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Mechanism of Methylglyoxal-Induced Oxidative Stress Injury in Diabetic Osteoporosis

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Abstract

Diabetic osteoporosis (DOP) is a severe chronic complication of diabetes affecting the skeletal system. Its incidence has been increasing year by year with the rising global prevalence of diabetes, making it a significant public health issue that threatens the quality of life of diabetic patients. Methylglyoxal (MG), a highly reactive carbonyl compound, accumulates abnormally under the hyperglycemic microenvironment in diabetes and serves as a key mediator linking glucose metabolism disorder with bone metabolic imbalance. Numerous basic and clinical studies have confirmed that MG-induced oxidative stress injury in bone cells is a core pathological link in the development and progression of DOP. Osteoblasts and osteoclasts serve as the two key effector cells that regulate bone homeostasis. However, these two cell types exhibit distinct cell-specific responses to MG and oxidative stress, and the underlying molecular regulatory networks remain largely unclear. This review systematically summarizes the pathophysiological role of MG in DOP. It focuses on the regulatory mechanisms by which MG accumulation induces both oxidative stress and mitochondrial dysfunction, two processes that mutually reinforce each other, ultimately leading to aberrant function of osteoblasts and osteoclasts. In-depth elucidation of the molecular mechanisms underlying MG-induced oxidative stress injury in bone cells will provide new theoretical support and potential intervention targets for the prevention and treatment of DOP, with significant value for basic research and clinical translation.

Keywords

Diabetic Osteoporosis, Methylglyoxal, Osteoblasts, Osteoclasts, Oxidative Stress, Mitochondria

1. Introduction

Diabetic osteoporosis (DOP) is one of the most common chronic complications

of diabetes. It is characterized by progressive bone loss, destruction of bone microarchitecture, increased bone fragility and a significantly elevated risk of fractures [1]. Epidemiological studies have shown that the risk of osteoporotic fractures in diabetic patients is 2 - 3 times higher than that in the non-diabetic population. Moreover, fracture healing is delayed, and the incidence of complications is high. This substantially impairs patients' quality of life, while also placing a significant burden on healthcare systems and increasing mortality rates. Given the continued growth of the global diabetic population, the annual incidence of DOP has risen, making it a significant public health concern that requires immediate action [2] [3].

The pathogenesis of DOP is complex and multifaceted. It is widely accepted that its core pathological feature is the disruption of bone homeostasis induced by the hyperglycemic environment, specifically the balance of osteoblast-mediated bone formation and osteoclast-mediated bone resorption [4]. Under physiological conditions, bone formation and bone resorption maintain a dynamic balance, which is fundamental to preserving the structural integrity and mechanical stability of the skeleton. Under diabetic conditions, however, hyperglycemia and its secondary metabolic disorders (such as accumulation of advanced glycation end products, oxidative stress, and inflammatory responses) can directly lead to a dysfunction in osteoblast and osteoclasts. The pathological changes including reduction of osteoblast number, impairment of osteoblast differentiation and maturation, as well as enhance the differentiation and activity of osteoclasts. This ultimately results in bone loss, structural damage, and the eventual development of DOP [5] [6].

Methylglyoxal (MG) is an endogenous toxic byproduct of glycolysis and a key precursor of advanced glycation end products (AGEs) [7]. Under physiological conditions, MG is maintained at low levels through multiple metabolic pathways, primarily the glyoxalase system, preventing its toxic effects on cells. However, under the hyperglycemic conditions of diabetes, disruptions in glucose metabolism and MG clearance lead to a significant increase in MG level. This results in abnormal accumulation of MG in body tissues and fluids, with concentrations 2 - 6 times higher than normal levels [8]. The high electrophilicity of MG enables it to undergo non-enzymatic reactions with biological macromolecules within cells, including proteins, nucleic acids, and lipids. By modifying their structure and function, MG induces cellular damage and dysfunction, acting as a significant driver in the development of various diabetic chronic complications, including diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy [9].

