

Diabetic oxidative stress and bone loss complications

Orlando L. Catanzaro¹, Nicole Brasquet¹ and Alejandra Arganaraz^{1,2}

¹Dental and Medical School -AOA Univ. Del Salvador,

²Department of Physiology -Univ. Argentina John F. Kennedy.

Corresponding Author: Orlando L. Catanzaro, Dental and Medical School -AOA Universidad Del Salvador, Facultad de Ciencias Médicas, Escuela de Odontología, Cátedra de Fisiología General y Neurofisiología. Buenos Aires, Argentina.

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Abstract

Diabetes mellitus is a group of metabolic disorder characterize by and absolute or partial insulin deficiency. Diabetic hyperglycemia is produce by the effect of homeostasis between proteolytic enzymes, their inhibitors and the antioxidants defense that protect and repair vital tissues and molecular components. Bone consist of both component and trabecular bone tissue. Organic matrix and albumin form part of noncollagenous of bone .Initiation of mineralization and collagen fibrils form the phase of mineral matrix. Calcium flux into and out of bone depend of osteoclastic and osteoblastic activity. The remodeling is initiated by resorption and new bone formation at the resorption site. Diabetic complication is a critical factor for bone pathology and could start early inflammatory stage even before hyperglycemia. Diabetic produces bone loss from reduce osteoblast activity. Partly insulin deficiency produce defective bone remodeling indirect by oxidative stress. The current treatment for defective bone in diabetes state include biophosphonate and cinaciguat. Biphosphonate inhibit bone resorption, but may worsen bone quality. A novel type of activation of sGMP is cinaciguat an NO independent activator of oxidative GC, increase c GMP synthesis on diabetic and restore proliferation and survival of osteoblasts. Chronic hyperglycemia interferes with the oseointegration of implants in diabetics. Both diabetic and aging plays a role in abnormal differentiation of osteroblasts. In diabetic patients may improve the oral health to have a positive impact if optimal glycemic control is emphasized. However with cinaciguat present as a novel paradigm enhancing bone formation under hyperglycemia and protect bone implants.

Keywords: diabetes mellitus; metabolic disorder; hyperglycemia; osteoclastic; osteoblastic activity

Diabetic mellitus is a group of metabolic disorders characterized by an absolute or partial insulin deficiency [1]. There are 4 types of diabetes: (i) type 1 diabetes, caused by destruction of pancreatic β -cells; (ii) type 2 diabetes, which is at least 90% of cases (occurs as a result of progressive defect in insulin secretion);(iii) gestational diabetes (occurs In the second or third trimester of pregnancy); and (iv) diabetes of other causes pancreatic anomalies, (eg. pancreatic fibrosis, drugs or chemical –induced or organ transplantation) [2]. A loss of homeostatic balance between proteolytic enzymes (neutrophil elastase) and their inhibitors (alfa-antitrypsin) and reactive oxygen species (ROS) and the antioxidant defense that protect and repair vital tissue, cell, and molecular components is believe to be responsible for the effect of diabetic hyperglycemia. The results from bone loss with the changes in remodeling during normal aging may be accelerated by extrinsic and intrinsic factors. Although bone appears inert, it is a dynamic tissue that receives about 10% of the cardiac output and remodels throughout life [3]. Bone consist of both compact and trabecular bone. The extracellular bone components include a solid mineral phase associated with 90-95 % of organic type 1 and collagen matrix. Noncollagenous is part of organic matrix and contains albumin, cell attachment/ signaling proteins as osteopontin and fibronectin, calcium binding proteins and osteocalcim, biglycan and decorin. The proteins of serum are responsible for the organization of collagen fibrils, initiation of mineralization and the mineral phase to the matrix. The skeleton contains over 99% of the

calcium in the adult body. There are high rates of calcium flux into and out of bone, mediated by osteoblastic and osteoclastic activity, the 0.5-1-0% of exchangeable calcium is within then extracellular fluid.

Calcium channels can be activated by hormones, metabolites or neurotransmitters affecting the 50% of total serum calcium that is ionized.

The ionized calcium is concentrated in the extracellular fluid by across renal and intestine epithelia mediated by the effect of parathyroid hormones, D_3 vitamin and calcium. In the control of calcium and phosphorus homeostasis, evidences has been demonstrated that vitamin D_3 and is synthetic analogs play a multiple functional role in the enhancement of antimicrobial peptide, expression and immunomodulatory actions [4, 5]. Current evidence indicates that Vit. D mediate activation and regulate genes that mediate osteoblast and osteolast functions [6]. Healthy bone models and remodels occurs throughout life as a dynamic effect of bone tissue. The skeleton increases in size in response in the stresses placed upon it. This involves new bone formation that is independent of tissue resorption and in this form can assume a new shape or cortical thickening. The remodeling is initiated by resorption and by new bone formation in the same place of resorptive site. Mechanical bone stresses are transmitted to osteoclast or osteoblast or to their precursors by osteocytes. Bone resorption reflex the sum of osteoclast recruitment and death, and the relation of the average cell degrades matrix [7]. Diabetes mellitus is associated with overproduction of inflammatory cytokines and oxidative stress in response to the state of

