

## Type 1 diabetes and osteoporosis: A review of literature

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### ABSTRACT

With better care and intensive insulin therapy, microvascular complications have reduced and longevity has increased in patients with type 1 diabetes (T1DM). Therefore, there is a need to change the focus from microvascular complications to cardiovascular disease and osteoporosis. Though number of studies from other parts of the world show that patients with T1DM are at increased risk of osteoporosis and fractures, there is a paucity of data from India. A number of factors and mechanisms affecting bone health in patients with T1DM have been proposed. The main defect in genesis of osteoporosis is osteoblastic function, rather than osteoclastic overfunction. Assessment of bone mineral density by dual X-ray absorptiometry and other risk factors for osteoporosis, as a part of diagnostic procedure can help to design tailored treatment plans. A physically active healthy lifestyle, prevention of diabetic complications and adequate calcium and vitamin D supplementation are the mainstay for prevention of osteoporosis. Treatment of osteoporosis is not evidence based but it is proposed to be similar to osteoporosis associated with other conditions. Bisphosphonates are the mainstay for treatment of osteoporosis in patients with T1DM. However, more studies are needed to make definitive guidelines on prevention and treatment of osteoporosis in patients with T1DM.

**Key words:** Fracture risk, osteoporosis, type 1 diabetes

### INTRODUCTION

Prevalence of type 1 diabetes (T1DM) is rising in India. There are only few epidemiological studies that estimated the prevalence of T1DM in India. The available published studies from different parts of India reveal the prevalence of T1DM in the range of 3.7 to 10.2 per 100,000 populations, with higher prevalence in urban area and in males.<sup>[1-4]</sup> With the advent of insulin in 1921-1922, there has been dramatic reduction in mortality due to acute complications in patients with T1DM. Furthermore, with the advancement

in newer insulin analogues and technologies like continuous glucose monitors and insulin pumps, more patients with T1DM are able to achieve goal A1c without significant hypoglycemia. Additionally, there has been a significant decline in microvascular complications.<sup>[5,6]</sup> As a result of this, the life expectancy in patients with T1DM has increased remarkably<sup>[7]</sup> and more patients with T1DM are now older than 60 years. Hence, there is need to focus more on other age related complications which can be potentiated by diabetes, including osteoporosis, cardiovascular disorders and cognition in older individuals with T1DM. Evidence based management of type 2 diabetes (T2DM) in older patients with various comorbidities is well- known, but is not clear for T1DM.<sup>[8]</sup>

Localized involvement of skeleton like Charcot's arthropathy is a well recognized complication of diabetes. Though Albright recognized generalized involvement of skeletal in 1948, there was not much attention focused on this area.<sup>[9]</sup> In the past decade, a number of epidemiological studies showed that there is an increase

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in the incidence of osteopenia, osteoporosis and fracture risk in patients with T1DM. A number of mechanisms have been proposed but none of them have been proven. There is lack of data in the therapeutic area for patients with osteoporosis and T1DM. This review will highlight the epidemiology, mechanisms, preventive strategies, treatment and future perspective in this important area.

## EPIDEMIOLOGY OF OSTEOPOROSIS IN PATIENTS WITH T1DM

Osteopenia was described in patients with T1DM even before the availability of bone mineral density (BMD) measurement technique.<sup>[9]</sup> Many studies, though not all, carried out with the older techniques to measure BMD, like single photon absorptiometry (SPA) or dual photon absorptiometry (DPA), demonstrated that BMD is lower in adolescents and adults with T1DM compared to control population.<sup>[10-14]</sup> Similar findings have been noted by the recent studies carried out using newer technologies to measure BMD like dual X-ray absorptiometry (DXA).<sup>[15-18]</sup> However, the data is not consistent among all the studies.<sup>[10-20]</sup>

Despite the lack of consistent evidence of reduced BMD in T1DM, combined study analysis have estimated that in T1DM fracture risk is increased by 1- to 2-fold at any skeletal site.<sup>[21]</sup> A recent meta-analysis revealed six-fold increased risk for hip fracture in patients with T1DM, which was higher than would have been expected on the basis of BMD.<sup>[22]</sup> Looking at the literature, it is quite clear that patients with T1DM are at high risk of osteoporosis and fracture.