Oxidative stress is a pathological state characterized by the overproduction of free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS). This overproduction exceeds the capacity of the body's antioxidant defense systems, leading to an imbalance between oxidation and antioxidation, which subsequently causes cellular damage. MG can induce oxidative stress in cells through multiple mechanisms. Mitochondria serve as both the primary sites of ROS generation and the most sensitive targets of ROS attack, and their dys-

function is closely associated with oxidative stress injury [10] [11]. In recent years, accumulating evidence has demonstrated that MG-induced oxidative stress injury in bone cells critically contributes to the disruption of bone homeostasis resulting from MG accumulation in DOP [12] [13]. However, the differential responses of osteoblasts and osteoclasts in this process and the underlying molecular mechanisms have not yet been thoroughly elucidated.

This review systematically summarized the pathophysiological role of MG in DOP. It focused on the multiple mechanisms by which MG induced oxidative stress in bone cells, including the regulation of related signaling pathways and mitochondrial dysfunction. Additionally, the distinct mechanisms of MG-induced injury in osteoblasts and osteoclasts are discussed. By integrating recent research advances in this field, we aim to provide a theoretical foundation and research perspectives for the prevention and treatment of DOP.

2. Metabolism and Pathological Significance of MG

2.1. Sources and Metabolic Pathways of MG

The endogenous production of MG primarily depends on the glycolytic pathway [9]. During glycolysis, glucose is gone through a series of enzymatic reactions converting into glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP). These two triose phosphates undergo non-enzymatic β-elimination, losing a phosphate group to form MG. In addition to the glycolytic pathway, MG can be generated through several other routes, including glucose auto-oxidation, degradation of glycated proteins, catabolism of ketone bodies during diabetic ketoacidosis, threonine catabolism, lipid peroxidation, and the metabolic activity of gut microbiota [14] [15]. Under physiological conditions, the conversion of glucose to MG is inefficient, and the body possesses robust MG clearance mechanisms. Consequently, MG is maintained at a low, dynamic equilibrium without exerting significant cytotoxicity.

The metabolic clearance of MG relies primarily on the glyoxalase system. This system consists of two key enzymes, including glyoxalase I (GLO I) and glyoxalase II (GLO II). MG undergoes a non-enzymatic reaction with glutathione (GSH) to form a hemithioacetal. Subsequently, GLO I catalyzes the conversion of this hemithioacetal to S-D-lactoylglutathione. Finally, GLO II hydrolyzes S-D-lactoylglutathione to D-lactic acid, regenerating GSH and completing the detoxification process [16]. Moreover, the body possesses other auxiliary metabolic pathways that participate in MG clearance, such as aldose reductase (ALR), aldehyde dehydrogenases (ALDHs), and the Parkinson's disease-associated protein DJ-1 [17] [18]. These enzymes contribute to MG clearance by converting it into non-toxic or low-toxicity products via distinct mechanisms, further ensuring the capacity for MG clearance.

2.2. MG Accumulation in Diabetes

Under diabetic hyperglycemic conditions, the balance between MG production

and clearance is disrupted, leading to its abnormal accumulation in cells and tissues. This accumulation is critically involved in the pathogenesis of diabetic chronic complications, including DOP. MG levels in the plasma and tissues (such as bone, kidney, and liver) of diabetic patients are 2 to 6 times higher than in healthy individuals [19] [20]. The increase in MG arises from a combination of increased production and impaired clearance. This mutual reinforcement establishes a vicious cycle that further exacerbates MG-induced toxicity.

2.2.1. Aberrant MG Generation

The elevated rate of MG generation under hyperglycemic conditions underlies its increased production, driving its subsequent accumulation. Under physiological conditions, the amount of MG precursors (G3P and DHAP) generated from glycolysis is limited, thereby maintaining low MG production. Under diabetic hyperglycemic conditions, elevated intracellular glucose levels result in excessive activation of the glycolytic pathway, leading to a marked increase in glycolytic flux. This results in the substantial accumulation of triose phosphate substrates like G3P and DHAP [14]. These precursors are rapidly converted to MG via non-enzymatic β-elimination, driving a marked increase in MG production and resulting in levels that far exceed the normal physiological range. Moreover, hyperglycemia also activates additional MG-generating pathways, including glucose auto-oxidation and the degradation of glycated proteins, which in turn further elevate MG production and promote its accumulation.

