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REVIEW

The Critical Role of Autophagy in the Pathogenesis of Diabetic Osteoporosis: Mechanisms and Therapeutic Measures

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Abstract: Diabetic osteoporosis (DOP) represents a significant skeletal complication of diabetes mellitus characterized by compromised bone quality and increased fracture risk. Autophagy, a conserved cellular homeostatic mechanism, serves as a key regulator of bone formation and resorption balance. This review comprehensively examines the pivotal role of autophagy in DOP pathogenesis and explores emerging therapeutic strategies targeting autophagic regulation. Under hyperglycemic conditions, dysregulated autophagy occurs through multiple signaling pathways, including ROS-mTOR, PINK1/Parkin-mediated mitophagy, FoxO transcription factors, AGEs-RAGE and TLR4/NF-κB cascades etc. These disturbances manifest distinctly in various cell types: impaired mineralization of osteoblasts, altered bone resorption of osteoclasts, compromised insulin secretion of pancreatic β-cells, diminished osteogenic differentiation of bone marrow mesenchymal stem cells and adipose-derived stem cells. Current therapeutic approaches targeting autophagy dysregulation include pharmacological interventions such as metformin, rapamycin and vitamin D analogs, autophagy enhancers such as resveratrol and AMPK activators, specific inhibitors regulating excessive autophagic activity, Chinese medicinal compounds and exercise regimens. Emerging strategies also include gene therapy, stem cell transplantation and combined therapeutic approaches that precisely modulate the dynamic balance of autophagic flux. Moreover, we underscore the critical importance of maintaining optimal autophagic activity—neither excessive nor insufficient—in bone cells to preserve metabolic homeostasis and prevent osteoporotic progression in DOP patients. Future research directions should focus on elucidating specific mechanisms of action, identifying optimal intervention timing and exploring synergistic therapeutic combinations to effectively manage this challenging metabolic bone disorder.

Keywords: diabetes, osteoporosis, autophagy, mechanism, therapeutic strategies

Introduction

Diabetes mellitus (DM) is a prevalent chronic endocrine disorder worldwide that can lead to multiple complications, with osteoporosis increasingly recognized as an emerging concern.[1,2] Diabetic osteoporosis (DOP) represents a common chronic complication in diabetes patients, macroscopically resulting from long-term metabolic dysregulation of carbohydrates, lipids and proteins, where bone resorption exceeds bone formation, leading to altered bone metabolism.[3,4] DOP is characterized by decreased bone mineral density, disrupted bone microarchitecture and increased bone fragility, significantly elevating fracture risk and diminishing life quality of patients.[5] Epidemiological studies indicate that diabetic patients have a higher risk of osteoporotic fractures compared to non-diabetic populations, with longer recovery periods and more complications, with incidence rising globally.[6] Therefore, DOP has emerged as a significant public health challenge, necessitating comprehensive exploration of its pathogenic mechanisms and treatment strategies.

Autophagy is a highly conserved cellular self-digestion process whereby damaged organelles and proteins are encapsulated by double-membrane vesicles to form autophagosomes, which subsequently fuse with lysosomes to create

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autolysosomes.[7] These structures ultimately degrade their contents through various lysosomal enzymes, maintaining cellular homeostasis by degrading and recycling damaged intracellular proteins and organelles.[8] Mounting evidence suggests that autophagy regulates bone metabolic balance, participating in the regulation of bone formation and resorption equilibrium. Under normal physiological conditions, moderate autophagy activity is essential for maintaining bone cell function. However, in hyperglycemic environments, dysregulation of autophagy signaling pathways is considered one of the core mechanisms underlying DOP pathogenesis.[9]

Currently, diverse aspects regarding the specific mechanisms of autophagy in DOP have been elucidated and investigated. Some studies suggest that excessive autophagy activity in hyperglycemic environments may promote bone cell apoptosis, while others indicate that insufficient autophagy activity results in organelle damage and functional impairment, subsequently affecting bone metabolism.[10] This phenomenon reflects the complexity and cell-specificity of autophagy regulation, highlighting that maintaining dynamic balance of autophagy is critical for bone metabolic health. Based on the significant role of autophagy in DOP, therapeutic strategies targeting autophagy regulation have become a research focus in recent years. Through precise modulation of autophagy levels, these strategies may improve bone cell function, restore bone metabolic balance and provide novel therapeutic options for DOP patients.[11]

This review systematically examines the mechanisms of autophagy in DOP pathogenesis, focusing on key signaling pathways. We analyze how these pathways regulate autophagy activity across different bone cell types and their functions in DOP pathological progression (Figure 1). Additionally, we explore various therapeutic strategies and their clinical potential, providing new insights and directions for both fundamental research and clinical management of DOP.

Mechanism

ROS-mTOR Signaling Pathway

Osteocytes

Autophagy dysregulation profoundly affects osteocyte function. In DOP, the high-glucose microenvironment disrupts bone metabolism through complex autophagy mechanisms centered on the AMP-activated protein kinase (AMPK)/ Rapamycin (mTOR) signaling axis.

Under high-glucose conditions, excessive ROS accumulation creates a pathological cascade affecting autophagy regulation. ROS directly damages osteocytes while activating the AMPK pathway.[12,13] As the cellular energy sensor, AMPK responds to glucose-induced ATP/AMP ratio alterations by phosphorylating Unc-51-like autophagy activating kinase 1 (ULK1) and upregulating autophagy-related genes, enhancing autophagic flux to clear damaged organelles.[14,15] This process operates in dynamic balance with the mTOR pathway, which negatively regulates autophagy.

However, high glucose disrupts this AMPK/mTOR balance through dual mechanisms (Table 1). Elevated ROS suppresses PI3K/Akt signaling and reduces mTOR activity, leading to aberrant autophagy activation and accelerated protein degradation.[16,17] Simultaneously, diabetic conditions inhibit AMPK function, impairing negative regulation of mTOR complex 1 (mTORC1) and causing sustained mTOR activation.[18] This imbalance triggers a vicious cycle of impaired autophagic flux, metabolic dysregulation and bone loss.

The AMPK/mTOR axis represents a critical regulatory network where AMPK promotes autophagy via ULK1-dependent pathways while mTOR inhibits this process.[15,19] Understanding this interactive regulation provides insights into autophagic dysfunction in DOP and suggests that dual modulation of the AMPK/mTOR pathway could be an effective therapeutic strategy for bone metabolic disorders (Figure 2).

Osteoblasts

The autophagy mechanism in osteoblasts is regulated through interconnected signaling pathways. ROS generated by oxidative stress dually affects autophagy by activating mTORC1 through Akt while simultaneously triggering AMPK signaling.[20] Similarly, AMPK promotes autophagy through two complementary mechanisms: direct phosphorylation of ULK1 and inhibition of mTOR signaling, thereby alleviating metabolic stress and enhancing autophagic flux.[21] Conversely, excessive mTOR activation suppresses autophagy-related factor expression, leading to reduced autophagic flux and compromised osteogenic capacity (Table 1).[22–24]

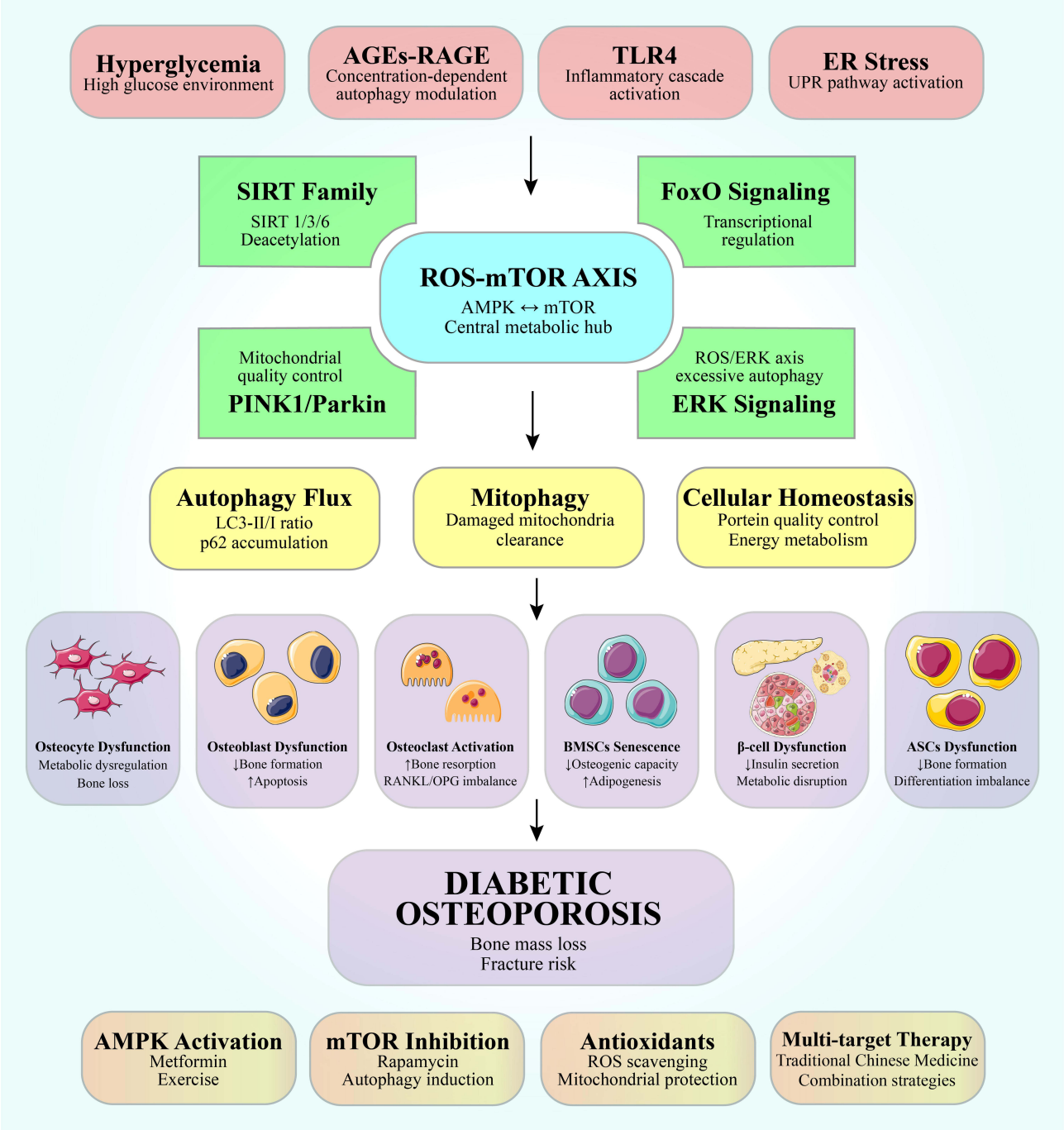

Figure 1 Interaction network of autophagy-related mechanisms in DOP. This schematic illustrates the convergence of four diabetic stressors (hyperglycemia, AGEs-RAGE interaction, TLR4 inflammatory cascade activation, and ER stress-induced UPR pathway) on the central ROS-mTOR axis, which serves as the metabolic hub coordinating cellular responses through AMPK-mTOR regulation. Key regulatory pathways—SIRT family (SIRT1/3/6-mediated deacetylation), FoxO transcriptional regulation, PINK1/Parkin mitochondrial quality control, and ERK signaling—modulate this central axis. The dysregulation manifests in three critical processes: disrupted autophagy flux (LC3-II/I ratio and p62 accumulation), impaired mitophagy (damaged mitochondria clearance), and compromised cellular homeostasis (protein quality control and energy metabolism). These alterations drive dysfunction across six bone cell types, including osteocyte metabolic dysregulation, osteoblast apoptosis, osteoclast activation with RANKL/OPG imbalance, BMSC senescence, β-cell insulin secretion impairment, and ASC differentiation imbalance, collectively resulting in DOP characterized by bone mass loss and increased fracture risk. Bottom panel indicates potential therapeutic interventions targeting this pathological network: AMPK activation (metformin/exercise), mTOR inhibition (rapamycin), antioxidants for ROS scavenging, and multi-target traditional Chinese medicine combinations.

