of pyroptosis-HMGB1 signaling to T2DM-related sarcopenia and its responsiveness to exercise intervention.

8. Conclusions and Future Perspectives

In summary, accumulating evidence suggests that metabolic inflammation, inflammasome activation, and HMGB1 signaling may collectively contribute to the complex pathophysiology of T2DM-related sarcopenia. The available literature indicates that hyperglycemia, lipotoxicity, and oxidative stress can create a metabolic environment that is permissive for inflammatory signaling pathways, including those associated with the NLRP3 inflammasome and pyroptosis. Under such conditions, the release of inflammatory mediators and damage-associated molecular patterns such as HMGB1 may further influence immune–metabolic interactions and cellular homeostasis. However, most mechanistic insights supporting these interactions are derived from experimental systems or non-muscle tissues, and direct evidence demonstrating coordinated activation of pyroptosis and HMGB1 signaling in skeletal muscle from patients with confirmed T2DM-related sarcopenia remains limited.

Within this conceptual framework, exercise represents a promising non-pharmacological strategy for improving metabolic and inflammatory disturbances associated with T2DM-related muscle dysfunction. Exercise training can influence several upstream metabolic regulators, including mitochondrial function, oxidative stress balance, and inflammatory signaling pathways. Activation of metabolic regulators such as the AMPK-PGC-1α axis, together with improvements in mitochondrial quality control and autophagic processes, may contribute to the overall anti-inflammatory and metabolic benefits of exercise. Nevertheless, these mechanisms should currently be interpreted as indirect regulatory pathways rather than direct evidence that exercise specifically inhibits a pyroptosis-HMGB1 signaling axis in skeletal muscle.

Future research should focus on clarifying the role of inflammatory cell-death pathways in diabetic skeletal muscle through integrated human and experimental studies. In particular, priority should be given to: (1) determining whether exercise interventions modulate intramuscular markers of pyroptosis and HMGB1 signaling in individuals with confirmed T2DM-related sarcopenia; and (2) defining the dose-response relationships and molecular mechanisms by which different exercise modalities influence immunometabolic regulation in skeletal muscle. Such studies will be essential for translating mechanistic insights into evidence-based exercise prescriptions for the prevention and management of T2DM-related sarcopenia.

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