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# DIABETIC OSTEOPOROSIS: A REVIEW ON HORMONAL, CELLUALR AND MOLECULAR PHYSIOLOGY OF BONE REMODELING UNDER HYPERGLYCEMIA.

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## ABSTRACT

Osteoporosis is a deteriorating bone disease characterized by loss of bone mass, resulting in pain, disability, compromise of quality of life and fractures. Though observed in both men and women, later ones are more affected due to loss of ovarian function following menopause. As bone is a key player in many of the physiological functions, gradual loss of bone health has cumulative effects on other physiological processes and vice versa. This article tries to focus on one of such condition – Hyperglycemia; trying to understand bone health, bone remodeling and mineral metabolism under hyperglycemic condition and role of bone as an endocrine organ during diabetes. We are also discussing the factors regulating bone remodeling and glucose metabolism; trying to provide a scientific base for better understanding on interplay of these two complex mechanisms.

**KEYWORDS:** Osteoporosis, Hyperglycemia.

## INTRODUCTION

Osteoporosis is a disease characterized by loss of bone mass, increased fragility of skeletal tissue and possibilities of fracture. It is mainly associated with postmenopausal estrogen deficit and age.[1,3] Other factors attributing to osteoporosis are increased levels of PTH, smoking, physical inactivity, overuse of corticosteroids.[4,5] Physiological abnormalities and diseases such as diabetes also adversely affect bone health, accelerating bone loss and contribute towards osteoporotic fractures.[1,6,8]

Bone is the central key player in the mineral metabolism of the body, responsible for maintenance of primary structural framework and provision of mechanical support for locomotion. It remodels continuously to adapt to mechanical stimuli, mineral requirement and growth[9], mainly attributed to 3 types of bone cells: osteoblasts, osteoclasts and osteocytes. Osteoblasts are responsible for the formation of bone and also play a role in regulation of osteoclast differentiation and activation. Osteoclasts on the other hand are responsible for bone resorption, digesting the mineralized bone matrix. Osteocytes are resting cells of bone matrix, acting as mechanosensors; translating the mechanical signals into chemical signals which in turn activate osteoblasts.[9,14] Bone remodeling is regulated by several factors such as hormones and cytokines among which calcitonin[15], growth hormone (GH).[16], parathyroid hormone (PTH)[17], Thyroid hormone[18], Cortisol[19], Estrogen[20] and Vitamin D[21] are the major hormones, while interleukin (IL)-1, IL – 6[22], insulin like growth factor (IGF)-1[23], tumor necrosis factor (TNF) α[24], transforming growth factor (TGF) β1[25], osteoprotegrin (OPG) and receptor activated nuclear factor kappa (RANK) ligand (L)[26] are the major cytokines. Bone health can be assessed by measuring different markers in both blood and urine such as Alkaline Phosphatase(ALP)[27], Procollagen type I amino terminal peptide and procollagen type I carboxy terminal peptide[28] for bone formation. Similarly, N-terminal cross linked telopeptides of type I collagen[29], Tartarate resistant acid phosphatase[30], Pyridinoline[31], Deoxypyridinoline[32] and Hydroxyproline[33] are used as clinical markers of bone resorption.

### Mechanism of bone remodeling

Bone remodeling is initiated when osteocytes are stimulated at the site of mechanical stress. This causes disruption in fluid flow in bone microcanaliculi. Osteocytes stimulate osteoblasts to initiate bone remodeling, which secrete Macrophage colony stimulate factor (MCSF) - a cytokine that promotes local recruiting of osteoclast precursor cells.[34] Along with MCSF, osteoblasts also secrete RANK L, inducing differentiation of osteoclast precursors into functional osteoclasts. MCSF and RANK L are the central key players of osteoblast mediated regulation of osteoclast recruitment and differentiation.[12] Osteoblasts check the activity of osteoclasts by secreting another cytokine – OPG which competitively binds with RANK L receptor on osteoclasts, thereby preventing osteoclastogenesis and activation.[26] Most of the hormones regulate bone remodeling through RANK L - OPG secretion including PTH, prolactin and estrogen.[35,41] Once activated, osteoclasts digest matrix through secretion of acids in the resorption pit. This is followed by secretion of proteases and cathepsin K like enzymes which digest the organic part of the matrix.[42] Digested end products of the osteolysis are transcytosed across osteoclast into the immediate environment, many of which such as Osteocalcin act as cytokines and promote bone formation; recruiting osteoblasts to the site of resorption to synthesize bone.[43,45]

Osteoblastic bone formation proceeds osteoclastic bone resorption, governed mainly by the local paracrine factors released from the digested bone.[38,46] Osteoblasts begin bone synthesis by laying down Type I collagen fibrils, followed by secretion of calcium and phosphate ions. This leads to mineralization of the matrix in the presence of ALP, ostepontin and osteocalcin.[29] Osteoblastic bone synthesis is also tightly regulated process by many of the bone anabolic factors such as IGFs, BMPs, GH and Sex hormones.[47]

From last few decade reports are indicating that insulin have significant anabolic effects on bone.[48,54] Zhang and his coworkers[55] reported that insulin has direct osteogenic effect as it promotes osteoblastic cell proliferation, increases ALP activity, promotes differentiation and synthesis of collagen and osteocalcin in MG 63 cells. Further studies reported that insulin has similar effect like that of IGF 1 and it promotes matrix mineralization.[56,57] Apart from these factors, many of the systemic cytokines also affect the bone remodeling process. For example, cyclooxygenase (Cox) 2[58], prostaglandins (PG) $E_2$[59], TNF – α[24], IL-1, IL-6, IL-11[22] have catabolic effects on bone as they promote recruitment and differentiation of osteoclastic cells, which is discussed later in the article.

