Free Radicals and Diabetic Bone Disorder

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Abstract

Diabetes mellitus is a pandemic metabolic disease characterized by hyperglycemia and induces alterations in bone and mineral metabolism. Diabetic bone disorder causes an increased frequency of bone fractures, delays the healing of fractures, and affects the quality of life. However, the mechanisms responsible for these complications have not been clearly identified. A major hypothesis is a diabetes-induced increase in oxidative stress because reactive oxygen species (ROS) increase under diabetic conditions and induce cellular dysfunction in a wide variety of cell types. Diabetes causes oxidative stress through six major mechanisms: (1) increased polyol pathway flux, (2) increased advanced glycation end-product (AGE) formation and receptor for AGE expression,

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(3) increased activation of protein kinase C isoforms, (4) mitochondrial overproduction of ROS, (5) increased activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and (6) reduced antioxidants. It is now widely accepted that ROS cause severe damage to DNA, proteins, and lipids. We have demonstrated that both streptozotocin-induced diabetic mice, an animal model of type 1 diabetes, and spontaneously diabetic Torii rats, an animal model of type 2 diabetes, have low-turnover osteopenia associated with increased oxidative stress and that markers of oxidative stress are inversely associated with histomorphometric parameters of bone formation. Growing evidence suggests that the increase in oxidative stress, in part, contributes to development of diabetic bone disorder. This review focuses on the impact of oxidative stress on the development of diabetic bone disorder.

Keywords
Advanced glycation end-product (AGE) • Diabetes mellitus • Hyperglycemia • Oxidative stress • Redox

Abbreviations

8-OHdG	8-hydroxydeoxyguanosine
AGE	Advanced glycation end product
BMD	Bone mineral density
NOD	Nonobese diabetic
OB	Osteoblast
RAGE	Receptor for AGE
ROS	Reactive oxygen species
SDT	Spontaneously diabetic Torii
STZ	Streptozotocin
TRX	Thioredoxin-1

Introduction

Diabetes mellitus is a pandemic metabolic disease characterized by hyperglycemia resulting from deficits in the secretion and/or actions of insulin. Diabetes is divided into type 1 and type 2. Type 1 diabetes has been mostly linked to genetics and production of autoantibodies that destroy pancreatic β-cells (Mehers and Gillespie 2008). Conversely, type 2 diabetes primarily results from insulin resistance and comprises >90 % of individuals diagnosed with diabetes (Wright et al. 2006). Both types of diabetes cause many complications including nephropathy, neuropathy, retinopathy, macrovascular and microvascular disease, and alterations in bone and mineral metabolism (Räkel et al. 2008). Although diabetic bone disorder increases bone fractures (Bouillon 1991; Forsén et al. 1999), delays the healing of fractures (Cozen 1972; Herskind et al. 1992), and affects the quality of life, few optimal therapies are available for this disorder, and the mechanisms responsible for it have not been clearly identified (Hamada et al. 2009a). One of the major hypotheses to

Table 131.1 Bone mineral disorder in type 1 and type 2 diabetes

	Characteristics of disease	Age of onset	BMD	Fracture risk
Type 1	Insulin deficiency	Younger	Typically low	Increased
	Destruction of pancreatic β-cells by autoantibodies			
Type 2	Insulin resistance	Older	Usually normal or elevated	Increased
	Hyperinsulinemia			
	More than 90 % of individuals diagnosed with diabetes			

BMD bone mineral density

explain the onset of diabetic complications is a diabetes-induced increase in free radicals. Therefore, this review focuses on the impact of oxidative stress in the development of diabetic bone disorder.

