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Review Article

Factors Influencing Bone Remodeling in Diabetes Mellitus

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Abstract

Diabetes Mellitus is group of metabolic disorder that occurs when the pancreas is no longer able to make insulin, or when the body cannot make proper use of the insulin it produce. Diabetes Mellitus increases risk of osteoporosis, interfere with bone formation and impairs bone remodeling. Human skeleton is an important structure in our body, which is influenced by diabetes mellitus. Both Type one diabetes mellitus (T1DM) and type two diabetes mellitus (T2DM) increase osteoporosis, bone formation, bone remodeling. There are different factors influencing bone remodeling in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). These factors are influence on osteoblasts and osteoclasts and reduce the numbers of osteoblasts and bone formation and bone remodeling. Increased advanced glycation end product (AGE) formation, hyper glycaemia, Reactive oxygen species (ROS) production and inflammation are among the common factors that influence the bone remodeling in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). The aim of this review was to explore factors influence bone remodeling both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM).

Keywords: *Diabetes Mellitus; Bone Fracture Remodeling; Factors*

Abbreviations

T1DM: Type One Diabetes Mellitus; T2DM: Type Two Diabetes Mellitus; AGE: Advanced Glycation End Product; ROS: Reactive Oxygen Species; Runt2: Runt- Related Transcription Factors 2; OS: Oxidative Stress; IGF-1: Insulin Likes Growth Factors-1; RAGE: Receptor for Advanced Glycation End Product; BMSC: Bone Marrow Stromal Cells; TNF-α Tumor Necrosis Factors, Alpha; IL-1: Interleukin 1; IL-6: Interleukin 6; OS: Oxidative Stress; PHT: Parathyroid Hormone; DAMP: Dentin Matrix Protein; FGF23: Fibroblast Growth Factors 23; MEPE: Matrix Extracellular Phosphor Glycoprotein; ANKL: Receptor Activator of Nuclear Factors Kappa B Ligand; s-CTX: Serum Terminal Cross Linked Telo-Peptide of Type-I Collagen; EPCS: Endothelial Progenitor Cells; VEGF: Vascular Endothelial Growth Factors Kappa B

Introduction

Human skeleton, internal skeleton that serve as frame work for the body which is made up of 206 bones [1]. It has important mechanical strength and fracture toughness, and plays a significant functions as an endocrinal organ in regulating the mineral and nutrient homeostasis [2]. It also acts as protection internal organs like heart, lungs and other organs and also help in movement by anchoring force

arising from muscles contraction [2]. Bone contains intrinsic capacity for regeneration as a part of, bone formation, bone development and bone remodeling in response to injury throughout Adult life [1,3]. Bone remodeling is a lifelong process is removed from the skeleton and new bone tissue is formed. Bone remodeling involves resorption of the bone by osteoclast and replacement of bone by osteoblast [4]. This result in acquisition of high bone mass [5].

Bone remodeling continues process synthesis and destruction which gives bone its mature structure and maintain normal calcium levels in the body [6]. Destructions of the bone in the body is called osteoclasts releases calcium in to the blood stream to meet the metabolic needs and at the same time allow osteoblasts that make new bone to maintain skeletal structure [7,8].

Impairment of bone remodeling is characterized by increased bone density caused and progression of bone to osteoporosis which is a major health problem in worldwide [9,10]. Bones remodeling depend on the balance between new bone formations by the process of osteoblast and degradation of bone through osteoclast [4,8,11]. The activity of bone remodeling is thought to be regulated by many local and systemic factors [12]. These are biochemical stress, nutritional status and humoral factors [12].

Diabetic Mellitus is one of the factors that effect on bone remodeling [13]. Diabetes Mellitus is a group of metabolic disorder characterized by high sugar level over a long period of time [14]. It occurs when the pancreas is no longer able to make insulin, or when the body cannot make proper use of the insulin it produce and leading to different serious micro vascular and macro vascular complication [15]. Diabetes Mellitus increases risk of osteoporosis, interfere with bone formation and impairs bone remodeling [7].

Type one diabetes mellitus also known as juvenile diabetes or insulin dependent diabetes, a chronic condition occurs due to the lack of insulin production by the pancreases [16]. Type two diabetic mellitus a progressive condition in which a body become resist the normal effects of insulin and/or gradually loses the capacity to produces enough in the pancreases [17].

