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Mini Review

Effect of Diabetes and other Risk Factors on Bone Health

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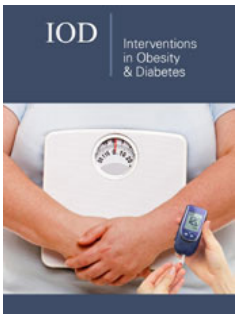
ISSN: 2578-0263



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Submission: January 21, 2022

Published: February 01, 2022

Volume 5 - Issue 5

How to cite this article: Debjita Mukherjee, Jhaleh Amirian. Effect of Diabetes and other Risk Factors on Bone Health Interventions Obes Diabetes 5(5). IOD. 000623. 2022.
DOI: 10.31031/IOD.2022.05.000623

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Abstract

Diabetes Mellitus (DM) affects a significantly large part of the population globally. Several kinds of research are being conducted every day around the world trying to understand the underlying mechanisms of the disease better to develop better treatments. One of the significant effects of diabetes is on the skeletal system of the patients. The disease affects the bone quality, mineral density, bone turnover and in turn bone health at large. This effect on bone health is worsened by several risk factors as well. This mini review aims at presenting some of the most important mechanisms behind this deterioration of bone health and how risk factors affect them according to latest research done in this field.

Keywords: Diabetes; Bone mineral density; Bone health; Risk factors

Introduction

Diabetes is a metabolic disease leading to increased levels of glucose in blood. This happens due to insufficient secretion of the hormone insulin like in Type 1 Diabetes due to destroyed beta cells in the pancreatic islets (auto-immune). Diabetes can also be caused by inability of the insulin to act on the glucose due to resistance towards it in the patient's system as in Type 2 Diabetes [1]. The insulin helps in breaking down glucose to glycogen which is accepted by cells for various metabolic activities. According to the statistics published by the International Diabetes Federation (IDF) for 2021, about 537 million adults and around 1.2 million children and adolescents are suffering from diabetes [2]. This value is estimated to increase by more than a 100 million within the next 10 years. The symptoms of diabetes include polyuria (frequent urination), polydipsia (increased thirst), polyphagia (increased hunger), fatigue, blurred vision, delayed wound healing, and skin problems [3,4]. Prolonged exposure to the disease leads to fatal conditions such as keto-acidosis, cardiovascular diseases, kidney disorders, and diabetes has also to be a co-morbidity factor for COVID-19 related deaths recently [4,5].

Bone Mineral Density (BMD) is the measure of the mass of bone minerals within the bone tissues which determines the strength of the bone. The BMD is highly useful for diagnosing conditions such as osteoporosis [6]. The bone quality of an individual is also a factor which results in bone defects or fractures. It affects bone strength independently from BMD. It includes several structural and compositional factors such as internal and matrix composition of the bone, bone turnover, mineralization, microarchitecture, and microdamage [7]. Bone health is also indicated by the Bone Turnover Markers (BTM) which are indicative of the interplay of the bone cells in bone development and metabolism [8]. The bone formation markers like procollagen type I N propeptide (PINP), osteocalcin or alkaline phosphatase are directly related to osteoblast activity. The resorption marker levels, on the other hand, indicate osteoclast activity. These include N-telopeptide of type I collagen (NTX), carboxy-terminal crosslinking telopeptide of type I collagen (CTX), and Deoxypyridinoline (DPD). Over the years, several research have shown diabetes to affect the BMD, bone quality, and bone turnover of the patients leading to increase in incidents of fractures and defects in the bone. This review will target on the recent findings showing how diabetes along with several risk factors affects these three factors resulting in bone fracture or defects.

