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REVIEW

Osteoporosis in diabetes mellitus: Possible cellular and molecular mechanisms

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Abstract

Osteoporosis, a global age-related health problem in both male and female elderly, insidiously deteriorates the microstructure of bone, particularly at trabecular sites, such as vertebrae, ribs and hips, culminating in fragility fractures, pain and disability. Although osteoporosis is normally associated with senescence and estrogen deficiency, diabetes mellitus (DM), especially type 1 DM, also contributes to and/or aggravates bone loss in osteoporotic patients. This topic highlight article focuses on DM-induced osteoporosis and DM/osteoporosis comorbidity, covering alterations in bone metabolism as well as factors regulating bone growth under diabetic conditions including, insulin, insulin-like growth factor-1 and angiogenesis. Cellular and molecular mechanisms of DM-related bone loss are also discussed. This information provides a foundation for the better understanding of diabetic complications and for development of early screening and prevention of osteoporosis in diabetic patients.

Key words: Bone remodeling; Bone strength; Diabetes; Fragility fracture; Insulin; Osteoblast; Osteoclast; Osteopenia; Osteoporosis; Pregnancy

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NORMAL BONE REMODELING

Being a primary structural framework of the body, bone undergoes dynamic microstructural remodeling throughout life to accommodate mechanical stress and calcium demand[1]. Bone remodeling is a coupled process of bone resorption and formation, and requires coordination of all three types of bone cells, namely osteocytes, osteoblasts and osteoclasts[1,2]. Under mechanical stress, osteocytes act as mechanosensors to detect changes in the flow of bone fluid within bone canaliculi, and respond by transmitting signals to the osteoblasts via their syncytial processes. Osteoblasts later stimulate osteoclast differentiation and subsequent bone resorption. Normally, osteoblast-mediated bone formation takes place at the same site to fill up the resorption pit with new bone[1,2].

Osteoclastic bone resorption occurs in areas of structurally weak bone caused by mechanical stress or disuse. At the cellular and molecular level, osteoclast-mediated bone resorption commences by osteoblasts initiating proliferation of osteoclast precursors and their differentiation into mature osteoclasts by secreting a cytokine called macrophage colony stimulating factor (MCSF)[2,3]. Osteoblasts also secrete the key mediator for osteoclastogenesis, receptor activator of nuclear factor-κB (RANK) ligand (RANKL), which binds to its receptor (RANK) on the plasma membrane of osteoclast precursors, thereby stimulating differentiation of pre-osteoclasts into mature osteoclasts. RANKL and MCSF are differentially upregulated by various osteoclastogenic factors, such as parathyroid hormone (PTH), PTH-related peptide and prolactin[2,4,5]. Moreover, to counterbalance RANKL action, osteoblasts synthesize and secrete osteoprotegerin (OPG), a soluble decoy receptor capable of inhibiting RANK-RANKL interaction and osteoclastogenesis[2,6]. In the presence of activated osteoclasts, bone resorption begins with dissolution of inorganic and organic components by hydrochloric acid, cathepsin K and lysosomal protease from osteoclasts[2,7].

Following bone resorption, osteoblast-mediated bone formation takes place to fill the resorption pits with newly mineralized bone. The type Ⅰ collagen fibrils secreted by osteoblasts are arranged into the organic matrix osteoid, which is subsequently mineralized by calcium and phosphate in the presence of alkaline phosphatase, osteocalcin and osteopontin. Eventually, hydroxide ions are gradually added and mature hydroxyapatite crystals $[Ca_{10}(PO_4)_6(OH)_2]$ are formed[1]. Humoral factors, such as insulin-like growth factor (IGF)-1, insulin, bone morphogenetic proteins and OPG, serve as anabolic signals to promote bone formation[5,8-10]. Among these anabolic mediators, liver-derived IGF-1 is of particular interest since profound growth retardation, small bone size, low bone mineral density (BMD) and osteoporosis were reported in IGF-1 and IGF-1 receptor deficiencies[5,10,11]. Furthermore, insulin was found to directly induce osteogenic action by increasing cell proliferation, differentiation, alkaline phosphatase activity and expression of type Ⅰ collagen and osteocalcin in human osteoblast-like MG-63 cells[12]. Matrix mineralization was also found to be enhanced by IGF-1 and insulin[11,12].