hyperglycemia [8, 9], and interleukin-1 β and tumor necrosis factor (TNF- α) that leads to the destruction of pancreatic β -cells [10]. Diabetic complications, including bone pathology, could start to develop the early inflammatory stages of the disease, even before establish the hyperglycemia and /or the glucosuria based diagnosis for diabetes [11]. Bone loss are frequent complications of diabetes [1]. Bone loss in diabetes type 1 is mainly from reduced osteoblast activity, thus, current osteoporosis therapies aimed at inhibiting osteoclast are inadequate [12, 13]. In diabetes type 2 bone formation decreased and increase fracture risk, but bone mineral density may normal or increased, while bone quality is impaired [14]. Inflammatory processes are well known to interact with remodeling of bone tissue in the vicinity, causing bone enhanced rate of bone resorption and new bone formation with the former usually being dominant [15, 16]. Pro-inflammatory mediators formed by the kallikrein-kinin system can stimulate bone resorption and synergistically potentiate bone resorption induced by IL-1 β and TNF- α . Bone loss due to increased number of activity resorbing osteoclasts observed in periodontal disease and rheumatoid arthritis and diabetes is usually considered being caused by excess of cytokines stimulating osteoclast genesis compared to those with inhibitory effects. Stimulatory cytokines include interleukin-1(IL-1),IL-6,IL-11, IL-17, leukaemia inhibitory factor(LIF), oncostatin M(OSM), tumor necrosis factor (TNF- α) and transforming growth factor- β (TGF- β), and the group inhibitory cytokines belongs IL-4, IL-10, IL-13, interferon - γ (ITF- γ) [17, 18]. Kinins can stimulate bone resorption *in vitro* [19, 20] and may more important synergistically potentiate the bone resorption effect of IL-1 an effect synergistic enhancement of prostaglandin biosynthesis [21]. Kinins have been known in a variety of biological effects including cardiovascular homeostasis inflammation, nociception and bone resorption [22, 23, and 18]. Kinins are formed from kininogen either by plasma kallikrein, which is activated early in the coagulation cascade, or tissue kallikrein, which is activated by proteases at injured sites [24]. They mediate biological effects by acting on two types of receptors namely B₁ and B₂. Molecular cloning of the bradykinin (BKB₁-R) B₁R receptors and the B₂R receptors (BKB₂-R) from a variety of species including humans, revealed that they belong to the family of G protein-couple receptors [25]. The BKB₂-R mediate many of the physiological effects of kinins are constitutively expressed and involved in the acute phase of the inflammation. The BKB₁-R, usually absent in normal tissues, are induced an over-expressed during tissue injury and following treatment with inflammatory mediators like endotoxin and cytokines. Furthermore the enhancement of B₁ and B₂ receptors expression and IL-1 β and TNF- γ was not only observed in the human osteoblasts cell but also in the intact mouse calvarial bones and primary culture of human gingival fibroblast [26]. Partly insulin deficiency produce defective bone remodeling in diabetes type 1, but current evidence indicates that hyperglycemia induce oxidative stress [27]. Increased reactive oxygen species (ROS) and decreased antioxidants defense mechanism contribute to diabetic tissue damage and bone loss [28, 29]. Patients with type 2 diabetes have decreased bone formation and increased fracture risk, but bone mineral density may be normal or increased, while bone quality is impaired [30]. Compared with other complications, diabetic disease increase the osteoporosis in bone fragility and fracture [31]. Current experimental evidences suggest that durable hyperglycemia, the most remarkable character of diabetes, could impair bone regeneration and delay bone healing rates [32]. There is an increase of alveolar ridge reabsorption in edentulous patients with osteoporosis [33]. Greater alveolar crystal height loss is noted with osteoporosis and osteopenia [34]. Osteoporosis and osteopenia are associated to diabetes and periodontitis, attachment loss and gingival recession [35]. Induced bone mineral density was associated with increased clinical attachment loss [36]. On the other hand weak or not significant association between systemic bone mineral and clinical attachment loss was observed [37]. However an association between osteoporosis and clinical attachment loss provided stronger evidences [38]. In postmenopausal women was