Under physiological conditions, autophagy maintains osteoblast homeostasis by clearing damaged mitochondria and aggregated proteins.[25] However, in diabetic conditions characterized by chronic hyperglycemia, this protective mechanism becomes compromised. High-glucose environments significantly impair MC3T3-E1 osteoblast proliferation through

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Table 1 ROS-mTOR Signaling Pathway-Centered Regulation in Different Types of Bone Tissue Cells in DOP

Cell Type	Main Pathological Effects
Osteocyte	Low ROS: Activate PI3K/Akt/mTOR pathway, inhibit autophagy, potentially exacerbate bone loss. High ROS: Inhibit PI3K/Akt/mTOR pathway, activate autophagy, potentially promote osteoporosis.
Osteoblast	ROS-triggered AMPK activation: Phosphorylate ULK1 to initiate autophagy, alleviate mTOR-mediated autophagy suppression, regulate osteoblast function.
Osteoclast	PI3K/Akt Pathway Activation: Inhibit mTORC1. NF-κB Pathway Activation: Suppress AMPK activity. Together: Reduce autophagy levels and impair osteoclast function.
BMSC	Upregulate autophagy signaling via ECM alteration and NADPH oxidase activation, concurrently inhibit autophagy via PI3K/Akt/mTOR activation and impair BMSC regenerative capacity.
Pancreatic β Cell	ROS Regulation: Inhibit autophagy via PI3K/Akt/mTOR activation, simultaneously promote autophagy via AMPK/SIRT1/PGC-1α pathway.
ASC	Block autophagy, downregulate autophagy-related proteins, inhibit Wnt and Notch signaling pathways, suppress osteogenic differentiation and promote adipogenic differentiation.

Abbreviations: ROS, Reactive oxygen species; AMPK, AMP-activated protein kinase; ULK1, Unc-51-like autophagy activating kinase 1; mTORC1, mTOR complex 1; NF-Kb, Nuclear factor kappa B; SIRT1, Sirtuin 1; ECM Extracellular matrix; BMSC, Bone marrow mesenchymal stem cell; ASC, Adipose-derived stem cell.

metabolic stress-induced mitochondrial dysfunction and cell cycle dysregulation.[26] Furthermore, sustained hyperglycemia triggers ROS accumulation and endoplasmic reticulum stress, activating the Caspase cascade and shifting the Bax/Bcl-2 ratio toward apoptosis.[27,28] When autophagic flux is insufficient, the resulting accumulation of damaged organelles and proteins exacerbates oxidative stress, inflammatory cytokine production and ultimately leads to reduced bone formation.[25,29]

Therefore, the therapeutic restoration of autophagic function through modulation of AMPK and mTOR pathways in osteoblasts represents a promising strategy for DOP treatment. By enhancing AMPK-mediated autophagosome formation and reducing mTOR-dependent autophagy suppression, it may be possible to restore osteoblast survival and bone-forming capacity in diabetic conditions.[20,29,30]

Osteoclasts

In DOP patients, hyperglycemia disrupts autophagic flux in osteoclasts through multiple interconnected signaling pathways. High glucose activates the PI3K/Akt pathway, which in turn activates mTORC1 and simultaneously suppresses AMPK activity.[31] Additionally, hyperglycemia activates the nuclear factor kappa B (NF-κB) pathway, which further inhibits AMPK and promotes mTOR activity, collectively reducing autophagic levels in osteoclasts.[32] These molecular alterations manifest as impaired osteoclast differentiation and function under high-glucose conditions, with experimental observations showing markedly reduced differentiation and bone resorption capacity. Specifically, the number of tartrate-resistant acid phosphatase ($TRAP^+$) multinucleated cells decreases, indicating hindered osteoclast differentiation, while the reduced expression of cathepsin K (CTSK) protein reflects compromised bone resorption function.[33]

The disruption of autophagy in osteoclasts involves specific changes in the AMPK/mTOR/ULK1 signaling cascade and autophagy-related proteins. High glucose-induced suppression of this pathway results in decreased levels of Beclin-1 and light chain 3 (LC3-II), indicating weakened autophagic activity, while P62 levels increase, suggesting obstructed autophagic flux. Importantly, when mTOR is pharmacologically inhibited and ULK1 phosphorylation is enhanced, autophagy in osteoclasts can be restored, confirming the central role of this pathway in regulating osteoclast autophagy.[33]

The impaired autophagy ultimately contributes to the pathogenesis of DOP through dysregulated osteoclast function and compromised bone remodeling (Table 1). Under normal conditions, the combination of receptor activator nuclear factor-κB (RANK) and RANK ligand (RANKL) promotes osteoclast differentiation by activating nuclear factor of activated T cells (NFATc1) and tumor necrosis factor receptor-related factor 6 (TRAF6) expression. However, AMPK activation can counteract these pathways by upregulating autophagy-related factors such as Beclin-1 and autophagy-related protein 5 (ATG5), thereby modulating osteoclast maturation and function.[34,35] Therefore, the autophagy machinery, primarily regulated by the AMPK/mTOR signaling pathway and associated molecular mechanisms, represents a promising therapeutic target for DOP treatment by restoring proper osteoclast function and bone metabolic balance.

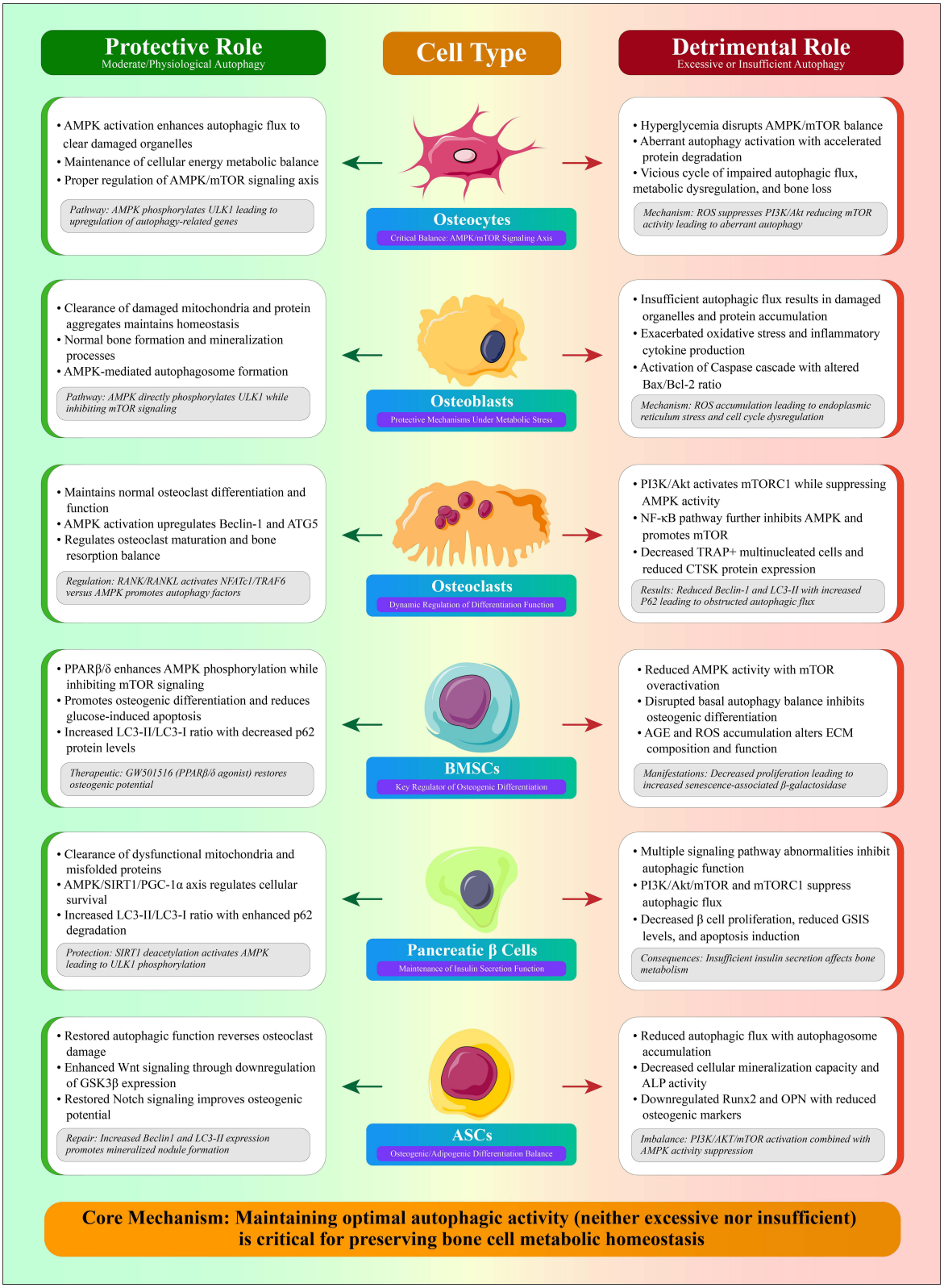

Figure 2 The Dual Regulatory Effects of Autophagy on DOP. The schematic illustrates cell-specific biphasic autophagy regulation in diabetic osteoporosis. Moderate physiological autophagy maintains bone homeostasis through AMPK activation, enhanced autophagic flux, and proper organelle clearance across six bone-related cell types. Conversely, hyperglycemia-induced autophagy dysregulation manifests as either excessive activation causing autophagic cell death or insufficient activity leading to damaged organelle accumulation. Cell-specific mechanisms include: osteocytes (AMPK/mTOR signaling disruption), osteoblasts (ROS-mediated autophagic stress), osteoclasts (RANK/RANKL-mediated differentiation imbalance), BMSCs (impaired osteogenic differentiation), pancreatic β-cells (compromised insulin secretion), and ASCs (disrupted osteogenic/adipogenic balance). These alterations converge through PI3K/Akt/mTOR activation, NF-κB dysregulation, and SIRT1/PGC-1α signaling disruption. The core therapeutic principle emphasizes maintaining optimal autophagic activity—neither excessive nor insufficient—to preserve bone metabolic homeostasis.