Nowadays, bone fragility, impaired remodeling and formation emerged as complication of diabetic mellitus, the exposure of diabetic environment leads to change in bone metabolism and impaired micro structure through variety of mechanism on molecular and structural levels [18,19]. Type one diabetes mellitus (T1DM) is associated with several disorder of skeletal health. Which include decreased bone mass, and increased risk of bone osteoporosis and poor bone remodeling and regeneration characteristics conditions which all depend, in part, upon an intramembranous component to bone formation [18-20]. In Type 1 diabetic the frequency lifetime fractures at any time has been reported to be increased as compared to counterpart without diabetes [21-23].

Type two diabetic mellitus (T2DM) associated with compromising bone microarchitecture by inducing abnormal bone cells cell function and matrix structure, with increased osteoblast osteoblasts apoptosis, interfere with osteoblast differentiation and enhanced osteoclast mediated bone resorption [24-26]. Currently, there has been increasing evidence suggesting type two diabetic mellitus (T2DM) affects the skeletal system, causing detrimental bone effects such as bone quality deterioration, loss of bone strength, increase fragility, and impaired bone remodeling [14,27-33].

Factors influencing bone remodeling in diabetes mellitus

There are different factors influencing bone remodeling in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). These factors are influence on osteoblasts and osteoclasts and reduce the numbers of osteoblasts and bone formation and bone remodeling. Increased advanced glycation end product (AGE) formation, hyper glycaemia, Reactive oxygen species (ROS) production and inflammation are among the common factors that influence the bone remodeling in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) [5,28,34-36].

Factors influencing bone remodeling in diabetes mellitus type 1 (T1DM)

Effects of type 1 diabetes on osteoblast progenitor cells

Gene expression of transcription factors involved in osteoblast differentiation is modified in type one T1DM [37]. Runt- related transcription factors 2 (Runx), it is regulators of osteoblast genesis, bone regulation, directs differentiation of mesenchyme cells in to pre osteoblast [38].

It regulate the expression of major genes necessary for bone matrix protein Ak2, integrin binding, sialoprotein, Dm1, Colla2, PHEX, Vdx, osteocalcin and osterix were all down regulated in the insulin – deficient, hyperglycemic diabetic [39,40].

The study shows that the insulinopenic, hyperglycemic environments effects on osteoblast, with the majority demonstrating decrease in bone formation, bone mineralization and poor osteoblast activity [41,42]. Parathyroid hormone associated with anabolic effects on the bone, is found to be low in children and adolescent with T1DM [36,43,44].

Inflammatory and hyperglycemic factors

During long run hyperglycemic in diabetes mellitus, glucose forms covalent adducts with plasma proteins through non enzymatic process and result in formation of Advanced glycation end products (AGE), Which is critical role in pathogenesis of diabetic mellitus complication like bone formation, bone remodeling and bone fracture [45]. Specifically, AGEs impair mineralization when present in high glucose environment [46].

Reactive oxygen species (ROS) is highly reactive molecules which contain a number of diverse chemical species which is related to osteoporosis and impair with continuous bone regeneration. Change in ROS and/or antioxidant system involved in pathogenesis of bone loses [45]. ROS induces the apoptosis of osteoblast and osteocytes and this favors osteoclasts genesis and inhibits the mineralization. This excessive osteocyte apoptosis associated with oxidative stress causing an imbalance of osteoclast genesis and turnover of bone remodeling.

Inflammatory cytokines are systematically up regulated in type one diabetes mellitus. Such as Tumor Necrosis factors alpha (TNF- α), interleukin 1 (IL-1) and Interleukin 6 (IL-6) have been shown to have negative effects on osteoblast proliferation and differentiation. As well as inhibition of bone fracture remodeling.

Insulin and IGF-1 factors

Type 1 Diabetic mellitus (T1DM) is associated with low insulin and insulin like growth factors (IGF-1) in human. IGF-1 and insulin have strong anabolic effect on boned density and also IGF-1 corporate with calcitriol activating collagen synthesis and mineralization. IGF-1 and insulin have similar molecular homology in which insulin has ability to bind and activate the IGF-1 receptor. Osteoblast activity and bone formation in type one diabetes mellitus was explained by absence or decrease of IGF-1 and insulin signaling in the cells of osteoblast lineage.