OSTEOPOROSIS AND RISK FACTORS

Osteoporosis is a global health care problem characterized by a reduction in BMD with increased porosity and susceptibility to fractures[13]. It can be caused by acceleration of bone resorption and/or deceleration of bone formation. Clinically, osteoporosis most often results from a combination of postmenopausal estrogen deficiency and age-related bone loss[2,14]. Irreversible bone loss can result from an imbalance between osteoclast and osteoblast activities, i.e. enhanced bone resorption and/or suppressed bone formation, resulting in an uncoupling event that can prolong duration of the bone remodeling cycle[5,13]. Other risk factors for osteoporosis are abnormally high plasma PTH levels, advancing age, genetic background, cigarette smoking, alcohol consumption, physical inactivity and the chronic use of some medications, such as corticosteroids. Low physical activity as found in the sedentary lifestyle of elderly, paralyzed or immobilized patients is also associated with accelerated bone loss[13,15-17]. Furthermore, other medical conditions, particularly hyperparathyroidism and diabetes mellitus (DM) are also risk factors for osteoporotic bone loss[13,16,17].

Regardless of the etiology, osteoporosis is initiated by the uncoupling of bone resorption and bone formation[5,13,17]. At the molecular level, enhanced bone resorption and osteoporosis generally result, in part, from the overproduction of RANKL and other cytokines/mediators regulating osteoclast differentiation and function. These include cyclooxygenase (Cox)-2, prostaglandin (PG) E_2, tumor necrosis factor (TNF)-α, interleukin (IL)-1, IL-6 or IL-11[5,18,19], all of which lead to recruitment and differentiation of pre-osteoclasts[5,18,19]. Thus, the greater the increase in the levels of these osteoclastogenic cytokines, the faster the progression of bone loss.

DM-INDUCED OSTEOPOROSIS

DM is a group of pandemic debilitating metabolic diseases featuring chronic hyperglycemia which results from defective insulin secretion and/or insulin actions[20]. Such chronic hyperglycemia typically elicits dysfunction and failure of various organs, particularly the eyes (diabetic retinopathy and cataract), kidneys (diabetic nephropathy), nerves (diabetic neuropathy), heart (diabetic cardiomyopathy) and blood vessels (microangiopathy)[20]. In addition, DM has been found to be associated with metabolic bone diseases, osteoporosis and low-impact fractures, as well as other bone-related events including falls in geriatric patients[15,21]. Indeed, DM not only aggravates osteopenia (T-scores between -1 and -2.5, as determined by dual energy X-ray absorptiometry; DXA) and osteoporosis (T-scores $\leqslant$ -2.5), but is also one of the "causes" of both conditions. Nevertheless, bone deteriorations differ markedly between type 1 and type 2 DM and possibly stem from different cellular and molecular mechanisms[22-27].

Type 1 DM, also known as insulin-dependent DM, results from insulin insufficiency which leads to hyperglycemia in the young[20]. Besides the usual neurovascular complications, both male and female patients with type 1 DM manifest low bone mass at the hip, femoral neck and spine (Table 1), which may eventually lead to an increased incidence of bone fractures[22-25,28,29]. In contrast, data on skeletal abnormalities in type 2 DM, or non-insulin-dependent DM, appear conflicting, and the exact explanation of this is still unknown[26,27,30]. For example, by using DXA Yamaguchi and colleagues demonstrated that, of 187 males with type 2 DM, there was an increase in BMD at the femoral neck with low prevalence of vertebral fracture in diabetic men with metabolic syndromes[26]. Similarly, Petit and colleagues reported a higher BMD in elderly patients with type 2 DM when compared to age-matched non-DM volunteers[27]. In contrast, several