**Diabetes and bone health**

Diabetes is a disease resulting from loss of insulin secretion or action; causing chronic hyperglycemia.[60] Inability to maintain blood glucose levels for prolonged duration leads to physiological stress[61], causing an array of organ failures such as eyes[62], kidneys[63], nervous system[64], cardiovascular system[65,67] and bone.[1,68] Hyperglycemia has been well documented to cause metabolic bone disease, inducing osteoporosis and increases the chances of fractures.[69,75] However, recent studies have shown that hyperglycemia induced osteoporosis follows different cellular and molecular mechanism in type I and type II diabetes.[70,76]

Insulin dependent diabetes mellitus (IDDM) or type I diabetes is characterized by decreased secretion of insulin from pancreatic beta cells, resulting in hyperglycemia.[61] Type I diabetes has many physiological complications including neurological, cardiovascular and skeletal complications. IDDM complications referring to bone were first described by Albright and Reifenstein in 1948.[77] In last 30 years, IDDM induced bone damaged is well documented by several authors and leads to lower bone mass, increasing the possibilities of fractures.[77,88]

Type II diabetes or Non-insulin dependent diabetes mellitus (NIDDM) is caused by insulin resistance as the cells are unable to respond to insulin, resulting in hyperglycemia.[76] There are contradictory reports regarding the effects of type II diabetes on bone health and the exact mechanism is yet to be explored.[89,91] Yamaguchi and his team[91] reported the type II diabetes individuals had higher bone density compared to non-diabetic age matched individuals. These results were strengthened by the investigations of Petit and his coworkers[90] reporting similar results even in elderly group. However, opposite to this, Yaturu and his coworkers[92] showed that NIDDM patients has significant lower bone density compared to healthy age matched group. Brown and Sharpless[74] also indicated that diabetic neuropathy is one of the causes of damaged to bone health, also called as charcot osteopathy.

Carolin and coworkers[93] provided a possible explanation to these contradictory results and suggested that diabetic individuals have, in general, normal bone density. However, fractures associated with diabetes are significantly higher and they were independent of bone density. Khosla[94] have suggested that NIDDM patients have abnormalities associated with bone mineral strength and bone microarchitecture. One of the reason behind the different effects of hyperglycemia in type I and type II diabetes is their onset, as evident by many researchers, indicating that insulin and IGFs levels were low in diabetic individuals.[57] As these are one of the key factors in achieving peak bone mass, type I diabetes individuals, who develop this complication at early age, are unable to attain healthy peak bone mass. Compared to this, type II diabetes develops after adulthood, where the individual has already acquired peak bone mass. Due to this difference in peak bone mass, Type II diabetic patients have sturdier bone compared to their counter parts in type I diabetes and it offers resistance to diabetic bone damage.[1,72,75,95] Effects of IDDM (Type I) and NIDDM (Type II) on bone are summarized in figure 1 and 2, respectively.

