Journal of Chemical Health Risks

www.jchr.org

JCHR (2026) 16(2), 1010-1018 | ISSN:2251-6727

Paradox of Diabetes and Bone Health: A Comprehensive Review on Silent Epidemic

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(Received: 16 January 2026 Revised: 25 February 2026 Accepted: 17 March 2026)

KEYWORDS

Type 2 Diabetes Mellitus, Bone Health, Bone Turnover Markers, Osteopathy, P1NP, CTX 1

ABSTRACT:

Introduction: The prevalence of diabetes is on the rise and an approximate figure of 530 million individuals globally have the disease. It is a long-term metabolic condition that simply implies that the body is unable to deal with glucose appropriately. The frequent complications of diabetes are cardiovascular disease, eye (retinopathy) and kidney complications. The fourth, which is osteopathy, is being researched by the researchers. In this narrative review, we are talking about the possibilities of diabetes being the cause of the osteopathy. Several researchers have reported that there is association bone health with type 2 diabetes mellitus. In type 2 diabetes mellitus bone mineral density (BMD) is can be normal or sometimes increased with shall indicate a false positive normal bone density in later one. In such cases although the BMD appears to be normal to high but the bone health is not adequate with later leads to complications such as bone fractures.

Objectives: The objective of this review is to emphasize on the bone health in individuals who are suffering from the condition of type 2 Diabetes Mellitus patients and emphasize on the bone formation and bone resorption markers for the assessment of bone health as researches have suggest that T2DM individuals might have normal to elevated bone mineral density despite of having deteriorated bone health.

Methods: Our search terms in the literature were "Type 2 Diabetes Mellitus and Bone Health", "P1NP and CTX1", "Diabetes and Bone Health", and "osteopathy and Diabetes". A systematic search was used to identify papers published within the last ten years in Scopus, PubMed, Embase, and Web of Science and kept open-access English articles, which involved clinical trials, cohort studies, cross sectional studies and case-control designs published till the end of December 2025.

1. Introduction

I have been researching on Diabetes Mellitus or DM as it is commonly referred to and it happens that it is one of the most widespread diseases in existence, and it is only becoming more widespread with each passing year. The International Diabetes Federation (IDF) (2021) indicated that there are approximately 530 million diabetic individuals across the globe. In the year 2045 alone, this number is expected to catapult to 780 million- talk of a huge surge. Diabetes gets in the way of glucose metabolism and may cause numerous complications. The common ones are diabetic nephropathy, neuropathy, retinopathy, and heart disease. According to the latest Diabetes Atlas (2025), approximately 11.1 percent or one in every nine adults aged 20 to 79 years has diabetes, and more than 40 percent of them have it without any knowledge whatsoever. According to studies of WHO, in developed countries, the largest proportion of new cases is in those 65 years and more. In India and other developing states, 45-64 bracket, which are still in their productive age, will experience the largest growth. This may be very damaging to the economies of the emerging countries. [1], Thus, as the world is ageing and altering their lifestyles, diabetes mellitus (DM) has become an

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JCHR (2026) 16(2), 1010-1018 | ISSN:2251-6727

epidemic issue in the society. It has become the third most prevalent non-communicable disease after cardiac disease and cancer. Diabetes is a set of metabolic diseases whose hyperglycemia is unremitting and the result of various factors. In the recent past, however, the interest in the effect of diabetes on the skeletal structures has been on the increase. [2]. In my notes, I have observed that diabetes mellitus, on the contrary, predisposes persons to bone loss and osteoporosis and the effects of type 1 (T1DM) and type 2 (T2DM) diabetes on bones is quite dissimilar [3]. T1DM is, in fact, a fact causing bone problems to be real bone knockers-downers. The fact that a person develops T1DM when in their teens is not good at all since the bones are at the stage of rapid growth. By implication, owing to the early development of the bones, they become highly probable to run into serious bone problems in the future. To add to that, the fact is that obesity as a metabolic condition only intensifies the bone-damage processes of the T2DM. [4].