2.2.2. Impaired MG Metabolism

The hyperglycemic environment significantly compromises the body's capacity to metabolize and clear MG, contributing to its accumulation. This metabolic impairment is mediated by several molecular mechanisms. First, hyperglycemia-induced oxidative stress can directly inhibit the expression and activity of GLO I. Reduced GLO I activity directly compromises the system's ability to metabolize and clear MG, preventing its timely conversion to non-toxic products [21]. The hyperglycemic environment enhances oxidative stress, leading to significant consumption and decreased levels of GSH. GSH deficiency limits the non-enzymatic reaction between MG and GSH, reducing the efficiency of MG detoxification [22]. Under hyperglycemic conditions, advanced glycation end products (AGEs) accumulate and further suppress glyoxalase system function via feedback regulation. This establishes a vicious cycle in which MG accumulation drives AGE formation, and subsequent glyoxalase inhibition further promotes MG accumulation [23]. Hyperglycemia also suppresses the activity of other auxiliary MG-metabolizing enzymes, such as ALR and ALDHs [20] [24] [25], further compromising overall MG clearance.

2.3. Cellular Toxicity of MG

The cellular toxicity of MG is primarily attributed to its high electrophilicity. This property enables it to undergo non-enzymatic nucleophilic addition reactions

with various intracellular biological macromolecules, including proteins and nucleic acids. By modifying the structure and function of these macromolecules, MG triggers cellular damage and dysfunction, which can be categorized into three main aspects.

2.3.1. MG-Induced Protein Modification

MG primarily reacts with arginine residues, and to a lesser extent with lysine and cysteine residues [26]. These reactions form covalent adducts that generate various AGEs, such as argpyrimidine and methylglyoxal-lysine dimer (MOLD) [27] [28]. These modifications directly alter the spatial conformation and function of proteins, resulting in loss of enzymatic activity, abnormal receptor binding capacity, and protein cross-linking and aggregation. Collectively, these changes impair normal cellular physiological functions [29] [30].

2.3.2. MG-Induced Nucleic Acid Modification

MG can react with guanine bases in DNA through nucleophilic addition, forming DNA adducts such as MG-guanine adducts. These modifications can lead to DNA strand breaks, nucleotide transversions, DNA-DNA cross-links, and DNA-protein cross-links, thereby inducing gene mutations, chromosomal damage, and ultimately leading to apoptosis or abnormal cell proliferation [31] [32]. Furthermore, MG modification of RNA can also affect gene transcription and translation processes, further exacerbating cellular dysfunction [33].

3. Mechanisms of MG-Induced Oxidative Stress

3.1. Pathways of ROS Generation

MG can significantly increase intracellular ROS levels through both direct and indirect pathways, a core mechanism underlying its induction of oxidative stress.

3.1.1. Direct Pathways

The production and metabolism of MG are directly accompanied by the generation of ROS. The conversion of MG to pyruvate catalyzed by glyoxal oxidase is accompanied by the generation of H_2O_2 [34]. Similarly, the conversion of aminoacetone to MG by semicarbazide-sensitive amine oxidase (SSAO) also releases H_2O_2 in rat aortic vascular smooth muscle cells [35]. MG can induce conformational changes in hemoglobin in human umbilical vein endothelial cells (HUVECs), promoting hemoglobin glycation. The resulting hemoglobin-advanced glycation end products (Hb-AGEs) significantly increase ROS production in HUVECs [36]. These generated ROS can directly attack intracellular biomacromolecules, initiating oxidative damage.

3.1.2. Indirect Pathways

MG can also indirectly increase ROS accumulation by activating intracellular ROS-generating systems. A primary mechanism is the activation of the NADPH oxidase (NOX) family [37]. MG can induce the expression of inducible nitric oxide synthase (iNOS) in macrophages, which generates nitric oxide (NO), a reactive

nitrogen species (RNS) that triggers nitrosative stress, a distinct but often concurrent form of redox imbalance [38]. Moreover, MG can bind to the receptor for advanced glycation end products (RAGE) on the cell surface, increasing oxidative stress and inflammation, contributing to various diseases [39]-[41]. MG can upregulate iNOS expression via p38 MAPK-NF κB pathway, stimulating iNOS activation and generating ROS through the activation of ERK and JNK in endothelial cell [42]. Additionally, MG promotes the generation of nitric oxide (NO), which rapidly reacts with superoxide anion ($\bullet O_2^-$) to form the potent oxidant peroxynitrite ($ONOO^-$). $ONOO^-$ has stronger oxidizing properties than ROS, further exacerbating intracellular oxidative damage by attacking DNA, proteins, and lipids, leading to cellular dysfunction [38].

