Materials Today Bio 23 (2023) 100835

Contents lists available at ScienceDirect

Materials Today Bio

journal homepage: www.journals.elsevier.com/materials-today-bio

Recent progress in bone-repair strategies in diabetic conditions

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ARTICLE INFO

Keywords:
Bone repair
Diabetic condition
Reactive oxygen species
Bone regeneration
Hyperglycemia

ABSTRACT

Bone regeneration following trauma, tumor resection, infection, or congenital disease is challenging. Diabetes mellitus (DM) is a metabolic disease characterized by hyperglycemia. It can result in complications affecting multiple systems including the musculoskeletal system. The increased number of diabetes-related fractures poses a great challenge to clinical specialties, particularly orthopedics and dentistry. Various pathological factors underlying DM may directly impair the process of bone regeneration, leading to delayed or even non-union of fractures. This review summarizes the mechanisms by which DM hampers bone regeneration, including immune abnormalities, inflammation, reactive oxygen species (ROS) accumulation, vascular system damage, insulin/insulin-like growth factor (IGF) deficiency, hyperglycemia, and the production of advanced glycation end products (AGEs). Based on published data, it also summarizes bone repair strategies in diabetic conditions, which include immune regulation, inhibition of inflammation, reduction of oxidative stress, promotion of angiogenesis, restoration of stem cell mobilization, and promotion of osteogenic differentiation, in addition to the challenges and future prospects of such approaches.

1. Introduction

Bone fracture is one of the most common types of trauma. As a regenerative process in response to injury, bone repair recapitulates many biological events of embryonic skeletal development including endochondral and intramembranous bone formation [1]. The same molecules and genetic mechanisms that regulate embryonic endochondral ossification are expressed during fracture healing [2,3]. In most cases, successful healing of damaged bone can be achieved. 5–10 % of fractures may end with delayed or even non-union, and more so in the case of co-morbidities such as diabetes mellitus (DM) [4].

With the aging of the population and changes in lifestyle, the incidence of DM has been increasing. The International Diabetes Federation (IDF) estimated that 536.6 million people are living with diabetes (diagnosed or undiagnosed) in 2021, and this number is expected to increase by 46 % to reach 783.2 million by 2045 [5]. In addition, it is estimated that around 50 % of people with diabetes are unaware of their condition [6,7]. Clinical studies have confirmed that DM leads to an increased risk of fractures and also affects the process of bone repair [8–12], posing a great clinical challenge, particularly for those with poor glycemic control [13–18]. Although the current classification of diabetes recognizes the forms of type 1 diabetes (T1DM), type 2 diabetes (T2DM), gestational diabetes, monogenic diabetes, and other less common types, the researches about bone and DM have mainly focused on T1DM and T2DM [16,19]. Stumpf et al. found a twofold increase in fracture rate in T1DM patients compared to healthy individuals after 10 years of follow-up, and fracture incidence was associated with increasing age and high HbA1c levels [20]. Individuals with T2DM had an increased risk of hip (relative risk (RR) 1.33, 95 % CI 1.19 to 1.49) and nonvertebral (RR 1.19, 95 % CI 1.11 to 1.28) fractures compared with those without T2DM. Furthermore, long duration of T2DM and insulin use were independently associated with an increased risk of hip fracture [21]. The increased risk of fracture in DM patients is multifactorial with both skeletal and non-skeletal contributions (hypoglycemic

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https://doi.org/10.1016/j.mtbio.2023.100835
Received 2 January 2023; Received in revised form 2 October 2023; Accepted 14 October 2023
Available online 20 October 2023

episodes, falls, age, female sex, and diabetic complications) [16,22]. T1DM, characterized by insulin-producing β cells of the pancreas being destroyed, leading to insulin deficiency, commonly presents in early life before peak bone mass and reduces bone formation during skeletal growth, which in turn leads to low bone mineral density (BMD), bone strength, and bone stiffness [23–25]. It has been confirmed that bone development is abnormal in youth with T1DM [26,27]. T2DM occurs when insulin resistance is present in the setting of innate and acquired deficiency in β cell function. Although patients may present with normal or increased bone density, impaired bone material properties and increased cortical porosity are associated with T2DM [28]. The treatment of T1DM and T2DM differ, T1DM must be treated with insulin; T2DM can be relieved by dietary control and taking hypoglycemic drugs and insulin is used when pancreatic islet failure or serious complications.

Use of hypoglycemic agents may also affect bone health. Thiazolidinediones (TZDs) have negative effects on bone and can alter bone remodeling by suppressing the bone formation and increasing bone resorption, resulting in decreased trabecular and cortical bone mass [29]. Increased fracture risk has been reported with sulfonylurea and insulin-based therapies, but it is unclear whether the increased fractures are due to falls from drug-induced hypoglycemia. In addition, the effect of SGLT2 inhibitors on bone health is controversial. Although Lecka-Czernik et al. proposed that the SGLT2 inhibitors may increase the risk for fracture, a meta-analysis conducted by Su et al. did not support this [28–33].

DM can also increase the risk of delayed union or non-union of fractures. In the last few years, researches have shed light on how the bone microenvironment and its cellular and noncellular components may respond to DM. Various approaches have been used to promote bone repair in patients with DM. In this review, we have outlined the mechanisms for the impaired healing of bone fractures with DM and assessed the therapeutic approaches including immune regulation, inhibition of inflammation, reduction of oxidative stress, promotion of angiogenesis, restoration of stem cell mobilization, and promotion of osteogenic differentiation, which are currently available or under development to promote the healing of bone fractures in individuals with DM.

2. Impaired bone repair in DM conditions

During development, bones are formed through two distinct mechanisms of ossification known as intramembranous and endochondral ossification. During intramembranous ossification, osteoblasts differentiate directly within the mesenchymal tissue. Examples of bones that form through intramembranous ossification during development include the flat bones of the skull, the mandible, the maxilla, the clavicles, and the patella. During endochondral ossification, bones are formed indirectly through the initial formation of a cartilaginous template, which is subsequently remodeled into bone. Long bones, such as the femur, tibia, and humerus, are formed through this process [34].

Bone repair involves a series of precisely coordinated and cascaded biological processes, with three consecutive stages: inflammation, repair, and remodeling [35,36], in which a variety of cellular and intercellular signaling pathways are involved [37]. During normal fracture healing, an inflammatory phase first occurs after the fracture, with a hematoma formed by local vasodilatation and massive exudation of plasma and leukocytes. Immune cells, including multi-nucleated neutrophils, macrophages, and lymphocytes, are successively recruited and secrete cytokines such as interleukin-1 (IL-1), tumor necrosis factor (TNF), receptor activator of nuclear factor-κB ligand (RANKL), angiopoietin-1 (Ang-1), and vascular endothelial growth factor (VEGF) to promote migration of endothelial cells into the hematoma to form new blood vessels. This provides nutritional support for follow-up processes and promotes stem cell migration. During the fibrous callus stage, fibroblasts form new collagen in the hematoma, which is gradually

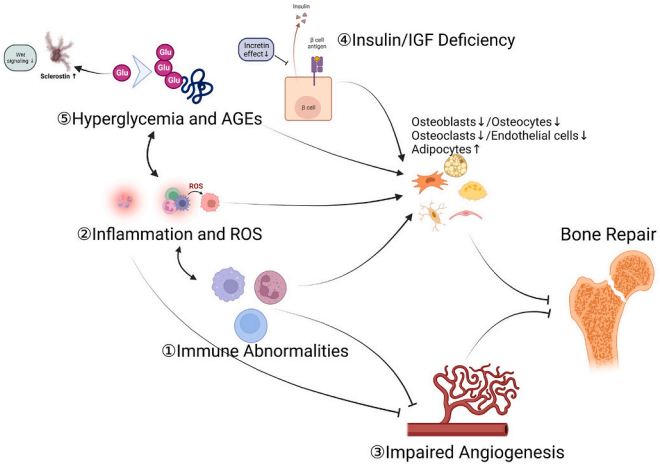

Fig. 1. Effect of DM on bone repair: DM affects bone repair through five main factors: ① Immune abnormalities; ② Inflammation and ROS; ③ Vascular system damage; ④ Insulin/IGF deficiency; ⑤ Hyperglycemia and AGES. There are complex interactions between such factors. ①,②,④, and ⑤ can make multiple cells dysfunctions, whilst ① and ② can promote it ③, which may ultimately lead to impaired bone repair.