Table 1 Bone changes in patients with type 1 diabetes mellitus

References	Sample size	Age	Gender (F/M)	Major findings
Hamilton *et al*, 2009	102	20-71	52/50	Adult males with type 1 DM had lower BMD at hip, femoral neck and spine compared with age-matched controls ($P \leqslant 0.048$). No significant difference in BMD between female type 1 DM *vs* age-matched controls.
Mastrandrea *et al*, 2008	63	2-37	63/0	Type 1 DM women $\geqslant$ 20 years of age had a reduction in BMD at hip, femoral neck and whole body. No significant difference in BMD between type 1 DM women < 20 years of age *vs* age-matched controls.
Soto *et al*, 2010	45	15-39	45/0	Adolescent and adult women with type 1 DM had lower BMD at spine, femoral neck and whole body. No correlation between decreased BMD and sex steroid hormones.
Saha *et al*, 2009	48	12-18	26/22	Adolescent men and women with type 1 DM had lower BMC at the proximal femur. Men with type 1 DM had lower cortical bone mass and cross-sectional size than age-matched women with type 1 DM.
Lumachi *et al*, 2009	18	36-51	8/10	Type 1 DM patients had ~60% lower BMD compared with age-matched controls.
Heilman *et al*, 2009	30	5-19	11/19	Type 1 DM patients had lower total BMC and lumbar BMD. Type 1 DM men had less physical activity than age-matched male controls.

DM: diabetes mellitus; BMD: bone mineral density; BMC: bone mineral content; F: female; M: male.

other investigators reported a negative effect of type 2 DM on BMD. For instance, Yaturu and colleagues found a significantly low BMD of hip in type 2 DM patients when compared to age-matched normal subjects[30]. Moreover, an increased fracture risk at several sites, including spine and hip has been reported[31]. However, these fractures and falls could have resulted from visual impairment (from diabetic retinopathy and cataract), gait imbalance (from peripheral neuropathy) and overweight, all of which are common clinical features in type 2 DM. Peripheral neuropathy in type 2 DM may also lead to local destruction of bones around the weight-bearing joints (especially in the ankle and foot), known as Charcot osteoarthropathy, which can cause pain, fracture and joint deformity[21].

Type 1 DM featuring low circulating insulin and IGF-1 levels usually occurs in young children prior to peak bone mass attainment, whereas type 2 DM is common in adults who have already attained peak bone mass[32,33]. Thus, type 1 and 2 DM induce detrimental skeletal complications of different magnitudes. Specifically, in both genders, BMD of the proximal femur appears to be significantly lower in type 1 DM than in type 2 DM[34]. This difference in severity might be because type 1 DM patients lack insulin, which is an osteogenic factor capable of stimulating osteoblast proliferation and differentiation[12]. Alternatively, different the time course of type 1 and 2 DM might contribute to their different outcomes and prognosis. A recent population-based investigation on 1964 diabetic patients in Rochester, Minnesota, revealed that the incidence of hip fractures, one of the most common osteoporotic fractures, increased only over 10 years of follow-up, and was not correlated with obesity or prolonged DM treatments[35]. However, other factors, including advanced age, previous fracture and long-term corticosteroid use, might also predispose DM patients to osteoporosis and low-impact fracture, whereas physical activity/exercise and high body mass index are protective[35].

