AGEs and Bone Ageing in Diabetes Mellitus

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Abstract

Type 1 and type 2 Diabetes mellitus are associated with a decrease in bone quality that leads to an increase in low-stress fractures, a condition called diabetic osteopathy. A growing body of evidence strongly indicates that one of the main pathological mechanisms of diabetic osteopathy is an excess accumulation of advanced glycation end products (AGEs) on collagen of bone extracellular matrix. This accumulation increases exponentially during ageing, and is further increased in conditions of substrate carbonyl stress such as chronically uncompensated Diabetes mellitus. AGEs can form covalent crosslinks throughout collagen fibrils, progressively increasing bone fragility and decreasing bone post-yield strain and energy, fracture resistance and toughness. In addition, bone marrow mesenchymal cells, osteoblasts and osteoclasts express receptors such as RAGE that can bind AGEs with high affinity, altering normal cellular homeostasis. Binding of AGEs by RAGE diminishes the osteogenic potential of mesenchymal cells, inhibits osteoblastic bone-forming capacity and induces a long-term decrease in osteoclastic recruitment and bone-resorbing activity. Altogether, these cellular effects of AGEs depress bone turnover, and thus induce an even greater accumulation of AGEs. Recent in vivo, ex vivo and in vitro evidence indicates that anti-diabetic and anti-osteoporotic treatment may prevent the deleterious effects of AGEs on bone cells, providing alternative options for the pharmacological treatment of diabetic osteopathy.

Keywords: Diabetes mellitus; Advanced glycation end products; Osteoporosis; Receptor for AGEs; Metformin; Strontium ranelate; Alendronate

Introduction

Diabetes mellitus (DM) and osteoporosis are highly prevalent global diseases and represent an increasing burden for health care systems. There is a growing body of clinical and experimental evidence reporting the association of type 1 and type 2 DM with bone abnormalities, including osteoporosis, and/or an increased incidence of low-stress fractures, in what has been termed diabetic osteopathy [1]. Many adult patients with type 1 DM show mild osteopenia. Although their decrease in bone mineral density (BMD) is frequently around 10% [2] and this would be expected to double hip fracture risk [3], in actual fact the incidence of low-stress fractures is 7-12 times that of age-matched non-diabetic individuals [4,5]. On the other hand, people with type 2 DM usually have normal or moderately elevated BMD that would be expected to be associated with a reduced incidence of osteoporotic fractures, however they actually show an approximately 2-fold increase in hip, extremity and vertebral fractures [3-7]. These clinical observations have been put forward as evidence for a significant decrease in the material properties of bone tissue (i.e., bone quality) associated with both types of DM [8].

Although not completely elucidated, several mechanisms have been implicated in diabetic osteopathy, such as disturbed glucose metabolism, systemic and local (bone) low-grade inflammation, alterations in levels of growth factors and/or cytokines, increased oxidative stress and excess accumulation of advanced glycation endproducts (AGEs) in bone. A chronic pro-inflammatory state develops during the early stages of DM, suggesting a loss of defence mechanisms. Thus, inflammation-associated cytokines such as TNFα are elevated and can directly affect the growth and apoptosis of bone cells [9]. Increased levels of reactive oxygen species (ROS) are also observed in DM, and they have been shown to induce cellular alterations in various tissues. Several mechanisms can contribute to this Diabetes-induced oxidative stress, such as AGEs accumulation, increased polyol pathways, activation of protein kinase C isoforms, glucose oxidation and/or superoxide overproduction [10].

Chronic hyperglycaemia in uncompensated diabetes leads to an excessive non-enzymatic glycosylation of proteins with accumulation of AGEs, especially on long-lived proteins such as collagen present in the extracellular matrix of connective tissues (e.g., cartilage, bone, tendon, and skin) [11-13]. AGEs accumulated on extracellular matrix (ECM) proteins, as well as circulating AGEs, can interact with cell-surface AGE-specific receptors. Three classes of receptors for AGEs have been described: AGER1, which is involved in the clarification of AGEs and in the suppression of ROS and inflammation induced by AGEs; AGER2 or Galectin-3; and RAGE (receptor for AGEs) [14]. RAGE is a member of the immunoglobulin receptor superfamily and binds multiple ligands, including high mobility group box 1 protein (HMGB1), S100 proteins, certain variants of amyloid β protein, and AGEs-modified proteins and lipids. The binding of AGEs to RAGE generates intracellular ROS production and pro-inflammatoryary responses, up-regulation of RAGE and a cascade of signal transduction pathways, which in pancreatic beta cells leads to impaired insulin secretion and in peripheral insulin-dependent tissues can induce insulin resistance and micro-vascular complications. The binding of several ligands to RAGE on different cell types activates various signalling pathways including p38, JNK MAP kinases, Rho GTPases, PI3K, JAK/STAT, as well as NF-κB signalling which induces ROS generation and oxidative stress. Thus, activation of