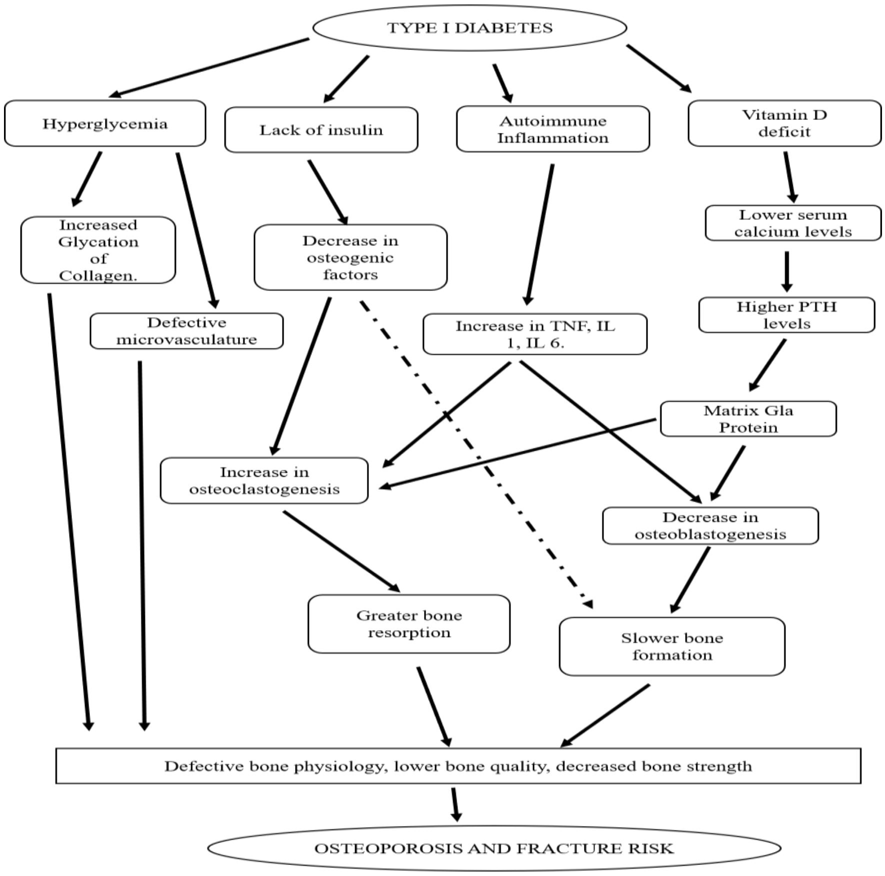


**Figure 1: Interplay of diabetes and bone remodeling in Type I.**

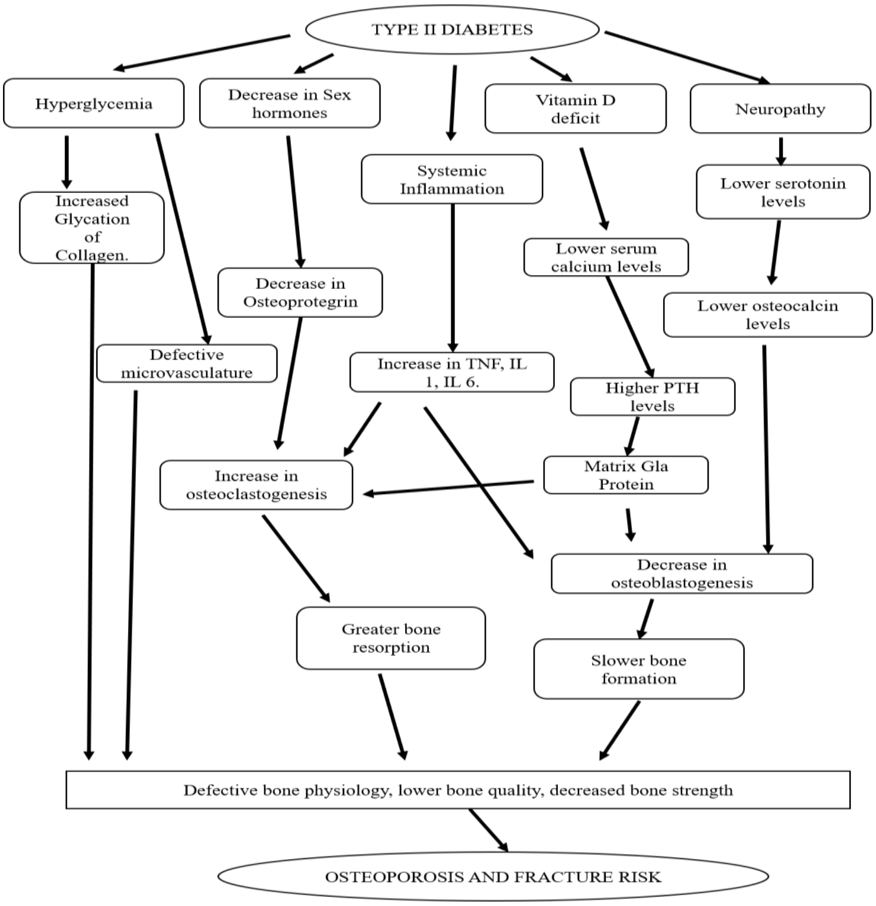


**Figure 2: Interplay of diabetes and bone remodeling in type II.**

**Hormonal synergism during diabetic bone remodeling**

**1. Role of sex hormones in hyperglycemia induced osteoporosis**

Estrogen and testosterone play a key role in bone remodeling. They mainly exert their effects via OPG – RANK-L receptor pathway. Estrogen/Testosterone deficiency stimulates osteoclast formation due to decreased OPG production, followed by increase in TNF α, RANKL and associated cytokines, leading to increased osteoclastic activity.[3,20] In our studies[27] we observed that in rodent model of postmenopausal bone loss, osteoblastic bone formation tries to follow up with the increased bone resorption. However, under chronic loss of Estrogen, ultimately bone formation fails to keep up with the pace of resorption, leading to progressive bone loss. This can be one of the primary causes of generalized bone loss during hyperglycemia, as aggravated inflammation and lower levels of sex hormone leads to increased osteoclastogenesis and the osteoblastic bone formation fails to keep up with the resulting chronic osteolysis. Barros and his team[20] reported similar results and showed that estrogen and estrogen receptors play a key role in pathogenic progression of diabetes and mineral metabolisms. In addition, it has been documented[45,83,96] that decreased levels of osteocalcin associated with diabetes decreases the production of sex hormones from testes and ovaries. As sex hormones are an important component of bone remodeling cycle, hyperglycemia can be hypothesized to have negative effects on this cycle, which is summarized in figure 3. Role of osteocalcin in diabetes and gonadal secretions is discussed later in the section.