2. Objectives

The objective of this review is to emphasize on the bone health in individuals who are suffering from the condition of type 2 Diabetes Mellitus patients and emphasize on the bone formation and bone resorption markers for the assessment of bone health as researches have suggest that T2DM individuals might have normal to elevated bone mineral density despite of having deteriorated bone health.

3. Methods

Our search terms in the literature were “Type 2 Diabetes Mellitus and Bone Health”, “P1NP and CTX1”, “Diabetes and Bone Health”, and “osteopathy and Diabetes”. A systematic search was used to identify papers published within the last ten years in Scopus, PubMed, Embase, and Web of Science and kept open-access English articles, which involved clinical trials, cohort studies, and case-control designs published till the end of December 2025. A total 540 papers were retrieved. Out of which only 07 articles were included in this comprehensive review.

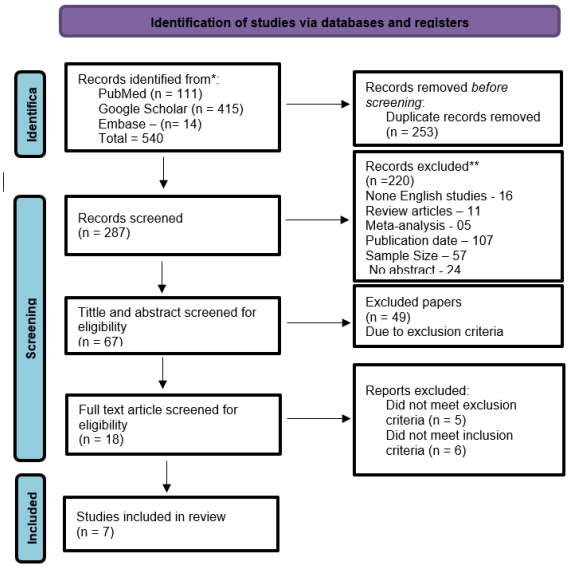

Fig. 1 Flow diagram for the study selection process.

Effects of Type 1 Diabetes Mellitus on Bone Metabolism:

The complications that are the majority in type 1 diabetes are basically driven by hyperglycemia. Scientists have discovered that individuals with such disorder are known to build harmful advanced glycation end products (AGEs). [5]. It happens that, in reality, this is really nothing more than a non-enzymatic reaction of glucose with lipids or proteins and that it is more prevalent in individuals who are not receiving sufficient glucose. What is even better is that these developed glycation end products actually cause mesenchymal cell death which prevents the transformation of mesenchymal cells into cartilage, fat cells or bone cells. [6]. The elevated glucose levels were observed to inhibit osteoblast production of the osteocalcin protein, which was found to be consequential in the lack of bone development after a long period of exposure to this condition [7]. In Type 1 Diabetes Mellitus mice, osteocalcin, matrix metallopeptidase-13 (MMP-13), vascular endothelial growth factor, and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) expression in osteoblasts is also shown to be inhibited, implying that chronic hyperglycemia can affect all stages of osteoblast development [8].Type 1 Diabetes Mellitus appears to affect the osteoblast microarchitecture The mesenchymal progenitor cells in the bone marrow of patients with type 1 diabetes are altered to promote adipogenesis. This is believed to be linked to some extent of difference manifestation of growth hormones, these

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are IGF-1 and TGF-b1. Mice with Streptozocin-induced diabetes resembling T1DM exhibited reduced concentrations of IGF-1, IGF-1 receptors, and insulin receptors with impaired bone development [9].

Type 2 Diabetes Mellitus Effect on Bone Metabolism:

