Shared mechanisms of musculoskeletal dysfunction in type 2 diabetes mellitus: Insights into future therapeutic directions (Review)

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Abstract. Type 2 diabetes mellitus (T2DM) profoundly affects the musculoskeletal system through multifactorial mechanisms. The present review systematically summarizes the impact of T2DM on skeletal muscle, tendon, tendon-bone interface (TBI), and bone, highlighting their shared and tissue-specific pathophysiological pathways. In skeletal muscle, impaired insulin signaling and mitochondrial dysfunction lead to reduced protein synthesis, enhanced proteolysis, and muscle atrophy. In tendons, advanced glycation end products accumulation and microangiopathy disrupt collagen metabolism and biomechanics. At the TBI, persistent hyperglycemia induces fibrocartilage fibrosis, impaired angiogenesis and disorganized stress transmission, ultimately weakening load-bearing capacity. In bone, the imbalance between osteoblast and osteoclast activity, coupled with microvascular dysfunction and metabolic acidosis, results in reduced bone formation and increased fragility. Although the manifestations of T2DM differ among skeletal muscle, tendon, TBI and bone, these tissues share common pathological drivers, including metabolic dysregulation, chronic inflammation, oxidative stress, extracellular matrix remodeling, and impaired regenerative capacity. A deeper understanding of these shared mechanisms may facilitate the identification of novel therapeutic targets. Emerging technologies, including single-cell RNA sequencing, regenerative medicine, and precision medicine, further provide new opportunities for early diagnosis and personalized management of diabetes-related musculoskeletal disorders.

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1. Introduction

According to the International Diabetes Federation (IDF), an estimated 537 million adults aged 20-79 years worldwide had diabetes in 2021. Projections indicate this number will rise to 783 million by 2045 (1). Notably, over 90% of these cases are type 2 diabetes mellitus (T2DM) (2). Inadequately managed T2DM can lead to numerous severe complications. Within the musculoskeletal system, T2DM induces multiple pathological alterations affecting bone, joints, muscles and the nervous system. These impairments not only directly compromise mobility but are also intrinsically linked to metabolic dysregulation, chronic inflammation and microvascular dysfunction. Physical exercise is an important intervention for diabetes management. Exercise activates adenosine monophosphate-activated protein kinase (AMPK) signaling, promotes glucose transport and lipid metabolism, and enhances mitochondrial function in skeletal muscle. It also improves insulin sensitivity and blood sugar control (3-8). However, a scientific exercise plan fundamentally relies on a stable and functional musculoskeletal system. Because of the detrimental impact of T2DM on the musculoskeletal system, early intervention is critical. Identifying effective treatment targets and preventive strategies may reduce the need for surgery and significantly

improve the quality of life for patients. This approach aligns with current priorities in the prevention and management of major diseases, emphasizing the integration of traditional Chinese and Western medicine, as well as multidisciplinary collaboration. The present review synthesizes current research to explain how T2DM affects the musculoskeletal system and identifies potential intervention targets, thereby laying a solid foundation for future investigations.

2. Systemic pathophysiology of T2DM in musculoskeletal tissues

Hyperglycemia and insulin resistance as the primary instigators. Hyperglycemia and insulin resistance represent the earliest pathological events that start musculoskeletal degeneration in T2DM. Persistent metabolic dysregulation disrupts glucose utilization, energy metabolism and cellular anabolic signaling. This creates a common pathological basis for abnormalities in skeletal muscle, tendon, tendon-bone interface (TBI) and bone. Although these tissues perform distinct physiological functions, they all exhibit impaired cellular metabolism and tissue homeostasis under chronic hyperglycemic and insulin-resistant conditions (Table I).

Skeletal muscle is the primary site for post-prandial glucose uptake and disposal, playing a central role in maintaining glucose homeostasis (9). Peripheral insulin resistance originating in skeletal muscle is a key driver in the development and progression of T2DM (10). Under normal physiological conditions, insulin promotes glucose uptake by activating glucose transporter type 4 (GLUT4). However, in T2DM, defects in the insulin signaling pathways lead to impaired translocation of GLUT4 to the cell membrane, which represents a core mechanism of insulin resistance (11,12). The resistance results in decreased activity of glycogen synthase in skeletal muscle and reduced glycogen storage. Reduced glycogen synthesis forces cells to rely on lipolysis for energy production. At the same time, impaired mitochondrial function decreases fatty acid oxidation, which exacerbates the accumulation of lipid intermediates (13,14). Among these metabolites, diacylglycerol (DAG) activates protein kinase C (PKC), attenuating insulin-stimulated insulin receptor substrate- phosphorylation and phosphoinositide 3-kinase (PI3K) activity. As a result, GLUT4 movement is further reduced, worsening insulin resistance (15,16). Moreover, prolonged exposure to free fatty acids or a high-fat diet increases DAG accumulation inside muscle cells. A high blood sugar environment further promotes fat synthesis and buildup, forming a vicious cycle of metabolic imbalance that progressively worsens energy metabolism (Fig. 1A) (16).

The metabolic disturbances initiated by hyperglycemia and insulin resistance also extend to tendon tissue. Tendons are highly organized connective tissues composed primarily of type I collagen, together with proteoglycans and glycoproteins (17). Chronic hyperglycemia suppresses the function of tendon stem/progenitor cell (TSPC). It also disrupts the balance between matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), promoting collagen degradation and preventing effective matrix remodeling (18-20). Consequently, collagen fibers become disorganized, losing elasticity and changing their mechanical properties. Experimental studies have demonstrated reduced elasticity and impaired mechanical performance in diabetes rats' tendons, highlighting the harmful effects of chronic hyperglycemia on tendon function (21,22). Similarly, the TBI is continuously exposed to the diabetic metabolic environment. As a specialized tissue responsible for transferring loads between tendon and bone, the TBI depends on coordinated cellular differentiation and extracellular matrix (ECM) homeostasis. Persistent hyperglycemia promotes abnormal collagen cross-linking and chronic low-grade inflammation, leading to a progressive worsening of the interface structure and function (23-25). Following an injury, the diabetic TBI heals mostly by forming fibrotic scar tissue rather than regenerating the normal fibrocartilage transition zone (26). The newly formed scar tissue is characterized by disorganized collagen fibers and poor biomechanical properties, leading to reduced load-bearing capacity and compromised interface function.

Bone tissue is likewise profoundly affected by chronic hyperglycemia and insulin resistance. Under diabetic conditions, hyperglycemia directly suppresses the expression of bone-forming markers, including osteocalcin, osteopontin, runt-related transcription factor 2 (Runx2) and alkaline phosphatase. Hyperglycemia also promotes the death of bone-forming cells, resulting in reduced bone formation and poor bone quality (27-30). In addition, insulin deficiency or resistance diminishes the anabolic effects of insulin and insulin-like growth factor-1 on osteoblasts, further impairing matrix synthesis and mineralization (31-33). Elevated glucose levels also induce aberrant differentiation of mesenchymal stem cells, resulting in increased bone marrow adiposity and impaired osteoblast formation (34-37). Furthermore, chronic hyperglycemia enhances the sensitivity of osteoclast precursors to macrophage colony-stimulating factor and receptor activator of nuclear factor κB ligand (RANKL), thereby facilitating osteoclast differentiation and fusion, and consequently increasing bone resorptive activity (38). These findings indicate that hyperglycemia and insulin resistance constitute the primary early drivers of diabetic musculoskeletal disorders. By disrupting glucose utilization, lipid metabolism, anabolic signaling and lineage commitment, they establish the pathological foundation for subsequent oxidative stress (OS), chronic inflammation, ECM remodeling, vascular dysfunction, and impaired tissue regeneration across skeletal muscle, tendon, the TBI and bone.

AGEs-RAGE signaling, OS, and chronic inflammation as interconnected pathogenic mediators. Following chronic hyperglycemia and insulin resistance, the excessive accumulation of advanced glycation end products (AGEs), persistent OS, and chronic inflammation constitute a connected pathogenic network that drives musculoskeletal degeneration in T2DM. Despite the tissue-specific signs of diabetes-related damage, these pathological mechanisms are remarkably similar across skeletal muscle, tendon, the TBI and bone (Table I). Under normal physiological conditions, the formation of AGEs is minimal and efficiently cleared from the body (39). However, chronic hyperglycemia greatly accelerates the non-enzymatic glycation of proteins and lipids, resulting in excessive AGEs generation and progressive accumulation within multiple tissues (40,41). Excessive AGEs alter the structural and

Table I. Shared pathogenic mechanisms of musculoskeletal dysfunction in T2DM.

Shared pathogenic mechanisms	Skeletal muscle	Tendon	Tendon-bone interface	Bone	(Refs.)
Hyperglycemia and insulin resistance	Impaired GLUT4 translocation → reduced glucose uptake; Reduced glycogen synthesis → reliance on lipolysis; DAG accumulation → PKC activation → IRS-1/PI3K Suppression; Impaired mitochondrial oxidative phosphorylation; metabolic dysfunction	TSPC function suppression; Disrupted MMP/TIMP balance → collagen degradation; Reduced collagen synthesis; Diminished tendon elasticity; Altered biomechanical	Abnormal collagen cross-linking; Chronic low-grade inflammation; Fibrotic scar formation; Reduced load-bearing capacity	Osteoblast apoptosis; Impaired matrix synthesis and mineralization; Aberrant MSC differentiation → marrow adiposity; Enhanced osteoclast precursor sensitivity to M-CSF and RANKL	(9,11-17,19,21, 22,25-27,31-34, 36,37)
AGEs-RAGE signaling	AGEs accumulation in ECM and collagen networks → fibrosis; RAGE activation → ROS and inflammation; Functional impairment and reduced muscle quality	AGEs cross-link collagen → reduced fiber sliding; Increased passive tension; Inhibition of collagen-related gene expression; Glycosylated collagen accumulation	Chronic inflammatory; TGF-β1/Smad3 activation → fibroblast hyperproliferation and fibrosis; Abnormal collagen; Increased ECM stiffness; Impaired mechanical buffering and load transmission	Reduced matrix elasticity and mechanical strength; Impaired osteoblast differentiation; Osteocyte senescence and apoptosis	(23,24,42,48-53, 56,58-63)
Oxidative stress	ROS; glucose autoxidation; Inflammation; ATP production; Mitochondrial DNA and respiratory chain damage PI3K/Akt/mTOR suppression	ROS damage tenocytes; Impaired tenocyte proliferation, differentiation, and metabolic function; Collagen degradation; Impaired tendon self-repair capacity	ROS damage endothelial cells → impaired angiogenic responses; Inflammation and hypoxia vicious cycle; Impaired angiogenesis; Disrupted stem cell differentiation	Osteoblast differentiation↓; Promote osteoclast activity; Hypoxia → premature Increased osteocyte RANKL → osteoclastogenesis	(70,73-77,97)
Chronic low-grade inflammation	IKKβ/NF-κB activation → TNF-α, IL-6, CRP increased; Cytokines impair insulin; UPS activation → accelerated proteolysis; JAK/STAT pathway activation → muscle loss; Impaired muscle regeneration	Immune cell activation; Pro-inflammatory cytokines release; Disrupted collagen fiber organization; M2 polarization → TGF-β /VEGF secretion → fibrosis and ECM deposition; Impaired biomechanical properties	Chronic inflammatory immune responses; Fibroblast hyperproliferation → fibrotic remodeling; Fibrocartilage replaced by scar tissue; Loss of stress-buffering capacity; Impaired force transmission	Inflammatory cytokines promote osteoclastogenesis; Bone marrow adiposity and inflammation; Imbalanced RANKL/OPG ratio → bone resorption; SASP from senescent osteocytes → further inflammation; Trabecular deterioration and bone loss	(38,79,81-84,95, 109,229,230, 261-263)

Table I. Continued.