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RAGE further increases ROS and inflammation in Diabetes and other chronic diseases [14].

In bone ECM, excess accumulation of AGEs occurs as a function of ageing and duration of Diabetes, and has been found to impair the mechanical properties of bone [15]. We and other researchers have demonstrated the expression of RAGE on bone cells, and found several deleterious effects of AGEs-RAGE interaction on the physiology of these cell types [16] (Figure 1). In addition, we have shown that anti-diabetic and anti-osteoporotic drugs can be useful to prevent in vivo, ex vivo and in vitro deleterious effects of AGEs on bone cells, and thus could provide useful options for the treatment of diabetic osteopathy [17-19].

**Enzymatic and Non-enzymatic Crosslinks in Bone Collagen**

The mechanical properties of bone are influenced by different factors, including the degree of mineralization of its individual basic structure units, micro-damage accumulation and formation of collagen cross-links [15]. In particular, collagen cross-links differ in their origin and localization, and have been classified in two categories: enzymatic and non-enzymatic.

Enzymatic cross-links are formed in a site-specific and closely controlled process by the combined action of the enzymes lysyl oxidase and lysyl hydroxylase. Initially these enzymes induce the formation of immature intra-fibrillar divalent keto-imines, which can then spontaneously form mature inter-fibrillar trivalent pyridinium cross-links [20]. Since a deficit in their enzymatic formation leads to a decrease in bone strength, these finely regulated divalent and trivalent cross-links are considered to have a beneficial effect on bone mechanical properties [21]. However, divalent cross-links are more prevalent in bone collagen and have thus been proposed to be more important in maintaining the mechanical properties of bone [15].

On the other hand, non-enzymatic intra- and inter-fibrillar cross-links are a sub-class of AGEs that include fluorescent structures such as pentosidine, and non-fluorescent moieties such as the more abundant glucosepane. These AGEs form intra- or inter-molecular covalent bonds in long-lived proteins such as collagen. Non-enzymatic cross-links can potentially be formed on any site in which there is an amino acid with appropriate side-chains (such as lysine or arginine), and their abundance relative to collagen depends on bone turnover (i.e. collagen half-life) and on the concentration over time of carbohydrate or lipid substrates that give rise to reactive carbonyl compounds (i.e., “carbonyl stress”). Thus, in clinical conditions with carbonyl stress such as DM, AGEs cross-links tend to accumulate at a far greater rate than in non-diabetic individuals [22]. As this accumulation is not controlled by cellular processes and is non-site-specific, it is generally believed to deteriorate the mechanical properties and biological functions of bone [23].

**Excess Formation of AGEs in Bone is a Hallmark of Diabetes and Ageing**

There is a growing body of evidence confirming the accumulation of...
AGEs in bone ECM and in the articular cartilage of ageing individuals. Almost 20 years ago, collagen non-enzymatic glycosylation and AGEs-associated fluorescence was shown to increase in the cortical bone of ageing and/or diabetic rats [24-26]. Several authors have also described a progressive accumulation of AGEs in human cortical and trabecular bone as a function of ageing. The levels of AGEs in aged human bone have been estimated both by measurement of collagen-associated fluorescence [27,28] and by determining levels of pentosidine in bone ECM as a marker of cross-linking AGEs [29-31]. Given that glucosepane has been shown to be the most prevalent AGE structure in skin ECM and glomerular basement membrane collagen [32], this non-enzymatic cross-link would also be expected to play an important role in the ageing of mineralized tissues. However, to date its accumulation in bone ECM has not yet been evaluated.