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Bone Marrow Mesenchymal Stem Cells

Bone marrow mesenchymal stem cells (BMSCs) are fundamental to bone regeneration and osteogenic differentiation, with their functional impairment being closely associated with DOP onset.[36,37] In high glucose environments, AMPK activity is reduced while mTOR is overactivated, disrupting basal autophagy balance and inhibiting BMSC osteogenic differentiation.[38] Conversely, peroxisome proliferators-activated receptor (PPAR) β/δ enhances autophagic activity by upregulating AMPK phosphorylation and inhibiting mTOR signaling, promoting rat BMSC osteogenic differentiation and reducing glucose-induced apoptosis. Experimental researches elucidated that PPARβ/δ agonist (GW501516) significantly increased LC3-II /LC3-I ratios and decreased p62 protein levels, restoring osteogenic potential through AMPK/mTOR-mediated autophagy regulation.[39,40] Additionally, PI3K/Akt/mTOR pathway activation directly inhibits autophagy and exacerbates cellular aging via oxidative stress, further compromising BMSC capacity to clear damaged organelles.[41]

High glucose also increases AGE and ROS accumulation, altering extracellular matrix (ECM) composition and function, with proteomic analysis revealing upregulation of 524 proteins and downregulation of 66 proteins, including ECM and osteogenic function-related proteins such as Fibulin-1, Fibulin-2, and COL6A3.[42] Under 25 mM glucose conditions, BMSCs exhibit reduced proliferation, increased senescence associated β-galactosidase (SA-β-gal) positive cells, and morphological shifts from elongated to flattened shapes, indicating critical functional damage in DOP development.[43] High glucose significantly upregulates autophagy-related proteins with increased autophagosome numbers, suggesting the dual role of autophagy in clearing damaged components while potentially accelerating senescence. When autophagy is inhibited using 3-Methyladenine (3-MA), autophagy-related proteins and autophagosome numbers decrease with reduced SA-β-gal-positive cells and restored proliferation, although apoptosis increases significantly.[43,44]

Antioxidant treatment reduces ROS levels, downregulates autophagy-related proteins, and decreases autophagosome numbers, confirming ROS-mediated oxidative stress as the mechanism for high glucose-induced autophagy and BMSC senescence.[45] Under coexisting high glucose and insulin conditions, BMSCs show significantly reduced autophagic levels with decreased LC3-II/LC3-I ratios and p62 accumulation, accompanied by impaired function and diminished osteogenic differentiation.[46] Early senescence markers increase significantly, indicating that high glucose and insulin weaken BMSC osteogenic potential by hindering autophagic function, promoting DOP occurrence and progression (Table 1).[47]

High glucose environments affect BMSCs through AMPK/mTOR signaling dysregulation and ROS-mediated oxidative stress, resulting in abnormal autophagy regulation that disrupts metabolic homeostasis, accelerates senescence, reduces osteogenic differentiation capacity and ultimately impairs BMSC regenerative function, directly contributing to DOP pathogenesis.

Pancreatic β Cells

The maintenance of functional homeostasis in pancreatic β cells is dependent on autophagy, which protects cells from damage by clearing dysfunctional mitochondria and misfolded proteins.[48] However, in hyperglycemic conditions, aberrant activation of multiple signaling pathways collectively inhibits β cell autophagic function, leading to cellular dysfunction and insufficient insulin secretion, thereby negatively impacting bone metabolism.[49,50]

Hyperglycemia disrupts β cell autophagy through multiple interconnected mechanisms. High glucose-induced oxidative stress generates ROS, which activate a series of signaling pathways including PI3K/Akt/mTOR and mTORC1, consequently suppressing autophagic flux.[31,51] This suppression is accompanied by reduced expression of autophagy-related proteins, preventing β cells from clearing damaged mitochondria and misfolded proteins, ultimately leading to cell dysfunction and death with loss of insulin secretion capacity. Furthermore, impaired autophagy significantly reduces pancreatic β cell proliferation capacity and glucose-stimulated insulin secretion (GSIS) levels while inducing apoptosis.[52]

The AMPK/Sirtuin 1 (SIRT1)/Proliferator-activated Receptor Gamma Coactivators-1α (PGC-1α) axis is essential in regulating β cell autophagy and survival. As an energy-sensing molecule, AMPK regulates cellular metabolic homeostasis by activating SIRT1 and PGC-1α signaling pathways.[53] SIRT1 promotes PGC-1α activation through deacetylation, enhancing mitochondrial function and anti-apoptotic capacity to maintain β cell viability.[54] Additionally, SIRT1 deacetylation activates AMPK, which promotes autophagic flux by phosphorylating ULK1 and inhibiting mTOR, thereby

improving β cell resistance to oxidative stress.[55] Active autophagy is characterized by an increased LC3-II/LC3-I ratio and enhanced p62 degradation, facilitating the clearance of damaged mitochondria in β cells.[56] Moreover, autophagy activation can mitigate chronic inflammatory damage to β cells in diabetic patients, although persistent inflammation may ultimately inhibit autophagic function.[57]

The blockade of autophagic flux under hyperglycemic conditions accelerates β cell degeneration and insulin secretion deficiency, subsequently disrupting bone metabolism. Therefore, preserving autophagy represents a critical mechanism for protecting β cell function and potentially ameliorating DOP.

Adipose-Derived Stem Cells (ASCs)

In patients with DOP, the osteogenic differentiation capacity of ASCs is significantly impaired, and this phenomenon is closely associated with autophagic dysfunction in a high-glucose environment. Under DOP condition, ASCs exhibit multiple functional defects including reduced proliferation, impaired migration, and suppressed osteogenic differentiation capacity.[58] At the cellular level, high glucose leads to reduced autophagic flux and accumulation of autophagosomes in ASCs, which directly correlates with diminished cellular mineralization capacity.[59] These changes are accompanied by decreased alkaline phosphatase (ALP) activity, reduced mineralized nodule formation, and downregulation of key osteogenic markers including runt-related transcription factor 2 (Runx2) and osteopontin (OPN).[58,60]

The molecular mechanisms underlying these impairments involve dysregulation of multiple signaling pathways. High glucose abnormally activates the PI3K/AKT/mTOR signaling pathway while suppressing AMPK activity, which disrupts normal autophagic function.[30,61] This is evidenced by reduced expression of autophagy-related proteins such as Beclin1 and LC3-I/II, alongside increased levels of negative regulatory factors including mTOR and GSK3β.[56,62] Furthermore, high glucose weakens the osteogenic capacity of ASCs by inhibiting the Wnt signaling pathway.[63] The Notch signaling pathway, another key regulator of osteogenic differentiation, also shows compromised function in DOP mice, with reduced expression of the intracellular domain of Notch (NICD) and downstream genes.[64]

Importantly, these pathological changes can be reversed through restoration of autophagic function. Activating AMPK restores autophagic flux, thereby improving the osteogenic differentiation capacity of ASCs in high-glucose environments.[62] Enhanced autophagy promotes Wnt signaling by downregulating GSK3β expression and restores Notch signaling, both of which significantly enhance osteogenic differentiation capacity.[65–67] Studies demonstrate that restoring autophagic function in ASCs from DOP patients can reverse osteoclast damage and improve osteogenic potential while enhancing the expression of Beclin1 and LC3-II promotes mineralized nodule formation.[66] However, the imbalance in ASC differentiation not only reduces bone formation but also accelerates osteoporosis progression by disrupting the bone marrow microenvironment.

Impaired autophagic function in ASCs could be led by high glucose-induced activation of the PI3K/AKT/mTOR pathway, coupled with inhibition of AMPK activity and interference with Wnt and Notch signaling. This cascade ultimately suppresses osteogenic differentiation while promoting adipogenic differentiation, triggering DOP and related complications (Table 1). Therefore, the decline in autophagy represents a core mechanism underlying ASC differentiation imbalance and bone metabolic disorders, suggesting that regulating autophagic function plays a critical role in improving ASC differentiation balance and restoring bone metabolic homeostasis.

PINK1/Parkin Signaling Pathway

The development of DOP is closely associated with mitochondrial dysfunction, wherein iron overload, oxidative stress and disrupted mitochondrial autophagy (mitophagy) pathways constitute critical pathological factors.

Mitophagy maintains cellular metabolic homeostasis by selectively removing damaged mitochondria, thereby reducing oxidative stress-induced bone cell damage, promoting metabolic stability, and decreasing ROS generation.[68] The PTEN induced kinase 1 (PINK1)/Parkin signaling pathway serves as the central mechanism for mitochondrial quality control. PINK1 accumulates on the outer mitochondrial membrane to identify damaged organelles and subsequently activates Parkin, which marks these compromised mitochondria through ubiquitination for clearance.[55,69] However, under hyperglycemic and inflammatory conditions, PINK1/Parkin-mediated mitophagy becomes suppressed, resulting in ROS accumulation, mitochondrial fragmentation and energy metabolic dysregulation that generates numerous dysfunctional mitochondria.[70] The

impaired clearance of damaged mitochondria leads to diminished oxidative phosphorylation capacity and further autophagy activation through ROS release, exacerbating metabolic burden and precipitating bone metabolic disorders.[47] This dysfunction is particularly pronounced in pancreatic β-cells, where accumulated damaged mitochondria generate excessive ROS, impairing cellular function and contributing to bone metabolic disorders.[17,71]

Iron overload is one of the major contributors to mitochondrial damage. Mitochondrial ferritin (FtMt), a key iron metabolism regulator, plays a significant role in DOP pathogenesis.[72] Studies demonstrate that both ferroptosis and altered FtMt expression occur in type 2 DOP rat models. Under high-glucose conditions, FtMt overexpression significantly reduces ferroptosis and ROS levels in osteoblasts, while FtMt silencing induces mitophagy through ROS/PINK1/Parkin pathway activation.[72] Similarly, NIPA2 is essential for DOP pathogenesis, with decreased expression observed in bone tissue and osteoblasts of type 2 DOP mouse models. Mechanistically, NIPA2 overexpression inhibits mitophagy and promotes osteogenic function by enhancing Mg^{2}+ influx, thereby decreasing LC3-II, PINK1 and Parkin expression. This regulation occurs through the NIPA2/PGC-1α/FoxO3a/mitochondrial membrane potential axis, where NIPA2 downregulates PGC-1α, subsequently promoting FoxO3a expression, activating BIM and increasing mitochondrial membrane permeability.[73–75]

The pathological cascade intensifies under high-glucose and high-fat conditions and disrupted mitochondrial membrane potential leads to organelle damage and dysfunction, further exacerbated by insufficient autophagic flux.[18] Supporting evidence includes findings from PINK1 knockout mice, which exhibit elevated mitochondrial superoxide levels in osteoblasts, reduced bone formation capacity and exacerbated bone mass loss.[72] Additionally, osteoblasts with low PINK1 expression demonstrate significant reductions in bone markers including ALP and osteocalcin, while showing increased mitochondrial fragmentation and ROS levels.[76]

PINK1/Parkin-mediated mitophagy dysfunction represents a central mechanism in DOP development. Mitophagy suppression under hyperglycemic conditions leads to damaged mitochondrial accumulation, intensifying oxidative stress and cellular dysfunction that ultimately disrupts bone metabolic homeostasis. Restoring PINK1/Parkin-mediated mitophagy function may therefore provide a novel therapeutic strategy for DOP management.

FOX Signaling Pathway

The FoxO transcription factor family, which includes FoxO1, FoxO3 and FoxO4, critically regulates autophagy in DOP. Under diabetic conditions, aberrant FoxO activation directly modulates autophagy-related mechanisms, promoting excessive autophagic flux that increases metabolic burden and accelerates bone tissue cell turnover, ultimately contributing to bone loss.[77]

FoxO1-mediated autophagy regulation represents a pivotal mechanism in bone metabolism. FoxO1 physiologically enhances osteoblast function through interaction with autophagy-related protein 7 (ATG7).[78] However, diabetic hyperglycemia fundamentally alters FoxO1 activity, correlating decreased osteoblast numbers with reduced bone mass and accelerated DOP progression.[79] Mechanistically, hyperglycemia-induced ROS elevation activates FoxO1, which directly upregulates autophagy genes including LC3 and Beclin1, enhancing autophagic flux.[80] While moderate FoxO1 activation maintains osteoblast homeostasis, excessive activation disrupts bone metabolic balance by inhibiting osteoblast function and enhancing osteoclast activity.[80,81] This dual role is confirmed by chloroquine-mediated autophagy inhibition, which reverses bone formation defects caused by FoxO1 overexpression.[78] Additionally, 1α,25-dihydroxyvitamin D3 protects diabetic bone formation by promoting FoxO1 nuclear-to-cytoplasmic translocation,[82] highlighting the importance of subcellular localization in FoxO1 function.