Shared pathogenic mechanisms	Skeletal muscle	Tendon	Tendon-bone interface	Bone	(Refs.)
Microvascular Dysfunction	Capillary rarefaction, basement membrane thickening; Endothelial dysfunction; mitochondrial dysfunction and energy deficiency; Impaired glucose utilization; peripheral neuropathy	Aberrant vascularization; Local hypoxia; Tenocyte damage and collagen degradation; Impaired stem cell migration; Delayed post-injury angiogenesis	Reduced expression of CD31 and endomucin; EPC and APC dysfunction; HIF-2α↑ → Scx suppression → impaired TSPC differentiation; Ectopic calcification; VEGF resistance	Reduced bone marrow capillary density; Reduced blood perfusion; Hypoxia; Trabecular structure disruption; Impaired bone remodeling and turnover	(89-91,93-95,99,115,118-121, 123-129,133,134)
Abnormal ECM	AGEs cross-linking increased ECM stiffness and fibrosis	AMPK/EGR1 inhibition → collagen synthesis decreased	MMP/TIMP balance disruption → excessive matrix degradation	Osteoclasts create acidic microenvironment → matrix	(59,137,138,141,144-148, 150-154,156)
Impaired cell regeneration	PI3K/Akt/mTOR ↓, NF-κB/FoxO↑; Reduced muscle fiber CSA and atrophy; MuSC dysfunction; Impaired muscle repair	TSPC proliferation↓; apoptosis↑; Aberrant osteogenic; Excessive vascularization; Persistent inflammation and fibrosis	TSPC apoptosis, proliferation↓; Fibrocartilage thinning and degeneration; Fibrotic scar replaces native transition zone	Bone marrow adiposity, osteoblast numbers; Bone formation, Trabecular deterioration, cortical thinning, skeletal fragility↑	(18,19,34-37,111,163-165, 167-172,175)

AGE, advanced glycation end product; Akt, protein kinase B; ALP, alkaline phosphatase; AMPK, AMP-activated protein kinase; APC, angiogenic progenitor cell; aP2, adipocyte protein 2; BH4, tetrahydrobiopterin; CKMT2, mitochondrial creatine kinase 2; CRP, C-reactive protein; CSA, cross-sectional area; DAG, diacylglycerol; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; EPC, endothelial progenitor cell; FoxO, forkhead box O; GLUT4, glucose transporter type 4; HIF-1α, hypoxia-inducible factor-1α; HIF-2α, hypoxia-inducible factor-2α; IGF-1, insulin-like growth factor-1; IKKβ, IκB kinase β; IL-6, interleukin-6; iNOS, inducible nitric oxide synthase; IRS-1, insulin receptor substrate-1; JAK, janus kinase; MAFbx, muscle atrophy F-box; M-CSF, macrophage colony-stimulating factor; Mfn1, mitofusin-1; Mfn2, mitofusin-2; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; mTOR, mechanistic target of rapamycin; MuRF1, muscle RING-finger protein-1; MuSC, muscle satellite cell; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor kappa B; NO, nitric oxide; OCN, osteocalcin; OPG, osteoprotegerin; OPN, osteopontin; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PI3K, phosphoinositide 3-kinase; PKC, protein kinase C; PPARγ, peroxisome proliferator-activated receptor gamma; RAGE, receptor for advanced glycation end products; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2; SASP, senescence-associated secretory phenotype; Scx, scleraxis; Smad3, mothers against decapentaplegic homolog 3; Sox9, SRY-box transcription factor 9; STAT, signal transducer and activator of transcription; TDSC, tendon-derived stem cell; TGF-β, transforming growth factor-β; TGase, transglutaminase; TIMP, tissue inhibitor of metalloproteinase; TNF-α, tumor necrosis factor α; TSPC, tendon stem/progenitor cell; UPS, ubiquitin-proteasome system; VEGF, vascular endothelial growth factor.

biochemical properties of the ECM, disrupt collagen integrity through non-enzymatic cross-linking, and trigger persistent signaling through the receptor for AGEs (RAGE) (42-45). The sustained activation of this pathway amplifies OS and inflammatory cascades, leading to mitochondrial dysfunction, impaired cellular differentiation, and cell death in multiple tissue types (46,47). These connected events ultimately compromise the balance between tissue formation and

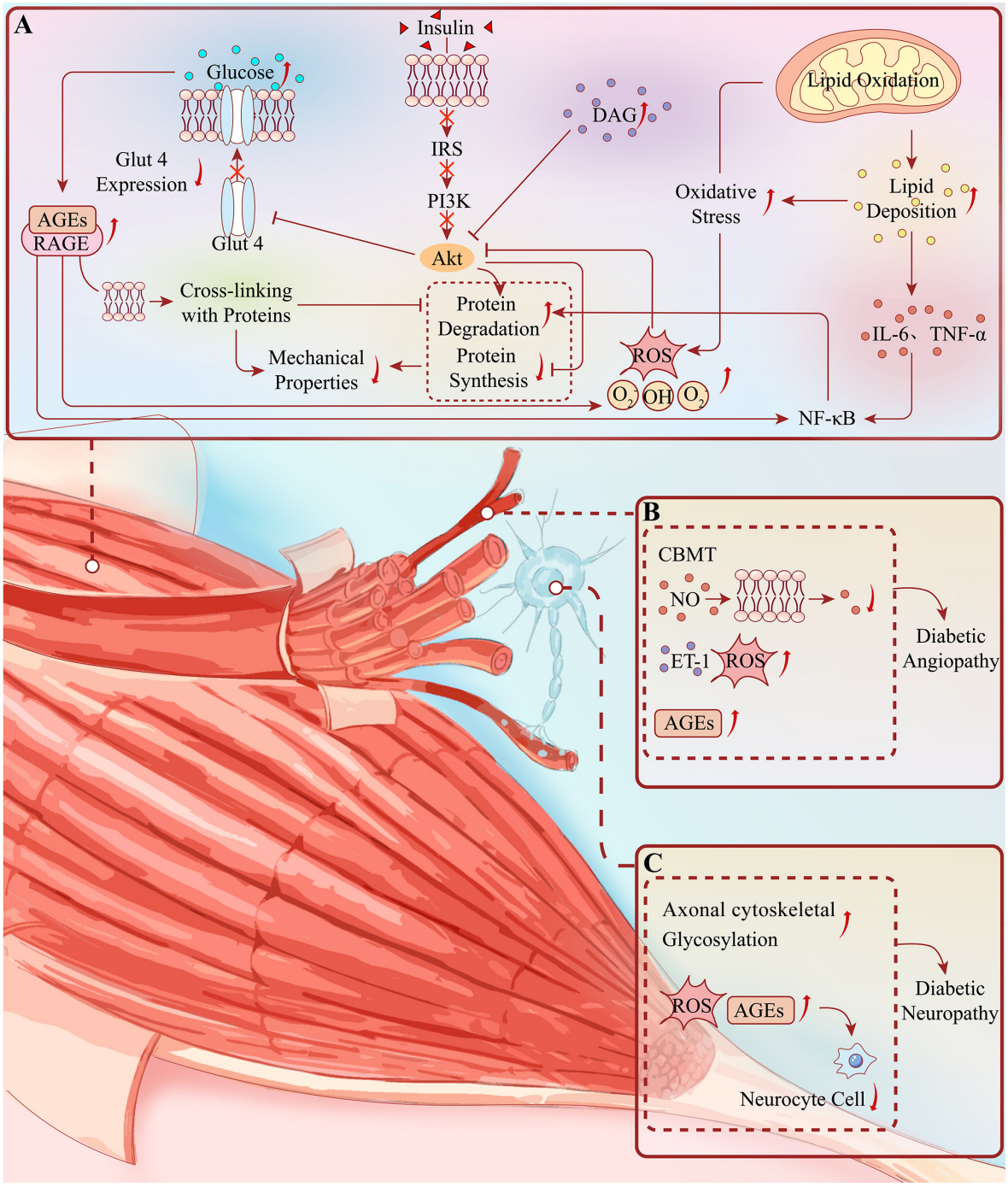

Figure 1. Mechanisms of skeletal muscle dysfunction in T2DM. (A) It highlights the role of glucose uptake), insulin signaling, and lipid oxidation leading to oxidative stress. This results in protein cross-linking with tissues, affecting the mechanical properties of muscle and triggering ROS generation, inflammation and protein degradation, which collectively contribute to muscle quality decline in T2DM. (B) It focuses on the role of CBMT and NO signaling in endothelial function, which leads to impaired blood vessel integrity. This is linked to the formation of ROS and AGE accumulation, which together contribute to diabetic angiopathy. (C) It involves axonal cytoskeletal glycosylation, AGE accumulation and ROS aggravation, leading to disruption in neurocyte function and contributing to diabetic neuropathy. T2DM, type 2 diabetes mellitus; ROS, reactive oxygen species; NO, nitric oxide; AGEs, advanced glycation end products; RAGE, receptor for AGEs; DAG, diacylglycerol; IRS, insulin receptor substrate.

degradation, weaken the biomechanical properties of muscles, tendons and bone, and destroy the coordinated function of the TBI.

AGE accumulation profoundly alters the mechanical properties of collagen-rich tissues throughout the musculoskeletal system. In skeletal muscle, AGEs accumulate within the muscle ECM and collagen networks, increasing collagen cross-linking, tissue stiffness, fibrosis and functional impairment (42,48-50). In tendon, AGEs impair biomechanics in multiple species by reducing tendon fibers sliding, resulting in increased passive muscle tension, reduced elasticity and decreased flexibility (51-53). In addition, AGEs directly inhibit the expression of collagen-related genes. Glycosylated collagen accumulates in connective tissues due to its insolubility and increased resistance to collagenase, leading to further AGE deposition (54-56). At the TBI, the persistent accumulation

of AGEs, along with hyperglycemia-induced OS, continuously activates AGEs-RAGE signaling and promotes chronic inflammatory immune responses (23-25). This pathological cascade activates the TGF-β1/Smad3 pathway, causing excessive fibroblast growth and fibrotic tissue remodeling. This is accompanied by abnormal cross-linking of collagen and proteoglycans, increased ECM stiffness, and loss of tissue elasticity, which impairs mechanical buffering and load transmission across the enthesis (24,53,57,58). In bone, excessive accumulation of AGEs within the bone matrix harms collagen structure through non-enzymatic cross-linking, reduces matrix elasticity and mechanical strength, and directly impairs osteoblast differentiation through activating RAGE-dependent signaling pathways (59-63). Major axonal cytoskeletal proteins, such as tubulin, neurofilaments and actin, are vulnerable to glycation under diabetic conditions. As essential components for maintaining axonal structure and function, their modification via glycation may alter structural integrity and functional properties of axons, leading to axonal atrophy, degeneration and slowed axonal transport (64-67). Studies indicate that AGE-modified myelin sheaths in peripheral nerves are more vulnerable to being consumed by macrophages. This process stimulates the release of enzymes and likely contributes to demyelination in diabetic neuropathy (68). Hyperglycemia-induced OS may accelerate the accumulation of AGEs, thereby exacerbating oxidative damage in peripheral nerves associated with neuronal disturbance and impaired Schwann cell signaling (67). In this manner, diabetic neuropathy promotes progressive nerve fiber loss and poor regeneration. Additionally, increased activity in the polyol pathway promotes the formation of 3-deoxyglucosone and methylglyoxal, which are precursors that contribute to the accumulation of AGEs. These AGEs alter neural cell components and, through engagement with the RAGE expressed on neural cells, trigger the production of various cytokines implicated in nerve injury (38,67). Thus, both hyperglycemia and polyol pathway-mediated AGE accumulation, along with AGE-RAGE interactions, are likely to occur within diabetic nervous and vascular systems. This highlights a cooperative relationship between the polyol pathway and AGE/RAGE-dependent signaling in promoting OS and nuclear factor kappa B (NF-κB) activation, which aggravates neurovascular dysfunction in experimental T2DM neuropathy (67).