In the study reported by Odetti and co-workers, pentosidine was measured in femoral and knee cortical bone samples obtained from 104 non-diabetic individuals. The concentration of this AGEs collagen cross-link was found to increase exponentially with patient age, with a doubling time of around 20 years [29]. Interestingly, these authors also found a significant positive correlation between pentosidine levels in serum and in cortical bone.

In articular cartilage the turnover of ECM is very low. Articular cartilage is thus a candidate tissue for progressive accumulation of AGEs with ageing. This has been demonstrated for human individuals by different authors [33,34] and has been proposed to be one of the causal factors of age-associated osteoarthritis [35]. However, recent studies have found that in vivo AGEs formation on cartilage by intra-articular injection of ribose as a glycat ing agent was not able to enhance disease progression in an animal model of spontaneous knee osteoarthritis [36].

In theory, the effect of Diabetes on the accumulation of AGEs in bone should be even greater than that of physiological ageing. Surprisingly, this effect of Diabetes has been studied in animal models but not yet in humans. A significant increase in non-enzymatic glycosylation of bone collagen was found in alloxan- and streptozotocin-induced models of type 1 Diabetes, in both young and ageing rats [8,24-26]. The accumulation of AGEs in bone was found to correlate positively with the duration of Diabetes and with the level of hyperglycaemia. Recently, bone AGEs content has also been evaluated in partially insulin-deficient spontaneously diabetic rats [37]. These authors found that as Diabetes evolved over time there was a progressive increase in pentosidine (AGEs) cross-links of bone collagen, together with a significant decrease in divalent immature enzymatic cross-links, which coincided with impaired bone mechanical properties.

**Accumulation of AGEs on bone ECM impairs its mechanical properties**

Bone is a two-phase composite material with an organic phase of cross-linked type 1 collagen molecules, and an inorganic phase of hydroxyapatite nanocrystals. The mechanical properties of bone (toughness, strength and stiffness) are derived from its structural properties at multiple length scales in its microarchitecture, ranging from nanometric covalent and non-covalent molecular interactions to near-millimetric osteonal organization [28]. The mineral phase provides stiffness whereas collagen fibres provide tensile strength, ductility and toughness. Thus, changes in enzymatic and non-enzymatic collagen cross-links can affect bone mechanical properties.

In physiological conditions, formation of divalent (immature) enzymatic cross-links and their maturation to trivalent moieties is closely regulated by bone collagen turnover, by the expression of lysyl hydroxylases and lysyl oxidases, and possibly also by interaction with proteoglycans and collagen-binding proteins such as periostin [38], in order to optimize the mechanical properties of collagen fibres within a narrow beneficial range. Indeed, the ratio of divalent to trivalent enzymatic cross-links in bone is usually very close to 2:1. In pathological situations this balance can be altered, affecting post-yield properties of bone. For example, in partially insulin-deficient rats, before their spontaneous development of Diabetes (i.e., in their pre-diabetic phase) a decrease in bone strength was observed which was attributed to a 25% reduction in divalent cross-links, while trivalent cross-links and AGEs remained unchanged [37].

On the other hand, formation of AGEs cross-links on bone collagen fibres is a non-regulated and accumulative process, believed to be an important determinant of the age- and Diabetes-related deterioration of bone post-yield properties such as ductility and toughness. This has been demonstrated by the in vitro induction of AGEs in bone samples, and determination of changes in their mechanical properties as a consequence of glycation. Several studies have found that the in vitro formation of AGEs cross-links on bone collagen generates an increase in bone fragility and a decrease in bone post-yield strain, energy, fracture resistance and toughness, in this last case due to multiple changes in bone tissue micro-damage mechanisms that lead to an overall reduction in its ability to dissipate energy [27,39,40]. AGEs have been proposed to stiffen the collagen matrix so that its fibrils dissipate less energy, and this would allow for an increase in the formation and propagation of micro-damage throughout bone ECM [41]. In a recent study, in vitro AGEs formation on bovine bone samples on one hand induced inferior cortical post-yield strain and flexural toughness, but on the other hand correlated positively with measures of strain accommodation and energy absorption before failure [42]. These results suggest that the increase in AGEs cross-linking cannot completely explain the embrittlement of bone associated with ageing and Diabetes.