replaced by granulation tissue rich in capillaries, cells, and collagen fibers [35,38]. Subsequently, precursor cells migrate and differentiate into chondrocytes and osteoblasts. The repair process itself typically occurs through one of two processes: either primary (or direct) bone healing, where the fractured bone is in close proximity and healing primarily happens through intramembranous ossification, or secondary (or indirect) bone healing, where a cartilaginous fracture callus forms and eventually remodeled into mature bone through endochondral ossification [39]. In the process of intramembranous ossification, the development of bone tissue from fibrous membranes, the growth of the microcapillary network extends into the mesenchymal region of the periosteum, and mesenchymal cells differentiate into osteoblasts and osteoprogenitors [40]. During endochondral ossification, mesenchymal progenitor cells accumulate, form dense clusters, and differentiate into chondrocytes. Proangiogenic factors are secreted by non-proliferative chondrocytes in the cartilage template, resulting in the invasion of blood vessels, which, along with osteoclasts and osteoprogenitors, form the primary ossification center [41]. As the vasculature expands, monocytes differentiate into osteoclasts and absorb the calcified cartilage. Stem cells differentiate into osteoblasts, producing new bone to fill the lacuna and form a woven bone with a trabecular structure. During the tissue remodeling stage, osteoclasts on the external surface are more active and the cells resolve, after which the woven bone is remodeled into lamellar bone [35,42–45]. The bone microenvironment refers to the specialized environment within the bone tissue that plays a crucial role during the repair process [46–48]. It consists of various cellular and noncellular components that work together to ensure the normal progress of bone repair. Cellular components in the bone microenvironment mainly include osteoblasts, osteoclasts, and osteocytes. Osteoblasts are responsible for the synthesis and deposition of bone matrix, whilst osteoclasts are involved in bone resorption. Osteocytes, the most abundant cells in bones, are known to regulate both osteoblast and osteoclast activity. Noncellular components of the bone microenvironment include the extracellular matrix and signaling molecules. The extracellular matrix provides structural support to the bone and contains collagen fibers, hydroxyapatite crystals, and other proteins [34]. Signaling molecules such as cytokines, growth factors, and hormones are involved in cell communication and regulation of bone repair process [49]. The importance of the bone microenvironment lies in its role in maintaining bone health. It can affect the balance between bone formation and resorption, which is crucial for maintaining bone strength and density.

Imbalances in this microenvironment can lead to various bone disorders and impair bone repair [50].

Both T1DM and T2DM compromised bone remodeling and bone turnover, which can affect the fracture healing process, including limited cell mobilization, impaired angiogenesis, and severe mineralization disorders [18,51]. Although the pathogenesis and treatment of T1DM and T2DM are different, their bone microenvironments ultimately undergo some similar abnormalities. Current studies on diabetic bone repair also do not strictly differentiate between the two types of DM. There are five main abnormal factors in the diabetic microenvironment: i) immune abnormalities, ii) inflammation and reactive oxygen species (ROS) accumulation, iii) vascular system damage, iv) insulin/insulin-like growth factor (IGF) deficiency, and v) hyperglycemia and production of glycation end-products (AGEs) (Fig. 1). Moreover, mutual promotion between these factors can produce a vicious cycle, resulting in multiple cells (osteoblasts, osteocytes, osteoclasts, adipocytes, endothelial cells) dysfunctions, which can impair bone repair and cause delayed union or non-union of fractures [9,52,53].

2.1. Immunological abnormalities

Diabetic hyperglycemia may lead to the dysfunction of immune cells, including neutrophils, macrophages, dendritic cells, innate lymphocytes, T cells, and B cells [54]. Immune cells are involved in the anabolism of acute inflammation during bone regeneration and in catabolism during bone resorption [46]. The effects of DM on bone immunology mainly involve the macrophages [55,56]. Studies have shown that macrophages play a vital role in regulating inflammation and the process of bone tissue healing. Macrophages in the microenvironment can be classified as the inflamed M1 type (classical activation) and M2 type (alternating activation) [57,58]. During bone tissue repair, M1-type macrophages are predominant in the early acute inflammatory phase, and can remove tissue fragments, secrete chemokines such as monocyte chemoattractant protein-1 (MCP-1), C-X-C Motif Chemokine Ligand 8 (CXCL8), and stromal cell-derived factor-1 (SDF-1), and ensure recruitment of mesenchymal stem cells, osteoprogenitor cells, and vascular precursor cells. M2-type macrophages predominate during the repair stage and secrete growth factors such as Interleukin-10 (IL-10), BMP-2, and arginase-1 to support bone tissue repair [59,60]. In the diabetic microenvironment, abnormal retention in the pro-inflammatory phase is accompanied by continuous activation of M1 macrophages; the phenotypic switch from M1 to M2 does not occur in time [61]. Thus, the ratio of M1/M2 macrophages is significantly dysregulated [62]. Studies demonstrating the importance of epigenetic regulation in macrophage polarization, including histone modifications, DNA modifications, and microRNAs, are associated with influencing macrophage phenotype in DM [63,64]. Increased levels of pro-inflammatory cytokines secreted by M1 macrophages can inhibit differentiation of bone marrow-derived mesenchymal stem cells (BMSCs) and osteoblasts by affecting multiple signaling pathways, promoting their apoptosis and osteoclast differentiation; the repair effect of M2 macrophages is weakened, which can ultimately lead to failed bone repair [58,65–67].

Neutrophils are involved in the early stages of bone repair. Following tissue injury, neutrophils are recruited to the site of phagocytosis. In a mouse model of bone fracture, neutrophil depletion resulted in impaired bone healing [68]. Activated neutrophils can express the membrane protein RANKL and activate osteoclast function through cell contact [69]. Studies have shown that the migration, phagocytosis, and microbicidal activity of neutrophils are impaired in patients with T2DM, resulting in an increased risk of infection [70]. Additionally, formation of extracellular traps (NETs) is increased in patients with DM, which can lead to vascular injury and impaired wound healing [71]. Thom et al. demonstrated that culturing neutrophils in a high-glucose medium can lead to cytoskeletal and membrane instability, which can enhance production of neutrophil microparticles and activation of inflammasomes [72]. Dendritic cells are absent in bone tissue under physiological conditions but can indirectly affect inflammation-related bone loss by activating regulatory T cell function, whereas dendritic cells are reduced in patients with T1DM and T2DM [73]. The regulatory effect of T cells on bone regeneration is primarily related to their subsets, cytokines, and environmental factors. B cells regulate bone regeneration by secreting osteoprotegerin (OPG) [46]. Dysfunction of B and T cells in DM has been demonstrated in numerous studies [74,75].