The binding of AGEs to RAGE represents the central molecular event linking metabolic disturbance with OS and inflammation. By activating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and the PI3K/protein kinase B (Akt) pathway, AGEs stimulate excessive reactive oxygen species (ROS) generation and activate NF-κB signaling, thereby establishing a self-amplifying cycle between OS and inflammation (41,43-45,69). Simultaneously, AGEs formation, glucose autoxidation, and inflammatory activation collectively induce excessive ROS production. This disrupts intracellular metabolic homeostasis, impairs insulin signaling, and promotes catabolic processes (70). ROS further attack mitochondrial DNA, respiratory chain complexes, and membrane phospholipids, leading to mitochondrial dysfunction (71). As the primary source of cellular energy, dysfunctional mitochondria fail to meet tissue energy demands, resulting in muscle atrophy, fatigue, impaired cellular differentiation and reduced exercise tolerance (72). Meanwhile, OS suppresses anabolic pathways, including PI3K/Akt/mammalian target of rapamycin (mTOR) signaling, and compromises tissue structural integrity. It also impairs angiogenesis and tissue repair, aggravates hypoxia, and ultimately contributes to delayed or failed healing across musculoskeletal tissues (73-77).

Chronic inflammation is another essential part of this pathogenic network. While T2DM has traditionally been defined by insulin resistance and progressive β-cell dysfunction, increasing evidence highlights chronic low-grade inflammation and immune dysregulation as equally central to disease progression (78). Persistent hyperglycemia, lipid overload, and the metabolic stress caused by compensatory insulin hypersecretion activate innate immune pathways. This environment releases signaling molecules that recruit monocytes to eliminate apoptotic β-cells. Under the regulation of NF-κB signaling, these recruited monocytes primarily differentiate into pro-inflammatory M1 and anti-inflammatory M2 macrophages. This process contributes to β-cell dysfunction and apoptosis. In particular, tumor necrosis factor α (TNF-α) impairs insulin signaling and diminishes insulin sensitivity (79,80). A vicious inflammatory cycle subsequently emerges. The IkappaB kinase β (IKKβ)/NF-κB signaling axis serves as a critical mediator in this process. It drives the systemic accumulation of pro-inflammatory mediators such as TNF-α, interleukin-6 (IL-6) and C-reactive protein (81-83). In turn, these cytokines further activate the IKK/NF-κB cascade, impair insulin signaling, and exacerbate β-cell dysfunction and systemic insulin resistance. They also promote the excessive breakdown of structural proteins and the ECM (79,84). Together with persistent ROS production, this inflammatory microenvironment progressively shifts tissue homeostasis toward catabolism, inhibits tissue regeneration, and amplifies structural degeneration throughout skeletal muscle, tendon, the TBI and bone.

Collectively, AGEs-RAGE activation, OS and chronic inflammation form a tightly connected pathological axis linking metabolic abnormalities to musculoskeletal degeneration. Rather than acting independently, these mechanisms reinforce one another through positive feedback, continuously exacerbating mitochondrial dysfunction, ECM abnormalities, impaired cellular differentiation, cell death and biomechanical deterioration. This sustained inflammatory and oxidative microenvironment provides the foundation for the subsequent development of microvascular dysfunction and defective tissue regeneration.

Microvascular dysfunction as a tissue-level amplifier. Microvascular dysfunction is a critical pathological consequence of persistent hyperglycemia and chronic metabolic stress. It acts as a tissue-level amplifier that accelerates musculoskeletal degeneration in T2DM (Table I). Under physiological conditions, an intact microvascular network ensures adequate oxygen and nutrient delivery while facilitating metabolite removal to maintain tissue homeostasis. However, prolonged exposure to hyperglycemia, insulin resistance, OS and chronic inflammation progressively impairs endothelial function, resulting in reduced nitric oxide (NO) bioavailability, excessive ROS production, endothelial cell

dysfunction, basement membrane thickening and poor blood vessel formation (76,85-87). Consequently, tissue blood flow declines, chronic hypoxia develops, and regenerative capacity is progressively weakened across skeletal muscle, tendon, the TBI and bone. Rather than representing an isolated pathological process, microvascular dysfunction reinforces metabolic stress, inflammation and ECM abnormalities, thereby establishing a vicious cycle that accelerates tissue degeneration.

Skeletal muscle is highly dependent on an extensive capillary network to support its substantial metabolic demand (88). In T2DM, diabetic microangiopathy features capillary rarefaction, basement membrane thickening, endothelial dysfunction, and reduced skeletal muscle blood flow. The consequent reduction in oxygen and nutrient delivery aggravates mitochondrial dysfunction and energy deficiency, which further impairs glucose utilization and insulin sensitivity (85,89-91). In addition, diabetic microvascular injury extends to the blood vessels of nerves, producing neural ischemia, axonal degeneration and peripheral neuropathy, which disrupt nerve-to-muscle communication (Fig. 1B and C) (92,93).

The detrimental effects of microvascular dysfunction extend to tendon tissue, which naturally has limited blood supply and therefore possesses a relatively poor intrinsic healing capacity (94). Diabetic tendons exhibit a significant increase in blood vessel density, with vessels extending into the central tendon region, leading to an enlarged vascular cross-sectional area (95). This aberrant vascularization disrupts the normal blood supply pattern and microcirculatory balance in tendons, leading to local tissue hypoxia, accumulation of metabolic waste and ROS generation. Ultimately, this compromises collagen fiber stability, increases tissue brittleness, and contributes to tenocyte damage and collagen degradation (21,74,95-97). Concurrently, this pathological environment triggers an inflammatory response characterized by immune cell activation and the release of pro-inflammatory cytokines. These cytokines disrupt the organized architecture of collagen fibers, leading to a decrease in fiber diameter, a reduction in density, fiber separation and impaired biomechanical properties (74). Furthermore, the impaired microenvironment hinders stem cell migration and differentiation and delays post-injury angiogenesis, collectively weakening the tendon's self-repair capacity (74,94,98,99). Besides, the hypoxic environment also directly impairs the proliferation, differentiation and metabolic function of tenocytes (100-102). Although local hypoxia upregulates vascular endothelial growth factor (VEGF) expression to stimulate angiogenesis, endothelial progenitor cell (EPC) dysfunction, reduced VEGF signaling, and the accumulation of ROS and AGEs result in the formation of aberrant, immature blood vessels that fail to meet the mechanical demands of the tendon (103-108). Moreover, hypoxia promotes M2 macrophage polarization, which accelerates fibrosis and scar formation, disrupting the balance of ECM turnover. This imbalance is reflected in aberrant protease activity, such as elevated MMP-13, leading to tendon structural degeneration and functional impairment (95,109). In summary, microangiopathy-induced local hypoxia and inadequate nutrient supply suppress tenocytes metabolic activity and impair the tendon's self-repair capacity and biomechanical properties. Hypoxia further exacerbates vascular endothelial damage through AGE accumulation and OS, increasing vascular permeability and promoting the release of inflammatory factors, thereby establishing a vicious cycle (Fig. 2).

Successful tendon-bone healing (TBH) proceeds through sequential inflammatory, proliferative and remodeling phases, all of which depend on adequate vascularization (110-112). Newly formed vessels deliver oxygen, nutrients, growth factors, and reparative cells to the healing interface, while insufficient blood supply delays tissue regeneration and compromises biomechanical recovery (77,113,114). Hyperglycemia disrupts vascular homeostasis through persistent OS and endothelial dysfunction. Excessive ROS damage endothelial cells and impair new blood vessel responses, creating a vicious cycle of inflammation and hypoxia (76,115). Demirag *et al* (116) reported that the degree of vascularization positively correlates with histological maturity of the TBI, particularly with the formation of Sharpey's fibers. Likewise, inhibition of VEGF expression at the TBI suppresses blood vessel formation, thereby reducing tendon maturation and biomechanical strength (117). Although VEGF expression is often elevated in diabetes, endothelial responsiveness to VEGF is diminished because of the reduced expression of VEGF receptors, particularly VEGFR2 (115,118,119). Consequently, angiogenic signaling becomes ineffective, resulting in defective neovascularization and delayed healing. Additionally, both CD31 and endomucin have been identified as critical markers involved in vascular development and TBH (120,121). Exosomes derived from bone marrow mesenchymal stem cells (BMSC-Exos) have been shown to markedly enhance the expression of CD31 and endomucin within the interface microenvironment (26,77). By contrast, diabetic conditions significantly impair the function of BMSCs and suppress CD31 and endomucin expression (122). Accumulating evidence also suggests that angiogenic progenitor cells (APCs) are dysfunctional in diabetes. Insulin resistance impairs the PI3K/Akt pathway and increases intracellular ROS levels, reducing APC mobilization, migration and homing capacity (123-129). Hypoxia further alters cell fate at the TBI. The fibrocartilage region is naturally hypovascular and maintains physiological expression of hypoxia-inducible factors (HIFs) (130). At this interface, progenitor cells expressing SRY-box transcription factor 9 (Sox9) and Scleraxis (Scx) give rise to TSPCs and fibrocartilage cells during early musculoskeletal development (131,132). Under diabetic conditions, chronic inflammation and elevated IL-1β drive excessive HIF-2α activation (79,131). This aberrant upregulation directly suppresses the tendon-specific transcription factor Scx, impairing the tenogenic differentiation of TSPCs and shifting their fate toward osteogenic and chondrogenic lineages, thereby promoting ectopic calcification or ossification at the TBI (131).

Bone remodeling is likewise highly dependent on an intact vascular network, as osteoblasts, osteoclasts, osteocytes, and skeletal stem cells require continuous vascular support to maintain normal bone turnover. Histological and morphological studies demonstrate that diabetes decreases hematopoietic tissue, increases marrow adiposity, and reduces microvascular density (133). Reduced bone marrow capillary density and microangiopathy further limit blood perfusion, leading to local hypoxia that suppresses osteoblast differentiation while stimulating osteoclast activity, ultimately resulting in direct disruption of the bone structure (133,134). Not only can hypoxia

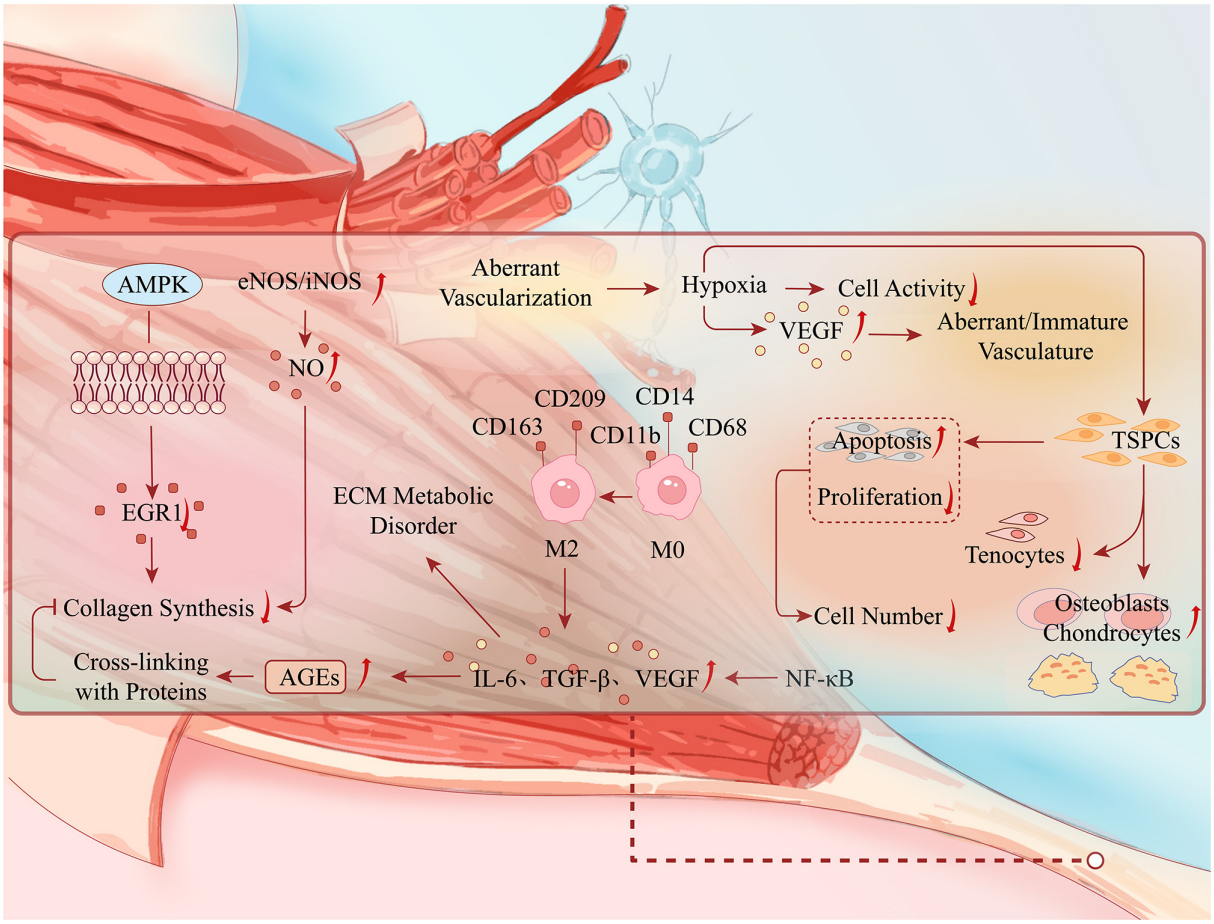

Figure 2. Dysregulation of the AMPK-eNOS/iNOS-NO pathway, coupled with hypoxia-induced excessive VEGF activation, leads to extracellular matrix metabolic disorder, aberrant and immature angiogenesis, activation of inflammatory signaling, and abnormal macrophage polarization. Collectively, these changes suppress cellular activity, promote apoptosis, inhibit proliferation, and impair the differentiation of TSPCs into tenocytes. NO, nitric oxide; eNOS, endothelial NO synthase; iNOS, inducible NO synthase; TSPCs, tendon stem/progenitor cell; AGEs, advanced glycation end products; VEGF, vascular endothelial growth factor.