Mechanisms Behind Diabetes Leading to Bone Fragility

Several complex mechanisms affect bone fragility in patients with Diabetes Mellitus (DM) based on its effect on the genetic expressions, biochemical pathways, bone formation process, and cell-signaling mechanisms. Insulin is involved in the differentiation and apoptotic cell-signaling pathways for osteoblasts [9]. It de-represses the CDK-2 (cyclin-dependent kinase) pathway by blocking p27, resulting in proliferation and maturation of osteoblasts. Also, insulin inhibits apoptosis by activating the PI3K (phosphatidylinositol 3-kinase) pathway which inhibits BAD (BCL-associated death promoter) by phosphorylation. The Wnt signaling pathway is also affected in the diabetic patients resulting in poorer bone quality. The Sirtuin class of proteins, seven of which are present in the mammalian genome, has been found to play an important role in apoptosis and senescence of cells thereby affecting aging [10,11]. The altered expression of the Silent Information Regulator of Transcription1 (SIRT1) gene has also shown to affect insulin resistance, beta cell dysfunction and alterations in metabolic regulations in both T2DM and T1DM [12]. The SIRT1 gene expression is directly related to bone mass and has also been identified as an important genetic factor in osteoporosis [13]. Hence, depending on SIRT-1 expression levels, bone health in diabetic patients can vary. Biochemical pathway disruptions in diabetic patients lead to effects like accumulation of Advanced Glycation End-Products (AGEs) and amylin over-secretion. In T1DM patients, autoantibodies destroy the pancreatic beta cells inhibiting insulin production, but it also increases amylin production [14]. The amylin destroys osteoclasts and promotes osteoblast formation thus affecting bone resorption. The non-enzymatic glycation of proteins, phospholipids, and nucleic acids lead to formation of AGEs which is observed in Type 1 collagen resulting in its cross-linking [9,15]. This prevents adhesion of the osteoblasts to the ECM (Extracellular Matrix) making bones fragile. This occurs if the body is in hyperglycemic state which commonly happens in diabetic patients. In T2DM, decreased vitamin D serum levels affect calcium and phosphate homeostasis [16]. Also, number and function of osteoblasts decrease as they differentiate into fat-storing adipocytes resulting in bone marrow adiposity. Inflammation increases due to micro hypoxia in bone niche and expression of cytokines and chemokines increase leading to accumulation of pro-inflammatory macrophages (M1).

Among structural issues due to diabetes, micro- and macro-architecture abnormalities and tissue material damage result in bone fragility. Patients with T1DM and T2DM diabetes respectively suffer from early bone loss or development of abnormal osseous architecture which incorrectly show increased or normal BMD. These at a later stage result in increase of incidents of bone fracture and defects [17]. Factors like increased frequency of falls also occur due to diabetic complications or treatment induced hypo-glycemia thereby leading to poor bone health and increased risk of fractures [18].

Bone Health Depends on other Risk Factors in Diabetic Patients

Other than the mechanisms indicated above, various risk factors such as age, sex, other diseases, treatment options and other lifestyle factors also contribute to poorer bone quality and/or BMD thereby leading to poor bone health. Some of the recently studied risk factors have been documented in the table below (Table 1) [19-28].

Table 1:

Risk Factors	Diabetes Type	Sample Analyzed	Test Group	Effects Observed	References
Early onset (before 20 years of age)	T1D	Lumbar spine, hip, distal radius [areal BMD (aBMD)]; tibia, ulna, outer forearm distal to proximal [volumetric BMD (vBMD)]; blood (for markers of bone health)	Post-menopausal women with and without T1D (47 patients total)	Lower trabecular vBMD observed at the distal radius compared to both late onset and non-diabetic patients; Cortical size deficit at tibia shaft also observed	Shah et al. [19]
Oral glucocorticoid (GC) therapy	DM	Lumbar Spine (LS)– BMD compared with Trabecular Bone Score (TBS)	Men and women with DM/ only on GC/on GC with DM, 55 years of age or above (477 patients in total)	Men with DM and on GC showed the lowest mean LS among all groups; Women with DM and on GC showed lowest LS-BMD; All-over TBS had a better correlation to diabetes	Xue et al. [20]
Metabolic syndrome and insulin resistance	T1DM	LS-BMD and TBS compared; blood analysis	T1DM patients (47 patients) and control group (47 people)	TBS was lower in T1DM patients; metabolic syndrome and insulin resistance, in addition, led to lower TBS	Shah et al. [21]
HbA1c levels, diabetes duration, Microvascular Disease (MVD)	T2DM	vBMD, distal radius and tibia strength, bone microarchitecture	Cross-sectional data for Radius (410 patients), tibia (198 patients) from normal/ prediabetic/T2DM affected patients	MVD showed no correlations; Pre-diabetics showed lower trabecular number (Tb.N) and cross-sectional (CS) area of tibia; HbA1c>7% showed lower cortical vBMD and thickness and higher porosity, higher Tb.N and lower trabecular thickness (Tb.Th);	De Waard et al. [22]