3.2. Weakening of the Antioxidant Defense System

MG directly depletes intracellular GSH, which is the most abundant non-enzymatic antioxidant in cells. The strong nucleophilicity of the thiol (-SH) group of GSH facilitates its nucleophilic addition with MG to form a hemithioacetal, leading to significant GSH consumption [43]. MG directly depletes GSH and inhibits the activity of key enzymes involved in its synthesis, such as γ-glutamylcysteine ligase (γ-GCL). Consequently, the cellular antioxidant defense system is weakened, leading to exacerbated oxidative stress and mitochondrial dysfunction, which ultimately cause cell injury [44] [45]. GLO I is a key enzyme for MG detoxification, and its activity directly impacts MG clearance efficiency. Excess MG can also inhibit GLO I activity. When GLO I activity is suppressed or deficient, MG clearance is compromised, leading to its accumulation. This accumulation subsequently triggers the AGEs-RAGE-NF-κB signaling axis, culminating in inflammation and oxidative stress [46] [47]. By inactivating GLO I, MG disrupts its primary detoxification pathway, leading to MG accumulation. This accumulation subsequently induces oxidative stress and mitochondrial dysfunction in osteoblastic MC3T3-E1 cells [48]. MG inhibits the nuclear translocation and transcriptional activity of Nrf2. This suppresses the Nrf2-mediated antioxidant defense system. As a result, the expression of antioxidant enzymes, including heme oxygenase-1 (HO-1), is downregulated. This further diminishes the cellular antioxidant capacity, leading to increased ROS production and exacerbating oxidative stress injury in myotubes [49].

3.3. Regulation of Oxidative Stress-Related Signaling Pathways by MG

3.3.1. AGEs-RAGE Axis and Inflammatory Signaling Pathway

AGEs formed by the non-enzymatic reaction of MG with intracellular proteins can bind to RAGE on the cell surface, activating the AGEs-RAGE axis and subsequently regulating multiple downstream signaling pathways. This is a key mechanism by which MG induces oxidative stress injury in bone cells [50] [51]. RAGE is a pattern recognition receptor widely expressed on the surface of various cells, including osteoblasts, osteoclasts, and bone marrow stromal cells [52] [53]. Bind-

ing of AGEs to RAGE can promote ROS generation by activating the NOX family, while simultaneously activating NF-κB and the MAPK cascade, initiating a vicious cycle of inflammatory response and oxidative stress [54] [55]. MG can activate the MAPK signaling pathway via the AGEs-RAGE axis, specifically activating the p38 and JNK signaling pathways, inducing the upregulation of osteogenic differentiation-related proteins such as RUNX2 and OPG [56]. Soluble RAGE (sRAGE) is a splice variant of RAGE that functions as a competitive inhibitor. It binds to AGEs in competition with membrane-bound RAGE, thereby blocking activation of the AGEs-RAGE axis and reducing oxidative stress and inflammation. Vitamin D treatment may possibly be beneficial to reduce AGE levels and to augment sRAGE levels in populations with vitamin D-deficient situations [57]. Studies have shown that in T1DM patients the sRAGE/RAGE ratio was significantly decrease, leading to overactivation of the RAGE signaling pathway and further exacerbating cellular oxidative stress injury on osteoblastic MC3T3-E1 cells [58] [59].