BONE LOSS IN DIABETIC MOTHERS

Pregnancy and lactation increase calcium demand for fetal skeletal development and milk production, respectively, and bone serves to supply calcium during these reproductive periods[36-38]. Although maternal BMD is not decreased during pregnancy in humans and rodents[36,37], our recent histomorphometric study in rats showed that osteoclastic bone resorption was indeed enhanced at trabecular sites from mid-pregnancy to late lactation[39]. Significant bone loss with a decrease in BMD was, therefore, observed in late lactation. Maternal BMD is usually restored within 12 mo post-weaning. However, some breastfeeding mothers manifest a long-term sequela known as pregnancy/lactation-induced osteoporosis, which features back pain, height loss and/or vertebral fracture[38,40].

Bone loss is, therefore, expected to be greater in mothers with previously diagnosed DM or even with gestational DM (GDM; which affects ~4% of all pregnant women without previous history of DM[41]). A recent densitometric study in GDM women revealed a reduction in vertebral BMD when compared with non-DM pregnant women[42]. Moreover, it has been reported that greater than normal bone loss is present in ~40% of GDM women within 3 mo postpartum[15]. Nevertheless, the effects of previously diagnosed DM on maternal bone resorption and the long-term sequelae remain to be elucidated.

POSSIBLE MECHANISMS OF DM-INDUCED OSTEOPOROSIS

Although several investigators have long addressed the question of how DM induces osteopenia and osteoporosis, the exact underlying mechanism is still elusive. However, it is widely accepted that hyperglycemia is a salient factor that has direct and indirect deleterious effects on osteoblast function and bone formation (Figure 1). At