Bone Mineral Disorder in Patients with Type 1 and Type 2 Diabetes

Patients with type 1 diabetes typically have reduced bone mineral density (BMD), whereas those with type 2 diabetes usually have normal or elevated BMD. A modest reduction in BMD is generally acknowledged as a characteristic of type 1 diabetes, primarily based on dual-energy x-ray absorptiometry measurements in children, adolescents, and middle-aged adults (Vestergaard 2007). In addition, results from the Nord-Trøndelag Health Survey from Norway showed a significant increase in hip fracture rates among female patients with type 1 diabetes (relative risk 6.9, 95 % confidence interval 2.2–21.6) compared with those among nondiabetic female patients (Forsén et al. 1999). Conversely, conflicting reports exist about BMD among patients with type 2 diabetes. Although hyperglycemia is not closely associated with lower bone mass in patients with type 2 diabetes (Schwartz et al. 2001), clinical evidence and animal models provide evidence that given the same bone density, diabetic bones are more fragile than nondiabetic ones. The characteristics of bone mineral disorder in type 1 and type 2 diabetes are summarized in Table 131.1.

Because bone strength reflects not only BMD but also bone quality, bone turnover, an important bone quality factor, must also be considered when evaluating bone disorder. Although most studies assessing bone turnover in patients with diabetes have included only a small number of patients, studies in patients with type 1 diabetes have generally shown low bone turnover (Bouillon 1991). Similarly, some studies in patients with type 2 diabetes have also suggested low bone turnover in this disease (Carnevale et al. 2004). Histomorphometry is necessary to accurately evaluate bone turnover. However, histomorphometry is rarely performed in humans because it requires a bone biopsy, which is invasive. Therefore, animal studies are needed.

Diabetic Bone Disorder in Animal Models

Some animal models of type 1 diabetes include streptozotocin (STZ)-induced diabetic mice (STZ mice) and rats, nonobese diabetic (NOD) mice, and spontaneously diabetic BB/OK rats. STZ and NOD mice exhibit low-turnover osteopenia because of decreased activities, low numbers of osteoblasts and osteoclasts, low osteoid surface percentage, and decreased mineral apposition rate (Hamada et al. 2007; Botolin and McCabe 2007). Poor bone formation is associated with histological evidence of osteoporosis and decreased bone strength in spontaneously diabetic BB/OK rats (Verhaeghe et al. 1990).

In the case of type 2 diabetes, some animal models such as *db*/*db* mice, *ob*/*ob* mice, Zucker diabetic fatty rats, WBN/Kob rats, and spontaneously diabetic Torii (SDT) rats are available. *db*/*db* mice exhibit osteopenia with decreased mineralization (Lorentzon et al. 1986). The Zucker diabetic fatty rat, which is an inbred model with a leptin receptor defect, also exhibits diabetic osteopenia (Shibata et al. 2000). WBN/Kob rats simultaneously exhibit decreased bone strength and BMD with the development of diabetes (Igarashi et al. 1994), and the increased bone fragility of these rats is closely associated with advanced glycation end-product (AGE) accumulation in bone collagen (Saito et al. 2006). The SDT rat is a newly established type 2 diabetic model derived by inbreeding from an outbred colony of Sprague–Dawley rats (Shinohara et al. 2000). The pathology of diabetes in SDT rats resembles that of common Asian type 2 diabetes without obesity. SDT rats have reduced BMD and bone strength and low bone turnover (Fujii et al. 2008). In summary, bone histology studies indicate that decreased bone formation is a critical mechanism for the reduction of bone mass in diabetes.

The Possible Mechanism of Diabetic Bone Disorder

Many human and experimental studies, including our own reports on diabetes mellitus complications (Hamada et al. 2007; Fujii et al. 2008), have demonstrated extensive alterations in bone and mineral metabolism. However, the mechanisms responsible for these alterations have not been clearly identified. Many disorders associated with diabetes, such as hyperglycemia, body weight loss, AGE formation, and oxidative stress, are involved in the pathogenesis of diabetic bone disorder.

AGE accumulation in bone is a possible reason for reduced bone strength independent of BMD, although this hypothesis is controversial. Protein glycation is a common posttranslational protein modification induced by the spontaneous condensation of glucose and metabolic intermediates (e.g., triose phosphate, glyoxal, and methylglyoxal) with free amino groups containing lysine or arginine residues. This process leads to irreversible AGE formation from an array of precursor molecules (Thorpe and Baynes 2003), which have significant pathogenic effects on cells and tissues.