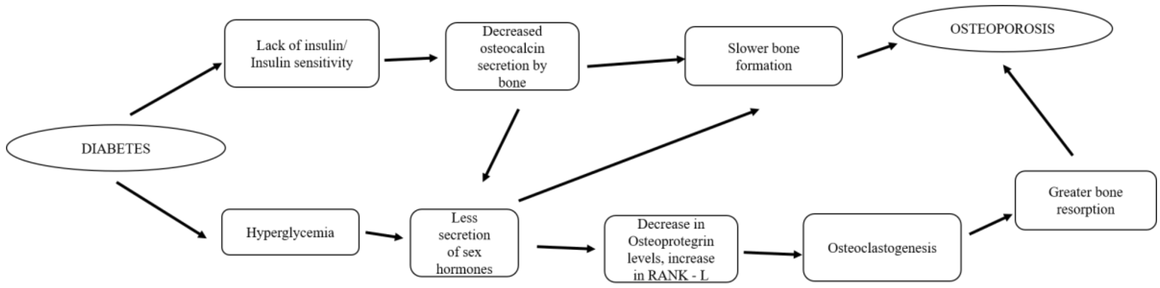


**Figure 3: Interplay of diabetes and bone remodeling under the influence of sex hormones.**

**2. Role of PTH**

PTH has been well documented for an array of bone remodeling effects, including its inhibitory effect on osteoblastic differentiation and activity.[4,5,97,98] Binding of PTH on its receptor – PTHR activates protein kinase A and through a complex intracellular mechanism it induces the expression of matrixs gla protein (MGP). MGP is a potent antagonist of BMP signaling, thereby checking osteoblast proliferation and differentiation. Moreover, binding of PTH with PTHR also forms a complex with TGFβR and induces endocytosis of this PTHR- TGFβR complex, thereby sequestering ongoing TGFβ signaling, responsible for osteoblastic activity.[99] Yamamoto and his team[100] has reported the increase in PTH levels associated with NIDDM patients and suggested hyperglycemia has multiple negative effects on bone remodeling as it lowers the level of Vitamin D and boosts the PTH hormone, resulting in negative bone remodeling and bone loss.

**3. Role of Vit D in diabetic osteoporosis**

Vitamin D is an important hormonal – nutritional factor that affects calcium metabolism and bone health. Its levels were shown to reduce during diabetes which may results in lower serum calcium, increased osteolysis and decreased osteogenesis.[101,104] Vitamin D stimulates the absorption of calcium from intestine, and reabsorption from glomerular filtrate in kidneys, thereby increasing serum calcium levels. Vitamin D also stimulates osteoblastic cells to secrete RANK L thereby promoting the bone remodeling cycle. Under the influence of Vitamin D, bone remodeling is faster and forms a healthier bone.[105] It has been hypothesized[106,109] that excessive urinary loss of vitamin D binding protein due to renal damage is the primary cause of lower levels of Vitamin D in diabetic patients. Deficiency of Vitamin D in serum sequesters absorption of calcium from intestine, thereby inducing the secretion of PTH. Elevated levels of PTH has dual negative effect on bone as it promotes osteoclastic bone resorption by activation osteoclasts and inducing the expression of MGP in osteoblasts, checking the osteoblastic bone formation.[110]

**4. Role of leptin hormone**

Leptin is an adipocyte derived hormone that has negative effects on bone remodeling.[111,112] Ducy and her team[113,114] reported that leptin leads to lower bone mass and leptin deficient mice has higher bone density. Furthermore, this report also showed that leptin is independent of gonadal control of bone remodeling and leptin deficient mice had stronger bones even in absence of sex hormones. Leptin modulates its effects through a hypothalamic relay using two neuronal mediators, i.e. sympathetic tone and cocain amphetamine regulated transcript-CART. These both mechanisms directly act on osteoblasts.[115] Leptin is transported through blood brain barrier into the brainstem where it binds with serotoninergic neurons and blocks the secretion of serotonin.[116,119] Serotonin checks catecholamines secretion from brainstem as catecholamines bind directly on β2 adrenergic receptors and blocks osteoblastic activity.[115,120,121] Hence, under the influence of leptin, serotonin is blocked, increasing the production of catecholamines and leads to decreased osteoblastic activity. Under hyperglycemic conditions, there is a marked increase in leptin levels, which negatively affects insulin secretions and has catabolic effects on bone remodeling.[114]

**Cellular mechanism behind hyperglycemia induced osteoporosis**

Hyperglycemia induces osteopenia and chronic elevated sugar levels result in osteoporosis, although the exact mechanism is yet to be established. Possible cellular mechanism of hyperglycemia induced osteoporosis through osteoblasts and osteoclasts is represented in figure 1 and 2, respectively, where black arrows indicate promotion while red lines indicate inhibition.