T2DM subjects were found to have high bone mineral density (BMD), whereas T1DM subjects had reduced BMD. Ma and colleagues evaluated the femoral spine, hip, and neck and reported that they observed that BMD was substantially higher in patients with T2DM, compared to both patients with T1DM and patients without T1DM or T2DM. This was done by conducting a meta-analysis study of 15 studies, encompassing 19,139 controls and 3437 patients with Type 1 and Type 2 Diabetes [10]. Well, this may not appear that well, however, it happens that an increase in BMD is actually accompanied by a decrease in total bone turnover. Various studies have indicated that we are in fact losing bone turnover indicators such as osteocalcin, type 1 cross-linked N-telopeptide (NTX) and type 1 cross-linked C-telopeptide (CTX-1). And, just to add, hyperinsulinemia in T2DM patients might be the cause of that increased BMD; the structural similarity of insulin allows it to bind to the IGF-1 receptor on osteoblasts. In both mouse and human models, IGF-1 is known to increase bone mineral density in an incredibly remarkable manner. [12]. It has been established that Type 2 Diabetes Mellitus is closely associated with obesity, which is a body mass index, or BMI of above thirty. In a follow-up study, BMI was the strongest predictor of type 2 diabetes in 2204 women. It has also been found that there is a positive association between obesity and BMD and numerous theories have been put forward to explain such an association. Adipose tissue also releases a variety of adipokines, including leptin which was observed to be raised in plasma of diabetic men relative to healthy men. [14]. I was researching on the mechanism of working of plasma leptin and discovered that it does not only decrease osteoclast formation by decrease the productions of the RANK - ligand, but also increases osteoblast production, which ultimately leads to bone formation. [15].

Anti-diabetic Medicines and Bone Metabolism:

Insulin-sensitizing drugs, incretin mimetics, secretagogues simulate the effect of gut hormones and have been implemented as a T1DM treatment. [16]. The treatment of T1DM bears very few possibilities due to total insulin deficiency. In T1DM, timing and regulation of meals, level of blood glucose and external insulin are also required by the patients. [17]. To minimize the potential negative outcomes, patients with T1DM and T2DM ought to be administered drugs with a positive or neutral effects on bones. Relatively smaller insulin deficit in Type 2 Diabetes Mellitus take advantage of more specifically available therapies. All these therapies are good, but they may cause weight gain and bone malfunction. The most common first-line therapy of T2DM is Metformin. Metformin is also demonstrated to enhance osteogenesis in vitro and in vivo and this could be the reason that these individuals have high BMD. [19]. In case of failure of metformin in helping the patient achieve his or her target plasma glucose level, alternative management interventions can be considered. Thiazolidinedione (TZDs) including rosiglitazone and pioglitazone are insulin sensitizing agents [20]. TZDs activate the nuclear receptor of PPAR-g that is located in the fat tissue and is involved in the regulation of insulin sensitivity. When PPAR-g is stimulated it leads to proliferation of adipocytes and insulin sensitivity that leads to accumulation of fatty acids and low concentration. Compared to other therapies, this therapy is superior in lowering the level of blood sugar but has serious side effects. The available large body of literature assessing the application of TZD in diabetes has demonstrated its adverse effect on bone. [21].

The Secondary Effect of Diabetes Mellitus Type 1 and Type 2 on Bone Health

There are similar secondary outcomes of T1DM and T2DM (skeletal microarchitecture, diminished bone cell differentiation potential, bone fractures). Diabetic patients are at risk of developing chronic renal disease, cardiac disease, osteoporosis, and neuropathy. Many of these secondary disorders will involve bone quality and cause the change of bone formation, and it is associated with microvascular disease (MVD) in diabetes mellitus. MVD changes blood circulation in cortical bone due to the decreased blood circulation and density of micro vasculatures in bone marrow. In combination with the inability to heal bone after the injuries, a deficient blood supply contributes to the development of small fractures. [23]. Osteoporosis is another serious comorbidity, which destroys bone mineralization, and bone structure in DM. The osteoporosis is very prevalent among the

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JCHR (2026) 16(2), 1010-1018 | ISSN:2251-6727

postmenopausal women as well as among those who have had the condition longer which only adds to the adverse effects on the bone further. [24]. T1D can lower the BMD and bone mass. This reveals the risk possibility of being affected by osteoporosis which causes bone weakness. [25]. T2D has high BMD as compared to low BMD seen in osteoporosis. Aggregation of AGE affects the crosslinking of type 1 collagen and makes the bones weak, thereby predisposing people to develop osteoporosis [23]. Patients suffering DM are prone to fracture due to long term symptoms of peripheral neuropathy and retinopathy. As the neuropathy is a damage done to the nerves, it causes the individual to experience numbness, weakness, and insensibility in the upper limb and lower limb. Diabetic retinopathy leads to partial or total blindness because that blood vessels of the retina are destroyed. Both disorders concerning diabetes expose one to falls because of loss of foot sensation and sight that makes walking challenging [26]. In addition to the expression of the negative bone outcomes caused by diabetes mellitus, the elevated risk associated with falls results into elevated risk of fractures eventually. [27].