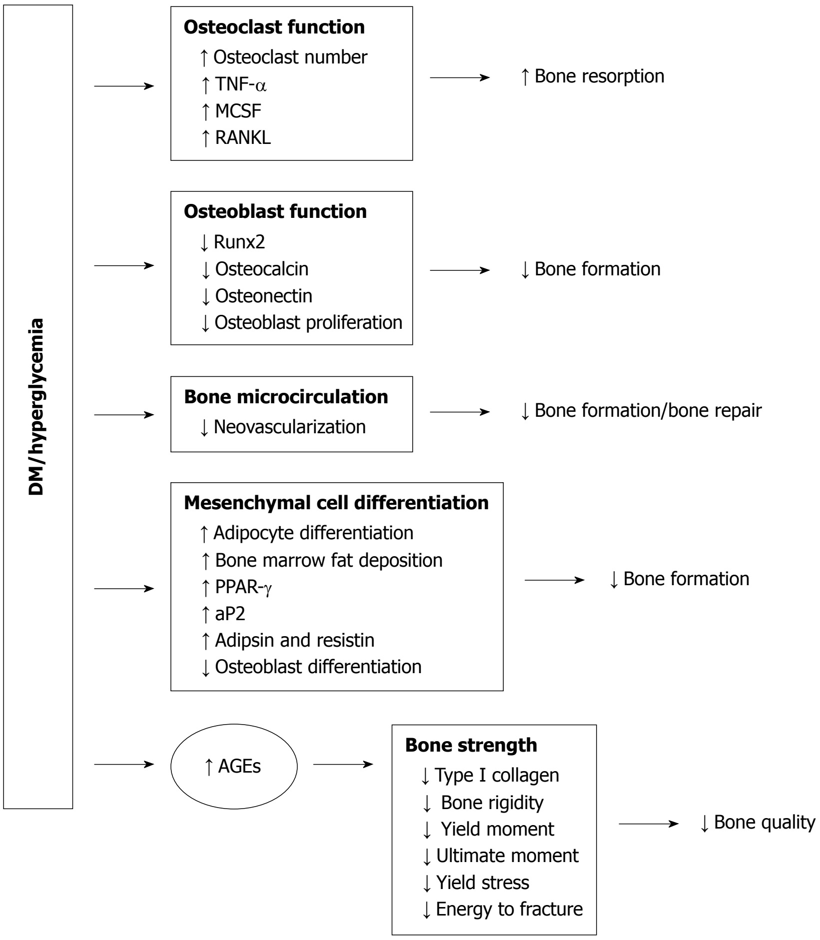

Figure 1 Possible deleterious effects of diabetes mellitus on bone metabolism and bone quality. Diabetes mellitus (DM) increases osteoclast function but decreases osteoblast function, thereby leading to accelerated bone loss, osteopenia and osteoporosis. DM/hyperglycemia induces production of macrophage colony stimulating factor (MCSF), tumor necrosis factor (TNF)-α and receptor activator of nuclear factor-κB ligand (RANKL), all of which are osteoblast-derived activators of osteoclast proliferation and differentiation. Moreover, DM/hyperglycemia suppresses osteoblast proliferation and function, in part, by decreasing *runt*-related transcription factor (Runx)-2, osteocalcin and osteopontin expressions. Adipogenic differentiation of mesenchymal stem cells is increased as indicated by the overexpression of adipocyte differentiation markers, including peroxisome proliferator-activated receptor (PPAR)-γ, adipocyte fatty acid binding protein (aP2), adipsin and resistin. A decrease in neovascularization may further aggravate bone loss. Bone quality is also reduced as a result of advanced glycation end products (AGE) production, which may eventually result in low-impact or fragility fractures.

the cellular level, a recent *in vitro* study in osteoblast-like MG63 cells demonstrated that high glucose concentrations markedly suppressed cell growth, mineralization, and expression of various osteoblast-related markers, including *runt*-related transcription factor-2 (Runx2), type Ⅰ collagen, osteocalcin and osteonectin, while stimulating the expression of adipogenic markers, such as peroxisome proliferator-activated receptor (PPAR)-γ, adipocyte fatty acid binding protein (aP2), resistin and adipsin[43,44]. Consistent with the *in vitro* findings, a histomorphometric analysis in streptozotocin-induced DM mice showed increases in osteoclast numbers and expression of osteoclastogenic mediators, including TNF-α, MCSF, RANKL and vascular endothelial growth factor (VEGF)-A[45]. Moreover, there were upregulations of PPAR-γ, aP2 and resistin mRNAs, as well as increases in lipid-dense adipocytes in the bone marrow of these streptozotocin-induced DM mice, whereas adipose tissues at other sites, such as liver and peripheral areas, were decreased[44]. It is thus plausible that, in addition to direct interference with osteoblast function and bone formation, DM also induces lipid accumulation in the marrow of long bones, thereby leading to the expansion of marrow cavity and thinning of cortical envelope. The osteoblast-to-adipocyte shift might also reduce the number of differentiated osteoblasts available for bone formation.

Other cell types, such as endothelial progenitor cells (EPCs) lining the blood vessels, are also affected by hyperglycemia. It was shown that the streptozotocin-induced DM mice exhibit a reduction in circulating bone marrow-derived EPCs when compared to non-DM control mice[46]. Such decreases in circulating EPCs could retard angiogenesis essential for the repair process at fracture sites. Moreover, as demonstrated by the three-point bending mechanical test, DM was found to be associated with a reduction in parameters, such as bone rigidity, yield moment, ultimate moment, yield stress and energy to fracture, all of which are related to bone strength or “bone quality”[47,48]. Regarding the possible mechanisms underlying impaired mechanical properties, several investigations have demonstrated an increase in advanced glycation end products (AGE) or non-enzymatic cross-links within collagen fibers, which, in turn, lead to deterioration in the structural and mechanical properties of bone, and eventually to a decrease in bone strength[47]. *In vivo* studies in both type 1 and type 2 DM rats have confirmed that an increase in AGE production is negatively correlated with BMD and bone strength[49,50].