affect osteoblast development at early stages, failing to provide proper signals for matrix maturation, but under hypoxic conditions, osteocytes can also increase RANKL expression via the HIF-1α signaling pathway (135,136). This promotes the differentiation of osteoclast precursors into mature osteoclasts and enhances bone resorption activity (136). The dual effects exacerbate the imbalance of bone remodeling, contributing to trabecular thinning and sparsity.

ECM dysregulation and impaired regeneration as convergent terminal pathways. ECM dysregulation and impaired regenerative capacity represent the converging pathways through which chronic metabolic disturbances ultimately compromise musculoskeletal integrity in T2DM (Table I). Following persistent hyperglycemia, AGEs-RAGE activation, OS, chronic inflammation and microvascular dysfunction, the coordinated balance between matrix synthesis and degradation is progressively disrupted. These pathological alterations not only impair the structural organization and biomechanical properties of the ECM but also compromise the regenerative potential of resident stem/progenitor cells, resulting in defective tissue remodeling and incomplete functional recovery.

Hyperglycemia suppresses collagen synthesis through multiple pathways. Inhibition of the AMPK and early growth response factor 1 (EGR1) pathway reduces the expression of collagen-related genes, including collagen type 1 alpha 1 (Col1a1), Col1a2, and biglycan (137,138). AGE deposition not only compromises cell viability but also disrupts the structure and function of the ECM, interferes with normal collagen cross-linking, and additionally suppresses collagen synthesis. Collectively, insulin resistance, suppression of AMPK/EGR1 signaling, and AGE accumulation reduce collagen synthesis and contribute to tendon degeneration. Collagen degradation is primarily mediated by MMPs, particularly MMP-9 and MMP-13 (139,140). Hyperglycemia increases their expression and activity, leading to excessive collagen breakdown and disruption of collagen fiber organization (141-143). Under physiological conditions, TIMPs maintain a balance with MMPs to preserve ECM integrity (144). However, T2DM reduces TIMP activity, resulting in excessive MMP-mediated collagen degradation (20). This systemic imbalance between synthetic and degradation drives tissue-specific structural disorder. In tendon, T2DM disrupts collagen homeostasis by reducing collagen synthesis while enhancing degradation, resulting in collagen disorganization, altered fiber architecture, and impaired biomechanical properties that predispose tendons to degeneration and injury (15). At the TBI, the ECM of the fibrocartilage region is primarily composed of collagens and proteoglycans, whose balance is tightly regulated by MMPs and TIMPs (131,145,146). Under diabetic conditions,

hyperglycemia, hypoxia and chronic inflammation disrupt the MMP/TIMP balance, resulting in excessive matrix degradation (146-153). Simultaneously, AGEs accumulate within the TBI and form abnormal cross-links with collagen and proteoglycans, reducing tissue elasticity and impairing cell-matrix interactions (50,58,70,154). In bone, osteoclasts degrade the bone matrix by creating an acidic microenvironment and secreting collagenases and other proteolytic enzymes (155). Additionally, the structural integrity of collagen fibers within the bone matrix is disrupted, with compromised fiber architecture and reduced matrix ductility and strength (59,156). These ECM-level abnormalities collectively undermine bone matrix quality and mechanical performance.

Simultaneously, the regenerative capacity of tissue-resident stem cells is severely compromised across all four tissues. Skeletal muscle satellite cells (MuSCs) are essential for muscle repair and regeneration, but increased inflammation and excessive OS impair MuSC function and suppress myogenic differentiation (157-160). Inflammatory mediators such as IL-6 and TNF-α inhibit PI3K/AKT/mTOR signaling while activating NF-κB and forkhead box O (FoxO) pathways, thereby impairing muscle regeneration (159,161,162). The reduction of myogenic regulatory factors, including MyoD1 and myogenin, further impairs muscle regenerative capacity, leading to reduced cross-sectional area of muscle fibers and atrophy (163). In tendon, TSPCs play a central role in maintaining tendon homeostasis and promoting tissue repair (164-166). Under T2DM conditions, TSPC proliferation is reduced while cell death is increased. Hyperglycemia and AGE accumulation alter TSPC fate, promoting abnormal osteogenic and chondrogenic differentiation at the expense of tenogenic differentiation, which contributes to tendon calcification, structural abnormalities and functional impairment (18,19,167,168). Impaired self-renewal, proliferation and differentiation of TSPCs directly compromise tendon regeneration, contributing to collagen disorganization, excessive vascularization, persistent inflammation, fibrosis and reduced biomechanical performance (19). Reduced collagen synthesis and enhanced degradation lead to impaired structural and mechanical properties, while TSPC dysfunction compromises the tendon's self-repair capacity and increases the risk of rupture. At the TBI, tendon-derived stem cells (TDSCs) are critical for fibrocartilage regeneration during tendon-bone healing (111,169-173). However, hyperglycemic conditions directly induce TDSC apoptosis, inhibit their proliferation, and deplete the available TDSC pool for repair (18,174). Consequently, fibrocartilage exposed to repetitive mechanical loading becomes increasingly vulnerable to thinning, structural disorganization and degeneration. Fibrotic scar formation replaces the native fibrocartilage transition zone, resulting in disorganized collagen fibers, poor biomechanical properties, and compromised load-bearing capacity (26). In bone, the osteogenic potential of MSCs is disrupted. Elevated glucose levels promote adipogenic differentiation through activation of adipogenic transcription factors, including peroxisome proliferator-activated receptor gamma (PPARγ) and adipocyte protein 2 (aP2), while suppressing osteogenic regulators such as Runx2 and Osterix (34,35). Consequently, MSCs preferentially differentiate into adipocytes rather than osteoblasts, resulting in increased bone marrow adiposity and reduced osteoblast numbers (36,37). The imbalance between osteoblast-mediated formation and osteoclast-mediated resorption, coupled with preferential adipogenic differentiation of MSCs, leads to reduced bone formation, trabecular deterioration, cortical thinning and increased skeletal fragility (175). Together, these tissue-specific stem/progenitor cell dysfunctions, coupled with systemic ECM remodeling abnormalities, establish a self-perpetuating cycle of structural degradation and failed repair across the entire musculoskeletal system. These findings highlight the critical need for therapeutic strategies that simultaneously target ECM homeostasis and endogenous regenerative mechanisms.

3. Tissue-specific pathological mechanisms underlying T2DM musculoskeletal disorders

Although hyperglycemia, AGEs-RAGE signaling, OS, chronic inflammation, microvascular dysfunction and ECM dysregulation collectively drive musculoskeletal degeneration in T2DM, each tissue exhibits distinct biological characteristics. These characteristics determine their unique pathological response to chronic metabolic stress. These tissue-specific mechanisms further contribute to the heterogeneity of diabetic musculoskeletal complications and represent potential targets for precision treatment interventions (Table II).

Skeletal muscle. Unlike other musculoskeletal tissues, skeletal muscle serves as the principal organ responsible for post-prandial glucose disposal and whole-body energy metabolism (9). A characteristic feature of diabetic skeletal muscle is the progressive disruption of intracellular energy metabolism. Defective insulin signaling impairs GLUT4 translocation and glucose uptake, forcing muscle fibers to rely increasingly on lipid oxidation (15,16). However, incomplete fatty acid oxidation results in the accumulation of toxic lipid intermediates, particularly DAG, which activates PKC and further suppresses insulin signaling, forming a vicious cycle of metabolic dysfunction (16). In parallel, mitochondrial dysfunction serves as a fundamental mechanism underlying insulin resistance and muscle atrophy (72,176). In patients with T2DM, skeletal muscle exhibits reduced mitochondrial density, impaired oxidative phosphorylation, and abnormal mitochondrial morphology, resulting in diminished adenosine triphosphate (ATP) production and compromised energy metabolism (14). These alterations contribute to the loss of muscle mass, elevated fatigue and reduced exercise tolerance (72). Mitochondrial dynamics are regulated by fusion proteins, including mitofusin-1 (Mfn1), Mfn2 and optic atrophy 1 (Opa1) (177). Reduced expression of Mfn2 and Opa1 in T2DM is associated with impaired mitochondrial fusion and decreased mitochondrial function (178-180). Hyperglycemia promotes excessive mitochondrial fission and ROS generation, further exacerbating mitochondrial damage and OS (97,178,181-184). In addition, mitochondrial creatine kinase 2 (CKMT2), an important regulator of oxidative phosphorylation and mitochondrial respiration (185,186). Decreased CKMT2 impairs phosphocreatine formation and ATP generation, leading to reduced glucose oxidation and worsening energy deficits (186). Together, mitochondrial dysfunction, OS, and impaired substrate utilization contribute to progressive muscle weakness and atrophy.

Table II. Tissue-specific mechanisms, signaling pathways, pathological alterations, and therapeutic strategies in T2DM-associated musculoskeletal disorders.