2.2. Inflammation and ROS accumulation

The diabetic microenvironment is usually accompanied by an increase in inflammatory factors such as TNF-α, IL-1β, and interleukin-6 (IL-6) [76,77]. The chronic inflammation is caused by multiple factors, including expansion of pro-inflammatory adipocytes in bone, Inhibition of efferocytosis, inflammatory polarized macrophages, the senescence-associated secretory phenotype of osteocytes, and hyperglycemia [16,78,79]. Alblowi et al. reported increased TNF-α and IL-1β in diabetic animals with periodontitis [80]. TNF-α and its receptor family members constitute the main initiators for apoptosis. In diabetic mice, TNF-α inhibitors reduced chondrocyte apoptosis [81]. Studies have shown that TNF-α-induced chondrocyte apoptosis is mediated by FoxO1 [82]. Moreover, TNF-α can also activate the transcription factor NF-κB to promote apoptosis [83]. A long-term increase in TNF-α is harmful to glucose metabolism, and can increase the release of fatty acids, inhibiting the insulin signaling transduction [84]. IL-6 is a cytokine mainly secreted by visceral adipose tissue; its plasma concentration is significantly increased in obese and diabetic patients [85]. IL-6 can phosphorylate serine residues in the insulin receptor substrate (IRS) and interrupt the transduction of insulin signaling [86]. White blood cells, adipokines, and C-reactive proteins may also increase in DM and negatively affect bone metabolism [87–89].

Moreover, downregulation of growth factors such as platelet-derived growth factor (PDGF), IGF-1, and epidermal growth factor (EGF) is observed in hyperinflammation, leading to osteogenic damage [90–93]. These factors play essential roles in the repair of vessel–bone coupling. Wieczór et al. reported a decrease in VEGF-A levels in diabetic patients [94]. High glucose levels can also destabilize the expression of hypoxia-inducible factor 1 (HIF-1), resulting in the loss of cellular response to hypoxia and dysfunction of multiple organs [95]. Streptozotocin (STZ)-induced diabetic mice showed impaired expression of platelet-derived growth factor B chain homodimer (PDGF-BB) [96]. It was recently discovered that SDF-1 levels are significantly decreased in STZ-induced diabetic rats [97].

DM can also enhance ROS accumulation, which leads to oxidative stress, impaired mitochondrial function, and suppression of osteoblast functions, affecting diabetic fracture healing [98]. Increased production of ROS is associated with hyperactivation of multiple molecular pathways resulting from hyperglycemia, including the mitochondrial pathway, polyol pathway, protein kinase C (PKC) pathway, hexosamine pathway, in addition to AGE formation and increased production of angiotensin II [99–101]. Among these, mitochondria are the primary source for ROS. Hyperglycemia can lead to excessive ROS production by mitochondria through excessive oxygen consumption and increased redox potential [53,100]. ROS derived from other pathways are mainly associated with abnormal activation of NADPH oxidase [99]. Elevated ROS levels can directly suppress osteogenic differentiation through the P13K/AKT signaling pathway [102,103]. In addition, ROS can lead to decreased expression of insulin genes, insulin secretion, and insulin resistance over time, which can damage osteogenic function. Moreover, accumulation of inflammatory factors and ROS can ultimately lead to impaired bone formation through induction of RANKL expression [104,105], activation of osteoclastogenesis, and suppression of osteoblast functions [106–108].

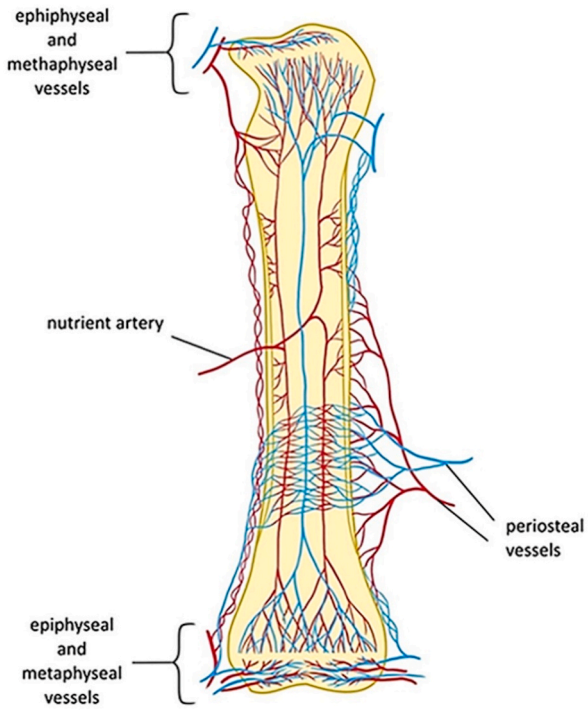

Fig. 2. Illustration of the vascular supplying system of long bones. Arteries/arterioles are marked in red and veins/venules in blue. Reproduced from Ref. [110] with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.3. Damages to vascular system

Bones are highly vascularized and receive 10–15 % of the resting cardiac output [29]. The vascular system provides essential oxygen, nutrients, and minerals to bone microenvironment [109]. An illustration of the vascular supplying system of long bones is shown in Fig. 2 [110]. Vascular regeneration plays a crucial role in bone development, regeneration and remodeling [110,111]. The two general mechanisms of bone tissue formation, intramembranous and endochondral ossification, are also regulated by the bone vasculature [112]. Macro- and micro-angiopathies are both observed in DM [113,114]. Progression of DM may lead to vasoconstriction and hamper blood supply to the bone, making uncouples bone formation and resorption and resulting in osteopenia and increased cortical porosity [16,115]. Generation of new blood vessels is reduced in diabetic fracture [116]. This may be attributed to AGE-induced vascular calcification, increased apoptosis of vascular smooth muscle cells, and impaired recruitment and migration of vascular endothelial precursor cells, which undoubtedly have a negative impact on bone repair [117–120].

2.4. Insulin/IGF deficiency

Studies have shown that both insulin and IGF induce osteogenesis and angiogenesis [121,122]. The binding of insulin to the insulin receptor (IR) on the surface of osteoblasts can lead to the phosphorylation of IR [123], specific activation of IRS and the downstream PI3–K/Akt pathway, and promotion of osteoblast proliferation and differentiation [124,125]. IRS of osteoblasts can also regulate the production of RANKL receptor activators and affect osteoclasts [126]. IGF, including IGF-1 and IGF-2, has a molecular structure similar to insulin and can bind to IR and insulin-like growth factor receptors (IGFR) to activate IRS and regulate the function of osteoblasts [127]. Endothelial cells can also express IR and IGFR. When these receptors bind to insulin and IGF-1, they promote the proliferation and differentiation of endothelial cells, which in turn promote angiogenesis [128,129]. IGF-1 combined with IGFR activates the ERK pathway to promote formation of vascular endothelial cells [130]. Moreover, the action of insulin on osteoblasts can enhance the expression of chemokine ligand 9 (Cxcl9), which is involved in VEGF signaling and regulates angiogenesis [131]. In DM, the relative deficiency of insulin and the diminished action of the IGF signaling axis can adversely affect the proliferation and differentiation of osteoblasts [122,132,133]. Compensatory insulin increase may occur during the progression of T2DM, and hyperinsulinemia can inhibit BMSC autophagy and osteogenic potential by up-regulating the transforming growth factor-β (TGF-β) [134]. The incretin effect is uniformly defective in T2DM, which reduces insulin secretion and contributes to hyperglycemia [135]. It also has additional effects on the diabetic bone system [136,137].

2.5. Hyperglycemia and production of glycation end-products

Hyperglycemia can directly affect the function of osteoblasts by

Table 1
Strategies for repair of diabetic bone defects.