In addition to hyperglycemia, dysautonomia and impaired leptin function may indirectly contribute to osteopenia and osteoporosis in DM since both the sympathetic nervous system and leptin are known to modulate bone remodeling in a complex interdependent manner (for review Reference[51]). The final outcome of sympathetic stimulation (bone loss *vs* bone gain) depends on the relative distribution of activated adrenergic receptor subtypes (β1, β2 or β3), expressed in osteoblasts[52]. β2-adrenergic receptor and leptin receptor knockout mice showed an increase in bone mass compared to normal mice, suggesting that β2 agonists and leptin are activators of bone resorption[53,54]. In contrast, osteoblast-like UMR106 cells exhibited the lower expression ratio of RANKL and OPG after exposure to β3-adrenergic agonist, suggesting a protective effect of β3-adrenergic receptor activation against bone resorption[52]. However, the possible direct link between the DM-induced autonomic neuropathy and impaired bone remodeling remains to be elucidated experimentally.

Several lines of evidence also suggest that DM-induced bone loss could be mediated, in part, by the humoral factors, kinins, which normally regulate blood circulation, inflammation and pain. Kinin dysfunctions could be responsible for several DM complications, such as hyperalgesia, cardiomyopathy and retinopathy[55-58]. In diabetic Akita mice with mutation in the insulin-2 gene, the lack of bradykinin receptor-1 (B1R) and receptor-2 (B2R) (i.e. B1R/B2R double knockout) induces profound diabetic complications, including massive albuminuria, glomerulosclerosis, reduction of nerve conduction velocity, and marked bone mineral loss[59]. It is thus possible that B1R/B2R and their related kinin signaling participate in the DM-induced bone loss.

PERSPECTIVES ON THE PREVENTION OF DM-INDUCED OSTEOPOROSIS

Since it is evident that most detrimental effects of DM on bone emanate from hyperglycemia and its consequences (e.g. AGE production and impaired vascularization), effective glycemic control and restoration of proper intraosseous blood supply should be of paramount importance for treatment and prevention of diabetic osteoporosis. The appropriate uses of antidiabetic agents should further help promote bone formation and/or prevent bone resorption. Recombinant insulin therapy might be a promising choice for diabetic intervention with its direct osteogenic effect through its receptors on osteoblasts. An *in vitro* study of insulin-treated bone marrow mesenchymal stem cells (BMSC; progenitors of both osteoblasts and adipocytes) cultured in high-glucose condition showed a significant increase in the activity of alkaline phosphatase, a representative of osteoblast differentiation, when compared to the control BMSC[60]. In addition, insulin also elicited synergistic effect when combined with supplementary 17β-estradiol by increasing type Ⅰ collagen production and bone mineralizing nodules *in vitro*[60]. Furthermore, insulin should indirectly benefit bone by reducing the negative effects of chronic hyperglycemia[61]. Besides lowering plasma glucose levels and promoting anabolic bone function, insulin also enhances production of proteoglycans, the components of the gel-like extracellular matrix of cartilage, in the articular cartilage of streptozotocin-induced DM mice, suggesting that insulin might also protect against osteoarthritis in overweighed DM patients[61].

Among the wide variety of antidiabetic drugs, some have been reported to be favourable to osteogenesis, through their direct actions on osteoblasts or BMSC, while reducing adipogenesis. For instance, a recent investigation in metformin-treated streptozotocin-induced DM rats showed positive effects of metformin on osteoblast differentiation and function, including upregulation of Runx2 and osteocalcin protein expression, as well as increases in alkaline phosphatase activity, type Ⅰ collagen synthesis and bone calcium accretion[62]. Similarly, glimepiride has been shown to stimulate proliferation and differentiation of primary rat osteoblasts *in vitro*[63]. In addition to synthetic drugs, certain herbal preparations, such as cinnamon bark extract, have been found to increase serum insulin levels and improve insulin sensitivity in adipose tissue by increasing serum adiponectin levels as well as upregulating PPAR-α and -γ mRNA expression[64], thereby inducing both antihyperglycemic and antihyperlipidemic actions. Thus, cinnamon extract probably helps reduce fat accumulation in bone marrow and indirectly facilitates bone formation[64].