Diabetes Mellitus and Bone Mineral Density.

Despite the fact that bone pathology and secondary diseases in T1D and T2D are similar, several pertinent differences between the two conditions are relevant with regard to the precise etiology of augmented danger of fractures. The BMD is the first distinction between two kinds of diabetes mellitus. T2D is a condition that is usually linked with high BMD and T1DM is also known to have a low BMD. [28]. The resulting conflicting information has led to silent research on the paradox of Type 2Diabetes Mellitus with an augmented BMD and the augmented hazard of fractures. This result is suggestive that there are other inspirational factors that lead to diabetes fractures and that BMD is not the sole predictor of fracture. [29]. Reduced levels of IGF-1 can be an explanation of why T1DM has poor BMD. It is among the significant causative factors in Type 1Diabetes Mellitus diminished trabecular bone tally, cortical thickness and bone turnover, which also augment the possibility of osteoporotic fractures. Rather, T2DM patients tend to eat improperly and they can also be obese and with chronic hyperglycemia. The hyperglycemia in the type 2 diabetes causes a rise in the AGE levels causing the breakdown of the type 1 collagen. Despite the fact that patients with T2DM possess large BMD, AGEs, oxidative stress and inflammation predisposes fracture in the patients [30].

Bone turnover Markers

BTMs or Bone turnover Markers are classified into two types viz. bone formation markers such as Bone Alkaline Phosphatase and P1NP and bone resorption markers such as CTX 1 and NTX.

Pro Collagen Type 1 N-Propeptide (P1NP)

Pro Collagen Type 1 N-Propeptide (P1NP) is trimeric peptide which is around 35,000 kDa in mass, and have two type 1 procollagen- α1 chains and a procollagen α2 chain which is binds noncovalently (Figure 2) [31]. Osteoblast and fibroblast synthesize Type 1 Procollagen, when procollagen turns into collagen, some proteases cleave the N and C terminal extension of Type 1 procollagen [32]. Subsequently bone matrix conjugated with procollagen type 1, consisting of P1CP and P1NP. P1NP being a bone development biomarker, serves as a unique sign of Type 1 collagen deposition. The interior cells release P1NP throughout the production of type 1 collagen synthesis in cells and is found in systemic circulation. P1NP typically releases in trimeric structure which is originated from the structure of trimeric collagen, which undergoes through a rapid transformation into a monomeric form because of the effect of thermal degradation [33]. Serum P1NP is a promising biomarker for assessing the bone health in osteoporosis. The monitoring is significant due to its moderately low sensitivity to changes in circadian rhythm and meal intake variability. Furthermore, is it also shows reasonable level of stability in typical conditions. The International Osteoporosis foundation (IOF) and the International Federation of Clinical Chemistry (IFCC) suggest that P1NP is an ideal biomarker for the assessment of bone health which they concluded after extensive examination of Bone Turnover Markers (BTMs) [34].

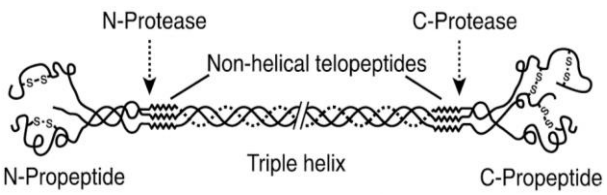

Figure 2. The structure of the collagen type I molecule.
(Figure courtesy of Simon Robins, Aberdeen, UK.)

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C-terminal Telopeptide of Type I collagen

CTX 1 is formed by the breakdown of type 2 collagen containing pyridinium cross links. Collagen type 1 telopeptides are investigated extensively and are used as the markers of bone resorption which includes Carboxy-terminal crosslinked (CTX-1) and amino terminal crosslinked (NTX-1). Both markers are released during the degradation of collagen [35]. CTX -1 is breakdown product of type 1 collagen which contains pyridinium cross links and excreted by kidneys [36]. Serum concentration are significantly correlated with histomorphometric measures of bone resorption [37]. CTX-1, a peptide compound which is made up of 8 amino acids sequence, and a product of cathepsin K digestion of type 2 collagen [38]. CTX-1 is currently in e of the promising bone resorption marker as it is released directly through bone digestion. Which results, estimating this biomarker may provide direct analysis of rate of bone resorption [39].