Recent experimental and clinical studies have reported the role of AGEs in bone metabolism. AGEs promote osteoblast (OB) apoptosis, thereby contributing to

deficient bone formation (Thorpe and Baynes 2003). AGEs also increase osteoclast-induced bone resorption (Alikhani et al. 2007). In addition, AGEs are specifically recognized by receptor for AGE (RAGE). AGE–RAGE interactions activate cytokines in RAGE-bearing cells, which contribute to alteration of bone healing and bone turnover (Santana et al. 2003). Conversely, we demonstrated that RAGE does not play an important role in diabetic bone disorder using RAGE null mice (Hamada et al. 2010).

In clinical studies, AGEs in cadaver or biopsy specimens were consistent with experimental observations, exhibiting higher pentosidine levels in bones from patients with fractures and a positive association between bone strength and skeletal pentosidine content (Saito and Marumo 2010; Viguet-Carrin et al. 2006; Vashishth et al. 2001). Other studies have demonstrated that serum and urine pentosidine levels in patients with type 2 diabetes are increased compared with those in age-matched controls and are positively associated with incident and prevalent fractures independent of BMD and other risk factors (Odetti et al. 2005; Yamamoto et al. 2008; Schwartz et al. 2009).

In addition, oxidative stress can be an influential candidate because it increases under diabetic conditions and induces cellular dysfunction in a wide variety of cell types. Moreover, reactive oxygen species (ROS) generated by high glucose concentrations are a causal link between hyperglycemia and other metabolic abnormalities during the development of many diabetic complications (Hamada et al. 2009a; Brownlee 2001).

The Relationship Between Oxidative Stress and Diabetes

Oxidative stress results from an imbalance between generation of oxygen-derived radicals and the antioxidant potential of the organism. Numerous studies have shown that diabetes mellitus is associated with increased formation of free radicals and decreased antioxidant defenses, including decreased cellular antioxidant levels and reduced activity of enzymes that metabolize free radicals. Because of these events, the redox balance in cells between free radical formation and protection is disturbed in both type 1 and type 2 diabetes. This leads to oxidative damage of components such as proteins, lipids, and DNA (Naziroğlu and Butterworth 2005). Diabetes causes oxidative stress through five major mechanisms: (1) increased polyol pathway flux, (2) increased AGE formation and RAGE expression, (3) increased activation of protein kinase C isoforms, (4) mitochondrial overproduction of ROS, (5) increased activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and (6) reduced antioxidants. Figure 131.1 summarizes the ROS sources in diabetes.

Increased Polyol Pathway Flux

The polyol pathway is based on a family of aldo-keto reductase enzymes that can use as substrates a wide variety of carbonyl compounds and reduce these by NADPH to their respective sugar alcohols (polyols). The main function of aldose