**In vivo**, many AGEs can be formed between lysine and arginine side-chains within the helical (non-telopeptide) domain of collagen. They would be expected to increase the resistance of collagen to enzymatic breakdown and thus its half-life, further promoting the accumulation of AGEs. This has been demonstrated in alloxan-induced type 1 Diabetes in rats [25]. In addition, Diabetes-induced AGEs accumulation in bone ECM has been associated with a decrease in femoral trabecular bone volume and cortical width [8,25], and with a decrease in long-bone stiffness, energy absorption, elastic modulus, maximum load and fatigue life [8,37].

Excess levels of AGEs in bone ECM have also been associated with incident and prevalent osteoporotic fractures in ageing non-diabetic human individuals [43,44]. In particular, Saito and co-workers have found an increase in pentosidine cross-links and a decrease in enzymatic cross-links in bone ECM from ageing patients with intra-capsular hip fracture versus gender- and age-matched post-mortem controls [44]. These results are similar to those found by the same authors in a rat model of spontaneous insulin-deficient Diabetes [37]. In combination, both studies suggest that absolute and/or relative changes in the levels of enzymatic and non-enzymatic collagen cross-links could be important determinants of bone quality in osteoporosis and diabetic osteopathy. Interestingly, in a recent study the accumulation of AGEs in skin was evaluated by non-invasive trans-cutaneous auto-fluorescence, and found to correlate negatively with calcaneal ultrasound osteosono
assessment index suggesting an inverse correlation between AGEs accumulation and bone strength [45]. Although both determinations used in this study were surrogate markers (for bone AGEs and mechanical properties respectively) the results suggest that this method could be useful for long-term prospective studies.

Turnover of AGEs-modified collagen generates low molecular weight AGEs-peptides, which localize to plasma prior to their renal excretion in urine [46]. Based on these considerations, different authors have evaluated the correlation between plasma or urine levels of AGEs moieties such as pentosidine and bone alterations such as osteoporosis, diabetic osteopathy and/or incident and prevalent fractures. As mentioned above, plasma pentosidine has been shown to have a significant linear correlation with cortical bone pentosidine [29]. In an interesting study by Hein and colleagues, serum pentosidine concentrations were found to be significantly higher in patients with osteoporosis than in age- and gender-matched controls [47]. However, the authors were only able to find a significantly positive correlation between serum pentosidine levels and participant age for the group of healthy controls, suggesting that osteoporosis could involve a more intensified generation of AGEs. Yamamoto and co-workers recently showed that in postmenopausal women with type 2 Diabetes, increased serum pentosidine was independently associated with prevalent vertebral fractures [48]. In a 5-year observational study with elderly non-diabetic women, prevalent and incident vertebral fractures were positively correlated with elevated levels of urinary pentosidine [49]. However, in another observational cohort study with elderly men and women with or without type 2 Diabetes, urine pentosidine levels were found to be independent predictors of clinical incident fractures and prevalent vertebral fractures in patients with type 2 Diabetes, but not in non-diabetic individuals [50].

As discussed above, the excess accumulation of AGEs on bone ECM that can be observed in ageing and Diabetes alters its mechanical properties and can thus predispose to increased fracture incidence. However, formation of AGEs such as pentosidine or glucosepane irreversibly alters the side-chains of arginine residues, and could thus also interfere with integrin-mediated interactions between RGD sequences of the ECM and bone cells. In order to prove this hypothesis, we demonstrated that the in vitro modification of type 1 collagen by AGEs decreased its free arginine residues, and thus significantly inhibited the attachment of osteoblasts via integrin receptors [51]. These effects, together with other specific actions of AGEs on bone-derived cells that will be described below, can further affect bone metabolism and contribute to osteoporosis, diabetic osteopathy and their clinical consequences including low-stress fractures.

### AGEs Modulate Bone Cell Metabolism via Specific Receptors

In many cell types, AGEs exert their deleterious actions via binding to specific receptors such as AGE-receptor 1, RAGE and Galectin-3 [14]. The presence of receptors for AGEs has also been demonstrated in bone cells. Osteoblasts express RAGE [52,53] and Galectin-3 [54], with receptor levels that depend on the stage of osteoblastic differentiation [55]. RAGE expression has also been shown in bone marrow mesenchymal/progenitor cells [56,57] and in osteoclasts [58].