Strategy	Approach	Type	Animal model	Type of regeneration	References
Immune regulation	1. Transformation of macrophages from M1 to M2; 2. Supplement macrophages	I, II	Sprague-Dawley rats	Calvarial bone defect, femoral defect, periodontal bone defects, tibial bone defect, mandibular periodontal fenestration defect	[159–163]
Inflammation inhibition	1. Chinese medicinal herbs 2. Anti-inflammatory drugs; 3. Gene therapy	I, II	Sprague-Dawley rats, Wistar rats, C57BL/6 mice	Tibial bone defect, maxillary alveolar bone defect, mandibular defect	[164–166]
Reduction of oxidative stress	1. Antioxidants; 2. Growth factors; 3. Biomaterials.	I, II	Sprague-Dawley rats, Wistar rats, New Zealand rabbits, C57BL/6 mice, Sheep	Calvarial bone defect, tibial bone defect, femoral defect, iliac bone defect, femoral/tibia bone defect	[167–171]
Angiogenesis promotion	1. Growth factors; 2. Exosomes; 3. Biomaterials	I, II	Sprague-Dawley rats, C57BL/6 mice, Wistar rats	Calvarial bone defect, tibial bone defect, periodontal defects, mandibular bone defect	[172–175]
Restoration of stem cell mobilization	1. Stimulating stem cell recruitment; 2. Supplementation of stem cells/products	I, II	Sprague-Dawley rats, Heterozygous Leprdb (db+/db−) mice, JAX mice	Calvarial bone defect, mandible bone defect, tibial defect model	[176–180]
Promotion of osteogenic differentiation	1. Cytokines and Hormones; 2. Genetic materials; 3. Drugs and small molecules; 4. Physical stimulation	I, II	Sprague-Dawley rats, Zucker Diabetic Fatty rats, Goto–Kakizaki rats, C57BL/6 mice, BALB/cByJ mice, New Zealand rabbits	Calvarial bone defect, femoral defect, tibial defect, metaphyseal tibia/radius defects, alveolar bone defect	[181–190]

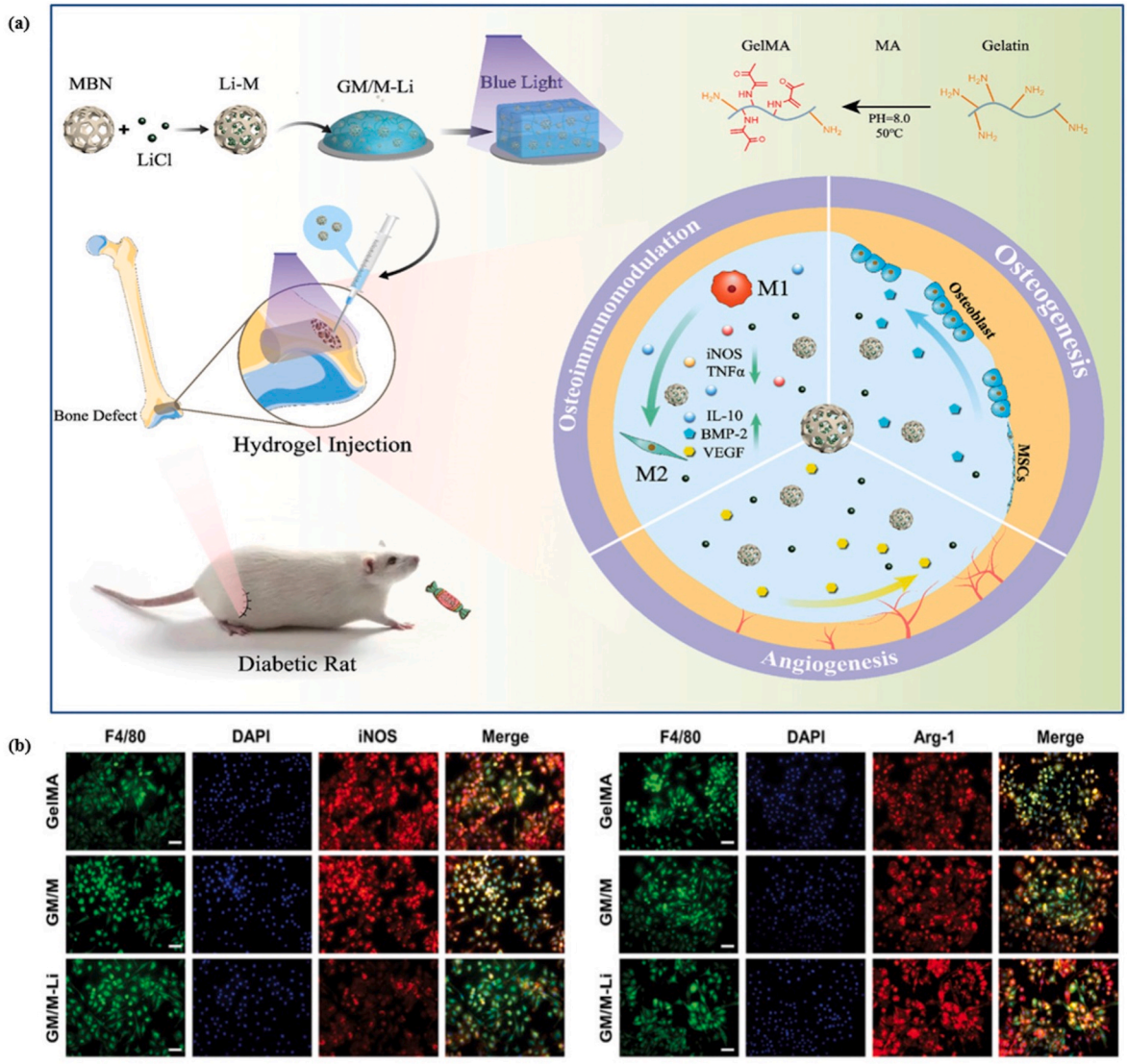

Fig. 3. Regulation of macrophage polarization in a high-glucose microenvironment using a lithium-modified bioglass-hydrogel: (a) Schematic illustration: With the release of Li+, GM/M − Li hydrogels triggered osteoimmunomodulation and drove the inflammatory microenvironment to a favorable osteogenic one, where macrophages were regulated from pro-inflammatory M1 to anti-inflammatory M2. (b) Immunofluorescence of RAW264.7 cells induced by LPS: red (M1 marker: iNOS and M2 marker: Arg-1), green (F4/80, a monoclonal antibody specifically directing against the mouse macrophage), and blue (DAPI). Reproduced from Ref. [160] with permission. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

increasing sclerostin production and inhibiting the pro-osteogenic Wnt signaling pathway, manifesting as decreased expression of osteoblast-related genes, including RUNX2, osteocalcin (OCN), and alkaline phosphatase (ALP), and reduced calcium absorption and mineralization ability of osteoblasts, which may impair bone formation [138–143]. High glucose can also stimulate the non-canonical Wnt/protein kinase C pathway and up-regulate peroxisome proliferator-activated receptor γ (PPARγ) to affect the differentiation of the BMSCs, resulting in weakened osteogenic differentiation and enhanced adipogenic differentiation [144–146]; increased lipogenesis in the bone marrow can impair bone health [147,148]. Studies have shown that hyperglycemia promotes osteoclast differentiation and bone resorption [149]. However, Hu et al. cultured rat bone marrow-derived osteoclasts in a 25 mM glucose solution and found that a high-glucose environment could inhibit differentiation of osteoclasts and suppress their degradation of the matrix [150]. Hyperglycemia can also stimulate production of ROS and enhance the expression of pro-inflammatory factors [151]. In addition, persistent hyperglycemia can increase the non-enzymatic glycosylation of proteins, resulting in production of AGEs [152], which can bind to AGE receptors (RAGE) on osteoblasts to inhibit synthesis of bone calcitonin and type 1 collagen. This may impair the mineralization function of osteoblasts, reducing osteogenesis [139,153–156]. AGEs are also a reason for increased production of pro-inflammatory factors and ROS [157].

3. Strategies for repair of diabetic bone defects

During the bone repair process, both cellular and non-cellular components of the microenvironment are involved. The pathological microenvironment of the DM includes multiple cellular and molecular abnormalities, leading to diabetic bone defects which are difficult to heal. Therefore, to regulate bone repair with the goal to maintain the microenvironmental balance may be an effective approach. Herein, we discuss previous experimental studies on diabetic bone defects and strategies to promote bone repair in DM, including i) immune regulation, ii) inflammation inhibition, iii) reduction of oxidative stress, iv) angiogenesis promotion, v) restoration of stem cell mobilization, and vi) promotion of osteogenic differentiation (Table 1). The pathogenesis and

treatment of T1DM and T2DM are different, as are the animal models used in experimental bone repair research, mainly the streptozotocin (STZ)-induced model for T1DM and the STZ plus high-fat diet model for T2DM [158]. However, the abnormal microenvironments that most studies have focused on are similar in the two types of DM. Therefore, current diabetic bone repair studies do not strictly distinguish between the two types of DM, and both animal models can be found in each strategy.