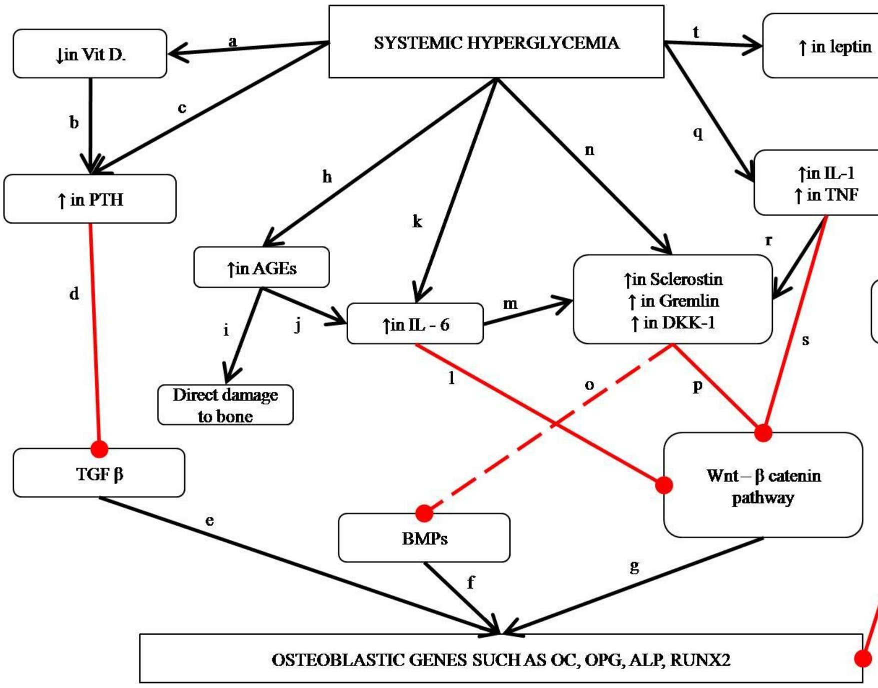


**Figure 1: Effects of systemic hyperglycemia (HG) on osteoblasts through various pathways.**

a. HG lowers the Vitamin D levels.
b. Lower Vitamin D leads to increase in PTH.
c. HG also influences increase in serum PTH levels independent of Vitamin D, as circulating calcium levels decrease.
d. Increased levels of PTH blocks TGFβ activation, thereby preventing osteoblastic differentiation, proliferation and maturation.
e. TGFβ is one of the 3 key players of osteoblastic differentiation, proliferation and activity. Other 2 are BMPs (f) and wnt-β catenin pathways (g)
h. HG increases AGEs which can (i) directly affect the bone matrix and decrease the bone strength and (j) increase the production of IL-6.
k. HG also leads to increase in production of IL-6 independt of AGEs, which can directly (l) check the wnt-β catenin pathways.
m. IL-6 can also boost the levels of sclerostin, gremlin and DKK-1.
n. HG can also increase levels of sclerostin, gremlin and DKK-1, independent of IL-6.
o. Sclerostin, gremlin and DKK-1 can directly block BMPs and (p) wnt-β catenin pathways.
p. HG increases the levels of IL-1 and TNF, which can (r) boost the levels of Sclerostin, gremlin and DKK-1 and (s) block the wnt-β catenin pathways.
t. HG also increases the production of leptin.
u. Leptin directly blocks the secretion of serotonin from hypothalamus.
v. Serotonin blocks catecholamines, which are required to check (w) osteoblastic activity and prevent osteogenesis. Hence, increase in leptin blocks osteoblastic bone synthesis.

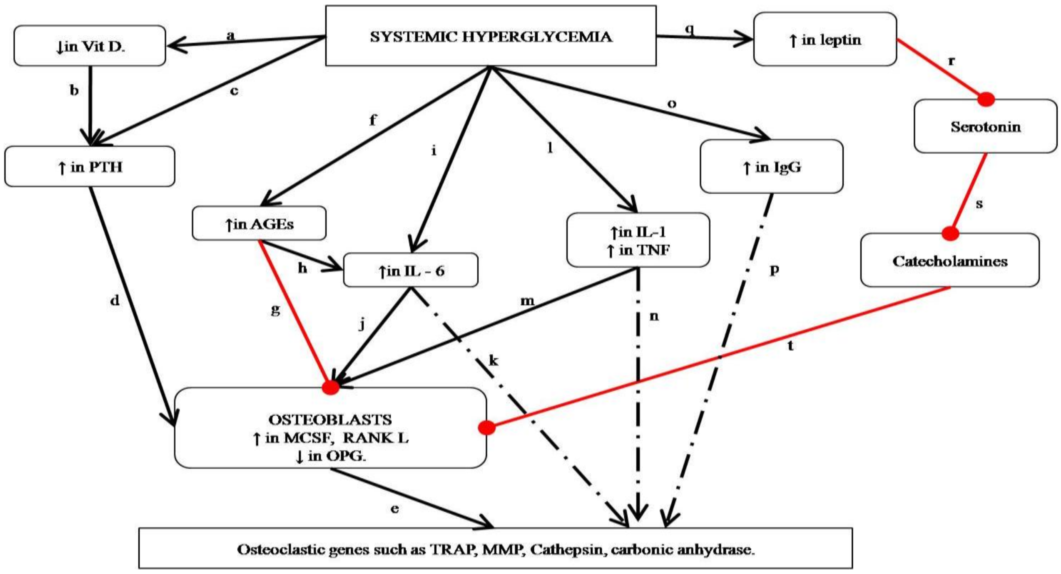


**Figure 2: Effects of systemic hyperglycemia on osteoclasts through various pathways.**

a. HG lowers the Vitamin D levels.
b. Lower Vitamin D leads to increase in PTH.
c. HG also influences increase in serum PTH levels independent of Vitamin D, as circulating calcium levels decrease.
d. Increased levels of PTH stimulates the osteoblasts to produce RANK-L, blocks the production of OPG. Also boosts the production of M-CSF.
e. This leads to triggering of osoteoclast specific genes and fusion of mononuclear osteoclastic precursor cells into multinucleated osteoclastic cells
f. HG increases AGEs which can (g) directly exert toxic effects on bone cells in general and lower the bone remodeling cycle or (h) increase the production of IL-6.
i. HG also leads to increase in production of IL-6 independent of AGEs, which can directly (j) boost the osteoblast stimulated development of osteoclastic cells through RANKL RANKL receptor.
k. IL-6 can directly stimulate osteoclastic precursor cells to mature into functional osteoclastic cells, independent of RANKL system.
l. HG increases the levels of IL-1 and TNF, which can (m) boost RANKL stimulated osteoclastic development and (n) directly stimulate osteoclastic cells through TNF receptors.
o. HG increases the levels of IgG which can (p) directly stimulate osteoclastic cells through IgG receptors.
q. HG also increases the production of leptin.
r. Leptin directly blocks the secretion of serotonin from hypothalamus.
s. Serotonin blocks catecholamines, which are required to block (t) bone remodeling cycle through RANKL system. Hence, increased leptin levels lead to slower bone remodeling cycle.