After its discovery 20 years ago as a receptor for AGEs, RAGE has been found to recognize certain proteins with high affinity, and so AGEs are currently considered to be accidental ligands for this member of the immunoglobulin superfamily of receptors. A physiological ligand for RAGE is the chromatin protein high mobility group box 1 (HMGB1), which is considered an “alarmin”, i.e. an endogenous molecule released by dead and dying cells that acts as a signal for tissue damage indicating the need for repair. HMGB1 has been shown to be released by apoptotic osteoblasts and osteocytes in vitro, and thus could act as an osteocyte alarmin to mediate normal bone remodelling and/or pathological bone loss [59]. In addition, HMGB1 can trigger the differentiation of human bone marrow mesenchymal cells into an osteoblastic phenotype [60]. Another family of physiological ligands that have been described for RAGE are the S100 proteins. Through in vitro studies these proteins have been found to inhibit osteoblast mineralization and increase osteoclast recruitment and differentiation, via binding to RAGE [61]. A pathological ligand for RAGE appears to be the Swedish mutation of amyloid precursor protein (APPsw), associated with early-onset Alzheimer’s disease. APPsw has been found to promote osteoclast activation in vivo and in vitro via RAGE, providing a potential mechanism underlying the increased bone fracture rate in patients with Alzheimer’s disease [62]. Interestingly, in RAGE-knockout mice [10,63] an increase in bone mineral density and a decrease in osteoclast development and function have been observed.

The effect of AGEs on bone cells was first observed 20 years ago [64]. In this study de-mineralized bone particles were modified in vitro with AGEs prior to their sub-cutaneous implantation in rats, as a model for endochondral bone formation. The presence of AGEs induced a 90% decrease in osteoblastic differentiation determined by alkaline phosphatase activity (ALP), in vivo calcium uptake and histological analysis. These results encouraged further studies to determine the direct effect of AGEs on individual bone-derived cells such as bone marrow mesenchymal cells, osteoblasts and osteoclasts.

Kume and co-workers found that AGEs increased the apoptosis and thus decreased the viability of human mesenchymal cells in vitro. AGEs, via interaction with RAGE and up-regulation of this receptor, also decreased the adipogenic, chondrogenic and osteogenic potential of mesenchymal cells [56]. However, most studies with bone cells have focused on the actions of AGEs on osteoblasts in culture.

In our laboratory we have found that AGEs (soluble or attached to a collagen matrix) decrease the attachment, proliferation, differentiation and mineralization of osteoblastic cells in culture [51,65,66] via an increase in intracellular reactive oxygen species (ROS), in the expression of nitric oxide synthase [66] and in the activation of extracellular-regulated kinases (ERK) [52]. In addition, we have shown that exposure to AGEs (a) modifies the secretory pattern of IGF-1 and its binding proteins inducing a decrease in the levels of free IGF-1 [67], (b) increases osteoblast apoptosis and (c) up-regulates the expression of RAGE and Galectin-3 to exacerbate the receptor-mediated effects of AGEs in these cells [68]. We have recently found that the AGEs-mediated increase in osteoblast apoptosis is secondary to a disruption of its actin cytoskeleton with formation of geodesic domes [69]. Similarly, other authors have also found that AGEs stimulate osteoblast apoptosis via MAP kinase pathways [70] and up-regulate osteoblastic expression of RAGE [53,71-73].

Simultaneously with our first studies, other researchers reported coincident anti-osteogenic effects of AGEs on primary osteoblasts of rat [24] and human origin [74], and additionally found that AGEs can stimulate osteoblastic interleukin-6 secretion suggesting their involvement in the modulation of bone remodelling. All in all, these and our results are in agreement with the immunohistochemical findings of Hein and co-workers in trabecular bone biopsies from patients with osteoporosis. These authors described a positive association of bone...
AGEs levels with patient age, and an inverse association with relative osteoblast-covered bone surface [47].

Recently, additional signal-transduction mechanisms have been described for RAGE-dependent anti-osteogenic effects of AGEs on osteoblasts. RAGE activation was found to consecutively suppress Wnt, PI3K and ERK signalling, thus inhibiting osteoblastic proliferation [75]. In another study, AGES increased the apoptosis and inhibited the proliferation and differentiation of osteoblasts by decreasing the expression of Runx2 and Osterix, two transcription factors that are essential for osteoblastic progression [76].