There is relative paucity of data on prevalence of osteoporosis and fracture in patients with T1DM from India. The only published study from western India by Joshi *et al.*, compared 86 patients of T1DM between 12- 45 years of age and mean disease duration of 14.6 years with age, sex and body mass index (BMI) matched controls. BMD of total body and lumbar spine was significantly lower in patients with T1DM compared to controls. Furthermore, patients with T1DM had 10% less bone mineral content (BMC) in comparison with controls.<sup>[23]</sup> This study suggests that Indian patients with T1DM are at higher risk for fracture.

## FACTORS INFLUENCING THE BONE IN PATIENTS WITH T1DM

The decrease bone formation and inadequate accrual peak bone mass in children with prepubertal onset T1DM has been proposed as a major contributing factor for low bone strength and osteoporosis in later life.<sup>[24]</sup> Men with T1DM tend to be particularly prone to osteopenia or

osteoporosis compared to women of similar ages.<sup>[19,25,26]</sup> Estrogen adequacy and/or use of estrogen-based oral contraceptive pills might be the reason for higher bone mass in women compared to men.<sup>[25,27]</sup> Furthermore, hypogonadism is quite common in men with T1DM and that may contribute to osteoporosis in males.<sup>[28,29]</sup> Another factor which may influence the BMD is body mass index (BMI). Studies have shown that lower BMI is associated with higher incidence of osteoporosis. The adipose tissue, apart from providing mechanical loading, also increases BMD through the activity of adipocytokines. Patients with T1DM have low BMI and hence, they are more prone to develop osteoporosis.<sup>[21]</sup> Patients with T1DM also have a negative calcium balance as a result of hypercalciuria during periods of hyperglycemia, functional hypoparathyroidism, vitamin D deficiency and alterations in vitamin D metabolism.<sup>[30-32]</sup>

A number of studies have shown that poor glycemic control in patients with T1DM is associated with osteopenia and osteoporosis.<sup>[22,23]</sup> Poor glycemic control for long period of time can result into microvascular complications and can aggravate the loss of bone density by various mechanisms. Retinopathy and neuropathy can predispose patients with diabetes to fall while nephropathy results into hypercalciuria and can alter the vitamin D metabolism causing vitamin D deficiency.<sup>[33-35]</sup> Furthermore, use of loop diuretics in patients with diabetic nephropathy is associated with low BMD as these drugs cause the renal excretion of calcium.<sup>[36]</sup>

Patients with T1DM have increased risk of other autoimmune disorders like autoimmune thyroid disease and celiac disease.<sup>[37]</sup> Clinical observation indicates that the clustering of three autoimmune diseases (Type 1 diabetes, celiac disease and thyroiditis) significantly increases the occurrence of osteopenia. It is possible that bone impairment might be considered not only a complication due to endocrine or nutritional mechanisms, but also a consequence of an immunoregulatory imbalance.<sup>[38]</sup>

In a study of 260 patients of T1DM from South India, Turner's syndrome was associated with 3.5% patients and Klinefelter's syndrome with 1.9% patients.<sup>[39]</sup> These associated syndromes in patients with T1DM can pose higher risk for osteoporosis.<sup>[40,41]</sup>

## POTENTIAL MECHANISMS FOR OSTEOPOROSIS IN T1DM

The growth of bone during early age and puberty is by a process called "modeling", which is different than remodeling that occurs in adults. In modeling, the osteoblast

functions to lay down the bone which is being shaped by osteoclast.<sup>[42]</sup> The number of hormones like gonadal steroids, insulin, growth hormones, growth factors and cytokines play vital a role in this process of modeling resulting in the achievement of peak bone mass. Any alteration in these hormones is associated with orchestrated bone modeling process which can result in osteopenia and osteoporosis. Many theories have been proposed for the development of osteopenia or osteoporosis in patients with T1DM. Most of the work has been carried out in animal models or *in vitro* analysis and none has been proven. Here, we summarize the possible detrimental consequences of insulin deficiency and hyperglycemia on bone development.