3.3.2. Cell Death Signaling Pathways

MG-induced oxidative stress can induce bone cell apoptosis through both the mitochondrial pathway and the extrinsic death receptor pathway, a critical mechanism underlying MG-induced dysfunction in bone cells. MG increases the Bax/Bcl-2 ratio, activates cleaved caspase-3, and inhibits the PI3K/Akt and Nrf2/HO-1 antioxidant signaling pathways in endothelial cell. Consequently, massive ROS production occurs, amplifying oxidative stress injury in a cascade and ultimately leading to apoptosis [60]. MG can also induce inflammatory pyroptosis by activating caspase-3, which subsequently cleaves gasdermin E (GSDME). Concurrently, by promoting the cleavage of non-muscle myosin heavy chain IIA (NMMHC IIA) and affecting the phosphorylation state of myosin light chain 2 (MLC2), MG further exacerbates cytoskeletal damage and vascular dysfunction in HUVECs [61]. Through ROS generation, MG activates the MAPK p38 signaling pathway and upregulates the transcription of the E3 ubiquitin ligase FBXO32, which catalyzes the ubiquitination and degradation of the transcription factor KLF4. This inhibits the transcription of the macrophage phagocytic receptor MerTK, ultimately impairing the ability of macrophages to clear apoptotic cells and hindering the resolution of inflammation and tissue repair [62].

3.4. Mitochondrial Dysfunction

Mitochondria are central to cellular energy metabolism and are both primary sites of ROS generation and primary targets of ROS attack. MG-induced mitochondrial dysfunction manifests primarily as impaired mitochondrial respiratory chain function, altered mitochondrial dynamics, abnormal mitophagy, and impaired mitochondrial biogenesis. This dysfunction leads to the release of cytochrome c (cytC) from the mitochondrial matrix into the cytoplasm, where it binds to apoptotic protease activating factor 1 (Apaf-1), activating caspase-9 and subsequently downstream caspase-3, ultimately triggering synaptic apoptosis [63]. MG induces mitochondrial dysfunction by downregulating the PI3K-Akt and

Nrf2-HO-1/NQO-1 antioxidant signaling pathways, decreasing mitochondrial membrane potential, and increasing lactate dehydrogenase (LDH) release. This activation of apoptotic markers such as p-P38, cleaved caspase-9/3, and Bax further leads to PC-12 cells apoptosis [64]. MG also reprograms metabolism in myoblasts, inhibiting the tricarboxylic acid (TCA) cycle and promoting fatty acid synthesis, while inducing mitochondrial morphological abnormalities. This results in a significant reduction in ATP production from mitochondria, triggering a cascade of oxidative stress responses and ultimately leading to myoblast cellular dysfunction and injury [65]. MG suppresses the expression of the mitochondrial antioxidant enzymes IDH2 and MGST1 in epithelial cells, while simultaneously downregulating the fusion protein MFN2 and upregulating the fission protein FIS1, leading to an imbalance in mitochondrial fusion and fission. This dynamic imbalance further exacerbates the loss of mitochondrial membrane potential and increases ROS production, creating a vicious cycle of oxidative stress and mitochondrial dysfunction [66]. MG induces excessive mitochondrial fission by downregulating the fusion proteins OPA1 and MFN1, leading to mitochondrial network fragmentation and subsequent dysfunction, thereby causing cellular injury. Enhancing GLO1 expression can restore OPA1 and MFN1 levels, reversing mitochondrial fission and mitigating endothelial cells' damage [67]. Increased mitochondrial fission and decreased fusion not only impair mitochondrial energy metabolism but also enhance the release of mitochondrial ROS (mtROS), further exacerbating cellular oxidative stress injury in a vicious cycle. Additionally, MG activates Parkin-1-mediated mitophagy. However, this excessive mitophagy disrupts mitochondrial homeostasis, leading to the downregulation of tight junction proteins (occludin, claudin-5, ZO-1) and compromising the barrier integrity of brain endothelial cells [68]. MG can also downregulate the expression of SIRT1 and PGC-1α, key regulators of mitochondrial biogenesis. This impaired biogenesis leads to a reduction in both the number and quality of mitochondria, while simultaneously weakening the activity of the endogenous antioxidant enzyme system (SOD, GPX). This creates an imbalance between ROS production and clearance, ultimately resulting in mitochondrial damage and cellular dysfunction [69].