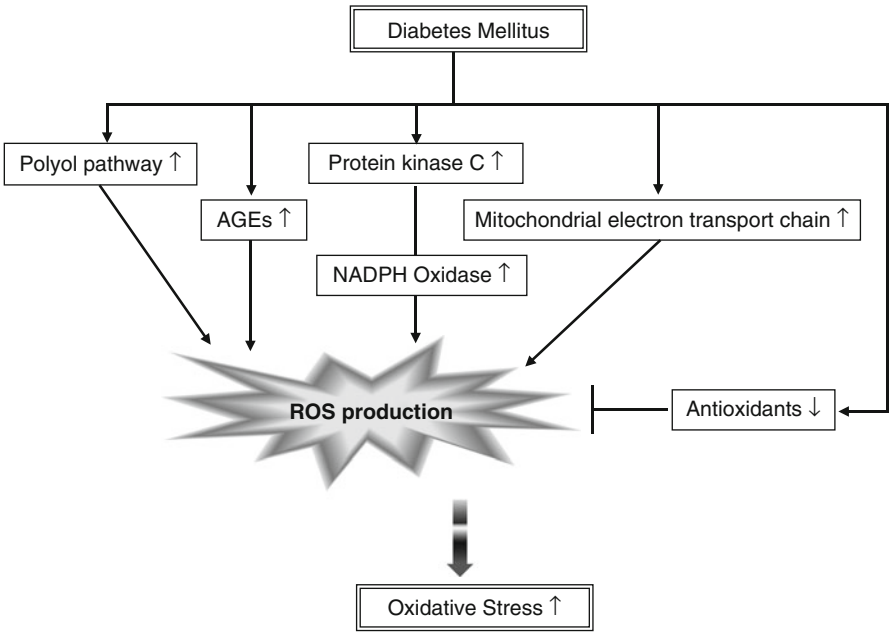

Fig. 131.1 Relationship between diabetes and oxidative stress. Reactive oxygen species (*ROS*) such as superoxide, the hydroxyl radical, hydrogen peroxide, and peroxynitrite arise from various mechanisms under diabetic conditions. These include the following: (1) increased polyol pathway flux, (2) increased advanced glycation end-product (AGE) formation and receptor for AGE (RAGE) expression, (3) increased activation of protein kinase C isoforms, (4) mitochondrial overproduction of ROS, (5) increased activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, and (6) reduced antioxidants

reductase is to reduce toxic aldehydes formed by ROS or other substrates to inactive alcohols. Under normal conditions, aldose reductase has a low affinity for glucose, with a very small percentage of total glucose converted to sorbitol by this pathway. Under diabetic conditions, there is an increase in the enzymatic activity and production of sorbitol, resulting in an overall decrease in NADPH. NADPH is a cofactor required to regenerate reduced glutathione (GSH), which is an important scavenger of ROS (Brownlee 2001). Taken together, increased glucose flux through the polyol pathway does not produce ROS directly but contributes to an overall redox imbalance in the cell that leads to oxidative stress.

Increased AGE Formations and RAGE Expression

AGEs are formed by the nonenzymatic reaction of glucose and other glycating compounds derived both from glucose and from increased fatty acid oxidation with proteins. AGEs are formed through the covalent binding of aldehyde or ketone groups of reducing sugars to free amino groups of proteins, creating a Schiff's base. The Schiff's base then spontaneously rearranges itself into an Amadori product, which is a more stable ketoamine. Amadori products can be directly converted to

AGEs or undergo autoxidation to form reactive carbonyl intermediates. Glucose can also undergo autoxidation to form reactive carbonyl intermediates. Glyoxal and methylglyoxal are the two main intermediates and then complete a complex series of chemical rearrangements to yield irreversible AGE structures (Sato et al. 2006). In diabetes, AGEs are accumulated in serum and various tissues. Accumulation of AGEs induces the production of ROS following bind to receptor for AGE (RAGE).

Increased Protein Kinase C Activation

PKCs are widely distributed in mammalian tissues. Hyperglycemia primarily activates the β- and δ-isoforms of PKC (Xia et al. 1994) and can contribute to the direct and indirect production of ROS via the activation of the DAG–PKC pathway (Brownlee 2001). The protein kinase C family consists of a number of different PKC isoforms, most of which are activated by the lipid second messenger DAG. Under diabetic conditions, there is an increase in the glycolytic intermediate dihydroxyacetone phosphate. Moreover, hyperglycemia can also activate PKC indirectly through ligation of AGE receptors and by the influx of the polyol pathway. In addition, activated PKC contributes directly to the oxidative stress by activating NF-κB and various membrane-associated NADPH oxidases, resulting in excessive ROS production (Brownlee 2001).