FoxO3 orchestrates autophagy-dependent cyto-protection against oxidative stress in DOP through multiple interconnected pathways. In hyperglycemic conditions, elevated ROS levels activate compensatory autophagy in osteoblasts via FoxO3-dependent mechanisms. The ROS/FoxO3 pathway involves serine 294 phosphorylation during mesenchymal stem cell (MSC) osteogenic differentiation, where FoxO3-induced autophagy creates a negative feedback loop to regulate ROS levels.[83,84] Parallel pathways include ROS/SIRT1/FoxO3 signaling, where SIRT1-mediated FoxO3 deacetylation promotes Bnip3 expression, enhancing autophagy and reducing osteoblast apoptosis and ROS/AMPK/FoxO3 cascade, where H_2O_2-activated AMPK phosphorylates ULK1 to promote FoxO3-mediated autophagy.[85,86] Conversely, inhibition of the Akt/mTOR pathway under diabetic conditions further amplifies FoxO3-dependent autophagy.[87] Despite the time-

dependent upregulation of FoxO3 during normal osteogenic differentiation, pathological diabetes overwhelms these protective mechanisms, resulting in osteoblast dysfunction and enhanced bone resorption.[88] Notably, excessive FoxO3 activation may exacerbate muscle atrophy through simultaneous upregulation of autophagy genes and the ubiquitin-proteasome system (UPS), indirectly affecting bone metabolism.[89]

FoxO transcription factors represent critical regulators of DOP pathogenesis through autophagy modulation. While physiological FoxO1/FoxO3 activation supports bone homeostasis, diabetic conditions promote excessive FoxO signaling that disrupts the delicate balance between bone formation and resorption. These findings suggest that targeted intervention of FoxO signaling pathways may offer novel therapeutic strategies for DOP management.[78,88]

SIRT Family

The SIRT family serves as a central regulatory role in DOP pathogenesis through precise modulation of autophagy pathways. Among these NAD^+-dependent deacetylases, SIRT1, SIRT3 and SIRT6 demonstrate distinct yet interconnected functions in maintaining bone metabolic homeostasis.

SIRT1-mediated autophagy regulation operates primarily through the AMPK/mTOR signaling axis.[90] Under hyperglycemic conditions, diminished SIRT1 expression impairs AMPK phosphorylation while aberrantly elevating mTOR activity, consequently blocking autophagy initiation.[91] This dysregulation leads to accumulation of damaged mitochondria and misfolded proteins in osteoblasts, ultimately inhibiting osteogenic differentiation and promoting cellular apoptosis. SIRT1 additionally enhances autophagy through direct deacetylation of FoxO transcription factors, facilitating their binding to autophagy-related gene promoters and maintaining autophagy-lysosomal system integrity.[92,93] At the autophagy-apoptosis interface, SIRT1 provides cyto-protection by deacetylating p53 and NF-κB to suppress pro-apoptotic transcriptional activity while simultaneously promoting ATG5-ATG12 complex formation to sustain protective autophagy levels.[94]

SIRT3 functions as the primary regulator of mitochondrial quality control through the PGC-1α/SIRT3/FOXO3 pathway. Hyperglycemia-induced SIRT3 downregulation compromises mitochondrial deacetylase activity, resulting in abnormal membrane potential, excessive ROS generation, and mitochondrial DNA damage.[95,96] Consequently, impaired PINK1/Parkin pathway activation prevents selective clearance of damaged mitochondria, leading to mitochondrial network collapse, ATP synthesis deficiency, and amplified oxidative stress that collectively inhibit osteogenesis while promoting bone resorption.[97,98] SIRT3 overexpression can rescue high glucose-induced osteogenic defects by enhancing ULK1 phosphorylation for autophagosome formation and activating the Bnip3/NIX pathway for specific mitochondrial elimination.[25,81] Additionally, SIRT3 strengthens mitochondrial antioxidant capacity through SOD2 deacetylation, reducing 8-OHdG accumulation and preventing excessive autophagy-induced cell death.[99]

SIRT6 contributes through multidimensional autophagy network regulation. Under hyperglycemic conditions, SIRT6 downregulation inhibits BMSC autophagy via the AKT-mTOR axis, causing autophagy flux obstruction that reduces osteogenic capacity while accelerating cellular senescence.[100] SIRT6 forms a positive feedback loop with KLF4, and KLF4 deficiency impairs SIRT6-mediated autophagy activation, particularly affecting endothelial cell autophagy homeostasis and subsequent vascular integrity.[101] Through histone H3K9 deacetylation, SIRT6 negatively regulates extracellular signal-regulated kinase (ERK) 1/2 signaling pathway and suppresses ATG5 and LC3B-II expression, exacerbating glucose-induced mitochondrial dysfunction and creating a positive feedback loop for bone cell apoptosis.[102,103]

The diabetic metabolic memory effect amplifies SIRT-autophagy axis dysfunction through epigenetic modifications. High glucose-induced histone H3K9 hyperacetylation promotes SIRT1 promoter chromatin condensation, while synergistic action with DNMT3b further suppresses SIRT1 transcription. This epigenetic silencing is amplified through the miR-128-3p/mmu_circ_0000250 regulatory loop, creating a self-perpetuating cycle of autophagy impairment.[104,105] Simultaneously, AGE-activated RAGE-JNK signaling promotes abnormal SIRT3 glycosylation at the K68 site, compromising mitochondrial localization and enzymatic activity.[106,107]

Cell-type-specific regulation within the bone microenvironment demonstrates the complexity of SIRT-mediated autophagy control. In osteoblasts, SIRT1 promotes autophagy-related lysosomal biogenesis through Hedgehog signaling, while in osteoclast precursors, it prevents excessive autophagy-induced differentiation by maintaining RANKL/OPG balance.[108,109] This dual regulatory mechanism underlies the bone formation-resorption imbalance characteristic of DOP.

BMSC osteogenic capacity depends on SIRT3-mediated mitochondrial autophagy-biogenesis coupling, coordinated through transcription factor EB (TFEB) nuclear translocation to ensure metabolic remodeling required for differentiation.[66]

These integrated mechanisms establish a SIRT-centered autophagy regulatory network whose dysfunction drives the characteristic bone microstructural deterioration in DOP, providing a molecular framework for understanding diabetes-associated bone metabolic disorders.

AGEs–RAGE Signaling Pathway in DOP

In the hyperglycemic milieu of diabetes, AGEs bind to their receptor (RAGE) and initiate downstream signaling cascades that modulate autophagic activity in a concentration-dependent manner.[110] Low AGE concentrations moderately activate autophagy, evidenced by increased autophagy-related protein expression, which promotes bone homeostasis through enhanced osteoblast proliferation, differentiation and expression of osteogenic markers including ALP and OCN. Conversely, high AGE concentrations trigger excessive autophagic activation, upregulating apoptotic mediators that damage osteoblasts and disturb bone metabolic balance.[81,111] This modulation occurs through direct RAGE signaling and indirect activation of the Raf/MEK/ERK pathway, which increases LC3-II expression and promotes autophagosome formation. ERK inhibition significantly attenuates AGE-induced autophagy and associated metabolic disturbances, confirming the critical role of RAGE-mediated signaling in DOP pathogenesis.[112,113]

AGEs also impair ASCs by reducing osteogenic differentiation markers (Runx2, OPN), decreasing the LC3-II/LC3-I ratio, and increasing p62/SQSTM1 expression, indicating autophagic suppression.[30,66] This autophagic inhibition increases intracellular ROS, disrupts cellular homeostasis, and diminishes osteogenic signaling pathway activity.[111] Additionally, AGE accumulation promotes ROS generation, impairing mitochondrial function and reducing membrane potential in osteoblasts—hallmarks of mitochondrial dysfunction underlying AGE-induced apoptosis.[20]

AGEs modulate autophagy through RAGE-mediated pathways in a concentration-dependent manner, with low levels supporting bone homeostasis and high levels promoting cellular damage and osteoporosis. Given the critical interplay between oxidative stress and autophagic regulation, therapeutic strategies targeting AGEs-RAGE signaling and autophagy balance represent promising approaches for DOP treatment.

ERK Signaling

ERK signaling is another important mediator in DOP pathogenesis by disrupting bone metabolism through autophagy dysregulation. Under hyperglycemic conditions, ERK activation operates via dual mechanisms to compromise bone homeostasis. First, ERK hyperactivation promotes excessive autophagy through the ROS/ERK axis, triggering abnormal autophagic death of osteoblasts.[114] High glucose stimulation enhances ERK-mediated ROS generation, leading to LC3-II lipidation and excessive autophagosome accumulation, ultimately impairing osteoblast differentiation. Second, ERK signaling cross-regulates the mTOR pathway, suppressing mTOR complex activity under diabetic conditions and releasing physiological autophagy inhibition.[115,116]

ERK-regulated autophagy exhibits notable cell-type specificity and dose-dependent characteristics. In osteoclasts, ERK activation enhances RANKL-mediated bone resorption by upregulating connective tissue growth factor (CTGF) expression, while in osteoblast precursors, ERK/autophagy axis dysregulation inhibits Wnt/β-catenin signaling, reducing bone formation.[117,118] Moderate ERK activation maintains bone cell homeostasis by clearing damaged mitochondria, whereas sustained pathological activation transforms into detrimental autophagy.[84,119] This pathological autophagy disrupts bone remodeling balance, decreasing bone mineral density (BMD), trabecular number (Tb.N) and trabecular thickness (Tb.Th), ultimately compromising bone formation capacity and integrity.[120,121]

ERK signaling represents a critical mediator of ROS-induced autophagy dysregulation under hyperglycemic conditions, offering a promising therapeutic target for DOP intervention.

TLR4 Signaling Pathways

Toll-like receptor 4 (TLR4) has been studied by researchers in DOP pathogenesis through dysregulation of autophagy via multiple interconnected signaling pathways. Under hyperglycemic conditions, elevated ROS levels activate TLR4, subsequently triggering inflammatory cascades that disrupt bone homeostasis.[122,123]

TLR4 influences autophagy through two primary mechanisms. First, TLR4 activation stimulates the Akt/mTOR signaling axis, which inhibits autophagy initiation and leads to mitochondrial dysfunction in osteoblast progenitor cells.[124,125] Second, TLR4 engages the NF-κB pathway, promoting nuclear translocation of NF-κB and enhancing inflammatory responses while suppressing autophagic flux through downregulation of autophagy-related proteins including Beclin1.[122] This dual inhibition slows osteoblast differentiation while promoting osteoclast hyperactivity.

The hyperglycemic environment further amplifies TLR4-mediated dysfunction by inducing abnormal release of inflammatory cytokines IL-6 and TNF-α via the TLR4/NF-κB axis, resulting in impaired autophagosome-lysosome fusion and blocked p62 degradation.[124,126] Additionally, upregulated high mobility group box 1 (HMGB1) /RAGE interactions activate aberrant Beclin-1-dependent autophagy while simultaneously inducing mitochondrial apoptosis.[124,125] TLR4 also mediates glucolipotoxicity-induced bone damage through RIAM/NF-κB interactions, further modulating autophagic responses.[127]

Recent investigations reveal additional regulatory layers whereby TLR4 overexpression correlates with abnormal m6A methylation modifications, potentially affecting autophagy activity by modulating mRNA stability of ATG5 and ATG7.[128] Furthermore, TLR4 influences autophagy-lysosomal gene expression by regulating TFEB nuclear translocation, establishing a critical link between autophagy defects and impaired bone matrix mineralization.[129,130] Notably, TLR4-mediated autophagy dysregulation exhibits context-dependent effects. While moderate autophagy activation clears damaged organelles and maintains bone homeostasis, excessive activation promotes osteoblast programmed cell death through LC3-II aggregation.[131,132] Supporting this concept, TLR4 gene knockout significantly reduces expression of autophagy-related proteins such as Beclin1 and LC3-II/LC3-I, improves disrupted bone metabolism, reduces osteoblast apoptosis and enhances bone formation capacity.[133] TLR4 knockout models demonstrate restored autophagy activity correlating with upregulated osteogenic markers such as bone morphogenetic protein-2 (BMP-2), ALP and OCN, reducing inflammatory cytokines including IL-1, IL-6 and TNF-α.[122,134]

These findings establish TLR4 as a central regulator of autophagy dysfunction in DOP pathogenesis, suggesting that therapeutic targeting of TLR4 signaling may represent a promising approach for DOP treatment.