4. Association between MG and Diabetic Osteoporosis

4.1. Disruption of Bone Homeostasis: A Core Pathological Feature of DOP

Bone homeostasis refers to the dynamic equilibrium maintained by osteoblast-mediated bone formation and osteoclast-mediated bone resorption, ensuring the stability of bone mass and microarchitecture. This balance is fundamental to normal skeletal physiology. Osteoblasts and osteoclasts, as the two key effector cells in this process, must maintain functional balance to preserve normal bone mass and structure [70] [71]. In the pathological process of DOP, the hyperglycemic environment and its secondary metabolic disturbances (such as MG accumulation, oxidative stress, and inflammation) disrupt this balance by suppressing os-

teoblast number and function while enhancing osteoclast differentiation and activity, leading to progressive bone loss and increased fracture risk [72].

Both type 1 (T1DM) and type 2 (T2DM) diabetes increase fracture risk, but via distinct bone phenotypes. T1DM typically exhibits low bone turnover and reduced bone mineral density (BMD), whereas T2DM often shows normal or high BMD with impaired bone quality [73]. Clinical and translational evidence directly links MG/AGE burden to adverse bone outcomes in both types. Elevated MG and AGE levels correlate with lower BMD in T1DM, reflecting low bone turnover and reduced bone formation. Bone biopsy studies in T1DM patients show increased AGE deposition in collagen, which contributes to reduced bone toughness and increased fragility [74]. The femoral cortical bone specimens from T1DM patients with >50 years disease duration exhibits 17% higher AGE levels, 30% lower bone toughness and decreased mineral crystallinity [75]. In patients with T2DM, skin autofluorescence-derived accumulation of AGEs is positively associated with low bone density/osteoporosis and major osteoporotic fractures. Elevated AGE levels also correlate with increased bone turnover markers (PINP, CTX), indicating that AGEs accumulation is an important risk factor for bone damage in T2DM [76]. The MG serum levels and gene expression of RAGE in PBMCs are higher in T2DM patients than control groups [77] [78]. Clinical translational evidence reveals that MG/AGE burden independently correlates with low bone mineral density in T1DM and with fracture risk in T2DM, implying that MG plays a pathogenic role in both diabetic populations, yet the underlying mechanisms differ.

4.2. MG and Osteoblasts

Osteoblasts, as the core effector cells for bone formation, are central to the insufficient bone formation seen in DOP. MG-induced oxidative stress can damage osteoblasts through multiple specific mechanisms, primarily by inhibiting osteoblast differentiation and mineralization, disrupting the cytoskeleton and adhesion, and promoting apoptosis. These effects collectively lead to impaired bone formation [79] [80]. MG treatment causes a significant decrease in mitochondrial membrane potential, reduced ATP production, and increased levels of mtROS and intracellular Ca^{2+} in osteoblasts. The increase in mtROS further damages the mitochondrial respiratory chain. CypD, a key component of the mitochondrial membrane potential, plays a crucial regulatory role in this process. PGAM5 acts as an upstream signaling molecule for CypD. MG can activate PGAM5, which in turn regulates CypD activity, promoting mPTP opening and leading to mitochondrial dysfunction and osteoblast injury [81]. MG induces the generation of intracellular ROS and mitochondrial superoxide in osteoblasts, while also promoting cardiolipin peroxidation. Additionally, it reduces GSH levels, inhibits GLO I and HO-1 activities, and downregulates Nrf2 expression. Collectively, these effects trigger mitochondrial dysfunction and inflammation, ultimately resulting in oxidative stress injury [59]. These findings suggest that targeting mitochondrial function may be an effective strategy to inhibit MG-induced osteoblast damage. Fur-

thermore, treatment of MC3T3-E1 osteoblasts with MG dose-dependently reduces cell viability, significantly inhibits the expression of osteogenic differentiation markers (ALP, OCN), and decreases the formation of mineralized nodules, indicating that MG directly suppresses osteoblast proliferation and differentiation and impairs their mineralization function [23].