Category	Skeletal muscle	Tendon	Tendon-bone interface	Bone	(Refs.)
Tissue-Specific Mechanism	GLUT4 translocation↓ → Impaired insulin-stimulated glucose uptake; Mfn1/Mfn2/Opa1↓, excessive fission → Mitochondrial dynamics imbalance; CKMT2 dysfunction → oxidative phosphorylation ↓, ATP↓; Type I oxidative fibers → type II glycolytic fibers; UPS-mediated proteolysis → MuRF1/MAFb x↑ via FoxO; Suppressed mTOR-dependent protein synthesis → PI3K/Akt/mTOR↓; Neuromuscular junction degeneration	Excessive collagen cross-linking through AGEs and TGase-mediated; TSPC dysfunction → proliferation↓, apoptosis↑; dysfunction; Aberrant osteo/chondrogenic differentiation; eNOS/iNOS-NO axis dysregulation → excessive NO, endothelial M2 macrophage polarization → TGF-β/VEGF secretion, fibrosis; Impaired mechanotransduction ECM disorganization	Impaired fibrocartilage regeneration; Defective osteochondral transition; Integrin-mediated mechanotransduction dysfunction → AGEs-modified RGD domain; Integrin α/β; Macrophage imbalance → pro-inflammatory and pro-fibrotic; Disrupted tendon-bone integration; TDSC dysfunction → apoptosis↑, proliferation↓	Osteoblast dysfunction → Runx2/Osterix↓, OCN/OPN/ALP↓; Enhanced osteoclastogenesis → RANKL sensitivity↑, M-CSF responsiveness↑; Osteocyte senescence and apoptosis → sclerostin↑, SASP↑, Wnt/β-catenin↓; BMSC adipogenic differentiation → PPARγ↑, Runx2↓; Cortical porosity and impaired bone quality	(28,34,36-38, 179-186, 190-192,198, 211,214,215, 217,221,223, 225,255,256, 259,260,263)
Major signaling pathways	mTOR; AMPK; FOXO; NF-κB; CKMT2; IGF-1/PGC-1α; MuRF1/MAFbx; PI3K/Akt/GLUT4; Mfn1/Mfn2/Opa1	NF-κB; MAPK; MMP/TIMP; TGF-β/Smad; Wnt/β-catenin; M2 polarization; eNOS/iNOS-NO; TGase-mediated crosslinking	Integrin α/β; FGF2; VEGF; PI3K/Akt; Wnt/β-catenin; BMP/TGF-β; RANKL/OPG	Notch; RANKL/OPG; PI3K/Akt; GF-β/Smad; Sclerostin/Wnt/β-catenin	(38,72,109, 115,118,119, 137,138,145, 146,178,186, 198,221,229, 230,252,253)
Representative pathological alterations	Sarcopenia; Impaired regenerative capacity; Mitochondrial dysfunction; Insulin resistance; Neuromuscular junction degeneration; Reduced muscle strength and endurance	Tendinopathy; Delayed healing; Increased stiffness, reduced elasticity; Impaired biomechanical properties; Increased rupture risk; Collagen disorganization and fiber separation	Delayed TBI healing; Poor fibrocartilage formation; Impaired osseointegration; Mechanotransduction dysfunction; Reduced biomechanical strength; Fibrotic scar replacement	Trabecular microarchitectural; deterioration; Cortical porosity; Reduced bone quality; Delayed fracture healing; Increased skeletal fragility	(14,22,26-30, 37,72,74,84, 133,134,154, 164,175,178, 186,207,208, 244,252-259)
Potential Therapeutic Strategies	Exercise: AMPK activation, improved insulin sensitivity; Metformin: AMPK activation, anti-inflammation, improved insulin signaling; Insulin sensitizers: thiazolidinediones;	AGEs-RAGE inhibition: reducing cross-linking and inflammation; Antioxidant therapy: reducing OS; TSPC-based therapy: promoting tenogenic differentiation;	MSC/exosome therapy: enhancing CD31/endomucin, angiogenesis; Macrophage immunomodulation: balancing M1/M2; Angiogenic factors: promoting neovascularization;	Anti-resorptive agents: RANKL inhibition; Anabolic therapies: sclerostininhibition, Wnt activation; Metformin: promotes osteogenesis, inhibits osteoclastogenesis; Wnt activation:	(3-8,26,40, 77, 113,210, 266-269, 273-277)

Table II. Continued.

Category	Skeletal muscle	Tendon	Tendon-bone interface	Bone	(Refs.)
	Mitochondrial-targeted antioxidants: reducing OS; Senolytics: clearing senescent cells	Anti-fibrotic therapy: targeting TGF-β/Smad; Exosome therapy: promoting regeneration	Bioactive scaffolds: providing structural support; Magnesium-based biomaterials: promoting osteogenesis	activation: bone formation; Senolytics: clearing senescent osteocytes; Antioxidant therapy: reducing OS	

AGE, advanced glycation end product; Akt, protein kinase B; ALP, alkaline phosphatase; AMPK, AMP-activated protein kinase; BMP, bone morphogenetic protein; CKMT2, mitochondrial creatine kinase 2; ECM, extracellular matrix; eNOS, endothelial nitric oxide synthase; FGF2, fibroblast growth factor 2; FoxO, forkhead box O; GLUT4, glucose transporter type 4; IGF-1, insulin-like growth factor-1; iNOS, inducible nitric oxide synthase; MAFbx, muscle atrophy F-box; M-CSF, macrophage colony-stimulating factor; Mfn1, mitofusin-1; Mfn2, mitofusin-2; MMP, matrix metalloproteinase; MSC, mesenchymal stem cell; mTOR, mechanistic target of rapamycin; MuRF1, muscle RING-finger protein-1; NF-κB, nuclear factor kappa B; NO, nitric oxide; OCN, osteocalcin; OPG, osteoprotegerin; OPN, osteopontin; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1 alpha; PI3K, phosphoinositide 3-kinase; PPARγ, peroxisome proliferator-activated receptor gamma; RAGE, receptor for advanced glycation end products; RANKL, receptor activator of nuclear factor-κB ligand; ROS, reactive oxygen species; Runx2, runt-related transcription factor 2; SASP, senescence-associated secretory phenotype; Smad, mothers against decapentaplegic homolog; STAT, signal transducer and activator of transcription; TDSC, tendon-derived stem cell; TGF-β, transforming growth factor-β; TGase, transglutaminase; TIMP, tissue inhibitor of metalloproteinase; TSPC, tendon stem/progenitor cell; UPS, ubiquitin-proteasome system; VEGF, vascular endothelial growth factor; Wnt, wingless-related integration site.

Skeletal muscle loss in T2DM results from both enhanced protein degradation and impaired protein synthesis (187). T2DM is associated with a shift from oxidative type I fibers toward glycolytic type II fibers, reducing oxidative capacity and insulin sensitivity while increasing susceptibility to muscle wasting (84,188-193). Insulin resistance suppresses the anabolic IRS/PI3K/Akt/mTOR pathway while concurrently activating the ubiquitin-proteasome system (UPS), which is the principal pathway responsible for protein degradation in skeletal muscle (72,194,195). The muscle-specific enzymes muscle RING-finger protein-1 (MuRF1) and muscle atrophy F-box (MAFbx/atrogin-1) are markedly upregulated during muscle atrophy (196). The FoxO transcription factors regulate the expression of MuRF1 and MAFbx (196,197). Reduced insulin signaling decreases FoxO phosphorylation, thereby activating the UPS and further amplifying proteolysis (84,198). Furthermore, inflammatory cytokines further enhance UPS activity through NF-κB and janus kinase/signal transducers and activators of transcription (JAK/STAT) signaling pathways, accelerating proteolysis and muscle loss (38,72,84,199-202). Under healthy conditions, insulin activates the PI3K/Akt signaling to promote glucose uptake and stimulate mTORC1-dependent protein synthesis (203,204). In T2DM, impaired signaling suppresses these pathways, resulting in diminished protein synthesis (73,205,206). Combined with diabetic peripheral neuropathy (DPN), neuromuscular junction degeneration and denervation-induced muscle atrophy, these metabolic abnormalities contribute to the progressive decline in muscle strength, endurance, and physical performance characteristic of diabetic sarcopenia.

Tendon. Compared with skeletal muscle, tendon pathology in T2DM is characterized primarily by disruption of collagen homeostasis and deterioration of biomechanical properties. Diabetes profoundly alters tendon mechanical behavior, reducing its ability to withstand and transmit mechanical loads. Structural abnormalities such as collagen disorganization, fibrosis and calcification compromise tendon integrity and increase susceptibility to injury (22,207,208). As mentioned previously, collagen cross-linking is essential for maintaining tendon mechanical properties. Enzymatic cross-linking enhances tendon stiffness and fatigue resistance by stabilizing collagen fibril arrangement. By contrast, non-enzymatic cross-linking, particularly AGEs, are minimal under physiological conditions but accumulate markedly in pathological states such as diabetes (209). Hyperglycemia accelerates non-enzymatic glycosylation, leading to AGE deposition between collagen fibers. This promotes abnormal intermolecular cross-linking that impede fibrillar sliding, increasing tissue stiffness, reducing overall elasticity and ductility (40,210-212). Transglutaminase (TGase) is an enzyme that catalyzes acyl-transfer reactions to form covalent cross-links between proteins, normally enhancing the mechanical strength and fatigue resistance of tissues (213). However, hyperglycemia elevates TGase activity within tenocytes, which exacerbates non-enzymatic cross-linking and impairs dynamic collagen sliding (74,214,215). These aberrant cross-links disrupt normal fibrillar organization and helical structure, ultimately reducing the elastic modulus of the tendon (216-219).

Hyperglycemia also activates endothelial NO synthase and inducible NO synthase, resulting in a short-term increase in the absolute production of NO (220,221). Elevated NO levels inhibit fibroblast proliferation and collagen synthesis, thereby reducing tendon elasticity (222). In the short term, excessive NO impairs vascular endothelial barrier function. The endothelial dysfunction further induces OS via activation of NADPH oxidase and glycolytic pathways, leading to a marked rise in ROS. The overproduction of ROS reduces NO bioavailability through both the degradation of tetrahydrobiopterin and direct oxidation of NO, thereby exacerbating endothelial dysfunction (223-227). Such

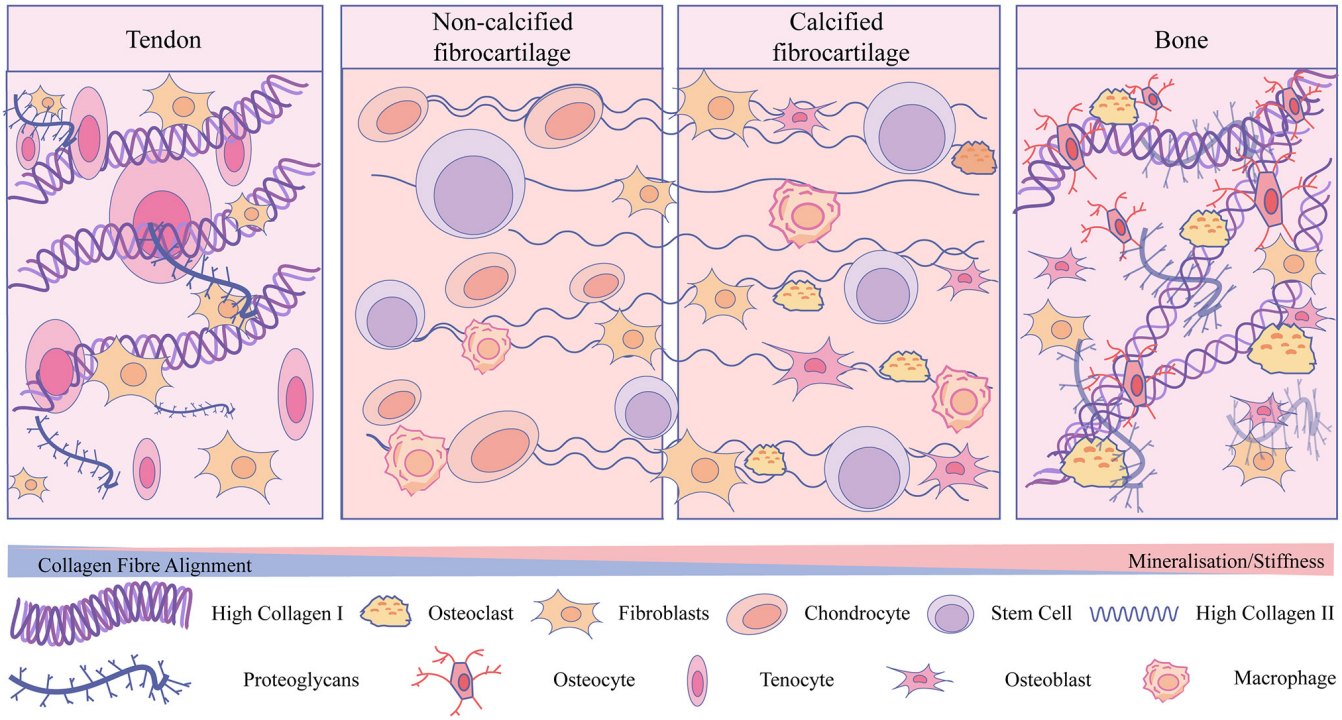

Figure 3. Schematic representation of the TBI illustrating its four gradient zones and corresponding cellular compositions. The native TBI exhibits coordinated gradients in cell phenotype, mineralization, and collagen fiber alignment across these distinct regions. TBI, tendon-bone interface.

impairment diminishes the regenerative potential of MSCs, compromising the tendon's repair capacity. Tendon elasticity relies on the organized arrangement of collagen and the homeostasis of elastin. Impaired repair results in abnormal collagen cross-linking and elastin degradation, collectively reducing elasticity and increasing brittleness (18,228). Concurrently, aberrant M2 macrophage polarization promotes the secretion of pro-fibrotic factors (for example, TGF-β and VEGF), which stimulate pathological scarring (109,229,230). These changes lead to stiffened tendon fibers, diminished tensile strength, and an elevated risk of rupture (Fig. 2).