Endoplasmic Reticulum (ER) Stress

The pathological mechanism of DOP is fundamentally linked to endoplasmic reticulum stress (ERS) and autophagy imbalance. Hyperglycemic conditions disrupt ER homeostasis, activating unfolded protein response (UPR) pathways including PKR-like ER kinase (PERK), inositol-requiring enzyme-1α (IRE1α), and activating transcription factor 6 (ATF6), which directly regulate autophagy-related protein expression and function.[135,136] ERS enhances autophagy initiation through the PERK/eukaryotic translation initiation factor 2α kinase (eIF2α) phosphorylation pathway, promoting LC3-II and Beclin-1 expression while reducing autophagy substrate p62 levels, thereby facilitating autophagosome formation to eliminate damaged organelles and misfolded proteins.[135,137]

In DOP pathogenesis, moderate autophagy maintains osteoblast function by clearing ERS-generated abnormal proteins and damaged mitochondria, as demonstrated by vitamin D metabolites inhibiting ERS-mediated osteoblast apoptosis through autophagy enhancement.[81,138] However, persistent ERS triggers excessive autophagosome accumulation via C/EBP homologous protein (CHOP) /c-Jun N-terminal kinase (JNK) pathway activation, ultimately causing autophagic osteoblast death.[135,139] Additionally, ERS modulates bone metabolic balance through the AMPK/PPARγ signaling axis, where metformin ameliorates high glucose-induced osteoblast autophagy dysregulation by activating AMPK to inhibit PPARγ-dependent ERS pathways.[140]

ERS simultaneously exacerbates bone resorption by promoting osteoclast differentiation through the IRE1α/x-box binding protein 1 (XBP1) pathway, which upregulates RANKL expression.[139,141] While autophagy normally inhibits this process by clearing damaged ER fragments, diabetic autophagy deficiency sustains ERS activation, further aggravating osteoclast activity and bone resorption imbalance.[142,143] The interaction involves key molecules such as FAM134B, an ER autophagy receptor that mediates selective ER autophagy by binding LC3, providing protection against diabetic bone loss.[137,144] This ERS-autophagy dysfunction extends beyond bone tissue to pancreatic β-cells, where hyperglycemia-induced ERS accumulates unfolded proteins and activates factors including CHOP and GRP78. Although autophagy-related protein expression increases in diabetic β-cells, p62 accumulation indicates impaired autophagic flux, preventing

clearance of unfolded proteins and damaged organelles.[120,145] This autophagy dysfunction exacerbates ERS-induced cell death, contributing to β-cell dysfunction and diabetes progression.

ERS-autophagy interaction represents a critical pathological mechanism in DOP, involving UPR pathways, selective autophagy receptors and metabolic signaling molecules. Hyperglycemia-induced imbalance impairs autophagic flux, causing protein and organelle accumulation that leads to osteoblast dysfunction, abnormal osteoclast activity and β-cell impairment. Therapeutic strategies targeting this axis may effectively ameliorate diabetic bone metabolism disorders.

Other Potential Mechanisms

Transforming growth factor-β1 (TGF-β1) expression is significantly upregulated in the hyperglycemic microenvironment, serving as a central regulator of autophagy dysfunction in osteoblasts. TGF-β1 inhibits osteoblast autophagy through activation of the TGF-β receptor II (TβRII)-dependent Smad2/3 signaling pathway, reducing autophagy markers Beclin1 and LC3-II/I ratio while increasing p62 accumulation.[47,146] This suppression impairs the clearance of damaged mitochondria and misfolded proteins, ultimately inhibiting osteogenic differentiation genes like Runx2. Additionally, TGF-β1 enhances mTORC1 activity via PI3K/Akt signaling, thereby blocking ULK1-mediated autophagy initiation.[147,148] The combined effects of insulin and TGF-β1 signaling intensify autophagy disruption through upregulation of TβRII, further accelerating DOP progression.

The long non-coding RNA Maternally Expressed Gene 3 (Meg3) has been studied in DOP through autophagy-dependent regulation of osteoblast function. In the diabetic bone microenvironment, upregulated Meg3 directly interacts with p62/SQSTM1, enhancing p62 stability and inhibiting autophagosome-lysosome fusion. This results in decreased LC3-II/LC3-I ratio and elevated p62 levels, creating an autophagy-inhibited state that triggers abnormal Runx2 degradation.[149,150] Mechanistically, p62 binds to ubiquitinated Runx2 via its UBA domain under diabetic conditions, promoting Runx2 degradation through the autophagy-lysosomal pathway. The consequent loss of Runx2 directly downregulates osteogenesis-related genes and inhibits bone matrix mineralization, establishing a vicious cycle of autophagy inhibition and osteogenesis impairment.[151,152]

Several additional pathways contribute to autophagy dysregulation in DOP, though their mechanisms require further elucidation. BMP receptor 1A (BMPR1A) influences osteoporotic bone formation by regulating the mTOR autophagy axis, with hyperglycemic conditions suppressing autophagy activity through mTORC1 activation.[153–155] BMP signaling also stabilizes β-catenin protein levels by inhibiting autophagy, potentially maintaining β-catenin homeostasis despite hyperglycemia-induced Wnt pathway disruption.[156,157] Additionally, BMP activation enhances mitophagy, facilitating clearance of ROS-generating organelles.[158] The acetyltransferase P300 represents another critical regulator, as hyperglycemic conditions promote P300-mediated acetylation of autophagy-related proteins including Beclin-1 and ATG7, thereby hindering autophagosome maturation and lysosomal fusion. This metabolic stress-induced dysfunction impairs osteoblast autophagy flux and activates osteoclast differentiation through RANKL/OPG axis imbalance.[159–161] The CCAAT/enhancer binding protein (CEBPA)-fibroblast growth factor 21 (FGF21) axis also modulates DOP through autophagy-lysosome pathway regulation. CEBPA directly regulates FGF21 expression, with reduced FGF21 levels potentially leading to excessive autophagy activation and intensified cellular stress responses.[162] FGF21 normally activates the SIRT1-mTOR signaling pathway to promote TFEB nuclear translocation, enhancing lysosomal biogenesis and facilitating clearance of damaged mitochondria and protein aggregates.[162–164] Finally, vesicle-associated membrane protein 7 (VAMP7) and acid sphingomyelinase (ASM) represent additional regulatory factors. VAMP7 facilitates autophagosome-lysosome fusion, with its absence impairing both β-cell autophagy and insulin secretion.[165,166] Hyperglycemia activates ASM, promoting ceramide production and triggering excessive autophagy that leads to GPX4 degradation and diminished osteoblast activity.[167]

Therapeutic Strategies for DOP

The management of DOP primarily focuses on targeting autophagy pathways, restoring the equilibrium of bone metabolism and mitigating both inflammatory responses and oxidative stress. Pharmacotherapy, as the foundation of DOP management, aims to inhibit bone resorption and stimulate bone formation, thereby improving bone quality in affected patients.

Targeted Therapeutics for Diabetes-Specific Molecular Pathways

In the context of DOP, restoring mitochondrial function and reducing oxidative stress-induced damage to osteoblasts have become critical therapeutic objectives. Targeting the PINK1/Parkin signaling pathway represents a promising approach to enhance osteoblastic function through mitophagy activation. PINK1/Parkin activators, which act as mitophagy inducers, augment mitochondrial clearance by restoring autophagic flux, thereby reducing ROS generation and improving metabolic homeostasis, ultimately alleviating diabetes-induced osteoporotic manifestations.[71,72] Additionally, delivering MEG3 via extracellular vesicles (EVs) to target miR-3064-5p can enhance PINK1/Parkin-mediated mitophagy, thereby improving osteoblast function.[69]

Emerging research on autophagy in MSCs has attracted increasing attention in DOP treatment. Evidence suggests that modulating autophagic processes, particularly by enhancing selective mitochondrial clearance, can restore the osteogenic and chondrogenic potentials of MSCs. This approach offers new avenues for reversing diabetes-induced MSC dysfunction.[168] Furthermore, VAMP7 enhancers demonstrate therapeutic potential by maintaining mitochondrial homeostasis and enhancing autophagic flux in metabolically stressed cells, as evidenced by improved insulin secretion in pancreatic β-cells under high-fat, high-sugar conditions.[166]

Inhibiting FoxO3 hyperactivity effectively reduces autophagy levels and alleviates diabetes-associated osteoporotic changes, making FoxO3 inhibitors a promising therapeutic approach.[88] As an upstream regulator, activated Akt can bidirectionally modulate autophagic flux, and combined use of Akt activators may synergistically balance autophagy and protein synthesis in bone tissue.[169] Targeting the AGE-RAGE signaling pathway provides another therapeutic avenue: RAGE suppression using RAGE-shRNA increases the LC3-II/LC3-I ratio and upregulates osteogenic genes such as RUNX2 and OPN, effectively restoring osteoblast osteogenic capacity.[111] Similarly, the MEK inhibitor PD98059 blocks AGE-induced MEK-ERK activation, restoring autophagic equilibrium and enhancing osteoblast function.[112]

1,25-Dihydroxyvitamin D_3 (1,25D) activates the PI3K/Akt pathway, inhibiting FoxO1 dephosphorylation and nuclear translocation, thereby attenuating FoxO1-mediated upregulation of autophagy-related genes.[170] By reducing ROS levels, 1,25D disrupts the positive feedback loop between ROS and autophagy, ultimately reducing diabetes-associated bone loss.[171] Combining ROS scavengers with targeted FoxO1 inhibition synergistically ameliorates bone metabolic disorders.[81] The BMP signaling pathway is essential in regulating bone cell energy metabolism. Enhancing BMP-2 activity can activate normal autophagic processes in bone cells, correcting diabetes-induced energy metabolic disturbances and enhancing bone formation while inhibiting bone resorption.[155]

ASM inhibition using ASM-siRNA markedly enhances BMD and improves trabecular architecture in type 2 DOP models by reducing serum iron ions, malondialdehyde (MDA) and ceramides. Antioxidants such as N-acetylcysteine (NAC) reduce high glucose-induced ROS accumulation, thereby lowering ASM activity and autophagic flux while mitigating lipid peroxidation damage to osteoblasts.[167] Tauroursodeoxycholic acid (TUDCA), an endoplasmic reticulum stress modulator, alleviates ERS, restores ER autophagy and reduces unfolded protein accumulation, thereby improving bone cell differentiation capacity.[41] Enhanced hCDC14A phosphorylation at Ser484 activates the AMPK signaling pathway, restoring autophagic flux and mitigating oxidative stress-induced damage. Moreover, zipper-interacting protein kinase (ZIPK) activators modulate hCDC14A phosphorylation status, further enhancing autophagic activity in pancreatic β-cells, reducing mitochondrial injury and suppressing apoptosis. However, clinical translation of hCDC14A phosphorylation strategies and ZIPK activators requires further investigation.[172]

These findings collectively suggest that combinatorial therapeutic approaches targeting multiple autophagy-related pathways hold substantial potential for treating DOP through restoration of cellular homeostasis and enhancement of bone formation.