Mitochondrial Superoxide Production

Mitochondria are the principal endogenous source of superoxide. Under physiological conditions, NADH and pyruvate are generated during glycolysis. NADH donates electrons to the mitochondrial electron transport chain by two different shuttle systems, whereas pyruvate donates reducing equivalents by entering the TCA cycle and producing NADH and FADH. Both NADH and FADH provide the electrons that fuel electron transport chain and ATP production. Under diabetic conditions, the number of substrates entering the TCA cycle is greatly increased, and consequently the number of reducing equivalents donating electrons to the electron transport chain is also increased. Once the electron transport chain reaches a threshold voltage across the membrane, the electrons begin to back up at complex III. These electrons are then donated to molecular oxygen, which in turn results in an increase in mitochondrial superoxide production (Brownlee 2001).

Increased Activation of NADPH Oxidase

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase is well characterized in neutrophils (Henderson and Chappel 1996). Since the NADPH oxidase in neutrophils was discovered, the enzyme complex or components have been identified in various cells such as smooth muscle cells, endothelial cells, and mesangial cells. In recent years, the role of NADPH oxidase in diabetic complications has been receiving a lot of attention.

Antioxidants

Cells and tissues contain antioxidant defense mechanisms, which prevent the overproduction of ROS and maintain the redox balance of the cells or tissues.

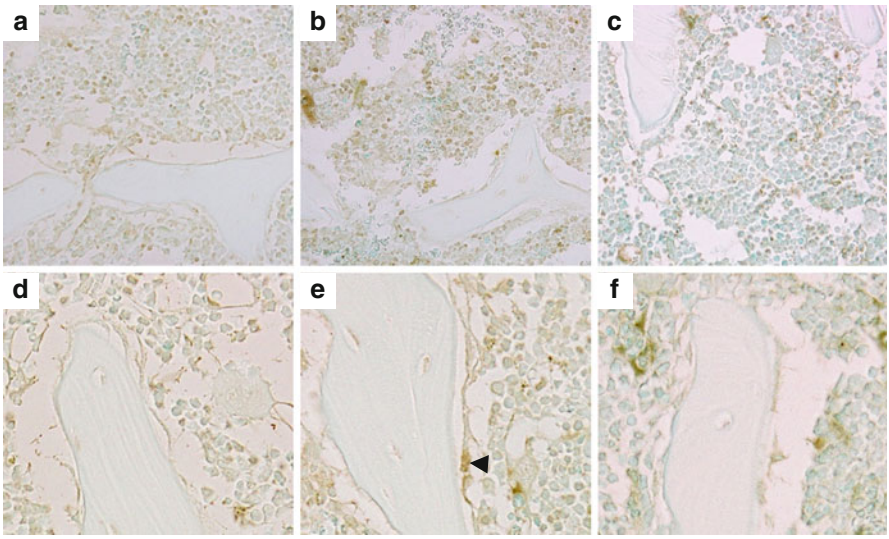

Fig. 131.2 Assessment of oxidative stress. Immunohistochemical staining of 8-hydroxydeoxyguanosine (*8-OHdG*) clearly intensified in bone tissues (**b**) including osteoblasts (**e**, *arrowhead*) of diabetic mice compared with that in control mice (**a**, **d**) and insulin-treated diabetic mice (**c**, **f**). **a**–**c**: 200× magnification. **d**–**f**: 400× magnification (Hamada et al. 2007)

It has been reported that diabetes is associated with reduced levels of antioxidants such as GSH, vitamin C, and vitamin E. In addition, glycation of antioxidative enzymes under diabetic conditions can impair cellular defense mechanisms, leading to the development of oxidative stress. Studies have reported that glycation of Cu–Zn superoxide dismutase (Kang 2003) and esterase (Sen et al. 2007) can inhibit their enzymatic activity. Moreover, it has shown that glycation of thioredoxin inhibits its antioxidant and organ-protective actions (Yuan et al. 2010).