found that periodontal disease and osteoporosis was associated with lower vitamin D and higher concentrations of RANKL and osteoprotegerin [39]. Between others, reduced bone mineral density is a critical risk factor for periodontitis rather than a casual factor between periodontal disease and reduced bone mineral density. As the natural teeth are more prone to loss and, as well also, osteoporosis, in diabetic periodontitis, two components to ameliorate all adverse effect of periodontitis on bone can be describe. The current medications for osteoporosis include calcium, vitamin D, parathyroid hormone, selective estrogen receptor modulators, calcitonin, bisphosphonates and cinaciguat. With increasing longevity, it is important to remember that osteoporosis in diabetes is common to both sex. Clinical therapy for osteoporosis is a lifelong - intervention. Diabetic hyperglycemia could delay bone healing rates, which is critical for the osseointegration of dental implants. Bisphosphonates are analogs of inorganic pyrophosphates. Bisphosphonates inhibit bone resorption, improve bone mineral density but may worsen bone quality by repressing bone formation. There are differences in the chemical and, physical structure of bisphosphonates, and these differences may explain variations in clinical observations, as potency at enzymatic level, binding affinity, distribution accumulation and release. Bisphosphonates of low affinity do not bind as tightly on the surface of the bone for removal by osteoclasts and the drug comes off easily from bone and its effect may shorter in duration. Bisphosphonate is derived from the base of the drug, with two phosphonate (PO₃) groups covalent linked to a central carbon. The carbon atom confers resistance to hydrolysis with two side chains. The short side-chain usually has a hydrolysis moiety and provide a strong affinity for calcium crystal and bone mineral. The long- side-chain determines the mode of action and the strength of the bisphosphonate. Bisphosphonates have low intestinal absorption and are excreted via renal. Bisphosphonates inhibition osteoclasts depend by two mechanisms: if long side-chain contains or not nitroside groups. When lack a nitrogen in the side-chains are metabolized by osteoclasts, interfere with osteoclasts and induce apoptosis. On the other hand the side with nitrogen contains side groups reduced osteoclasts recruitment and induced osteoblasts to produce an osteoclast inhibiting factor. In experimental animals, bisphosphonate (alendronate) has been showed to inhibit repair of normal micro damage, so micro damage accumulation may occur [40]. To date bisphosphonates trials, specific gains in bone quality architecture, turnover, damage accumulation and mineralization have not been reported in human maxilla or mandible. As a matter of fact hyperglycemia induces oxidative stress and loss bone mineral density and reduce bone mass. These two factors could impair bone regeneration which is critical for the osseointegration implants in patients with diabetes [41]. More effective methods in reverse the bone loss in diabetes could be an important factor. As a vital molecule NO can diffuse into target cells and activate intracellular receptor, the soluble guanylate cyclase (sGC). Cyclic guanosine monophosphate -5 (cGMP) is generated by cytoplasmic sGC and hydrolyzed by phosphodiesterase -5 (PDE5) which stimulates protein kinase G(PKG), and produce a series of biological effects as reversing oxidative stress, inducing osteoblast generation [42]. In diabetic conditions existing evidences that the cGMP/PKG II could be disturbed [43], such as increased expression of PDES and decreased bioavailability of cGMP [44] soluble guanidine cyclase (sGC) drug have been discovered to resist interfered cGMP/PKG II pathway. A novel type of activator of sGC is Cinaciguat (Bay 58-2667), an NO-independent activator of oxidative guanylate cyclase increase cGMP synthesis under diabetic conditions and restore proliferation, differentiation, and survival of osteoblasts. The effect of the drug increase trabecular and cortical bone in type 1 mice by improving bone formation and osteoblasts. In type 1 diabetes bone loss is due from reduced osteoblast activity. On the other hand defective bone remodeling in diabetes is partly due to insulin deficiency. Insulin requires NO/cGMP/PKGII signaling for proliferative effect in osteoblasts. Under hyperglycemia conditions decrease insulin activation of the NO/cGMP/PKGII in osteoblasts expose to high glucose

.Restoring cGMP synthesis reduces oxidative stress, recovers osteoblast functions, decreases osteocyte apoptosis, and prevent bone loss in the insulin –deficient mice. According to Joshua et al [45] cinaciguat produce a transient decline in systolic pressure. Research shows that cinaciguat could improve cardiac dysfunction in type 1 diabetic rats [46], which indicated that it may play a protective role in glucotoxicity environments. Have been demonstrated that cinaciguat could reverse the damage of osteoblasts caused by high glucose and protect the osteogenic function in T1D mice [47]. Osseointegration is a combination of living bone tissue and implants and the first stage of bone implants interactions is essential for the formation of osseointegration interface. It is difficult to explain the molecular effects of cinaciguat on osteointegration under hyperglycemia condition. Studies in diabetic rats (Zucker or STZ) showed that chronic hyperglycemia interferes with the osseointegration of implants by determining expression of fibronectin and integrin alpha 5-beta -1[48]. Advanced glycation end products accumulate in body tissues with the age's progression, and under hyperglycemic conditions inhibit osseointegration and compromise the biochemical properties of the bone implant interface. Persistent hyperglycemia plays a role in abnormal differentiation of osteoblasts, making bone tissue more susceptible to resorption [49]. Diabetes is associated with peri-implant soft tissue, crystal bone loss and even implant failure. Implant survival and primary stability parameters in diabetes conditions varying with hemoglobin A1c, and increase in proportion with the rising hemoglobin A1c levels. Peri-implant plaque index, bleeding on probing depth and crest bone loss are significantly higher in diabetic than in control. In diabetic patients may improve the oral health to have a positive impact if optimal glycemic control is emphasized. No/cGMP/PKG pathways activator with cinaciguat present a novel paradigm for enhancing bone formation under conditions of hyperglycemia and oxidative stress.

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