Recent studies have shown that in IDDM, osteoblastic proliferation and differentiation is directly inhibited. Moreover, IDDM also induces lower osteoblastic activity as marked by low levels of osteocalcin and mineralization rate, lower osteoblastic population and osteoblastic cell death.[81,99,122] A recent study[123] on bone histoarchitecture of streptozotocin induced diabetic mice showed that there was significant increase in the number of osteoclasts and damage to microarchitecture of the bone. This study also supported their data with molecular findings, revealing that there was significant up regulation of TNF α, MCSF, RANK L and PPAR γ, confirming that diabetes has deleterious effects on bone, as it promotes osteoclastogenesis and bone resorption. Interestingly, this study also discovered that there is significant increase in the lipid dense adipocyte in the marrow cavity. As osteoblasts and adipocytes share a common lineage, this osteoblast to adipocyte lineage shift may also contribute to decrease in osteoblastogenesis, bone formation and contribute towards negative bone remodeling.

Supporting this hypothesis, few studies[124,128] showed similar results in vitro. It was documented that high glucose levels in culture medium has direct effects on MG63 cells, resulting in diminished cell growth, defective mineralization and lower expression of osteoblast markers such as Runx2, type I collagen, osteocalcin and osteonectin. Apart from damaging the molecular controlling mechanism of bone remodeling, hyperglycemia has direct effects on bone health.[69,71,82,85] In both type I and type II diabetes animal models, it has been established that advanced glycation end products (AGEs) affect bone health, decrease bone mineral density and compromise bone health.[129,134]

**Hypoinsulinemia and lower levels of IGF 1 affects bone health**

It has been established by many authors that insulin and IGF 1 has anabolic effects on bone and low level of insulin and IGF 1, characteristic of serum profile of diabetes, is known to affect bone health.[16,23,50,55,57] Insulin receptors are expressed by almost all stages of osteoblastic life cycle, i.e. preosteoblasts to mature osteoblastic cells.[51,55] It has previously been suggested[56,57] that insulin and IGF 1 also play a key role in osteoblast lineage determination as osteogenic Bone marrow stem cells are also insulin and IGF 1 receptor positive. Many studies have indicated that insulin and IGF 1 can directly affect the Runx2 and BMP 2 pathways, indicating the major preosteogenic role of insulin and IGF 1 and how diabetes might be affecting osteoblast development.[135,138] In few recent studies[139,142] it was reported that in diabetic rodents, insulin[143,145] receptors and important proteins which are responsible for insulin and IGF – 1 signaling were decreased in osteoblasts and osteoblastic progenitor cells. Hence, one can conclude that diabetic condition with lower insulin and IGF – 1 level hampers osteoblastic differentiation, proliferation and activity, resulting in compromised bone formation and contributing towards osteoporosis. Apart from producing insulin, pancreatic beta cells also produce amylin and preptin. Amylin has positive effect on bone remodeling as it prevents osteoclastic bone resorption while promoting osteoblastic osteogenesis.[146,149] Preptin has potent osteogenic effects as it induces osteoblastic differentiation and mineralization and prevents apoptosis.[150,152] However, detailed mechanism is yet to be explored for the osteoprotective effect of amylin and preptin.

**Osteocalcin – insulin interaction in diabetic osteoporosis**

Osteocalcin is the key hormone secreted by bone and connects it to an array of physiological activities, including glycemic control.[45] Osteocalcin is the major constituent of non-collagenous protein component of bone. It is secreted by osteoblasts and it is a structural component of mineralized matrix.[153,155] When exposed, it attracts circulating monocytes and osteclast precursor cells, playing an important role in osteoclastic activation.[156] Apart from its role in bone remodeling, recent findings[157,162] suggest that osteocalcin also plays an important role in glucose homeostasis by acting as a molecular connection between bone and pancreas.

**Molecular connection between osteoblasts and pancreatic β cells**

Recent finding suggests that there is a connection between osteoblasts and pancreatic β cells.[51,55] When mineralized bone is digested, osteocalcin is released in the form of undercarboxylated fraction.[45] It stimulates β cells to produce insulin and acts on adipocytes to produce adiponectin[163] (Ferron *et al.*, 2008). Apart from osteocalcin having positive effect on glycemic control, there is also a reciprocal loop between osteoblasts and pancreatic β cells.[158] Similar to osteocalcin's positive effect on glucose metabolism, Insulin promotes entire bone remodeling cycle. It increases the proliferation and differentiation of osteoblastic cells and promotes osteoclastic bone resorption. This leads to a healthier bone, increases in bone mineral density and also elevates circulating levels of undercarboxylated fraction of osteocalcin which has positive effect on insulin as discussed.[49,55,86]

Mice lacking osteocalcin gene has severe abnormalities such as decreased beta cell proliferation, decreased insulin production and hyperglycemia.[45] This condition can be reversed by administration of osteocalcin and wild type phenotype can be restored. Ferron and his co-workers (2008) extended this hypothesis further and showed that injecting wild type mice with osteocalcin induced beta cell proliferation, enhanced insulin secretion and offered a protective role against hyperglycemia and obesity.[54] Various studies have proved that serum osteocaclin levels are inversely associated with glycemic levels, insulin resistance and diabetes.[45,50,52,96,157,158,160,162,164,165] Interaction of insulin, osteocalcin and pancreas along with gonads and adipose tissue is represented in figure 3.