Autophagy Regulator

Autophagy Enhancer

Metformin

Metformin, a widely prescribed antidiabetic agent, exhibits therapeutic potential in DOP primarily through autophagy modulation via the AMPK/mTOR signaling pathway. By activating AMPK while inhibiting mTOR, metformin enhances autophagy, as evidenced by increased LC3-I/LC3-II conversion and accelerated p62 degradation.[21,173,174]

In bone tissue, metformin promotes osteogenic differentiation under hyperglycemic conditions while suppressing RANKL-induced osteoclast-related genes such as TRAP, MMP9 and CTSK, thereby reducing bone resorption. The drug restores autophagic flux in MSCs under high-glucose conditions, upregulating autophagy-related proteins while inhibiting mTOR and GSK3β activity to enhance Wnt signaling. This results in increased mineralized nodule formation, elevated ALP activity and upregulation of osteogenic markers including RUNX2 and OPN.[62,175] Combined AMPK activation with Wnt signaling enhancement offers innovative therapeutic strategies for bone defect repair in DOP patients.[176,177]

Additionally, metformin protects pancreatic β-cells through the AMPK/SIRT1/PGC-1α pathway, improving glucose-stimulated insulin secretion (GSIS) and reducing apoptosis by increasing the Bcl-2/Bax ratio.[12,140] When combined with irisin, synergistic pathway activation further amplifies β-cell protection.[12] Importantly, autophagy inhibitors like chloroquine and SIRT1 inhibitors like Ex527 significantly attenuate therapeutic efficacy of metformin, confirming the indispensable roles of autophagy and SIRT1 in maintaining pancreatic function.[12,178]

Resveratrol

Resveratrol, a natural polyphenolic compound found in grapes, berries and nuts, demonstrates significant therapeutic potential for DOP through autophagy modulation. This compound activates multiple autophagy-regulating pathways. It enhances SIRT1 activity, leading to increased expression of autophagic markers LC3 and Beclin-1, while simultaneously downregulating the PI3K/Akt/mTOR signaling pathway.[179] Additionally, resveratrol activates AMPK and upregulates GATA-1 expression and nuclear translocation, further promoting autophagy-related protein expression.[180] These mechanisms collectively improve bone density and architecture by enhancing the proliferation and differentiation of pre-osteoblastic cells, as evidenced by increased LC3-II/LC3-I ratios, elevated Beclin1 expression and reduced p62 levels in MC3T3-E1 cells.[179] These findings establish autophagy modulation as a pivotal mechanism underlying the bone-protective effects of resveratrol and provide theoretical foundation for developing autophagy-targeted therapeutic strategies against diabetes-associated bone metabolic dysfunction.[180,181]

Rapamycin

Rapamycin (Rapa), a mTOR inhibitor, demonstrates bone-protective effects in diabetes-induced osteoporosis by modulating autophagic signaling to attenuate excessive osteoclast differentiation and enhance osteoblast osteogenic capacity.[112,182] This mechanism significantly improves bone mineral density and mitigates trabecular degradation, contributing to its therapeutic efficacy in treating DOP. However, since maintaining dynamic balance in autophagic regulation is crucial for optimal outcomes, precise modulation of autophagic levels becomes essential. Consequently, a combined therapeutic strategy employing Rapa with anti-AGEs agents has been proposed to synergistically reduce AGE accumulation while activating autophagic function, thereby comprehensively improving bone metabolism and promoting trabecular repair.[111]

AdipoAI

AdipoAI exerts its therapeutic effects on DOP primarily through enhancing autophagic flux in osteoclasts. Experimental data demonstrate that AdipoAI markedly reduces osteoclast number and bone-resorptive activity, leading to increased bone mineral density and alleviated bone resorption in animal models. Validation experiments using the autophagy inhibitor 3-MA confirm that autophagy inhibition completely reverses the suppressive effects of AdipoAI on osteoclast-mediated bone resorption, underscoring the critical role of autophagic regulation in its mechanism.[22] Beyond bone-protective effects, AdipoAI significantly reduces fasting blood glucose levels and inflammatory markers in experimental animals, providing a comprehensive therapeutic approach addressing bone metabolism, metabolic dysregulation and inflammation in DOP.[183] Clinical translation may benefit from combining AdipoAI with anti-inflammatory agents or metabolic modulators to further enhance therapeutic efficacy. The development of autophagy enhancers targeting the Akt/mTOR pathway represents a promising breakthrough in DOP treatment, though clinical efficacy and long-term safety require further investigation.[22,184]

Torin1

Torin1, an mTOR inhibitor, exerts therapeutic effects by activating autophagy. In ASCs, Torin1 significantly enhances autophagic activity, evidenced by increased LC3-II/LC3-I ratios and elevated Beclin1 expression. This autophagy activation concurrently restores osteogenic markers including Runx2 and OPN, ultimately improving BMD and osteogenic differentiation in DOP mice.[66,147,185] Moreover, Torin1 treatment upregulates Notch signaling components (NICD, Hes1 and Hey1), indicating potential crosstalk between autophagy and Notch pathways in promoting osteogenesis.[64] These mechanistic insights support a combinatorial therapeutic strategy employing mTOR inhibitors alongside Notch activators to synergistically enhance bone formation and optimize trabecular architecture in DOP management.[67,186] Importantly, long-term Torin1 administration demonstrates sustained BMD improvement without significant adverse effects, highlighting its therapeutic potential for DOP treatment.[66,147]

Gw501516

The PPARβ/δ agonist GW501516 enhances bone regeneration under hyperglycemic conditions by potentiating autophagy via the AMPK/mTOR pathway.[39] Experimental studies demonstrated that GW501516 significantly increases BMD and bone volume fraction while promoting osteogenic differentiation, new bone formation and collagen synthesis, concurrently protecting osteocyte function through reduced apoptosis. Critically, administration of autophagy inhibitors significantly attenuated these osteogenic effects, confirming autophagy as the central mechanism underlying PPARβ/δ-mediated bone metabolism regulation.[39,187] These mechanistic insights suggest that combination therapy incorporating AMPK activators with PPARβ/δ agonists could optimize treatment outcomes. Further validation in a rat cranial defect model demonstrated improved bone regeneration and mineralization, supporting the clinical translational potential of PPARβ/δ agonists as molecular targets for DOP treatment.[39]

Empagliflozin

Empagliflozin, a selective SGLT-2 inhibitor, demonstrates dual therapeutic benefits by exerting hypoglycemic effects while enhancing osteogenic differentiation of DOP-ASCs through autophagy activation. Mechanistically, empagliflozin modulates autophagy via dual pathways: inhibiting PI3K/AKT/mTOR signaling to augment autophagic flux and restore autophagosome degradation evidenced by LC3-II and p62 regulation and activating AMPK/mTOR and PINK1/Parkin pathways to promote mineralized nodule formation.[30,147] In DOP mice, empagliflozin treatment significantly improved trabecular thickness and bone volume fraction while upregulating osteogenic genes such as RUNX2 and OPN and reducing osteoclast activity, thereby maintaining bone metabolic homeostasis. Furthermore, combining empagliflozin-treated DOP-ASCs with GelMA hydrogel in bone tissue engineering approaches enhances bone defect repair by mitigating inflammation and oxidative stress-induced adverse effects on bone cells.[30]

Other

AMPK activation represents a key mechanism in emerging DOP treatment, with studies demonstrating that the AMPK activator 5-aminoimidazole-4-carboxamide ribonucleotide (AICAR) significantly enhances osteoblast differentiation and mineralization through autophagy-related molecule induction.[14,188] Similarly, adiponectin and its receptor agonists promote osteogenic differentiation via AMPK pathway activation and autophagic regulation.[189] Experimental evidence further supports the synergistic effects of combined BMP-2 and AICAR therapy, which enhances osteoblast differentiation and bone-implant integration strength, emphasizing the critical role of early AMPK activation in optimizing osteogenic efficiency and bone restoration.[14,190]

Beyond AMPK modulation, other autophagy enhancers show therapeutic potential. Resolvin D3 (RD3) activates autophagic flux through the AMPK/LC3 axis, simultaneously alleviating endoplasmic reticulum stress and improving mitochondrial function.[191] Additionally, autophagy activation facilitates metabolic normalization under hyperglycemic conditions by repairing ECM and clearing reactive oxygen species, with upregulated Fibulin-1 and Fibulin-2 proteins contributing to bone metabolic protection through enhanced autophagy and ECM stability.[192] Complementary targeting

of PI3K/Akt and Wnt/β-catenin signaling pathways can further improve osteoporosis outcomes by promoting osteogenic differentiation while inhibiting osteoclastic activity.[42,157]

Autophagy Inhibitor

Melatonin functions as an endogenous hormone that effectively inhibits excessive autophagy while providing antioxidant protection. Administration results in decreased LC3-II and Beclin-1 expression with concurrent p62 elevation in bone tissue, indicating successful autophagy suppression. This effect occurs through AMPK/mTOR pathway modulation, where melatonin partially restores mTOR activity that is typically diminished in diabetic conditions, thereby counteracting AMPK-mediated autophagic activation. Consequently, melatonin preserves osteoblast viability, improves bone microstructure and increases bone mineral density in animal models, effectively slowing DOP progression.[121]

TLR4 inhibition represents another promising approach, reducing osteoblast autophagic activity under hyperglycemic conditions while decreasing inflammation and apoptosis. Multiple therapeutic agents, including methionine, dioscin, miR-1906 mimic and artesunate, have demonstrated efficacy through TLR4 inhibition.[133] Combined with autophagy inhibitors, this therapy enhances osteoblast survival and increases BMP-2 and OCN secretion.

PD98059, an ERK pathway inhibitor, mitigates AGE-induced excessive autophagy through Raf/MEK/ERK signaling suppression. This intervention restores osteoblast function, increases osteogenic markers (ALP and OCN) and improves bone mineral density and trabecular structure.[112,118]

Chinese Medicine

Timosaponin BII (TBII)

TBII significantly enhances osteoblast autophagy through mTOR/NF-κB signaling pathway inhibition, evidenced by dose-dependent upregulation of LC3-II/LC3-I ratio and Beclin1 expression.[193] Under hyperglycemic conditions, TBII restores autophagic capacity while reducing apoptosis by a decreased Bax/Bcl2 ratio and mitigating oxidative stress through lowered H_2O_2 levels and improved mitochondrial function.[131,194] In vivo validation using diabetic rat models demonstrates that TBII-mediated autophagy modulation markedly improves trabecular architecture, with increased bone volume fraction, Tb.Th and Tb.N, alongside reduced trabecular separation (Tb.Sp) (Table 2).[131,195] Mechanistic validation reveals that autophagy inhibitor 3-MA abolishes protective effects of TBII, while rapamycin co-administration enhances them, as demonstrated by increased LC3B puncta formation, reduced ROS levels and decreased apoptosis.[131] These findings establish the autophagy-activating properties of TBII as a promising therapeutic approach for DOP, warranting further investigation into its molecular targets and integrated signaling mechanisms.

Yin-Nourishing and Kidney-Tonifying Formula (Ziyin Bushen Fang, ZYBSF)

Research indicates that ZYBSF exerts protective effects against DOP through dual autophagy-modulating and antioxidant mechanisms.[25] In vitro studies demonstrate that under hyperglycemic conditions, ZYBSF suppresses excessive autophagy in osteoblasts by downregulating LC3-II/I and Beclin-1 expression levels, thereby significantly enhancing cell viability.[112] Simultaneously, in MC3T3-E1 osteoblasts, ZYBSF markedly reduces intracellular ROS levels, augments superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activities, restores mitochondrial function and inhibits ERK signaling pathway overactivation.[121,196] In vivo validation using a type 1 diabetic rat model confirmed that ZYBSF significantly improved bone microarchitecture by increasing BMD, Tb.N and Tb.Th while reducing Tb.Sp, with dose-dependent efficacy where moderate to high doses yielded more pronounced osteoprotective effects (Table 2).[25] These findings on ZYBSF collectively demonstrate therapeutic potential for DOP through synergistic cellular mechanisms, suggesting that combination with other autophagy modulators may further optimize bone metabolic functions and enhance therapeutic efficacy.