4.3. MG and Osteoclasts

Current research suggests that MG exerts a bidirectional regulatory effect on RANKL-induced osteoclast differentiation, which may be closely related to factors such as MG concentration, cell type, and exposure time. This regulation also involves various specific mechanisms, including mitochondrial dysfunction and metabolic reprogramming, ultimately influencing osteoclast differentiation and bone resorption activity [82]. Under hyperglycemic conditions, increased MG production simultaneously inhibits the expression of osteoblast markers (ALP, OCN, OPG) and downregulates the osteoclast-associated receptor (OSCAR), thereby impairing the differentiation function of both osteoblasts and osteoclasts and leading to delayed bone defect healing [83]. It has been reported that treatment of RAW264.7 cells with 300 - 600 μM MG for 4 days during RANKL-induced osteoclastogenesis significantly inhibited TRAP activity and osteoclast differentiation. MG significantly inhibits RANKL-induced osteoclast differentiation by inhibiting GLO I activity, leading to impaired MG metabolism, inducing mitochondrial dysfunction, and decreasing intracellular calcium concentration [84]. However, other studies have shown that treatment of RAW264.7 cells with a lower concentration of MG (50 - 200 μM) for 3 days enhanced osteoclast differentiation via JNK activation and upregulating the expression of osteoclast marker genes CTSK, OSCAR, and TRACP5, suggesting that MG mediates osteoclast activation via the JNK pathway, thereby contributing to the bone remodeling imbalance in diabetes-related osteoporosis [85]. This bidirectional effect may be closely related to MG concentration, cell type (e.g., osteoclast precursors vs. mature osteoclasts), and exposure time. High-dose MG (e.g., 300 - 600 μM) may inhibit osteoclast differentiation by inducing excessive oxidative stress, while moderate oxidative stress induced by low-dose MG (e.g., 50 - 200 μM) may act as a signal promoting osteoclast differentiation. Additionally, differences in cell models (RAW264.7 vs. bone marrow-derived macrophages), differentiation stage (early vs. late osteoclastogenesis), and exposure timing (continuous vs. intermittent) may also contribute to the observed discrepancies. The specific molecular mechanisms underlying this bidirectional regulation are not yet fully understood and require further investigation.

4.4. MG and the Bone Matrix

The adhesion capacity and cytoskeletal integrity of osteoblasts are fundamental to their bone-forming function, as osteoblasts need to adhere to the bone matrix surface to synthesize and mineralize it. MG can also modify type I collagen in the

bone matrix, altering the biomechanical properties of the bone and increasing its fragility [86] [87]. Type I collagen is the main component of the bone matrix, and its structural integrity directly affects the mechanical strength of the skeleton. The non-enzymatic reaction of MG with type I collagen to form AGEs can lead to collagen cross-linking and aggregation, altering its physicochemical properties. This not only reduces the mechanical strength of the bone but can also diminish the adhesion capacity of osteoblasts to the bone matrix proteins, further inhibiting the bone formation process and exacerbating bone loss and structural damage [88].

5. Intervention Strategies and Therapeutic Prospects

Given the central role of MG-induced oxidative stress injury in bone cells in the pathogenesis of DOP, current intervention strategies primarily focus on clearing MG, inhibiting oxidative stress, protecting mitochondrial function, and regulating bone cell function. Approaches such as antioxidant intervention, natural product protection, mitochondrial-targeted therapy, and MG scavengers have shown preliminary research progress, offering potential avenues for the clinical treatment of DOP.

5.1. Antioxidants

Since oxidative stress is a central role in MG-induced bone cell injury, antioxidants represent a potential strategy for intervening in DOP. N-acetylcysteine (NAC), a classic antioxidant and precursor of GSH, can significantly increase intracellular GSH levels, enhancing cellular antioxidant capacity [89]. NAC effectively ameliorates MG-induced mitochondrial dysfunction, osteoblast apoptosis, and impaired osteogenic differentiation. Studies show that NAC pretreatment significantly reduces MG-induced ROS levels in osteoblasts, restores mitochondrial membrane potential and ATP production, decreases the number of TUNEL-positive cells, and upregulates the expression of osteogenic marker genes like ALP and OCN, thereby improving osteoblast differentiation and mineralization function [81]. Trolox, a water-soluble analog of vitamin E, possesses potent antioxidant activity and can mitigate cellular damage by scavenging ROS and inhibiting oxidative stress [90]. Additionally, natural antioxidants like vitamin C and vitamin E protect bone cell function by alleviating oxidative stress injury [91] [92], offering simple and feasible strategies for DOP intervention.