TBI. The TBI is a specialized transitional tissue that comprises two distinct insertion types, which are direct and indirect insertions, enabling efficient load transfer between tendon and bone (231,232). It consists of tendon, unmineralized fibrocartilage, mineralized fibrocartilage, and bone, forming a graded structure characterized by progressive changes in cellular phenotype, collagen composition, and mineral content (Fig. 3) (112,233-238). The indirect insertion is characterized by Sharpey's fibers, which anchor tendon directly into bone (239). The two insertion types differ primarily in collagen maturity and extent of new bone formation. Biomechanically and biologically, indirect insertions exhibit inferior properties compared with direct insertions (26).

By providing a gradual transition in stiffness, this native fibrocartilage interface minimizes stress concentration between tissues with vastly different mechanical properties, ensuring effective force transmission (240-244). However, this transmission relies heavily on both the structural integrity of the interface and the capacity of resident cells to sense and respond to mechanical stimuli. Biomechanical studies have shown that diabetes significantly reduces the Young's modulus, stiffness and ultimate failure load of the TBI (22,154). Diabetes-induced fibrosis disrupts the hierarchical architecture by replacing fibrocartilage with scar tissue. This loss of fibrocartilage, alongside reduced vascularization and collagen disorganization, severely compromises the interface's stress-buffering capacity. Consequently, these alterations impair force transmission and contribute to a higher incidence of rotator cuff tears, Achilles tendinopathy, postoperative retears, and delayed healing in diabetic patients (244). Experimental studies further demonstrate that diabetic animals exhibit reduced fibrocartilage formation, poorer collagen organization, and lower biomechanical strength following rotator cuff repair compared with healthy controls (154).

Beyond structural degradation, cells within the TBI depend on mechanotransduction pathways to continuously sense mechanical cues from the extracellular environment (245-246). Integrins, which are heterodimeric transmembrane receptors composed of α and β subunits, are key mediators of this process. By linking the ECM to the actin cytoskeleton, integrins convert mechanical forces into intracellular biochemical signals that regulate tissue remodeling and repair (247,248). Multiple studies indicate that hyperglycemia impairs this integrin-mediated signaling. AGEs can modify the Arg-Gly-Asp (RGD) domain of fibronectin, disrupting its interaction with integrins, thereby altering ECM stiffness and attenuating mechanotransduction efficiency (249). Furthermore, in human proximal tubular epithelial (HK-2) cells cultured under high-glucose conditions, the expression of specific integrin subunits is significantly reduced (250). Chronic hyperglycemia has also been reported to delay fibronectin and integrin expression, impairing the integration of implants into bone (251). These findings suggest that diabetes downregulates integrin expression, disrupts interactions between integrins and ECM

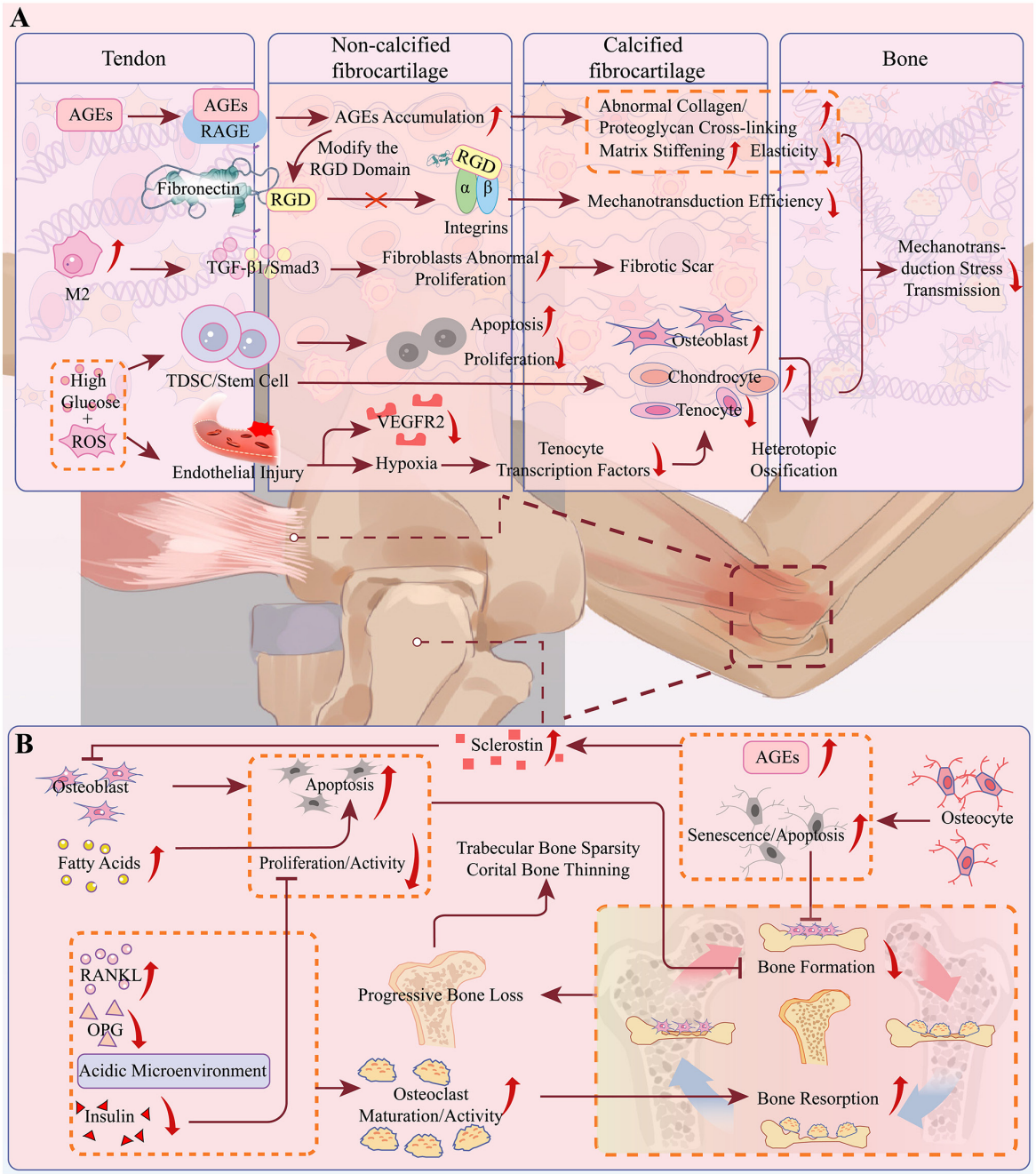

Figure 4. Mechanisms of tendon-bone and bone quality decline in type 2 diabetes mellitus. (A) Hyperglycemia and oxidative stress drive persistent accumulation of AGEs at the TBI, leading to sustained activation of AGEs-RAGE signaling and chronic inflammatory immune responses. This pathological cascade activates the TGF-β1/Smad3 pathway, which promotes fibroblast proliferation and fibrotic remodeling. Meanwhile, abnormal cross-linking of collagen and proteoglycans reduces tissue elasticity and compromises interface integrity. In addition, AGEs modify the RGD domain of fibronectin, disrupting integrin binding, altering extracellular matrix stiffness, and impairing mechanotransduction. These structural abnormalities weaken the mechanical buffering capacity and force transmission of the enthesis. Concurrent endothelial dysfunction and aberrant hypoxia signaling further disrupt stem cell differentiation and tenocyte transcriptional programs. Collectively, these changes promote fibrocartilage calcification and heterotopic ossification, ultimately leading to structural deterioration and functional failure of the TBI. (B) The accumulation of AGEs, lipid metabolic disturbances, and chronic inflammatory microenvironment suppress osteoblast proliferation and differentiation while promoting apoptosis, leading to markedly reduced bone formation. In parallel, AGEs-induced osteocyte senescence and apoptosis upregulate sclerostin expression, thereby inhibiting osteogenic signaling pathways such as Wnt/β-catenin and further impairing bone anabolism. Meanwhile, remodeling of the bone microenvironment, characterized by an imbalanced RANKL/OPG ratio, acidic conditions, and disrupted insulin signaling, promotes osteoclast differentiation, maturation and resorptive activity. Driven by the combined effects of suppressed osteogenesis and enhanced osteoclastogenesis, bone remodeling shifts from homeostatic balance toward negative balance, ultimately resulting in trabecular bone sparsity, cortical thinning and progressive bone loss, which define diabetic bone degeneration and skeletal fragility. AGEs, advanced glycation end products; TBI, tendon-bone interface; RAGE, receptor for AGEs; RGD, Arg-Gly-Asp; ROS, reactive oxygen species; TDSC, tendon-derived stem cell; RANKL, receptor activator of nuclear factor-κB ligand; OPG, osteoprotegerin.

components, and consequently impairs mechanosensation, leading to abnormal mechanical stress transmission at the TBI (Fig. 4A).

Bone. Bone exhibits a distinct pathological response to diabetes because its homeostasis depends on the dynamic coupling of osteoblast-mediated bone formation,

osteoclast-mediated bone resorption, and osteocyte-mediated mechanosensation (252-255). A hallmark of diabetic bone disease is uncoupled bone remodeling. As noted previously, hyperglycemia suppresses osteoblast differentiation while simultaneously promoting excessive osteoclast development and bone resorption. Another distinctive mechanism involves osteocyte dysfunction. Osteocytes are the most abundant and essential cellular component of the skeletal system, acting as the primary sensors of mechanical and biochemical stimuli and playing an irreplaceable role in bone remodeling (256). They are derived from osteoblasts, and a subset of osteoblasts becomes embedded within the mineralized bone matrix to differentiate into osteocytes. These cells are interconnected through a complex network and produce a variety of signaling molecules that regulate osteoblast and osteoclast activity (255). Hyperglycemia impairs the mechanosensory function of osteocytes, accelerates cellular aging, and compromises bone strength (37,257). It can also directly induce osteocyte death, disrupting the integrity of the osteocyte network and impairing skeletal mechanical adaptability (258,259). Cellular aging is a stress-responsive cell fate characterized by durable growth arrest, extensive chromatin remodeling, and acquisition of a proinflammatory secretory program known as the senescence-associated secretory phenotype (SASP) (260). The accumulation of AGEs and senescent cells compromises osteocyte viability and function through the activation of RAGE signaling and the secretion of proinflammatory SASP factors, ultimately enhancing the production of sclerostin by osteocytes. When sclerostin binds to Wnt co-receptors, it inhibits bone formation and reduces osteocyte mechanosensitivity, thereby contributing to poor bone quality in diabetic patients (261-263). Meanwhile, hyperglycemia drives BMSCs toward a metabolically stressed adipogenic lineage rather than osteoblasts. This shift not only causes marrow fat accumulation and impaired trabecular formation, but it also triggers inflammation mediated by hyaluronan, ultimately exacerbating trabecular demineralization (37). These alterations collectively impair fracture healing, reduce bone quality, and increase skeletal fragility despite relatively preserved bone mineral density in numerous patients (Fig. 4B).