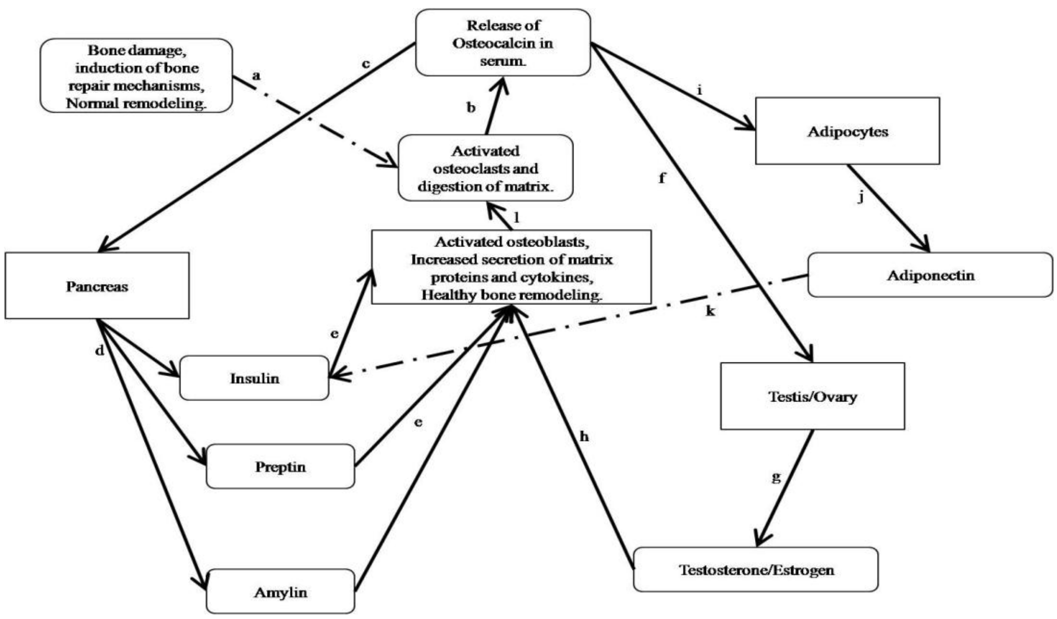


**Figure 3: Interaction of osteocalcin with gonads and pancreas.**

a. A mechanical stimulus leads to repair of microarchitecture of bone or under the normal remodeling, osteoclasts are activated to digest the mineralized matrix.
b. Digestion of matrix releases minerals and proteins, including undercarboyxlated fraction of ostocalcin.
c. Osteocalcin stimulates pancreas to (d) produce more insulin, preptin and amylopectin.
e. These 3 pancreatic hormones, more importantly insulin stimulate osteoblasts, increases their proliferation, differentiation and forms healthy bone.
f. Osteocalcin also stimulates Testis/Ovary to produce (g) more of Testosterone and estrogen which act (h) on osteoblastic cells, increases the production of OPG which binds competitively with RANKL receptor on osteoclastic cells and prevents bone resorption.
i. Osteocalcin also stimulates adipocytes to produce (j) more of adiponectin.
k. Adiponectin increases the sensitivity of insulin.
l. interaction of osteocalcin, insulin, testosterone and adiponectin stimulates osteoblasts to keep a check on osteoclastic resorption and initiate a healthier bone remodeling cycle.

**Role of BMP proteins in hyperglycemia induced bone loss**

BMPs, the members of TGF β superfamily, are one of the key players of bone formation as they induce osteoblast formation, increase collagen synthesis and favor mineralization.[136,137] BMPs are considered the major regulators of osteoblastogenesis. Binding of BMP with BMP receptor on osteoblast leads to phophorylation of SMAD proteins, SMAD binding element and induces the transcription of osteoblast specific genes such as RUNX-2, OPG and osteocalcin.[166] Different BMPs have been documented for varied important roles in bone and cartilage remodeling. BMP-2, BMP-4, BMP-5, BMP-6 and BMP-7 have been well documented to have osteogenic role.[167,172] BMP-2, BMP-4 and BMP-6 have been shown to increase osteoblastogenesis and chondrocytogenesis.[171] Opposite to the effects of these BMPs, BMP-3 has negative effects on osteoblasts, preventing osteoblastogenesis.[173] Recent findings have suggested that BMPs were getting altered in diabetic animals with delayed callus formation, distorted healing process in diabetic rats.[174] This study also discovered that there was a marked decrease in TGFβ and BMP2 expression in diabetic animals, which was directly correlated with delayed recovery of fractured bones.

**Role of TGFβ in hyperglycemia induced osteoporosis**

One of the key players of osteoblastic maturation from Mesenchymal stem cells is TGFβ which is responsible for proliferation, differentiation and commitment to osteoblastic lineage.[25] Binding of TGFβ with its receptor TGFβR follows a pathway similar to BMPs, as it activates SMAD proteins and SMAD binding elements to induce osteoblast specific genes. Moreover, binding of TGFβ with TGFβR also activates non SMAD pathway in which it activates MAPK to induce osteoblast specific genes.[136,168] Xu and his team (2016) showed that TGFβ plays equally important role in bone healing and in diabetic animals there was significant decrease in bone healing which was associated with decrease in TGFβ levels.[175]

**Wnt β catenin signaling**

The Wnt/β catenin pathway plays a key role in bone formation and bone repair.[176,179] This pathway is activated by binding of Wnt glycoproteins with Frizzled receptors and LRP 5 and 6 (Low density receptor like proteins). This in turn activates a cascade of events which leads to the expression of OPG and Runx2, one of the most important genes of osteoblastic activity.[180,184] Wnt pathway is negatively regulated by the expression of sclerostin which is a potent bone anabolic protein.[185,188] It has been recently reported that IDDM has negative effects on wnt β catenin pathway, leading to slower osteoblastic cycle, impaired osteogenesis and negative bone remodeling.[164,176,177,179] A study by Uluçkan and his team[189] has shown that under the influence of proinflammatory cytokines such as IL-17 there is a marked decrease in wnt signaling mechanism followed by diminished osteoblastic activity, suggesting that systemic inflammation has negative effect on bone remodeling, and diseases with systemic inflammation will lead to negative remodeling through decreased wnt signaling.