3.1. Immune regulation

Abnormalities in the immune microenvironment of diabetic patients significantly affect fracture repair. The pro-inflammatory M1 phase of macrophages may be prolonged during the diabetic bone healing process, and the transition to the anti-inflammatory state is inhibited. Based on existing osteoimmunology studies, promoting the transformation of macrophages from M1 to M2 or supplementing local macrophages to restore the MI/M2 ratio can regulate the local immune environment, which is a reliable method for promoting bone repair in DM [159–161]. Cytokines mediate cell–cell interactions, regulate immune response, and accelerate cell growth. The immunomodulation effects of interleukins have been utilized to promote the repair of diabetic bone defects [163,191]. Interleukin 4 (IL-4) transforms M1 macrophages into M2 macrophages. Hu et al. combined IL-4 with heparin and loaded IL-4 into injectable nanofibrous gelatin microspheres. Thus, IL-4 can be slowly released to accelerate the transformation of the M2 phenotype from M1 macrophages to promote bone regeneration in diabetic conditions [163]. Sun et al. loaded macrophages, BMSCs, and mesoporous silica particles with BMP-4 factors into a 3D-bioprinting scaffold to promote the repair of diabetic bone; BMP-4 regulated the local immune microenvironment by accelerating polarization of RAW264.7 to the M2 macrophages [191]. IL-10 is also commonly used to regulate the polarization of M2 macrophages. Li et al. designed a dual-network hydrogel that responded to blood glucose fluctuations, ROS, and matrix metalloproteinase 9 in a diabetic environment by carrying IL-10 and BMP-2. IL-10 regulates inflammation, and BMP-2 promotes osteogenic differentiation. Hydrogels can regulate cell function and promote diabetic bone defect repair [192]. In T1DM, adrenomedullin 2 (ADM2) promotes M2 polarization by inhibiting NF-PPAR B signaling through activation of PPARγ, inhibiting the impairment of BMSC function resulting from AGEs [162]. Bone immunomodulatory biomaterials can directly or indirectly regulate local immune responses and promote repair of diabetic bone defects [193]. In Lu's study, using gelatin methacryloyl as a template, a lithium-modified bioglass hydrogel for diabetic bone regeneration was developed that could sustain the release of ions to regulate macrophages in a high-glucose microenvironment. In vitro and *in vivo* results demonstrated better bone regeneration in the diabetic microenvironment (Fig. 3) [160]. A polyglutamic acid hydrogel compounded with magnesium oxide/hydroxyapatite nanocrystals (HA/MgO) with high mechanical strength was used to repair femoral defects in DM rats. HA/MgO can effectively reduce the invasion of pro-inflammatory macrophages, promote angiogenesis, and promote the proliferation and differentiation of BMSCs in diabetic bone defects [194]. Dai et al. used ferroelectric nanocomposite membranes to simulate the endogenous electrical environment of native bone tissue. Polarized BaTiO3/polyvinylidene fluoride nanocomposite membranes promoted repair of diabetic bone defects by attenuating the hyperglycemia-induced polarization of M1 macrophages and transitioning them into M2 macrophages, which in turn promoted the osteogenic effect of BMSC by inhibiting the expression of AKT2 and IRF5 in the P13K-AKT signaling pathway [55]. Studies have also shown that bioelectrical signals promote bone repair by regulating macrophages [55,161,195]. Dai et al. showed that the implantation of a polarized BaTiO3/P(VDF-TrFE) nanocomposite membrane suppressed macrophage-mediated inflammation and enhanced bone defect healing [55].

Other immune cells including neutrophils, dendritic cells, innate lymphocytes, T cells, and B cells may also directly or indirectly affect the repair process. Neutrophils contribute to local inflammation; high concentrations of neutrophils can lead to a decrease in the number of BMSCs and reduce their ALP activity [196]. Activated T cells participate in the regulation of vascular smooth muscle cells [197]. Although these cells can be affected to some extent in the diabetic microenvironment, few studies have explored the possibility of promoting bone repair in DM by intervening with these cells. Immunomodulation plays a crucial role in the repair of diabetic bones. Macrophages are the most common immunomodulatory targets. Promoting conversion of M1 cells to M2 alone is not a natural repair process; early pro-inflammatory response is beneficial for repair. Thus, studies should consider the timing of M1 and M2 transition. Immunomodulation is a multi-cellular process. Further studies are required on other immune cells affected by diabetes.

3.2. Inhibition of inflammation

Inhibition of inflammation can effectively maintain homeostasis of the microenvironment and facilitate the progress of bone defect repair [165,198]. Wang et al. used a glucose-sensitive TNFα-antibody-delivery system for long-term control of local inflammation and improvement of osteogenesis in diabetes. Enhanced osteogenesis-associated proteins promoted alveolar bone healing in a diabetic rat model [199]. Chinese medicinal herbs such as epigallocatechin-3-gallate, doxycycline, and proanthocyanidins have been used to treat diabetic bone defects due to their anti-inflammatory effects [166,200–202]. Moreover, the repairing effects of anti-inflammatory drugs have been assessed in diabetic bone defects. Yu et al. used salicylic acid-based polymers to continuously release salicylic acid at the defect area, which effectively inhibited local inflammation, reduced osteoclastogenesis, promoted osteoblast proliferation and differentiation, and promoted bone regeneration in diabetic rats [203]. Chondroitin sulfate has been shown to alleviate the limited bone repair caused by DM [204]. Incretin-related drugs promote bone repair in DM by inhibiting inflammation and regulating bone resorption and bone formation [205]. In addition, gene therapy has shown that use of lentiviral shRNA targeting the NLRP3 inflammasome can inhibit the expression of pro-inflammatory cytokines such as caspase-1 and IL-1, upregulate the expression of osteogenic genes such as RUNX-2 and osteocalcin, and ultimately promote the repair of alveolar bone defects in DM rats [167]. Although studies have shown that inhibiting inflammation can improve bone repair in diabetic waves, concentration-related complications are associated with the local use of active factors and/or small-molecule drugs, and the success rate of gene therapy is still unclear.

3.3. Reduction of oxidative stress

Oxidative stress is a cause of impaired bone repair in DM. relieving DM-induced oxidative stress is important to ensure normal bone repair. The use of antioxidants is an effective way to reduce oxidative stress; antioxidants currently applied in the repair of diabetic bone defects are mainly drugs and small molecules such as curcumin, α-lipoic acid, water fly thrips, and coumaric acid [168,169,206–209]. In a study by Li and Zhang, curcumin-loaded microspheres were incorporated into fish collagen nanohydroxyapatite scaffolds. The results showed that curcumin was continuously released from the scaffolds, inhibiting the overproduction of ROS and effectively promoting diabetic bone repair [210].