4. Conclusion and perspective

Critical appraisal of the evidence, knowledge gaps and future directions. Although the preceding sections summarize the proposed mechanisms underlying diabetes-related musculoskeletal disorders, the strength of evidence supporting each pathway warrants critical evaluation. Much of the available evidence, particularly for AGEs-RAGE signaling and chronic inflammation, comes from *in vitro* and animal studies. Therefore, its direct translation to human pathophysiology should be interpreted with caution. For instance, AGE accumulation is consistently associated with increased tendon stiffness and reduced elasticity in rodent models. However, evidence from human studies is largely correlative and is often confounded by disease duration and comorbidities (22,52,216). Likewise, mitochondrial dysfunction is considered a central feature of numerous proposed mechanisms. However, current evidence mainly comes from associative studies showing reduced oxidative capacity and abnormal mitochondrial morphology in diabetic muscle (14,178). Whether these mitochondrial alterations initiate insulin resistance or arise as a consequence of the diabetic metabolic milieu remains unresolved (264).

Notable contradictions exist within literature. For example, although chronic hyperglycemia is widely accepted to impair angiogenesis, some studies report elevated VEGF levels in diabetic tissues such as the retina. This finding suggests a paradoxical upregulation in response to hypoxia under certain pathological conditions (103,104). By contrast, peripheral tissues such as skeletal muscle and tendon exhibit reduced VEGFR2 signaling and poor neovascularization (115,118,119). These observations suggest that the overall angiogenic response depends on the complex interplay of multiple dysregulated pathways and may be tissue dependent. A significant knowledge gap remains in the understanding of the TBI. While the role of TGF-β1 in fibrosis is well-established, the precise molecular triggers that shift tissue repair from regenerative fibrocartilage formation to pathological scarring in diabetes remain largely unknown (244,265). In addition, the specific contributions of different immune cell subpopulations, particularly the dynamic phenotypic switching of macrophages, remain incompletely understood. Most available evidence comes from a limited number of studies. Finally, most current evidence is derived from single-tissue or single-mechanism studies, making it difficult to understand the integrated, system-level response to diabetes. Future research should prioritize longitudinal human studies, apply multi-omics approaches to capture the complexity of the disease, and develop experimental models that simultaneously investigate interactions among skeletal muscle, tendon, bone and their interfaces. Such integrative approaches will facilitate the identification of robust therapeutic targets and their translation into effective interventions for diabetes-related musculoskeletal complications.

Conventional antidiabetic and anti-osteoporotic therapies bridging metabolism and musculoskeletal health. Conventional antidiabetic medications and anti-osteoporotic therapies not only improve systemic metabolic homeostasis but also exert pleiotropic effects on musculoskeletal tissues by targeting shared pathological mechanisms underlying T2DM-associated musculoskeletal disorders. Rather than acting solely on glucose metabolism or bone remodeling alone, these therapies serve as an important bridge between metabolic regulation and musculoskeletal health through coordinated modulation of inflammation, OS, AGEs, and stem cell function.

Among conventional antidiabetic agents, metformin has been the cornerstone of first-line pharmacological therapy for T2DM for over six decades because of its well-established efficacy, excellent safety profile, minimal risk of hypoglycemia, favorable effects on body weight, cost-effectiveness, robust long-term clinical evidence, and pleiotropic metabolic benefits (266). Beyond its glucose-lowering effect, metformin activates AMPK, thereby suppressing NF-κB-mediated inflammatory signaling and reducing the production of pro-inflammatory cytokines such as TNF-α and IL-6 (267). It also inhibits the formation and accumulation of AGEs, consequently attenuating AGEs-RAGE signaling, OS, apoptosis, and tissue fibrosis (267-269). Since excessive AGEs

accumulation disrupts the stem cell microenvironment and impairs proliferation and lineage commitment, metformin may indirectly preserve stem cell function by reducing glycation stress (270-272). Moreover, accumulating evidence suggests that metformin promotes osteogenic differentiation while suppressing osteoclast activity through multiple signaling pathways, including AMPK, Nrf2/HO-1, SIRT1 and mTOR (273,274). Combination therapy with metformin and anti-osteoporotic agents has also been shown to improve both glycemic control and diabetes-induced bone loss in experimental models (275). Anti-osteoporotic therapies primarily restore skeletal integrity by re-establishing the balance between bone resorption and bone formation. Antiresorptive agents, including RANKL-neutralizing antibody denosumab, suppress osteoclast differentiation and induce osteoclast apoptosis, thereby reducing excessive bone resorption (276). By contrast, anabolic agents such as sclerostin-neutralizing antibody romosozumab directly stimulate osteoblast differentiation and bone formation (277). Beyond increasing bone mineral density and reducing fracture risk, these therapies improve the musculoskeletal microenvironment by preserving bone remodeling homeostasis, thereby providing a favorable niche for stem cell-mediated tissue regeneration.

Conventional antidiabetic and anti-osteoporotic therapies share complementary mechanisms that extend beyond their primary therapeutic indications. By simultaneously improving metabolic control, suppressing chronic inflammation and OS, limiting AGEs accumulation, and preserving stem cell activity, these agents help maintain musculoskeletal tissue homeostasis and strengthen the link between systemic metabolism and the musculoskeletal system.

Application of emerging technologies in diabetes. In recent years, rapid advances in emerging technologies have transformed the prevention, diagnosis, monitoring and management of diabetes. Continuous glucose monitoring, artificial intelligence-assisted decision support systems, digital health tools, biosensors, and advanced drug delivery approaches are reshaping current models of diabetes care. Meanwhile, progress in omics research, big data analytics, and regenerative medicine has provided new insights into disease mechanisms and facilitated the development of personalized therapeutic strategies. The integration of biotechnology, data science and clinical practice marks the beginning of a new stage in precision diabetology, with an emphasis on improving glycemic control, preventing complications, and enhancing the overall quality of life for individuals with diabetes.

Single-cell RNA sequencing (scRNA-seq) reveals the heterogeneity of the diabetic microenvironment. With the rapid development of high-throughput sequencing technologies, the genetic and transcriptomic mechanisms underlying diabetes have been progressively uncovered. The precise regulation of glucose homeostasis depends on the coordinated activity of multiple endocrine cell types within the pancreatic islets (278). Human pancreatic islets are composed mainly of β cells (~54%), α cells (35%) and δ cells (11%), along with smaller populations of γ/PP and ε cells (279,280). Increasing evidence suggests that alterations in the proportion or function of these endocrine cells are closely associated with the pathophysiological processes of monogenic diabetes, T1DM and T2DM (278). However, because pancreatic islets account for only ~1% of pancreatic tissue and contain rare cell populations such as δ and ε cells, whole-genome sequencing at the single-islet level has long been technically challenging (281). The emergence of scRNA-seq has overcome numerous of these limitations. It enables detailed investigation of the molecular mechanisms underlying diabetes and provides new opportunities for clinical diagnosis and treatment (278,282).

Yang *et al* (283) applied scRNA-seq to pancreatic islets from T1DM mouse models and generated a comprehensive single-cell atlas, identifying 11 major cellular subpopulations. Their results revealed marked heterogeneity among α and β cell subsets and demonstrated a significant reduction in the number of mature α and β cells, which was further confirmed by flow cytometry. These observations highlight the potential roles of specific α- and β-cell subpopulations in T1DM progression (283). Honardoost *et al* (284) conducted scRNA-seq analyses of peripheral blood mononuclear cells (PBMCs) from patients with T1DM. Their study demonstrated widespread immune dysregulation across 13 immune cell types, consistent with abnormalities observed in pancreatic islets. Based on these findings, the authors developed a T1DM Meta-Gene Z-score (TMZ score) model, providing a framework for personalized therapeutic strategies in diabetes (284). Analysis of pancreatic islets from patients with T2DM further showed that even the rare δ and ε cells specifically expressed important molecules such as the GHRL receptor and GHRL, suggesting that these rare cell subpopulations may play unique roles in the regulation of islet function (285). Diabetic foot ulcers (DFUs) represent another major complication of diabetes, affecting ~19-34% of patients during the course of the disease (286). Human skin is composed primarily of keratinocytes and fibroblasts, along with immune cells, melanocytes, adipocytes and endothelial cells (287,288). Among these, keratinocyte dysfunction is considered a major contributor to delayed wound repair (282,289). Luo *et al* (290) combined bulk RNA sequencing with scRNA-seq to investigate the mechanisms of mitochondrial programmed cell death in DFUs. They identified key genes, including BCL2 and LIPT1, that were downregulated in DFU tissues, with keratinocytes identified as the most affected cell type (290). Similarly, Wang *et al* (291) applied scRNA-seq to explore wound-healing mechanisms in DFUs and identified 1,948 differentially expressed genes between healing and non-healing wounds, including 1,198 upregulated and 685 downregulated genes. Functional enrichment analysis further demonstrated that the CCL2-ACKR1 signaling axis plays a crucial role in regulating endothelial cell activity and promoting wound healing in diabetic ulcers (291). Collectively, these studies suggest that scRNA-seq serves as a powerful tool for decoding the molecular basis of keratinocyte dysfunction and the complexity of wound repair in T2DM. By revealing disease-specific signaling pathways and potential therapeutic targets, this technology provides opportunities for precision medicine in chronic wound management. Beyond mechanistic studies, scRNA-seq is gradually evolving from a powerful tool for elucidating disease mechanisms into an important technological platform for translational diabetes research. By resolving cellular heterogeneity across pancreatic islets, immune cells and diabetic wounds, and identifying disease-associated molecular signatures, scRNA-seq may

provide clinically relevant insights for biomarker discovery, patient stratification and therapeutic target identification. For example, scRNA-seq-based quality assessment of donor islets before transplantation may facilitate donor selection and potentially improve transplantation outcomes. Moreover, the PBMC-derived TMZ score has shown significant associations with established prognostic immune biomarkers and clinical trial drug responses in T1DM, suggesting its potential utility in identifying patient populations that are more likely to benefit from immunomodulatory therapies. Overall, integrating scRNA-seq with advanced computational and multi-omics techniques holds great promise for developing personalized therapeutic interventions based on the molecular profiles of individual cells.

Although the widespread application of scRNA-seq in both basic research and clinical studies continues to expand, several technical challenges remain. The single-cell capture procedure often compromises cellular integrity and viability, highlighting the need for further optimization to improve throughput and precision. In addition, scRNA-seq produces high-dimensional datasets that are inherently noisy, and reducing this noise remains a major challenge for reliable data analysis. Moreover, cell differentiation and proliferation are inherently dynamic processes, making it difficult for current scRNA-seq methods to accurately distinguish between cell types (292). Beyond these technical limitations, the relatively high cost of scRNA-seq also limits its broader adoption as a routine research tool. Clinical translation of scRNA-seq is further challenged by the limited accessibility of disease-relevant tissues, the lack of standardized analytical workflows, and the need for large-scale prospective validation to ensure the reproducibility and clinical interpretability of single-cell findings across diverse patient populations. Continued improvements in sequencing technologies, bioinformatics algorithms, analytical standardization and cost efficiency will be essential for advancing the application of scRNA-seq in diabetes research and clinical practice.

Targeted delivery systems enhance local therapeutic efficacy. Precision medicine has become a key strategy for managing a wide range of diseases, and targeted drug delivery systems (TDDS) are now emerging as one of its central technologies in diabetes treatment. Insulin remains the fundamental therapy for maintaining glucose homeostasis in patients with T1DM and advanced T2DM. However, conventional insulin therapy relies primarily on frequent subcutaneous injections, such as rapid-acting insulin before meals and long-acting insulin at bedtime, to mimic physiological secretion patterns (293). Repeated injections often lead to pain, local tissue injury, infection and neuropathy, resulting in poor patient compliance (294). In addition, factors such as injection site, depth and dosage can significantly affect insulin absorption kinetics, further increasing the uncertainty of glycemic control (295). To overcome the limitations of injection-based therapy, research has increasingly focused on non-invasive and intelligent TDDS strategies. These systems enable targeted drug delivery to diseased sites and achieve rhythm-synchronized release in response to physiological demands. By improving local therapeutic efficacy while minimizing systemic side effects and reducing dosage requirements, TDDS provide new opportunities for personalized diabetes management. They also optimize pharmacokinetics, regulate drug biodistribution and enhance patient adherence, makes them highly promising for the treatment of complex chronic diseases (296).