Scutellaria Baicalensis Root Extract (WSB)

WSB activates autophagy through the AMPK signaling pathway, enhancing insulin secretion and reducing apoptosis of pancreatic β-cells under hyperglycemic conditions.[197] This autophagy mechanism is critical for maintaining insulin storage and secretion homeostasis, as evidenced by studies showing that autophagy deficiencies, such as ATG7 deletion,

Table 2 Autophagy Mechanisms and Therapeutic Effects of Traditional Chinese Medicine-Derived Compounds in DOP

Compound	Autophagy Regulation	Primary Signaling Pathway	Cellular Target	Key Therapeutic Evidence	Mode of Action
Timosaponin BII (TBII)	Enhances autophagy	mTOR/NF-κB inhibition	Osteoblasts	↑ Bone volume fraction, Tb.Th, Tb.N; ↓ Tb.Sp in diabetic rats	Dose-dependent ↑ LC3-II/LC3-I ratio, ↑ Beclin1; validated by 3-MA inhibition
Gymnemic acid I (GA I)	Enhances autophagy	mTOR inhibition	Pancreatic β-cells	↓ IAPP aggregation, improved insulin secretion	Synergistic with rapamycin, ↓ apoptosis-related signaling
Scutellaria baicalensis root extract (WSB)	Activates autophagy	AMPK pathway activation	Pancreatic β-cells	Enhanced insulin secretion, ↓ β-cell apoptosis	Maintains insulin granule homeostasis; active compound: baicalin
Delphinidin	Activates autophagy	AMPK-mediated activation	Pancreatic β-cells	β-cell protection from high-glucose apoptosis	↑ LC3-II levels, ↓ p62 expression; protective effect abolished by 3-MA
Xiao Ke Ping (XKP)	Induces autophagy	mTOR inhibition	Pancreatic β-cells	↓ β-cell apoptosis	↑ LC3-II/LC3-I ratio, ↓ p62 levels; active components: berberine, astragalus polysaccharides
Yin-nourishing and kidney-tonifying formula (ZYBSF)	Suppresses excessive autophagy	ERK signaling inhibition	Osteoblasts (MC3T3-E1)	↑ BMD, Tb.N, Tb.Th; ↓ Tb.Sp with dose-dependent efficacy	Dual mechanism: ↓ LC3-II/I, ↓ Beclin-1 + antioxidant (↑ SOD, ↑ GSH-Px)
Puerarin	Suppresses autophagy	Akt/mTOR pathway activation	Skeletal muscle cells	Restored metabolic homeostasis, improved muscle quality	↑ Akt and mTOR phosphorylation, ↓ LC3II/LC3I ratio
Magnolol	Inhibits autophagy	Akt/FoxO/mTOR modulation	Multiple cell types	Anti-inflammatory, ↓ oxidative stress, ↑ antioxidant enzymes	↑ Akt phosphorylation (Ser473), ↓ FoxO nuclear translocation, ↓ LC3/Bnip3

Notes: ↑, upregulation; ↓, downregulation.

Abbreviations: Tb.Th, trabecular thickness; Tb.N, trabecular number; Tb.Sp, trabecular separation; BMD, bone mineral density; SOD, superoxide dismutase; GSH-Px, glutathione peroxidase; IAPP, islet amyloid polypeptide; 3-MA, 3-methyladenine.

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result in diminished insulin granule numbers and compromised insulin release (Table 2).[198] The therapeutic potential of autophagy-based strategies for treating DOP is further supported by active compounds like baicalin in traditional Chinese medicinal formulations.

Puerarin

Puerarin effectively suppresses hyperglycemia-induced autophagy through Akt/mTOR pathway activation, thereby restoring cellular metabolic homeostasis and improving skeletal muscle quality. Mechanistically, puerarin treatment significantly enhances Akt and mTOR phosphorylation while decreasing the LC3II/LC3I ratio, confirming autophagic inhibition (Table 2).[199,200] This metabolic restoration may contribute to bone homeostasis maintenance, providing therapeutic potential for DOP management.

Magnolol

Magnolol modulates autophagy through multiple complementary mechanisms. It promotes Akt phosphorylation at Ser473, thereby inhibiting FoxO activation and nuclear translocation, which subsequently downregulates autophagy-related genes including LC3 and Bnip3. Furthermore, magnolol enhances mTOR phosphorylation and activates its downstream targets, facilitating protein synthesis and muscle mass restoration. Additionally, magnolol reduces inflammatory cytokines and oxidative stress markers while enhancing antioxidant enzyme activities, collectively suppressing autophagy induction (Table 2). Although direct effects on bone tissue remain unexplored, these comprehensive autophagy-modulating properties provide theoretical foundation for therapeutic potential of magnolol in DOP treatment.[201]

Gymnemic Acid I (GA I)

In high-glucose environments, GA I significantly enhances autophagic flux through mTOR inhibition, thereby reducing IAPP aggregation in β-cells and improving insulin secretion to restore islet function (Table 2). Experimental evidence demonstrates that GA I exhibits synergistic effects with autophagy regulators such as Rapa, enhancing cellular protection through suppression of apoptosis-related signaling pathways. Given the critical role of GA I in maintaining β-cell homeostasis by regulating autophagy, therapeutic strategies targeting autophagic modulation represent a promising approach for addressing metabolic dysregulation in multiple cell types, including osteocytes.[202,203] Collectively, this GA I-centered autophagy-based interventions may offer innovative therapeutic opportunities for optimizing pancreatic function while simultaneously alleviating DOP.

Xiao Ke Ping (XKP)

As a traditional Chinese medicine, XKP demonstrates significant therapeutic efficacy in diabetes through autophagy-mediated mechanisms. Under hyperglycemic conditions, XKP treatment reduced pancreatic β-cell apoptosis from 23.24% to 10.92%, while simultaneously increasing the LC3-II/LC3-I ratio and decreasing p62 protein levels, indicating enhanced autophagic flux. This cytoprotective effect is attributed to bioactive constituents of XKP, particularly berberine and astragalus polysaccharides, which exhibit potent autophagy-inducing properties.[204] Furthermore, the ability of XKP to enhance β-cell survival through mTOR inhibition-mediated autophagy induction provides a mechanistic basis for its therapeutic benefits (Table 2).[204,205] Given its established clinical approval for diabetes treatment and demonstrated autophagy regulatory mechanisms, XKP represents a promising pharmacological intervention for diabetes-related complications, including DOP.[206]

Delphinidin

Delphinidin, a natural bioactive compound, protects pancreatic β-cells from high-glucose-induced apoptosis through AMPK-mediated autophagy activation. This cytoprotective mechanism is evidenced by elevated LC3-II levels and decreased p62 expression, both hallmarks of enhanced autophagic flux (Table 2). The critical role of autophagy in β-cell survival is further supported by experiments showing that autophagy inhibition with 3-MA exacerbates apoptosis, while AMPK inhibition diminishes protective efficacy of Delphinidin.[55] These findings collectively demonstrate that therapeutic potential operates via the AMPK-autophagy axis, providing mechanistic insights relevant to diabetes-associated complications such as DOP.

Others

Dihydromyricetin (DHM) induces autophagy by activating the AMPK signaling pathway, significantly elevating LC3-II levels and promoting p62 degradation in high-fat diet-induced insulin resistance models. DHM simultaneously restores IRS-1 and Akt phosphorylation, improving insulin resistance and glucose metabolism. Co-administration with autophagy activators such as Rapa further enhances DHM effects, suggesting synergistic therapeutic potential.[23] Similarly, sciadopitysin upregulates mitochondrial biogenesis regulators in osteoblastic cells, enhancing mitochondrial biosynthetic capacity and potentially attenuating diabetes-associated skeletal disorders.[207] Silibinin, the primary flavonoid of silymarin, exhibits comparable benefits by downregulating RAGE expression while reducing mitochondrial oxidative stress and membrane potential alterations in osteoblast models, establishing its potential for DOP prevention and treatment.[208] Additional compounds including quercetin, curcumin and salvianolic acid B demonstrate complementary mechanisms: quercetin activates mitophagy via the AMPK/PGC-1α pathway while reducing ROS levels and enhancing insulin sensitivity; curcumin promotes mitochondrial biogenesis and induces autophagy through mTOR pathway modulation; salvianolic acid B decreases mitochondrial fission protein expression, reducing fragmentation and preserving mitochondrial function.[71,209–211] These natural compounds collectively offer promising therapeutic strategies for DOP through integrated autophagy and mitochondrial function enhancement, warranting further clinical investigation (Table 2).

Exercise

Exercise therapy demonstrates significant therapeutic efficacy in patients with type 2 DOP, achieving superior clinical outcomes compared to conventional treatments through autophagy-mediated mechanisms.[212] Mechanistically, exercise activates the SIRT1/AMPK/mTOR signaling axis via mechanical loading stimulation, promoting autophagy flux in bone marrow mesenchymal stem cells (BMSCs) and enhancing osteogenic differentiation.[213] Experimental evidence confirms that 8-week aerobic training combined with vitamin D3 inhibits mTORC1 activity through AMPK phosphorylation, upregulates LC3-II/Beclin-1 expression, and restores osteocyte autophagy-lysosomal function in hyperglycemic conditions, ultimately improving trabecular bone microstructure.[214] Additionally, combining exercise with caloric restriction may enhance metabolic function and benefit bone health in type 2 diabetes patients.[71]

High-intensity exercise modalities, including high-intensity interval training (HIIT) and downhill running, demonstrate enhanced therapeutic effects through distinct autophagy pathways. HIIT significantly increases Beclin1/LC3 II expression while decreasing p62/Meg3 levels, modulating the Meg3/p62/Runx2 pathway to promote osteoblast differentiation and bone formation.[149] HIIT-induced lactic acid accumulation further activates the PI3K/AKT pathway, promoting autophagosome formation and alleviating high glucose-induced osteoblast apoptosis.[215] Downhill running enhances bone formation markers including alkaline phosphatase activity and modulates serum calcium and phosphate levels, though its effects on mitophagy markers BNIP3 and LC3B require further investigation.[216] Swimming training similarly improves femoral neck strength in diabetic models, with effects positively correlated with increased ATG5/p62 autophagy marker ratios.[217]

Exercise-induced autophagy activation exhibits dose-dependent characteristics, with moderate exercise at 60% maximum oxygen uptake promoting bone formation, while excessive exercise may trigger bone degradation through autophagy overactivation.[213,218] Whole body vibration (WBV) represents an alternative approach, enhancing skeletal muscle autophagy and metabolic balance in diabetic models. A 12-week WBV intervention improved muscle morphology, reduced blood glucose levels and optimized lipid profiles by increasing high density lipoprotein (HDL) and decreasing low density lipoprotein (LDL) concentrations.[219]

Exercise therapy improves DOP through multi-target autophagy network regulation, though optimal dosing protocols and underlying molecular mechanisms require further investigation. Current clinical practice incorporates exercise therapy as first-line non-pharmacological treatment, with future research focusing on synergistic combinations with autophagy modulators and validation through large-scale cohort studies.[220–222]