Relationship Between Oxidative Stress and Diabetic Bone Disorder

Although few studies have examined the relationship between oxidative stress and diabetic bone disorder in vivo, their results have suggested that oxidative stress may be involved in the pathogenesis of diabetic bone disorder. Urinary excretion of 8-hydroxydeoxyguanosine, an oxidative DNA damage marker, in STZ mice, a type 1 diabetes model, is elevated compared with that in nondiabetic mice. Immunohistological studies have shown intensified immunostaining of a bone oxidative stress marker in osteoblasts (Fig. 131.2) (Hamada et al. 2007), and similar results were obtained in SDT rats, a type 2 diabetes model (Fujii et al. 2008). Thus, we demonstrated that both STZ mice and SDT rats have low-turnover osteopenia associated with increased oxidative stress.

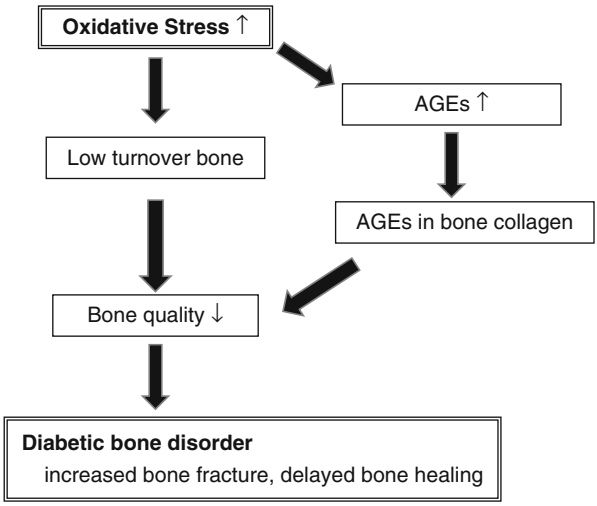

Fig. 131.3 Hypothesis of the influence of oxidative stress in diabetic bone disorder. Increased oxidative stress under diabetic conditions contributes to the development of diabetic bone disorder through low bone turnover and accumulation of advanced glycation end products (*AGEs*) in bone collagen

The finding that insulin treatment suppresses oxidative stress under diabetic conditions accompanied by recovery from diabetic osteopenia (Hamada et al. 2007; Fujii et al. 2008) suggests that oxidative stress plays an important role in diabetic bone disorder. In addition, oxidative stress markers in serum and bone tissue are inversely associated with histomorphometric parameters of bone formation (Hamada et al. 2007). Although our results have not fully clarified the main cause of diabetic osteopenia, they suggest that the increase in oxidative stress at least partly contributes to the development of diabetic osteopenia.

Moreover, we have reported the effect of thioredoxin-1 (TRX) overexpression, a major intracellular antioxidant, on the development of diabetic bone disorder using TRX transgenic mice (Hamada et al. 2009b). TRX overexpression does not affect either body weight or glycated hemoglobin levels. Conversely, TRX overexpression partially restores reduced BMD and prevents the suppressed bone formation observed in diabetic wild-type mice, accompanied by suppression of oxidative stress. In summary, these results demonstrate that increased oxidative stress under diabetic conditions contributes to the development of diabetic bone disorder. Our hypothesis of the influence of oxidative stress on diabetic bone disorder is shown in Fig. 131.3.

Conclusion

Our results suggest that oxidative stress plays an important pathophysiological role in the onset and development of diabetic bone disorder. In addition, because diabetic osteopenia is characterized by impaired osteoblast function, drugs should be prescribed to stimulate osteoblast function. For instance, one such class of drugs may be statins, which inhibit 3-hydroxy-3-methylglutaryl coenzyme A reductase and suppress

oxidative stress. A retrospective study reported that statins, primarily used to treat hyperlipidemia, increase femoral BMD in male patients with type 2 diabetes mellitus during 15 months of treatment (Chung et al. 2000), although contradictory findings have also been reported. Further studies linking diabetic bone disorder to oxidative stress and bone turnover should be performed to clarify the mechanism of diabetic bone disorder.

Further research will help to delineate the exact mechanisms by which diabetes affects bone and the most effective approaches to reduce diabetic bone disorder. In addition, other diabetic bone disorder such as Charcot arthropathy, that is one of the diabetic neuropathy and causes weakened and fractured bones, should be also paid attention.

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