Growth factors such as erythropoietin and adiponectin can alleviate the inhibitory effects of bone repair in DM through anti-oxidation [170,211]. Biomaterials can regulate ROS homeostasis through surface modifications to promote bone formation with DM [212]. Chitosan is a natural macromolecule with antioxidant activity [213]. Li et al. used chitosan-coated porous titanium alloy implants to promote osseointegration through reactivation of the P13K/AKT pathway [171]. Ma et al. coated a composite chitosan/hydroxyapatite on a titanium alloy surface to promote titanium-bone integration with DM. Wang et al. developed a

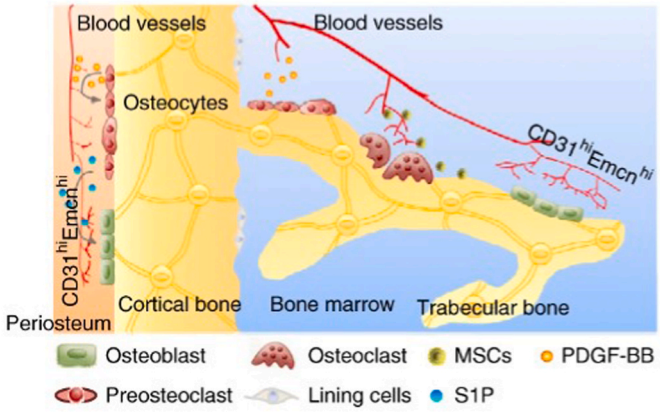

Fig. 4. Coupling process of vasculogenesis and angiogenesis. In periosteal bone modeling, preosteoclast secretion of PDGF-BB can induce formation of CD31hiEmcnhi vessels and stimulates secretion of S1P to promote osteoblast differentiation. In trabecular bone, CD31hiEmcnhi vessels induced by preosteoclast secretion of PDGF-BB can improve the transport of nutrients, oxygen, minerals and metabolic wastes during bone remodeling. Reproduced from Ref. [215] with permission.

coating targeting mitochondria composed of polyetheretherketone moieties to enhance bone remodeling and osteointegration with DM by scavenging ROS in diabetic states [214].

3.4. Promotion of angiogenesis

As a coordinated process, bone regeneration involves the coupling of angiogenesis and osteogenesis (Fig. 4) [215,216]. Intramembranous and endochondral ossifications are regulated by the bone vasculature [112]. Re-establishment of bone vasculature is vital for diabetic bone defects, whether it promotes angiogenesis or recovers the inhibitory effect of DM on angiogenesis [172,217–219]. Various bioactive factors can be used to promote angiogenesis; this has become a reliable method that can be used in combination with pro-osteogenic differentiation factors. Wallner et al. used a collagen sponge loaded with angiogenic factors (VEGF) and fibroblast growth factor (FGF-9) to promote local revascularization of the defect, which accelerated osteogenic repair in the calvarial bones of T2DM rats [173]. Local addition of fibroblast growth factor (FGF-2) can also promote the repair of periodontal defects in DM by regulating local angiogenesis [174]. Kuchler et al. loaded angiogenic prolyl hydroxylase onto a bone substitute and observed a significant increase in neovascularization [220]. Platelet-rich plasma is rich in cytokines that can promote angiogenesis; FGF and VEGF applied in diabetic defects can promote diabetic bone repair by stimulating generation of new blood vessels [175,221]. Jing et al. used apical papilla-derived exosomes with an excellent capacity to facilitate angiogenesis and improve bone regeneration in diabetic rats [222]. Tao et al. developed a hyaluronic acid (HA)/poly-L-lysine (PLL) layer-by-layer (LbL) self-assembly coating on β-TCP (β-tricalcium phosphate) scaffolds to provide immobilization of modularized engineered small extracellular vesicles to facilitate bone defect regeneration with DM. Bioactive membranes are designed to overcome the limitations of bone tissue regeneration in diabetics by creating an angiogenesis-inductive microenvironment [223]. This strategy was effective in promoting the repair of diabetic bone defects by enhancing angiogenesis, promoting osteogenesis, and inhibiting osteoclast formation [164]. Bone repair is a continuous process. Although early intervention to promote angiogenesis is conducive to bone repair, the damage caused by continuous high glucose to blood vessels remains. Further studies are needed to verify whether the quality of newly formed bone is affected.

3.5. Restoration of stem cell mobilization

The pathological environment in DM may also affect stem cell recruitment. Restoring stem cell mobilization is an alternative intervention to promote diabetic bone regeneration [224,225], and can be accomplished by stimulating stem cell recruitment or exogenous supplementation of stem cells and/or their products [176]. Various bioactive factors and pharmacological methods have been used to restore stem cell mobilization. Yu et al. used adiponectin to promote the mobilization and recruitment of BMSCs for treatment of diabetic bone defects to regulate SDF-1 through Smad1/5/8-mediated signaling pathways [226]. Insulin also has a positive effect on stem cell mobilization, which may be attributed to its direct action on these cells and the improvement of blood glucose control [227]. Studies have shown that factors such as erythropoietin and granulocyte colony-stimulating factors can also affect the mobilization of diabetic BMSCs [228,229], though this has not yet been applied for treating diabetic bone defects. As demonstrated by research in other fields, statins, which can stimulate the mobilization of bone marrow-derived progenitor cells through the PI3–K/Akt/eNOS pathway, have also been used to treat diabetic bone defects [230–232]. Ganli et al. found that gelatin sponges loaded with simvastatin implanted into critical-sized skull defects promoted bone repair in diabetic rats [146]. Camacho-Alonso et al. used hydroxyapatite combined with simvastatin to promote the repair of mandibular bone defects in diabetic rats, which was attributed to the pharmacological effects of simvastatin on the recruitment of stem cells [177,233]. Other drugs, including valproic acid, cobalt chloride, deferoxamine mesylate, and Alpinia oxyphylla miq, can also accelerate stem cell mobilization, but have not yet been fully assessed [234].

Exogenous stem cell supplementation for diabetic bone defects primarily involves the use of BMSCs and adipose-derived stem cells (ADSCs). BMSCs are important cells for repairing bone defects. Camacho et al. have used bioceramics with BMSCs to improve bone regeneration in critical-sized defects in mandibular bones in healthy, diabetic, osteoporotic, and diabetic-osteoporotic rats [235]. Zhu et al. found that exosomes derived from normal stem cells could better promote osteogenic differentiation and angiogenesis than exosomes derived from DM, and proposed the use of normal stem cells and exosomes to promote the repair of bone defects in T1DM [236]. Wang et al. found that exosomes derived from BMSCs could accelerate the osteoblastogenesis of BMSCs in diabetic bone regeneration through the inhibition of plexin B1 expression, the receptor of Sema4D, and the plexin B1/RhoA/ROCK pathway [237]. Compared to BMSCs, ADSCs are more accessible to mesenchymal stem cells, promoting local angiogenesis and significantly increasing osteoblast proliferation and differentiation when applied to a mouse model of tibial defects with T2DM [179,238,239]. Xu et al. reported a satisfactory restorative effect in a T2DM skull defect model by loading the ADSC sheets into Bio-Oss® bone particles combined with local injection of Seam3A [180]. Liang et al. seeded ADSCs onto bovine bone and transplanted them into critically sized vertical calvarial defects in rats with DM. An obvious increase in new bone formation was observed in the ADSC/bovine bone scaffolds [179]. Wallner et al. isografted mouse adipose-derived stem cells (mASCs) (db-/db-) transfected with a green fluorescent protein vector into tibial defects and noted significantly increased neovascularization and bone formation in diabetic mice [238]. Compared with exogenous supplementation of stem cells or cell derivatives, which have problems of difficult maintenance and heavy workload, drug stimulation of stem cell homing seems to be a good choice. Effective and safe release of the drug is yet to be determined.