Discussion

Hou et. al. [40]in their study highlights significant deterioration in bone health among type 2 diabetes mellitus patients, primarily driven by impaired bone formation rather than accelerated bone resorption. Serum Osteocalcin and P1NP, key markers of osteoblastic activity and collagen synthesis were notably decreased, indicating suppressed anabolic processes likely due to high blood glucose levels and insulin resistance. On the contrary, serum CTX 1 level, which reflects osteoclast mediated bone breakdown, remained unchanged, suggesting no high turnover state but rather a low formation imbalance that comprises bone quality and elevates fracture risk. This pattern aligns with T2DM known skeletal complications where net bone loss occurs despite normal BMD in many cases, emphasizing the need for targeted monitoring. Jacob et. al. [41] conducted study on Danish population which reached a parallel conclusion, confirming significant bone health deterioration in T2DM patients through similar biomarkers. There was reduced serum osteocalcin and P1NP indicates suppressed bone formation, with unaltered or declining CTX 1 showing no ride in bone resorption. Safarova et. al. [42] in their Azerbaijan based study, demonstrated the utility of bone remodelling markers for the evaluation of bone health in type 2 diabetes patients, emphasizing their sensitivity to T2DM disrupting effects on bone microarchitecture, and recommended P1Np and CTX 1 as reliable indicators of bone formation and bone resorption respectively.

Authors	Study Type	Study Population	Key Observations
Hou Y et al 2023 [40]	Case-Control Study	Han Chinese	The study suggested that there was significant deterioration of bone health. Serum Osteocalcin and P1NP was decreased whereas the serum levels of CTX1 was not significantly altered.
Jakob et. al.2021 [41]	Case-Control Study	Danes	There was a significant decline in the serum concentration of Bone Formation and Bone resorption markers, CTX 1 and P1NP 1 respectively.
Safarova.2019 [42]	Cross Sectional	Azerbaijan	They have concluded that bone remodeling markers like P1Np and CTX 1 are useful for assessing the bone architecture in diabetes patients whereas bone health cannot be screened by bone mineral density.
Chenhe Zhao et. al. 2020 [43]	Cross Sectional	Chinese	Serum levels of Osteocalcin, P1NP, and CTX were inversely correlated with BMD levels in males across three sites and with total lumbar BMD in women with type 2 diabetes; the correlation varied between femur neck and whole hip BMD in women.
Kirsa Skov-Jeppesen et. al.2024 [44]	Randomized, Placebo-Controlled, Crossover Study	Danes	In Type 2 Diabetes Mellitus individuals, GIP and GLP2 markers are elicit acute suppression on bone formation and bone resorption.
Khandelwal et. al.2024 [45]	Cross Sectional	Indians	They found a significant decrease in bone formation and increase in bone resorption and suggested that all Type 2 Diabetic patient should be screened regularly for osteoporosis as there is a silent bone deterioration without any alteration in bone mineral density.
Reema et. Al 2020 [46]	Cross Sectional	Indians	They concluded that those patients who are obese and have uncontrolled high blood glucose level are more vulnerable for the bone disease and healthcare providers should keep them screen regularly for the osteopenia and osteoporosis.

Table 1. Summary of the studies about the impact of Type 2 Diabetes Mellitus on Bone Health and its microarchitecture.