In osteoclasts the effects of AGES have been poorly defined, and published reports are controversial [58,77]. Using unfractonated mouse bone marrow cultures that included osteoclasts among other cell types, Miyata and co-workers found an increase in resorption pits (but not in osteoclast number) when the cultures were incubated for 4 days on AGES-modified dentin slices [77]. In the other published report on this issue, Valcourt et al. found that both human and rabbit osteoclasts expressed significant levels of RAGE, and that when cultured on ivory slices modified with the AGES-cros-link pentosidine, osteoclasts transiently increased their resorptive action after 3 days but were greatly inhibited if cultures were extended to 8 days [58]. Thus, it appears that although the presence of AGES may initially increase the activity of osteoclasts, exposure to AGES for longer (and more clinically relevant) periods of time greatly diminishes their recruitment and activity. While further research is necessary to confirm these results, they are in agreement with the vision of diabetic osteopathy as an adynamic bone disease.

Bone healing also appears to be affected by the presence of AGES. In an interesting study by Santana and co-workers, cranioynt defects healed significantly less (and expressed greater levels of RAGE) in streptozotocin-induced diabetic mice than in non-diabetic animals. A similar decrease in bone healing was observed when AGES were applied locally to defects in non-diabetic mice [78]. Thus, AGES-RAGE interaction appears to modulate the process of bone repair, although this must be confirmed in studies with weight-bearing bones of endochondral formation. Recently, a unifying mechanism has been proposed suggesting that inflammatory signalling secondary to excess AGES and ROS increases osteoblast and chondrocyte apoptosis, as well as initial osteoclast survival, thus inducing impaired bone regeneration in Diabetes [9].

**Pharmacological Treatment can Modulate the Deleterious Effects of AGES on Bone**

In recent years our research group has tested the hypothesis that pharmacological treatment may prevent the deleterious effects of AGES on osteoblasts by mechanisms related to a decrease in the generation of oxidative stress, and by modulation of survival signals and of RAGE expression. In particular we have evaluated whether an anti-diabetic or pharmacological treatment may prevent the deleterious effects of AGEs on bone [17,18,69]. Other authors previously demonstrated that the bisphosphonates inadronate and minodronate were able to suppress anti-angiogenic effects of AGES in vitro [94,95].

For both strontium ranelate and alendronate, the initial mechanism of action against AGES-induced cytotoxicity is activation of L-type calcium channels. However, the downstream cascades appear to be different. On one hand, low doses of alendronate prevent intracellular oxidative stress and in consequence revert morphological changes and apoptosis induced by AGES, but do not affect expression of ERK [18,69]. On the other hand, strontium ranelate prevents the osteoblastic secretion of IL-1beta and TNF-alpha induced by AGES, an effect that is downstream to the activation of ERK. In addition, strontium ranelate...
also prevents the AGEs-induced decrease of beta-catenin activation, a key regulator of osteoblastic function [17].

In vivo studies are currently under way in our laboratory to evaluate the possible preventive effects of orally administered alendronate or strontium ranelate, on bone alterations induced in models of type 1 and type 2 Diabetes.

Conclusions and Perspectives

Chronically elevated ROS, glucose levels and/or carbonyl stress associated with uncompensated Diabetes mellitus induce an excess accumulation of AGEs on long-lived proteins such as bone collagen. Excess AGEs in bone ECM reduce bone quality, strength and post-yield properties. In addition, collagen AGEs can interact with RAGE expressed by bone cells, impairing the homeostasis and activity of mesenchymal cells, osteoblasts and osteoclasts. This in turn decreases bone turnover inducing an even greater accumulation of AGEs with development of diabetic osteopathy, thus increasing fracture risk (Figure 1). Pharmacological treatment with anti-diabetic and anti-osteoporotic drugs may prevent the deleterious effects of AGEs on bone cells.

The progressive accumulation of AGEs in diabetic bone would be expected to correlate with the deterioration in bone quality. This has been shown in animal models, but surprisingly has not been demonstrated yet in patients with Diabetes. Studies to prove this hypothesis are necessary in order to design specific strategies to prevent diabetic osteopathy and its associated bone fractures.

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