3.6. Promoting osteogenic differentiation

Formation of new bone is impaired in diabetic bone defects, associated with impaired osteogenic differentiation of BMSCs, limited secretion of the bone matrix by osteoblasts, and impaired mineralization function. Once the stem cells are recruited to the bone defect site, to

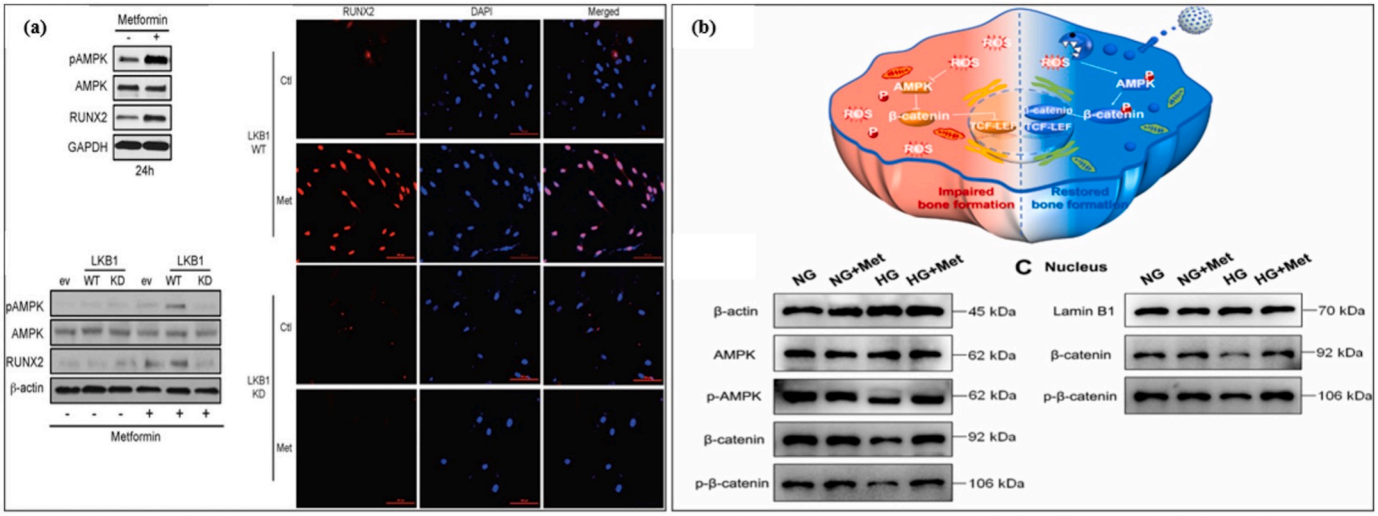

Fig. 5. Metformin promotes the MSC osteogenesis under HG conditions. (a) Metformin induces an osteogenic effect via LKB1/AMP-activated protein kinase (AMPK) signaling activation; (b) Metformin promotes rBMSC osteogenesis under HG conditions through the ROS/AMPK/β-catenin pathway. Reproduced from Refs. [264, 265] with permission.

enable the local microenvironment to promote stem cell differentiation toward osteogenesis may provide another strategy to promote the bone repair. Researchers have attempted to restore bone formation and attain better repair of diabetic bone defects by directly promoting osteoblastic differentiation and eliminating the inhibitory effect of DM on osteoblasts [181,217,240], mainly through growth factors, genetic materials, drugs and/or small molecules, and physical stimulation.

3.6.1. Cytokines and hormones

Growth factors are soluble signaling proteins secreted by cells that can induce specific biological activities. Growth factors can have different effects on bone repair at different stages. BMP is the most commonly used growth factor in bone tissue engineering and can be used alone or in combination. BMP-2 promotes the repair of bone defects by activating the Wnt signaling pathway [183]. *In vitro* and *in vivo* studies have shown that BMP-2 can promote healing of diabetic bone defects [182,183,241]. Increased plasma BMP-2 levels can lead to atherosclerosis and heterotopic ossification [242,243]. This has cautioned researchers regarding the dose and administration mode of BMP for diabetic bone defects. Treatment of diabetic rats with insulin or IGF-1 may enhance osteoblast proliferation, differentiation, and the bone matrix [184–186,244–246]. The role of parathyroid hormone in the regulation of bone formation has been demonstrated in many studies. Parathyroid hormones can partially reverse the detrimental effects of T2DM on bone mass, bone strength, and fracture healing in rats [187,247]. Thrombomodulin (TMD) is a transmembrane glycoprotein. Chen et al. showed that TMD2/3 could promote MG63 cell migration, proliferation, and mineralization *in vitro*, and improve the *in vivo* healing of injured calvaria in mice following local administeration. This beneficial effect is mediated via the fibroblast growth factor receptor (FGFR)/ERK signaling pathway [248]. Wang et al. found that melatonin encapsulated in a biodegradable poly coating on a polydopamine-modified titanium surface promoted osteogenesis and osteointegration in T1DM mice with tibial bone defects [249]. Other growth factors, including TGF-β [250], rhPDGF-BB [251], periostin [252], and semaphorin3B [253], have also been used to promote bone repair by enhancing BMSCs or osteoblastic differentiation in diabetic bone defects [248,254,255]. Use of biological factors in diabetic bone defects has shortcomings such as short half-life, uncontrollable release, large local dosage, and heterotopic ossification, which must be overcome by further improvement of drug carrier materials and growth factor recombination technology.

3.6.2. Genetic materials

Genetic materials in the form of DNA or RNA can provide an alternative for the delivery of growth factors that induce osteogenic differentiation by affecting transcriptional or post-transcriptional modifications. Chen et al. transfected the osteoblast-related gene *RUNX2* to overexpress in the BMSCs and showed that it could reduce the inhibitory effect of high glucose on osteoblast differentiation by regulating the PI3K/AKT/GSK3β/β-catenin pathway [188]. Khorsand et al. utilized two types of plasmid DNA encoding either BMP-2 or fibroblast growth factor (FGF-2) to transfect human BMSCs and demonstrated that the co-delivery of BMP-2 and FGF-2 could significantly improve bone regeneration in a diabetic rabbit model [256]. Diabetic BMSCs transfected with BMP-2 maintained their BMP-2 secretion for a long time and promoted bone regeneration through the canonical Wnt/β-catenin and Smad signaling pathways [257]. Inhibition or overexpression of specific ncRNAs can also promote osteogenic differentiation in diabetic bone defects [258–261]. As shown by Wang et al., miR-214–3p can inhibit osteogenic differentiation of BMSCs by targeting the 3′-UTR of β-catenin in DM; knockdown of miR-214–3p can ameliorate the inhibitory effect of high glucose on the BMSCs [261]. Cao et al. found that miR-29c-3p reduced bone loss in rats with diabetic osteoporosis [262]. As more genetic materials targeting osteogenesis have been discovered, genetic material-mediated repair of diabetic bone defects has become a feasible therapeutic option.

3.6.3. Drugs and small molecules

Some drugs and small molecules act through specific signaling pathways to promote bone repair. In response to BMSC dysfunction induced by a high-glucose environment, Sun et al. used morroniside to trigger Glo1 signaling to further inhibit the formation of AGEs and RAGE expression, which eliminated the adverse effect of DM on osteogenesis [263]. As an effective hypoglycemic agent, metformin activates AMPK, a crucial regulator of osteogenic differentiation (Fig. 5) [264,265]. Studies have demonstrated its beneficial effects on the repair of diabetic bone defects [264,266–269]. Molinuevo et al. found that administration of metformin *in vivo* and *in vitro* could increase alkaline phosphatase activity, type I collagen synthesis, osteocalcin expression, and extracellular calcium deposition in bone marrow progenitor cells [270]. Picke et al. used sulfated hyaluronic acid-coated scaffolds to repair bone defects in T2DM and found that sulfated hyaluronic acid could bind to osteopontin, which in turn could ameliorate the inhibitory effect of DM on Wnt signaling in osteoblasts [271]. Similarly, Hamann et al. found that