A typical TDDS consists of three essential components: The therapeutic target, the active pharmaceutical ingredient (API), and the carrier or delivery vehicle. The therapeutic target refers to the specific organ, tissue, or cell that requires intervention, whereas the API provides the therapeutic effect. The carrier transports the API to the target site with spatial and temporal precision. An ideal carrier should exhibit favorable biocompatibility, biodegradability, low toxicity and specific recognition of the target site (297). Various carrier systems, including liposomes, aptamers and tetrahedral framework nucleic acids, have been extensively investigated. These carriers can improve the bioavailability and tissue penetration of therapeutic molecules, thereby enhancing efficacy. According to their delivery mechanisms, TDDS can be classified as active or passive targeting systems. Active targeting relies on ligand-receptor interactions to achieve precise drug localization, whereas passive take advantage of pathological features such as increased permeability to enhance drug accumulation in diseased tissues (297). The combination of micro-nanotechnology with TDDS represents a major advancement in diabetes therapy. Encapsulating drugs within micro- or nanoscale carriers improves drug stability, bioavailability and local concentration, enhancing therapeutic efficacy and reducing adverse reactions (293,298). For example, polymer-based nanoparticle systems for insulin delivery, constructed from biocompatible and biodegradable materials, such as chitosan, poly(lactic-co-glycolic acid) (PLGA) and polycaprolacton, can effectively overcome the limitations of traditional injection therapy. These nanocarriers protect insulin from enzymatic degradation and acidic conditions during oral administration, significantly increasing its bioavailability and enabling controlled and targeted release (299). Similar benefits have been observed with other oral hypoglycemic agents. A PLGA-based metformin delivery system demonstrated remarkable changes in pharmacokinetic properties. Compared with conventional formulations, PLGA-loaded metformin achieved more than a 10-fold increase in mean residence time and a substantially larger apparent distribution volume, even at 1/10 of the standard dose (300). These findings support PLGA as an efficient sustained-release delivery platform with great potential in diabetes treatment.

As β cells play a central role in the onset and progression of diabetes, designing delivery systems capable of specifically targeting the islet microenvironment is crucial for effective therapy. Ghosh *et al* (301) developed functionalized nanoparticles by conjugating the targeting peptide CHVLWSTRKC to a PLGA-b-PEG-COOH polymer and loading it with genistein. These nanoparticles bound to islet endothelial cells with 3-fold greater affinity through specific interaction with the EphA4 receptor, resulting in a 200-fold enhancement in the immunosuppressive activity of genistein (301). These results demonstrate the feasibility and potential of islet-specific drug delivery. In addition to targeting peptides, antibodies and aptamers have been widely used to construct nanoscale delivery systems for gene therapy, demonstrating considerable potential for precise genetic modulation in diabetes. These systems use

antibody- or aptamer-mediated targeting to deliver therapeutic genes into specific cells and employ disease-responsive promoters to achieve controlled gene expression. This approach helps restore disrupted gene networks and recover cellular function (302). Among these ligands, aptamers have received growing attention for their unique advantages as single-stranded DNA or RNA oligonucleotides with high affinity and selectivity (303). Compared with antibodies, aptamers are smaller, enabling deeper tissue penetration, and they exhibit low immunogenicity and high stability *in vivo*, making them suitable for long-term treatment. Their easy synthesis and chemical flexibility also facilitate the development of personalized therapeutic platforms for diabetes (304,305). Yamada *et al* (306) provided strong experimental evidence for the concept by designing a β-cell-targeted nanocarrier system known as β-MEND. This carrier efficiently delivered nucleic acids into pancreatic β cells. β-MEND successfully internalized into MIN6 cells and delivered antisense RNA targeting microRNA (miR)-375, leading to a marked reduction in miR-375 expression. As a result, Pdk1 and Mtpn were upregulated, significantly enhancing insulin secretion (306). These findings demonstrated that aptamer-based nanocarriers can effectively regulate β-cell function and provide a viable route toward gene therapy in diabetes. Collectively, these advances indicate that TDDS are gradually evolving from experimental delivery platforms toward clinically applicable therapeutic strategies. Recent advances in oral nanoplatforms have achieved efficient insulin delivery, glucose-responsive drug release and sustained glycemic control in preclinical models, highlighting the promising translational potential of precision drug delivery. For example, a milk-derived nanovesicle-based oral insulin delivery system achieved ~20% oral bioavailability with sustained glucose-lowering efficacy in diabetic pigs, highlighting the feasibility of non-invasive insulin replacement therapy (307). Similarly, the recently developed the MOP@T@D (MON-Proteins@Transferrin@Deoxycholic acid) oral nanoplatform in a T2DM rat model achieved an oral bioavailability of 10.6%, increased islet area by 26.7% after treatment, restored insulin secretion to 74.6% of the physiological level, and maintained normal blood glucose levels for up to two weeks after treatment cessation (308). By enabling sustained drug release and selective delivery to diseased tissues or cells, these strategies may facilitate individualized therapeutic interventions while reducing systemic adverse effects, thereby providing a feasible route for future clinical translation.

Despite these encouraging advances, TDDS still face significant challenges in clinical translation. Each type of carrier has inherent limitations. Nanoparticles often exhibit poor physical stability and tend to aggregate or undergo oxidative degradation. In addition, their manufacturing processes are complex (309). Polymer-based also face challenges such as complicated synthesis routes, high production costs and limited structural stability. These limitations may lead to aggregation and, in some cases, inflammatory reactions *in vivo* (310).

Application of artificial intelligence in early diagnosis and prognostic assessment. As a systemic metabolic disorder, diabetes is not only inherently complex but also closely associated with numerous severe complications, which substantially increase patient morbidity and mortality (311). Therefore, treatment alone is insufficient to address the full spectrum of health challenges associated with diabetes. Early intervention through prevention and timely diagnosis is equally important. Consequently, the integration of artificial intelligence (AI) into diabetes management, through machine learning, deep learning and other AI-based analytical approaches, has the potential to transform diabetes care. By leveraging advanced data analysis, feature extraction and predictive modeling, AI provides a data-driven framework for screening, diagnosis, treatment, prognostic assessment and preventive interventions, thereby opening new avenues for disease management (312).

AI applications in diabetes primarily focus on four key domains: Screening for diabetes and its complications, clinical decision support systems (CDSS), population risk prediction and patient self-management tools (313,314). In the field of diabetes screening, AI offers the potential for early, non-invasive, rapid, and cost-effective detection of pathological changes (314). Shu *et al* (315) utilized facial texture analysis combined with a support vector machine model, achieving an accuracy of 99.02%, sensitivity of 99.64% and specificity of 98.26% in diabetes detection. Similarly, Li *et al* (316) integrated tongue color and texture features with machine learning models to predict diabetes risk, reporting an average accuracy of 0.821. However, neither study included external validation, limiting the generalizability of the findings. AI-based early detection of diabetic retinopathy (DR) has emerged as a cost-effective alternative, potentially reducing diabetes-related ocular complications and preventable blindness (317). The American Diabetes Association formally recognizes the clinical value of autonomous AI systems in detecting DR and macular edema (318). Keel *et al* (319) demonstrated that an AI-based DR screening model is highly feasible in endocrinology outpatient settings, showing a sensitivity of 92.3% and specificity of 93.7%, and a patient satisfaction rate of 96%, providing strong evidence for integrating AI screening into routine clinical practice. DPN is another common yet often overlooked complication, largely because of limited screening tools and insufficient diagnostic sensitivity (320). Deep learning algorithms trained on corneal confocal microscopy images have shown promise in detecting DPN. Williams *et al* (321) developed a deep learning algorithm that demonstrated rapid and accurate localization for quantifying corneal nerve biomarkers. Preston *et al* (322) developed a ResNet-50-based model that achieved precisions value of 0.83 in healthy volunteers, with 0.92 and 1.0 for non-neuropathic and neuropathic individuals, respectively.

AI can also assist in optimizing treatment strategies for patients with complex diabetes by identifying optimal therapeutic targets and supporting clinical decision-making. Murphree *et al* (323) conducted a retrospective study of 12,147 patients initiating metformin therapy, using a machine learning model to predict 1-year glycemic control outcomes. Baseline HbA1c, initial metformin dose and complications emerged as key predictors of treatment failure. The best-performing model achieved an area under the curve of 0.75, providing evidence for early identification of high-risk patients and personalized treatment planning (323). Additionally, AI-driven CDSS based on treatment pathway modeling can simulate HbA1c responses under different therapeutic strategies in T2DM, offering critical guidance

for individualized care (324). By analyzing patients' lifestyle behaviors, physical and mental health parameters, and social network activities, machine learning-based health recommendation systems can predict disease risks (324). Decision tree models have also been applied to predict the risk of T2DM development in women with gestational diabetes, achieving discrimination performance of 83.0% in training datasets and 76.9% in independent test sets, outperforming traditional fasting glucose monitoring (325). AI models integrating genetic and medical imaging data have demonstrated strong predictive performance for T2DM risk assessment. Huang *et al* (326) employed XGBoost to combine polygenic risk scores, multi-modality imaging risk scores and demographic variables (for example, age, sex and family history of diabetes) in 68,911 participants, achieving an Area Under the Receiver Operating Curve (AUC) of 0.94. This model effectively identified high-risk populations with specific genetic and imaging features, enabling precision prevention and early intervention for T2DM (326). These advances suggest that AI is gradually transitioning from a research-oriented analytical tool to an integrated component of precision diabetes care. In clinical practice, AI-based systems may facilitate earlier identification of individuals at risk, improve screening efficiency for diabetes complications, and support individualized therapeutic decision-making through integration with continuous glucose monitoring, electronic health records, and digital health platforms. Among current AI-enabled therapeutic strategies, personalized insulin adjustment based on reinforcement learning, prediction of treatment responses to glucose-lowering medications, and AI-guided lifestyle interventions have shown promising potential for improving glycemic control and optimizing long-term disease management.

Self-management, particularly maintaining blood glucose within recommended ranges, remains a cornerstone of diabetes care. This involves active glucose monitoring, regulation of physical activity and diet, and appropriate insulin administration (327). Dietary and exercise interventions are primary strategies for preventing T2DM in high-risk populations (328). Personalized applications provide tailored dietary plans, while wearable devices track daily activity and use behavioral incentives to promote healthy habits, thereby helping prevent chronic diseases including T2DM (314). In addition, accurate prediction of blood glucose fluctuations in patients with T2DM facilitates improved glycemic control, reduces hypoglycemic events, and lowers diabetes-related morbidity and mortality, ultimately enhancing quality of life. Deng *et al* (329) developed a predictive model using deep transfer learning and data augmentation on continuous glucose monitoring data recorded every 30 min, forecasting blood glucose 5 min to 1 h ahead with over 95% accuracy and 90% sensitivity. Wang *et al* (330) proposed a reinforcement learning-based dynamic insulin titration regimen, improving glycemic control without increasing hypoglycemia risk, achieving personalized insulin dose optimization for patients with T2DM. These technological advances enable both healthcare providers and patients to proactively manage diabetes, adjusting insulin doses and lifestyle behaviors to prevent hyperglycemia or hypoglycemia and associated complications. Despite the promise of AI in research, its real-world application remains challenging, particularly across diverse populations (331). Training datasets lacking balanced representation in terms of age, sex, ethnicity, or risk factors may exacerbate biases, leading to misdiagnosis or inappropriate treatment for underrepresented groups (332). Therefore, inclusive data collection strategies are essential. Given the potential for AI errors, ethical challenges arise, underscoring the need for robust supervision and clear accountability guidelines in AI-driven diabetes care. Furthermore, ensuring data privacy is critical. Securing data during development and deployment remains challenging, and global-scale implementation intensifies these risks, necessitating stringent protection measures.

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Availability of data and materials

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Authors' contributions

ZH conceptualized the study. ZH, HL, YL and YY conducted investigation and data visualization, wrote the original draft, and wrote, reviewed and edited the manuscript. SL conducted investigation, and wrote, reviewed and edited the manuscript. TZ supervised the study, conducted project administration, and wrote, reviewed and edited the manuscript. DB conceptualized and supervised the study, conducted project administration, acquired funding, and wrote, reviewed and edited the manuscript. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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