P1NP releases during osteoblast collagen synthesis and CTX 1d, a product of osteoclast collagen degradation, provide dynamic insight in turnover imbalances, often showing P1NP suppression from diabetic hyperglycemia with variable CTX1 reflecting low resorption states that degrades trabecular integrity and elevates fracture risk without BMD changes. Chenhe Zaho et. al. [43] in their study on Chinese population, found that serum levels of osteocalcin, P1NP and CTX1 were inverse correlated with Bone Mineral Density (BMD)in both males and females with Type 2 diabetes (T2DM), meaning lower marker concentrations aligned with reduced BMD and heightened osteoporosis risk. Osteocalcin and P1NP, as formation markers, dropping alongside CTX 1 (resorption) suggest a low turnover state where diminished remodelling fails to maintain bone mass, exacerbated by T2DM's metabolic causes like insulin resistance and Advanced Glycation Endproducts (AGE's) impairing osteoblast-osteoclast coupling. This inverse relationship underscores these biomarkers prognostic value for BMD decline, unlike in non-diabetics where high turnover dominates, validating their use in research for predicting fragility. Kirsa et. al. [44] further concluded that bone deterioration in T2DM through biomarkers analysis, revealing disruption in bone turnover that align with the low formation, low to

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JCHR (2026) 16(2), 1010-1018 | ISSN:2251-6727

normal resorption pattern is reported. By measuring markers like osteocalcin, P1NP (formation) and CTX 1 (resorption), they likely observed significant declines, attributed to T2DM induced osteoblast dysfunction from hyperglycemia and insulin resistance leading to microarchitectural decay and elevated fracture susceptibility despite potentially persevered BMD. Khandelwal et. al. [45] In their study focused on Indian population concluded that Type 2 Diabetes significantly deteriorates bone structure and they have advocated for the regular osteoporosis screening intervals to mitigate elevated fracture risk in this high prevalence fracture risk in this high prevalence group. Reema et. al. [46] in their study on another Indian regional population determined that obese individual with uncontrolled blood glucose levels face heightened vulnerability to bone disease in type 2 diabetes mellitus patients recommending vigilant monitoring by healthcare providers to prevent complications. This synergy obesity and poor glycemic control promoting AGE's that impairs bone formation and accelerates microarchitectural deterioration, low turnover and fracture risk. The studies have suggested that there is a negative impact on bone health in T2DM patients. Currently the BMD is gold standard technique aimed for the assessment for the bone health however the changes in the BMD is slow and takes around 2 years to assess the treatment effectiveness. Although BMD measured by DEXA is used to diagnosed osteoporosis according to WHO recommendations [47].

Conclusion

Fragility of the bones among diabetic patients is actually common but somewhat unknown. The need to identify and manage bone frailty in the early stages of diabetic patients is supported by a plethora of studies on pathophysiology, clinical practice, and epidemiology. How osteoporotic drugs affect people with type 2 diabetes and how fracture prevention may affect the long-term mortality and the overall life quality will also be explored in my future sleep research. Diabetes is not an isolated entity and there are many factors contributing to the risk of fractures and poor bone healing. Bone weakness can be caused by different systems and enzymes, and it leads to a high risk of fractures. In my opinion, further research should be done to determine the key variables that can spur bone repair. That would help to prevent osteoporotic fractures in patients with Diabetes Mellitus. There are some promising emerging biomarkers like P1Np and CTX 1 which are very sensitive in early stages changes for the bone formation and bone resorption activity respectively and can be a gold standard for assessing the bone health in T2DM individual so that their bone health shall be monitored regularly.

Limitation

Honestly speaking, the diabetes crisis could not really be simply compared to the bone health as the studies differ enormously, some are more extended, some take into account more factors. Anyway, we are quite knowledgeable about the fact that diabetes is a risk factor. We had sliced up a fairly sizeable portion of papers in an effort to take in all of them but we probably had missed on quite a few which were mere conference abstracts.

Finally, some degree of bias will be present as we have not accessed non-English papers. Most of the systematic reviews that purely use English stuff are killed by that, though.

Acknowledgement

This work is acknowledged under Integral University manuscript number IU/R&D/2025-MCN0003999. The authors are also grateful to the Department of Allied and Healthcare Sciences, Faculty of Health and Medical Sciences, Integral University, Lucknow, Uttar Pradesh, India.

Disclosures

No conflicts of interest to declare.

Data Availability

The concept of data sharing is not applicable to the article because no data sets were developed or analyzed as part of the current research.

Funding

The study received no particular support from public, commercial, or non-profit agencies.

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