Sclerostin

The association between increased circulating sclerostin levels in type one diabetes mellitus reduced osteocyte activity or osteocyte survival. This indicate that it impair the bone remodeling, osteocyte apoptosis paired with increased sclerostin, may contribute to uncoupling of bone remodeling to favor bone resorption.

DMP1, MEPE, FGF23

In type one diabetes mellitus osteocyte- expressed protein like Dentin Matrix Protein-1 (DMP-1), Fibroblast growth factors 23 (FGF23)

and Matrix Extracellular phosphoglycoprotin (MEPE) negative effect on osteocyte formation. An increment of osteocyte secretion of FGF23 direct effect of pro-inflammatory cytokinesis on osteocyte formation [14,18].

Factors influencing bone remodeling in diabetes mellitus type 2 (T2DM)

Alterations of cellular and molecular composition of the diabetic of bone in diabetes mellitus

High level of non- enzymatic cross linking of collagenous matrix, increasing advanced glycation end products (AGE) cause lessened of the bone strength [31]. Collagen I is a main protein that maintain bone biomechanical strength due to its capacity to generate intermolecular cross links with adjacent collagen molecules in the bond [27].

Recently, it was reported the mineralization and alkaline phosphatase activity of bone marrow stromal cells (BMSCs) derived from the study done on rat under type two diabetes mellitus condition was significantly decreased when compared to the counterpart [34]. This Impairment in osteogenic activity was explained by reduced in gene expression of β- catenin, cyclin D1, and c-myc thus inhibiting signaling in Cellular and Molecular pathway during bone formation, remodeling [14].

Endocrine factors of bone remodeling in diabetes mellitus

Parathyroid hormone (PTH) is an endocrine hormone that activates osteoclast in order to prevent hypocalcaemia which cause osteoporosis [35]. It was linked to osteoclast in type one diabetes mellitus due to its association with markers serum tartrate resistant acid phosphatase-5b in patients with type two diabetes mellitus [26]. Serum levels of tartrate resistant acid phosphatase-5b and bone formation/remodeling marker osteocalcin (OC) have been found to be decreased in Type two diabetic mellitus [45]. It was suggesting that individual with type two diabetes mellitus (T2DM) present a decreased in bone turnover [23].

Vascularization for bone remodeling in T2DM

For proper functioning and development of bone blood supply to bone is very important. It provides oxygen, nutrients, and minerals for bone regeneration and bone remodeling. Different studies have addressed the main role of vasculature, angiogenesis in bone formation/bone remodeling and evaluating the contribution of elements such as endothelial progenitors cells (EPC), Ischemia and pro-angiogenic factors like vascular endothelial growth factors (VEGF). In addition angiogenesis, a crucial step in bone regeneration, is often altered in the diabetic patients [12,23].

In Type two diabetes mellitus the arterial calcification is caused by the bio mineralization of vascular cells, impairing the arterial vessels system and the functionality of the vasculature [15,36]. In T2DM Advanced glycation end product and Advanced glycation end product receptors seem to play key role in vascular calcification [17]. Other mechanism of AGE - induced diabetic calcification using also the same cell line. This indicate AGE accumulation is detrimental for vascularization and thus for bone tissue health in T2DM [18].

Effects of hyperglycemia bone remodeling in diabetes mellitus

Following long term hyperglycemia in T2DM there is accumulation of AGE. This is a direct consequence of high blood glucose levels that increase the non-enzymatic glycosylation reactions that takes place when glucose reacts with circulating molecules [19]. In presence of hyperglycemia, bone tissue changed in quality, biochemical properties and composition these can result in impair bone formation and

bone remodeling [13,34]. Reduced immune-histochemical cell proliferation rate in the diabetes mellitus decreased number of osteoblasts apart of mechanism for impaired bone remodeling [12,13].

Inflammatory effects on bone remodeling in diabetes mellitus

Inflammation is a part of Diabetes mellitus pathogenesis that could leads to bone loss which is called inflammation mediated osteopenia and peak bone mass

Diabetes mellitus changes several factors involved in the mechanism of bone remodeling and promote the activation of inflammatory mediators such as Reactive oxygen species, advanced glycation end products that help in bone remodeling. This inflammation related factors and members of inflammation mediators like TNF-α play role in initiation of bone apoptosis, endothelial cell proliferation impairment, suppressed VEGF expression in bone remodeling [27].