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Adolescence	T1DM	vBMD of non-dominant tibia; blood analysis for 25(OH)D vitamin and HbA1c	Children and adolescents (95 patients in total) 59 boys, 36 girls	T1DM patients had lower trabecular BMD, stress-strain index, cortical thickness, lower relative muscle power and force; cortical BMD was increased	Maratova et al. [23]
Osteoporosis and osteoarthritis	T2DM	BMD of total hip and femoral neck; Femoral head sample analysis; biochemical tests	Patients with hip fracture (OP) with and without T2DM (36 and 54 patients respectively), with osteoarthritis (OA) with and without T2DM (22 and 28 patients respectively) (140 patients total)	Compared to OA group, the OP, OP-T2DM, and OA-T2DM groups showed decrease in bone volume fraction, in Tb.N and Tb.Th, and in biomechanical parameters; Structural Model Index (SMI) and trabecular bone pattern factor (Tb.Pf) increased	Giner et al. [24]
Treatments with insulin, metformin, and rosiglitazone	T2DM	Blood Plasma analysis for Bone Turnover Markers (BTM) for bone resorption (CTX) and formation (PINP)	Diabetic patients administered human insulin, metformin, rosiglitazone, and/or placebo combinations till 24 months (371 patients in total)	BTMs generally remained high from 12 to 24 months of treatment; Metformin and metformin+rosiglitazone showed lower amount of BTM-PINP indicating better bone formation; No such effect was seen with insulin or only rosiglitazone;	Stage et al. [25]
Bone Alkaline Phosphatase (BAP)	DM	BMD analysis for head, left arm, pelvis, LS, trunk, and whole body	Diabetic (143) and non-diabetic (4054) patients (aged 8 years or older, 4197 persons in total)	All BMD values decreased significantly in DM patients (except head) and normal persons on increasing BAP concentration; Lifestyle factors like smoking, obesity, and others affected BAP concentrations	Chen et al. [26]
Conventional insulin therapy and Autologous Non-myeloablative Hematopoietic Stem-Cell Transplantation (AHST)	T1DM	BMD and TBS, Bone Marrow Adipose Tissue (BMAT) in L3 vertebra, Visceral and Subcutaneous Adipose Tissue (VAT and SAT), Intrahepatic Lipids (IHL),	Normal persons (24), T1DM patients (23) and T1DM patients treated with AHST (9)	Lower TBS observed in L3-LS in all T1DM patients; No effects seen on adipose tissues irrespective of the type of treatment administered; No excess fat deposition observed in liver even in overweight diabetic patients	Carvalho et al. [27]
Non-Alcoholic Fatty Liver Disease (NAFLD)	T2DM	Liver (for NAFLD progression check); blood analysis (for vitamin D3, BTMs)	Post-menopausal women with NAFLD with fibrosis (10) and without fibrosis (52), and free from steatosis (15)	Women with NAFLD and significant fibrosis had significantly higher sclerostin levels and lower BMT levels (DKK-1, RANKL and sCTX) compared to other groups.	Mantovani et al. [28]

Conclusion

The poor quality and mineral density of bones make managing the already complicated diabetes much more difficult. Keeping the risk factors and mechanisms in mind, newer therapies should be developed which will help make the lives of the patients easier. This mini-review attempts at shortly summarizing the most recent research done in this aspect for researchers. Not only that, but it also aims at increasing awareness among the patients and their relatives regarding the potential risk factors responsible for worsening the disease.

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