In contrast, thiazolidinediones antidiabetic drugs, such as rosiglitazone, should be used with caution especially in postmenopausal DM patients since they may contribute to bone loss and fracture. Thiazolidinediones may decrease bone formation and BMD, while increasing bone resorption, as indicated by the reduced syntheses of alkaline phosphatase, osteocalcin, and procollagen type Ⅰ N-terminal propeptide[33,65]. However, further investigations are needed to better understand the effects of thiazolidinediones on bone remodeling in DM patients at the cellular and molecular level.

Alleviation of microangiopathy and restoration of microcirculation in diabetic bone may be additional benefits of insulin and antihyperglycemic drugs. Xu and coworkers (2009) demonstrated that injection of BMSC treated with pancreatic extract into streptozotocin-induced DM rats not only normalized plasma glucose and prevented apoptosis of islet cells, but also elevated production of VEGF, IGF-1 and basic fibroblast growth factor (bFGF), all of which are known to have anti-apoptotic and angiogenic effects[66]. A recent *in vivo* study in type 2 DM (db^-/db^-) mice with ischemic hind limbs showed that injection of epidermal growth factor (EGF)-treated BMSC into the affected hind limbs increased angiogenesis by over 90%[67]. Such angiogenesis was due to the fact that the injected BMSC differentiated into new microvessels (neovascularization), using intercellular adhesion molecule-1 and vascular cell adhesion protein-1 for adhesion and migration[67].Overall, it is possible that antidiabetic agents with angiogenic activity could be used to enhance blood flow to fracture sites, which may in turn accelerate bone healing, and might also prevent osteopenia/osteoporosis. Conversely, certain rheological drugs, such as pentoxifylline, which increase blood flow and osteoblast activity, might be promising as anti-osteoporotic agents in both DM and non-DM patients[68].

In addition to medications, alternative interventions often prescribed to DM patients, such as exercise/physical activity, may be indirectly useful since they are expected to mitigate microangiopathy in bone by increasing neovascularization and blood flow. *In vivo* investigation in swimming rats showed higher bone capillary vascularity compared with sedentary controls[69]. Such higher vasculogenesis following exercise has been postulated to result from an increase in circulating EPCs[70,71]. Adams and colleagues demonstrated the elevation of EPC levels after single-exercise stress in patients with coronary artery disease[70]. An increase in EPC level was accompanied by an elevation of plasma VEGF[70,71], a crucial growth factor for EPC proliferation, differentiation and migration[70,71]. Thus, certain physical activities/interventions, such as appropriate endurance exercise, should improve perfusion in bone and alleviate bone loss in DM patients. Nevertheless, in "high-risk" individuals, including DM patients with very low BMD, previous low-impact/non-traumatic fractures and/or chronic use of corticosteroids, specific treatments for osteoporosis are still necessary (for reviews regarding the treatments of osteoporosis in DM patients, please see Refrences [15,21]).

CONCLUSION

In addition to neurovascular, ocular and renal complications, osteopenia and osteoporosis are important debilitating problems in DM patients. Osteoporosis and several other DM complications (e.g. visual impairment and gait imbalance) increase the risk of falls, fragility and low-impact fractures. It is apparent that hyperglycemia in DM directly suppresses osteoblast-mediated bone formation, while conversely promoting osteoclast-mediated bone resorption, adipogenic differentiation of mesenchymal stem cells (also precursors of osteoblasts), and fat accumulation in the marrow cavity, all of which deteriorate bone quality and strength and increase susceptibility to fracture. Therefore, an effective glycemic control should be the hallmark of prevention and treatment of DM-induced osteoporosis. Lowering of plasma glucose by appropriate antidiabetic drugs, recombinant insulin, herbal medications and/or lifestyle interventions (e.g. exercise) should help promote osteoblast function, angiogenesis (neovascularization) and bone perfusion, and help reduce fat accumulation in the marrow cavity, all of which eventually lead to better bone health for the DM patients.

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