Conclusion

Diabetes Mellitus is group of metabolic disorder that occurs when the pancreas is no longer able to make insulin, or when the body cannot make proper use of the insulin it produce. Both Type one diabetes mellitus (T1DM) and type two diabetes mellitus (T2DM) increase osteoporosis, bone formation, bone remodeling. Increased advanced glycation end product (AGE) formation, hyper glycaemia, Reactive oxygen species (ROS) production and inflammation are among the common factors that influence the bone remodeling in both type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) are factors that influence bone remodeling in diabetes mellitus.

Competing Interests

The authors of this review declare that they have no competing interests.

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Author's Contribution

Both Urge Gerema and Diriba Dereje involved in literature searching, writing manuscript and managing the overall progress of the manuscript. Finally, both authors read and approved the final manuscript.

Bibliography

1. Partridge NC and Remodeling B. "REVIEWS Physiological Bone Remodeling: Systemic Regulation and Growth Factor Involvement". 52 (2020): 233-245.
2. Hu C and Qin Q. "Bone remodeling and biological effects of mechanical stimulus". 7 (2020): 12-28.
3. Id CFA., *et al*. "Bone remodeling: A tissue-level process emerging from cell-level molecular algorithms" (2018).
4. Crockett JC., *et al*. "Bone remodelling at a glance Bone Remodelling at a Glance". (2011): 991-998.
5. Prof A Ph D. "Bone remodelling in diabetes mellitus". 13 (2002): 221-226.

6. Follak N., *et al*. "Delayed remodelling in the early period of fracture healing in spontaneously diabetic BB/OK rats depending on the diabetic metabolic state". *Histology and Histopathology* 19.2 (2004): 473-486.

7. Remodeling B. Bone Remodeling (2007).

8. Article R. "The bone remodelling cycle". 55.3 (2018): 308-327.

9. Chau DL., *et al*. "Osteoporosis Among Patients With Diabetes: An Overlooked Disease". (2003): 1-5.

10. Hygum K., *et al*. "Osteoporosis and Sarcopenia Diabetes and bone". *Osteoporos Sarcopenia* 5.2 (2019): 29-37.

11. Miner V., *et al*. "Vitamins and Minerals Zinc and Lifestyle - Related Disease - with Focus on Diabetes Mellitus and Osteoporosis". (2013): 10-13.

12. Sims NA and Gooi JH. "Bone remodeling: Multiple cellular interactions required for coupling of bone formation and resorption". (2008).

13. Retzepi M and Donos N. "The effect of diabetes mellitus on osseous healing". *Clinical Oral Implants Research* 21.7 (2010): 673-681.

14. Endocrinology MIN. "Diabetes mellitus, a state of low bone turnover - a systematic review". 4 (2017).

15. Paula FJA De and Rosen CJ. "Diabetes mellitus". 3 (2010).

16. Abdissa D., *et al*. "Prevalence of Diabetic Foot Ulcer and Associated Factors among Adult Diabetic Patients on Follow-Up Clinic at Jimma Medical Center, Southwest Ethiopia, 2019: An Institutional-Based Cross-Sectional Study". *Journal of Diabetes Research* (2020).

17. La Fontaine J., *et al*. "Type 2 Diabetes and Metformin Influence on Fracture Healing in an Experimental Rat Model". *The Journal of Foot and Ankle Surgery* 55.5 (2016): 955-960.

18. Dhaon P and Shah VN. "Type 1 diabetes and osteoporosis: A review of literature". *Indian Journal of Endocrinology and Metabolism* 18.2 (2014): 159-165.

19. Safarova S. "Evaluation of Bone Turnover in Patients With Type 1 Diabetes Mellitus". 8.1 (2018): 2-5.

20. Brasília HU De. "Bone mass in Type 1 diabetes mellitus". 1.1 (2016): 1-4.

21. Arkkila PET. "Musculoskeletal disorders in diabetes mellitus: an update". 17.6 (2004): 945-970.

22. City SL. "Bone mineral acquisition in adolescents with type 1 diabetes" (2004).

23. Thrailkill KM., *et al*. "Bone Formation Is Impaired in a Model of Type 1 Diabetes". 54 (2005): 2875-2881.

24. Mousavi SF. "Fracture risk in patients with type 2 diabetes mellitus and possible risk factors: a systematic review and meta-analysis". (2017): 455-468.