Other Form of Therapy

Antioxidants improve bone metabolism imbalance in DOP through precise regulation of autophagy pathways. Rosmarinic acid (RA) demonstrates superior efficacy compared to traditional anti-osteoporosis medications by

simultaneously inhibiting NACHT-LRR-PYD domains-containing protein 3 (NLRP3) inflammasome activation in osteoclasts and restoring osteoblast autophagy flux.[222] Glucosamine (GlcN) counteracts this disruption by restoring PINK1/Parkin-mediated selective mitophagy, thereby enhancing osteoblast mineralization capacity.[223,224] Similarly, NAC significantly reduces hyperglycemia-induced ROS levels and improves autophagic flux by restoring AKT and mTOR phosphorylation status, consequently reducing osteoblast apoptosis and promoting cellular proliferation.[26] To address challenges of low bioavailability and insufficient targeting specificity, novel nano-delivery systems such as berberine-loaded nanocarriers have been developed to enhance targeted accumulation of therapeutic agents in bone tissue while maintaining autophagy-lysosomal system integrity.[225]

Building upon these mechanistic insights, stem cell and gene therapies have emerged as promising autophagy-targeted interventions. The impaired osteogenic differentiation potential of ASCs and BMSCs in DOP can be restored through autophagy activation. Genetic intervention or pharmacological blockade of the PI3K/Akt/mTOR pathway induces autophagy activation, promoting expression of osteogenic markers including RUNX2 and OCN in ASCs.[131,147] Exosomes secreted by ASCs deliver regulatory microRNAs (miRNAs) such as miR-152-5p, which target autophagy-related protein ATG14 to modulate oxidative stress and autophagy levels, thereby inhibiting osteoclast activity and enhancing bone mineral density.[226,227] In animal models, transplantation of genetically modified BMSCs over-expressing long non-coding RNA (lncRNA) TUG1 activates autophagy through the AMPK/mTOR/autophagy axis, restoring trabecular bone microstructure.[228] Additionally, gene therapy approaches, including adenovirus-mediated TLR4 silencing and CRISPR/Cas9-based editing of core autophagy genes, have shown efficacy in promoting bone formation through enhanced Beclin1 and LC3-II expression.[131,182,229] However, clinical translation faces significant challenges including gene vector toxicity, low stem cell homing efficiency and long-term safety concerns.[230,231]

The therapeutic success of autophagy modulation in DOP ultimately depends on achieving optimal balance, as both excessive stimulation and suppression negatively affect bone metabolism. Autophagy in osteocytes facilitates degradation and recycling of cellular components, supplying ATP and biosynthetic substrates essential for maintaining osteoblast energy homeostasis.[155] Future therapeutic strategies require integration of single-cell sequencing technology to precisely characterize spatiotemporal autophagy specificity within the diabetic bone microenvironment, alongside development of intelligent responsive systems with bidirectional autophagy regulatory capabilities.[232] These advances represent the evolution from adjunctive to precision-targeted treatment, offering critical insights for optimizing therapeutic strategies in DOP management.

Discussion

This review comprehensively elucidates the central role of autophagy in both the pathogenesis and therapeutic management of DOP. We have conducted a detailed analysis of how key signaling pathways regulate autophagy activity in hyperglycemic environments and subsequently influence bone metabolic homeostasis. Through systematic examination of existing research, we have identified that autophagy plays a dual role in DOP (Figure 2). Therefore, moderate autophagy activity is essential for maintaining bone cell function and bone metabolic balance, while either excessive enhancement or inhibition of autophagy levels can lead to bone metabolic disorders, accelerating DOP onset and progression.

From a molecular mechanism perspective, the ROS-mTOR signaling pathway exhibits abnormal activation in hyperglycemic conditions, inhibiting autophagic flux and resulting in reduced bone cell function. PINK1/Parkin-mediated mitophagy impairment disrupts bone cell energy metabolism, accelerating bone loss. Abnormal activation of FoxO transcription factors enhances expression of autophagy-related genes, causing excessive autophagy and functional impairment in bone cells. Meanwhile, the AGEs-RAGE signaling pathway interferes with autophagy levels through Raf/MEK/ERK cascade reactions, compromising osteoblast function. These pathways exhibit extensive cross-interaction, collectively forming a complex network underlying DOP pathogenesis (Figure 1).

Regarding cell specificity, this review analyzes how autophagy dysregulation affects different bone cell types, including osteocytes, osteoblasts, osteoclasts, BMSCs, pancreatic β-cells and ASCs. We discovered significant variation in how different cell types respond to changes in autophagy levels. This cell-specific response likely represents an important characteristic in DOP pathology and provides a foundation for individualized therapeutic strategies.

Based on the critical role of autophagy regulation in DOP, we have summarized various potential therapeutic approaches. Pharmacological interventions include autophagy modulators such as Metformin, Rapamycin and torin1, which restore autophagy balance by regulating signaling pathways like AMPK/mTOR, thereby improving bone metabolism. Traditional Chinese medicine compounds such as TBII and ZYBSF demonstrate promising autophagy regulatory and bone-protective effects. Exercise interventions, including high-intensity interval training and whole-body vibration therapy, can activate bone tissue autophagy and improve bone microstructure. Emerging gene and stem cell therapies offer more targeted treatment possibilities for DOP.

Despite the broad prospects of autophagy regulation in DOP treatment, several challenges remain. First, the dual nature of autophagy necessitates precise control of therapeutic interventions, as excessive modulation may lead to adverse consequences. Second, existing research is primarily based on animal models, requiring further validation for clinical translation. Additionally, the complexity and cell specificity of autophagy pathways increase the difficulty in determining therapeutic targets.

Future research should focus on several key directions. Elucidate the fine mechanisms of autophagy regulation in different bone cell types, particularly the interaction between autophagy and other cellular processes such as apoptosis and ferroptosis. Develop more precise, controllable autophagy regulation strategies, such as cell-specific autophagy modulators or targeted delivery systems. Explore the value of autophagy markers in early DOP diagnosis and therapeutic monitoring. Strengthen translational medicine research to advance laboratory findings toward clinical applications, and investigate combination therapeutic strategies that integrate autophagy regulation with traditional anti-osteoporosis treatments or glycemic control to achieve synergistic effects.

In conclusion, autophagy, as a critical link connecting hyperglycemic environments to bone metabolic disorders, provides a new perspective for investigating DOP pathogenesis and developing therapeutic strategies. Through deeper understanding of the role of autophagy in DOP and development of targeted interventions, there is potential to improve bone health in diabetic patients, reduce fracture risk and enhance quality of life. As research continues to advance and technologies progress, individualized precision therapies based on autophagy regulation will bring new breakthroughs in DOP management, offering patients more effective treatment options.

Conclusions and Perspectives

Based on comprehensive analysis, current autophagy-targeted therapeutic strategies for DOP face critical challenges: the dual nature of autophagy necessitates precise balanced modulation to avoid excessive stimulation or inhibition; most studies rely on animal models, requiring clinical translation validation; cellular specificity variations complicate therapeutic target identification. Mechanistically, DOP pathogenesis involves complex interplay among multiple autophagy pathways (ROS-mTOR, PINK1/Parkin, FoxO, SIRT, AGEs-RAGE, ERK, TLR4, ER stress), exhibiting cell-specific and concentration-dependent effects. Future research should prioritize developing cell-specific autophagy modulators, intelligent bidirectional regulatory systems, single-cell sequencing-guided precision therapies, and synergistic strategies combining autophagy regulation with conventional anti-osteoporotic treatments. Furthermore, future investigations should elucidate pathway crosstalk mechanisms and develop spatiotemporal-specific regulatory strategies. These advances represent the evolution from adjunctive to precision-targeted therapy, offering enhanced therapeutic efficacy for DOP management.

Abbreviations

1,25D, 1,25-Dihydroxyvitamin D_3; 3-MA, 3-Methyladenine; AGE, Advanced glycation end product; AICAR, 5-aminoimidazole-4-carboxamide ribonucleotide; ALP, Alkaline phosphatase; AMPK, AMP-activated protein kinase; ASC, Adipose-derived stem cell; ASM, Acid sphingomyelinase; ATF, Activating transcription factor; ATG, Autophagy-related gene; BMD, Bone mineral density; BMP, Bone morphogenetic protein; BMPR1A, BMP receptor 1A; BMSCs, Bone marrow mesenchymal stem cells; BV, Bone volume; CCCP, Carboacylcyanom-chlorobenzene hydrazide; CEBPA, CCAAT/enhancer binding protein; CHOP, C/EBP homologous protein; CTGF, Connective tissue growth factor; CTSK, Cathepsin K; DHM, Dihydromyricetin; DM, Diabetes mellitus; DOP, Diabetic osteoporosis; ECM, Extracellular matrix; eIF2α, Eukaryotic translation initiation factor 2α kinase; ER, Endoplasmic reticulum; ERK, Extracellular signal-regulated kinase; ERS, ER stress; EV, Extracellular vesicle; FGF21, Fibroblast growth factor 21; FoxO, Forkhead box O; FtMt,

Mitochondrial ferritin; GA I, Gymnemic acid I; GlcN, Glucosamine; GSH-Px, Glutathione peroxidase; GSIS, Glucose-stimulated insulin secretion; hCDC14A, Human cell division cycle gene 14A; HDL, High density lipoprotein; HIIT, High-intensity interval training; HMGB1, High mobility group box 1; IL, Interleukin; IRE1α, Inositol-requiring enzyme-1α; JAK, Janus kinase; JNK, C-Jun N-terminal kinase; LC3, Light chain 3; LDL, Low density lipoprotein; lncRNA, Long non-coding RNA; MDA, Malondialdehyde; Meg3, Maternally expressed gene 3; MEK, Mitogen-activated protein kinase; miRNA, MicroRNA; MMP, Mitochondrial membrane potential; mPTP, Mitochondrial permeability transition pore; MSC, Mesenchymal stem cell; mTORC1, mTOR complex 1; NAC, N-acetylcysteine; NFATc1, Nuclear factor of activated T cells; NF-κB, Nuclear factor kappa B; NICD, Intracellular domain of Notch; NIPA2, Prader-Willi/Angelman syndrome region protein 2; NLRP3, NACHT-LRR-PYD domains-containing protein 3; NOX, NADPH oxidase; OCN, Osteocalcin; OPN, Osteopontin; PERK, PKR-like ER kinase; PGC-1α, Proliferator-activated receptor gamma coactivators-1α; PINK1, PTEN induced kinase 1; PPAR, Peroxisome proliferators-activated receptor; RA, Rosmarinic acid; RAGE, Receptor of advanced glycation end product; RANK, Receptor activator of nuclear factor-κB; RANKL, Receptor activator of nuclear factor-κB ligand; Rapa, Rapamycin; rBMSCs, Rat BMSC; RD3, Resolvin D3; ROS, Reactive oxygen species; Runx2, Runt-related transcription factor 2; SA-β-gal, Senescence associated β-galactosidase; SIRT1, Sirtuin 1; SOD, Superoxide dismutase; SQSTM1, Sequestosome 1; STAT, Signal transducer and activator of transcription; Tb.N, Trabecular number; Tb.Sp, Trabecular separation; Tb.Th, Trabecular thickness; TBII, Timosaponin BII; TFEB, Transcription factor EB; TGF-β1, Transforming growth factor-β1; TLR4, Toll-like receptor 4; TNF, Tumor necrosis factor; TNF-α, Tumor necrosis factor alpha; TRAF6, TNF receptor-related factor 6; TRAP, Tartrate-resistant acid phosphatase; TUDCA, Tauroursodeoxycholic acid; TV, Total volume; TβRII, TGF-β receptor II; ULK1, Unc-51-like autophagy activating kinase 1; UPS, Ubiquitin-proteasome system; WBV, Whole body vibration; WSB, Scutellaria baicalensis root extract; XBP1, X-box binding protein 1; XKP, Xiao Ke Ping; ZIPK, Zipper-interacting protein kinase; ZYBSF, Ziyin Bushen Fang.

Data Sharing Statement

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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