**Role of other extra and intra cellular proteins**

An array of extracellular, intracellular and transcriptor inhibitors have been identified in recent years which are responsible for controlling bone synthesis, mainly by attenuating BMPs and TGFβ induced osteoblastic recruitment, proliferation and differentiation. Matrix gla protein (MGP)[110], Noggin[190], dickkopf-related protein 1 (DKK-1)[191], Sclerostin[188], Gremlin[192], Ski, Smurf-1, Smurf-2, twisted gastrulation (Twsg1)[193], IL-6[22] and TNFs[24] are few of these which can directly check the activity of BMPs and TGFβ and reduce bone synthesis. MGP directly competes with BMP 2 for binding with its receptor BMP-2R on osteoblastic precursor cells, thereby preventing osteoblastic activity.[194] In two of the recent studies[142,164] it has been reported that diabetes mellitus induces the expression DKK-1, decreases osteoblastogenesis through inhibition of wnt signaling. Garcia-Martin with his team[195] has reported that serum levels of sclerostin were significantly higher in NIDDM patients. Following this study, Gaudio and coworkers[196] reported that increased sclerostin levels were associated with inhibition of the Wnt/β-catenin signaling and reduced bone turnover in type 2 diabetes mellitus. These results were further confirmed by Gennari and his team[197] who reported that sclerostin levels were significantly higher in NIDDM patients and were associated with time and control of the disease. Gremlin levels were also found to be increased in diabetic conditions[198,200], defecting the normal osteoblastogenesis.

**Role of hyperglycemia, Advanced glycation end products and generalized oxidative stress in bone health**

Elevated blood sugar levels, irrespective of the origin, have direct toxicological effects on osteoblasts and disrupt osteoblastic signaling pathways.[128] Hyperglycemia also increases osteoblastic oxidative stress and elevates reactive oxygen species levels, non-enzymatic glycosylation of proteins and DNA damage.[201,204] Chronically elevated glycemic index leads to progressive accumulation of advanced glycation end products (AGEs), which starts getting deposited in various tissues, including bone.[82,129,131,132] One of such AGEs, Pentosidine, deposits primarily at cortical bone, tampering with bone remodeling process and cellular activities.[73,205,206] Silva and his team[207] believe that it is the central mechanism behind fragile bones, risk of fractures, especially of long bones in IDDM. Furthermore, Sanguineti with his team[205] has demonstrated that culturing osteoblastic cells in presence of pentosidine induced a significant drop in ALP, collagen and osteocalcin. One Japanese study[208] provided further insight of type II diabetes and showed that serum pentosidine levels were directly associated with vertebral fractures, which was independent of BMD. These recent studies provide the multifactorial explanation for a common defective bone remodeling in both type I and type II diabetes.

**Hyperglycemia, inflammation and osteoporosis**

One of the important systemic features of diabetes is elevation in inflammatory cytokines. A recent study[209] reported that there was a marked increase in intracellular TNF α in CD4+ and CD 8+ lymphocytes under hyperglyemica. TNF α is well documented to have negative effect on bone remodeling as it activates osteoclastic cells and induces osteoblastic apoptosis.[24,26] In animal models, it has been shown that increased expression of TNF α in bone marrow and bone leads to decreased osteblastic activity and osteoblastic cell death. On this same model, it was shown that TNF α antibodies have ameliorating effect on hyperglycemia induced osteoblastic cell death and restored bone formation.[210,214] Previously, Botolin and co-workers[128] had established that inflammatory cytokines induce the expression of adipogenic genes. This leads to more of adipocytic cells and less of osteoblastic cells, leading to lower bone formation and fat accumulation in bone marrow. Devaraj and his team[215] reported that hyperglycemia induces production of various inflammatory cytokines including IL-6, which has been well documented to have negative effect on bone remodeling as it attenuates osteoblastic activity by down regulating the activity of BMP-2 and TGFβ.[216] Furthermore, hyperglycemia induced AGEs and angiotensin II upregulates the expression of IL -6, thereby contributing towards already increased levels of IL-6 and further diminishes bone formation.[129,130] Uluçkan along with his team[189] demonstrated inhibition of wnt signaling and diminished osteoblastic activity by IL-17, released during chronic skin inflammation, suggesting that systemic inflammation leads to a diminished osteogenic physiology, resulting in osteoporosis.

**CONCLUSION**

Hyperglycemia is known to cause many complications, but of these, possibly bone damage is most neglected problem, with more and more data warning us about this serious cause of secondary osteoporosis. Apart from compromised bone health, cardiovascular and neurological problems increase the possibility of fall and fractures. It is now well established that irrespective of type, diabetes directly suppresses osteoblast differentiation and activity while contributing towards increased osteoclastsic bone resorption. Recent findings suggest that though both type I and type II diabetes patients are prone to osteoporosis, severity of the disease is more in type I patient as they are not able to achieve a healthy peak bone mass due to lower levels of IGF-1 and insulin. Type II diabetes patients, though less prone, follow an additional mechanism and studies suggests that it is mainly attributed to increased levels of sclerostin and AGEs like pentosidine which inhibit bone formation. Further research is needed to understand the role of secondary hormones of pancreas in bone remodeling and modulation of newly discovered proteins like semaphorins under hyperglycemia.

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