25. Ahmad T. "Diabetic osteopathy" (2003).

26. Valentini A., *et al*. "Nutrition, Metabolism and Cardiovascular Diseases Osteoprotegerin in diabetic osteopathy". *Nutrition, Metabolism and Cardiovascular Diseases* 30.1 (2020): 49-55.

27. Johnson AW and Iv OMS. "An Osteopathic Approach to Type 2 Diabetes Mellitus". 111.9 (2011).

28. Karoli Y., *et al*. "Musculoskeletal Disorders in Patients with Type 2 Diabetes Mellitus". *International Journal of Health Sciences and Research* 6.7 (2016): 99-104.

29. Sanches CP., *et al*. "The impact of type 2 diabetes on bone metabolism". *Diabetology and Metabolic Syndrome* 9.1 (2017): 1-7.

30. Wu Y., *et al*. "Diabetes mellitus related bone metabolism and periodontal disease". (2015): 63-72.

31. Bayani MA., *et al*. "The Relationship Between Type 2 Diabetes Mellitus and Osteoporosis in Elderly People: a Cross-sectional Study". 2.1 (2016).

32. He H., *et al*. "Diabetes Causes Decreased Osteoclastogenesis, Reduced Bone Formation, and Enhanced Apoptosis of Osteoblastic Cells in Bacteria Stimulated Bone Loss". *Endocrinology* 145.1 (2004): 447-452.

33. Starup-Linde J and Vestergaard P. "Diabetes and osteoporosis: Cause for concern?" *European Journal of Endocrinology* 173.3 (2015): R93-99.

34. Murray CE and Coleman CM. "Impact of diabetes mellitus on bone health". *International Journal of Molecular Sciences* 20.19 (2019).

35. Hofbauer LC., *et al*. "Osteoporosis in patients with diabetes mellitus". *The Journal of Bone and Mineral Research* 22.9 (2007): 1317-1328.

36. Graves DT., *et al*. "Impact of Diabetes on Fracture Healing". *Journal of Experimental and Clinical Medicine* 3.1 (2011): 3-8.

37. Lu H., *et al*. "Diabetes interferes with the bone formation by affecting the expression of transcription factors that regulate osteoblast differentiation". *Endocrinology* 144.1 (2003): 346-352.

38. Fowlkes JL., *et al*. "Runt-related transcription factor 2 (RUNX2) and RUNX2-related osteogenic genes are down-regulated throughout osteogenesis in type 1 diabetes mellitus". *Endocrinology* 149.4 (2008): 1697-1704.

39. Wu H., *et al*. "Genomic occupancy of Runx2 with global expression profiling identifies a novel dimension to control of osteoblastogenesis". *Genome Biology* 15.3 (2014): 1-17.

40. Botolin S., *et al*. "Increased bone adiposity and peroxisomal proliferator-activated receptor-γ2 expression in type I diabetic mice". *Endocrinology* 146.8 (2005): 3622-3631.

41. Locatelli V and Bianchi VE. "Effect of GH/IGF-1 on Bone Metabolism and Osteoporsosis". *International Journal of Endocrinology* (2014).

42. Hamada Y., *et al*. "Histomorphometric analysis of diabetic osteopenia in streptozotocin-induced diabetic mice: A possible role of oxidative stress". *Bone* 40.5 (2007): 1408-1414.

43. Hamed EA., *et al*. "Parathormone - 25(OH)-vitamin D axis and bone status in children and adolescents with type 1 diabetes mellitus". *Pediatric Diabetes* 12.6 (2011): 536-546.

44. Motyl KJ., *et al*. "Amelioration of type I diabetes-induced osteoporosis by parathyroid hormone is associated with improved osteoblast survival". *Journal of Cellular Physiology* 227.4 (2012): 1326-1334.

45. Santana RB., *et al*. "A role for advanced glycation end products in diminished bone healing in type 1 diabetes". *Diabetes* 52.6 (2003): 1502-1510.

46. Miranda C., *et al*. "Influence of high glucose and advanced glycation end-products (ages) levels in human osteoblast-like cells gene expression". *BMC Musculoskeletal Disorders* 17.1 (2016): 1-9.

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