5.2. Natural Small Molecule Compounds

Many natural small molecule compounds, characterized by their multi-target effects and low toxicity, exhibit significant protective effects against MG-induced bone cell injury, representing a potential source for DOP drug development. Glabridin, a major active component of licorice, possesses strong antioxidant and anti-inflammatory properties. Glabridin alleviates oxidative stress-induced osteoblast apoptosis by activating the Akt signaling pathway, subsequently phosphorylating and regulating downstream GSK-3β and NF-κB p65 proteins [93]. Crocin,

a major active component of saffron, exhibits significant antioxidant and mitochondrial protective effects. Crocin significantly restores succinate dehydrogenase (SDH) activity, reverses the loss of mitochondrial membrane potential and mitochondrial swelling, while reducing ROS generation, malondialdehyde (MDA) levels, and maintaining GSH content. By preserving mitochondrial redox homeostasis and energy metabolism, crocin protects cells from oxidative stress injury [94].

5.3. Mitochondrial-Targeted Therapy

Mitochondrial dysfunction is a central link in MG-induced oxidative stress injury in bone cells, making mitochondrial-targeted therapy a new direction for DOP intervention. Cyclosporin A (CsA) is a specific inhibitor of the mPTP. By blocking mPTP opening, CsA protects mitochondrial membrane potential, reduces cytochrome c release, and inhibits mitochondrial pathway-mediated apoptosis, thereby preventing MG-induced osteoblast toxicity. Studies have shown that CsA pretreatment significantly restores MG-induced mitochondrial function in osteoblasts, reduces ROS production, increases cell viability, and improves osteoblast differentiation function [81]. Furthermore, mitochondrial-targeted antioxidants, such as MitoQ, can specifically target mitochondria, scavenge mtROS, and protect mitochondrial function, effectively inhibiting osteoclast differentiation and osteogenic mineralization function [95] [96], providing new avenues for DOP intervention.

5.4. Scavengers of MG

Since abnormal MG accumulation is a prerequisite for MG-induced bone cell injury, directly clearing excess MG in the body using MG scavengers to reduce its toxic effects on bone cells is a potential strategy. Aminoguanidine is a classic MG scavenger that specifically reacts with MG to form non-toxic adducts, reducing MG accumulation in the body. It can reverse MG-induced ROS generation, mitochondrial dysfunction, and cytotoxicity in osteoblasts, block MG-triggered oxidative stress and cellular dysfunction, upregulate the expression of osteogenic marker genes like ALP and OCN, and improve osteoblast differentiation and mineralization function, thereby restoring the osteogenic differentiation capacity of BMSCs [23].

6. Summary

As a key metabolic toxicant associated with diabetic hyperglycemia, MG plays a central regulatory role in the development and progression of DOP by inducing oxidative stress injury in bone cells. Current research has revealed the multifaceted mechanisms by which MG induces oxidative stress in bone-related cells, including both direct promotion of ROS generation and weakening of the cellular antioxidant defense system. Furthermore, MG can damage mitochondrial function (including respiratory chain impairment, altered dynamics, mitophagy abnormalities and biogenesis defects) by regulating signaling pathways such as the

AGEs-RAGE axis and MAPK/NF-κB. This leads to inhibition of osteoblast function and aberrant activation of osteoclasts, ultimately disrupting bone homeostasis and promoting DOP development. However, several scientific questions in this field remain to be addressed. The molecular mechanisms of MG-induced oxidative stress injury in bone-related cells require further refinement. The coordinated regulatory relationships between the AGEs-RAGE axis, MAPK/NF-κB signaling pathways, and mitochondrial dysfunction, as well as the crosstalk mechanisms among these signaling molecules, have not yet fully analyzed. Current intervention strategies are often singular and lack specificity. And their clinical efficacy, safety, and administration methods require further optimization and validation. The molecular mechanisms of MG-induced oxidative stress injury in bone cells will be further elucidated. Novel intervention strategies developed based on this knowledge will provide stronger theoretical support and clinical options for the prevention and treatment of DOP, potentially improving the skeletal health of diabetic patients and reducing the risk of osteoporosis and fractures. This area holds significant value for basic research and clinical translation.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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