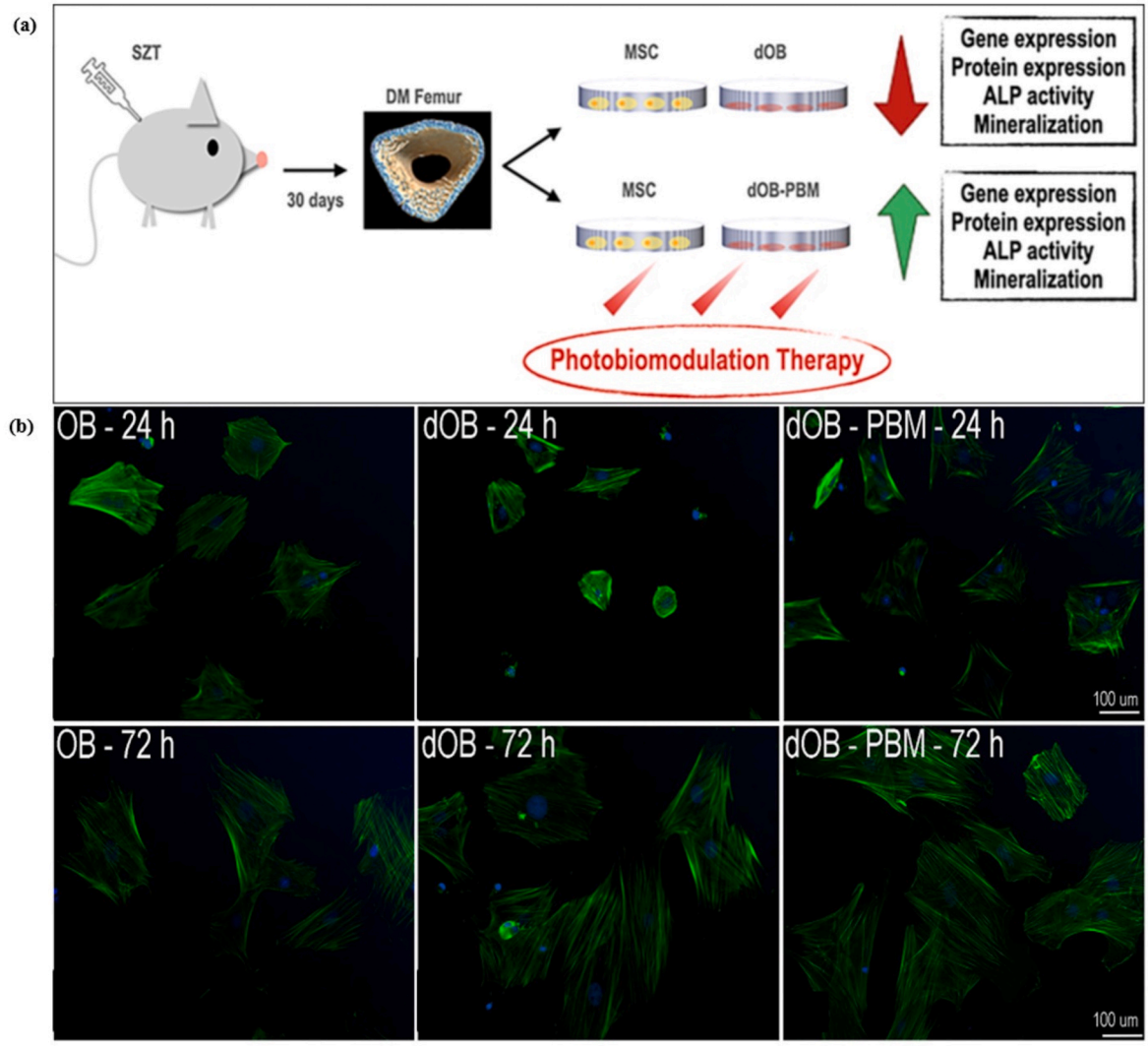

Fig. 6. Promoted osteoblastic differentiation of the BMSCs by PBMT. (a) Recovery of osteoblastic differentiation potential of mesenchymal stem cells derived from diabetic rats by PBMT; (b) Photomicrographs of osteoblasts derived from healthy rats (OB), streptozotocin-induced diabetic rats (dOB) and dOB exposed to PBMT for 24 h and 72 h. Reproduced from Ref. [281] with permission.

sclerostin-neutralizing antibody therapy could reverse the adverse effects of T2DM on bone mass and strength and promote the regeneration of skull defects in rats [272]. Wang et al. reported that AdipoRon ameliorated cell apoptosis and promoted formation of neocartilage to accelerate bone repair in diabetic mice [189]. Li et al. found that mangiferin attenuated the decrease in cell viability in diabetic conditions and improved the delayed healing of alveolar bone defects in diabetic rats [273].

3.6.4. Physical stimulation

As a highly mechanosensitive system, bones can adjust their metabolism in response to physical stimuli while maintaining their structure. Appropriate physical stimulation plays an important role in bone defect repair [274–277]. In a rabbit model for TIDM, stimulation with an exogenous pulsed electromagnetic field induced activation of the Wnt/β-catenin signaling pathway in the osteoblasts and promoted bone repair [274]. Jing et al. used whole-body vibration (WBV) therapy to enhance osseointegration in rabbits with T1DM [278]. In addition, it has been shown that photobiomodulation therapy (PBMT) can also promote osteoblast function during diabetic bone repair [190,279–281]. Lee et al. assessed the effect of PBMT at 660 nm on healing of bone defects in diabetic rats. Compared to non-irradiated rats, rats treated with PBMT showed higher osteogenic differentiation both *in vitro* and *in vivo* [282]. Bueno et al. demonstrated that PBMT can recover the morphology, viability, and expression of osteoblastic markers in BMSCs in DM conditions (Fig. 6) [281]. Although physical stimulation is non-invasive, has fewer side effects, and incurs lower costs, there are also some interference factors. The frequency, amplitude, dose, and subject posture may cause significant differences in the results that require further exploration.

4. Conclusions and future perspectives

Our understanding of the mechanisms by which DM affects the healing of bone fractures remains incomplete; interference with any link during the precisely coordinated cascade may hamper repair. Factors that may impair diabetic bone repair are mutually influenced. Most of the current treatments for diabetic bone defects are monotherapies, which may be insufficient to solve the multifactorial problem. Studies have shown that bone defect healing is more likely to be impaired in low-compensation diabetic metabolic states, which can be improved by strict control of diabetic metabolism [283,284]. Further studies aimed at promoting bone repair through regulation of metabolic abnormalities are warranted. As the diabetic bone microenvironment may vary with

the duration of DM, fluctuation of blood glucose, and type of DM, static treatment methods may have difficulty matching the dynamic changes in the local microenvironment. In addition, DM may also affect adequate healing at the stage of bone remodeling, which involves bone resorption by osteoclasts and bone formation by osteoblasts; however, studies in this area are rare. As DM is a common disease, its impact on human bone health should not be neglected. Further research is needed to determine the abnormalities at different stages of diabetic bone healing and how this differs between types of DM. It is important to fully consider the adverse effects of each factor and dynamically adjust the local microenvironment to accelerate bone repair in DM conditions.

Studies on the effects of DM have focused mainly on skin and soft tissues; its impact on bone repair is attracting increasing attention. DM leads to bone structural abnormalities that increase the risk of fracture, and also suppresses the process of bone repair. The factors include immune abnormalities, inflammation and ROS accumulation, vascular system damage, insulin/IGF deficiency, hyperglycemia, and the production of AGEs. These factors affect the normal functions of multiple cells and cytokines during diabetic bone regeneration. Current methods for promoting diabetic bone repair are mainly based on research using rodent models that simulate the diabetic environment, and although these approaches have shown promise, their efficacy is still limited. Therefore, it is necessary to study the impact of diabetic environment on the bone repair process in depth and develop more efficient therapeutic strategies and/or biomaterials to address the increasing demand for diabetic bone repair in clinical practice.

Declaration of competing interest

There are no conflicts to declare.

Data availability

Data will be made available on request.

Acknowledgment

This work was supported by the National Natural Science Foundation of China (32171351, 82202705), the “1.3.5” Project for Disciplines of Excellence, West China Hospital, Sichuan University (ZYJC18002, ZYPY20003 and ZYPY20004), Natural Science Foundation of Sichuan Province (2022NSFSC0717), Project of the Science and Technology Department of Sichuan Province (2023YFS0063, 2023NSFSC1738), the Frontiers Medical Center, Tianfu Jincheng Laboratory Foundation (TFJC2023010002).

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