T1DM is characterized by autoimmune destruction of beta cells resulting in near complete deficiency of insulin causing hyperglycemia.<sup>[6]</sup> Hyperglycemia affects the bone development in various ways; (1) it damages osteoblast either by osmotic damage or by suppressing gene expression responsible for osteoblast maturation.<sup>[43]</sup> (2) it increases PPAR $\gamma$  that promote adipogenesis from mesenchymal stem cells at the expense of bone formation thus reducing bone accrual and peak bone mass.<sup>[44,45]</sup> Glitazones, like pioglitazone, are agonists of PPAR $\gamma$  and they are linked to more fractures and low bone mass.<sup>[46,47]</sup> (3) The mice model and *in vitro* studies showed that hyperglycemia directly inhibits the bone formation as shown by expression of transcription factor RUNX2, biochemical markers and histomorphometric analysis.<sup>[48,49]</sup> (4) hyperglycemia also induces the expression of proinflammatory cytokines like

TNF $\alpha$  which inhibits osteoblast differentiation and activity, thus increasing osteoblastic apoptosis.<sup>[50,51]</sup> (5) hyperglycemia may results in the generation of increase reactive oxygen species which in turn can increase osteoclast formation and activity.<sup>[52]</sup> (6) Chronic hyperglycemia leads to development of microvascular complication like retinopathy, neuropathy and nephropathy.<sup>[53]</sup> Advance retinopathy increases the risk of fall by impairing vision which is further aggravated by the presence of diabetic neuropathy. Additionally, nephropathy can result in increase in protein loss which aggravates osteoporosis in patients with diabetes.<sup>[21,54,55]</sup> [Figure 1]

The distinct reduction of peak bone mass in some patients with T1DM has led to the hypothesis that insulin has anabolic effects on bone.<sup>[56]</sup> Hence, patients with T1DM who are deficient in insulin are at risk of osteoporosis. This hypothesis is being substantiated by the fact that BMD is higher in patients with T2DM who are hyperinsulinemic. The mechanism underlying the anabolic effect of insulin may be either by direct stimulation of osteoblast or indirectly by increasing the transcription of RUNX2.<sup>[57,58]</sup> Furthermore, it is known many of the effects of insulin are mediated by Insulin- like Growth Factor-1 (IGF).<sup>[59]</sup> In patients with uncontrolled T1DM, the levels of free IGF-1 are low due to increase in IGF- binding proteins particularly IGFBP3.<sup>[60]</sup> Hence, low IGF-1, as a result of insulin deficiency may result in low accrual of peak bone mass. Furthermore, intensive insulin therapy has been shown to stabilize the BMD in patients with T1DM.<sup>[21]</sup> [Figure 1].

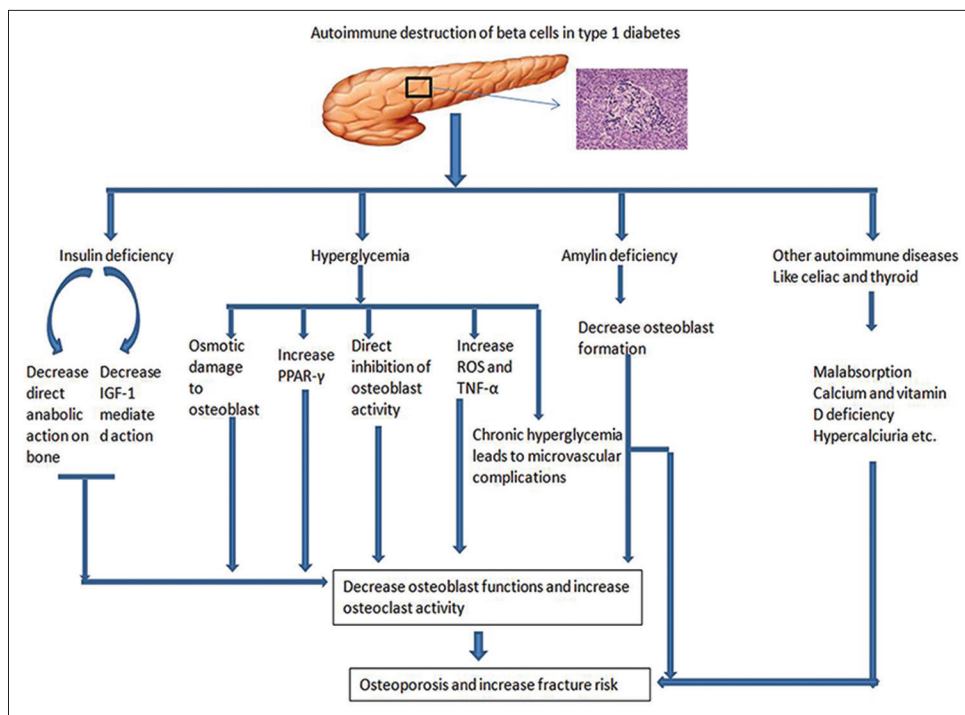


Figure 1: Potential mechanisms leading to osteoporosis in patients with T1DM

In addition to insulin, patients with T1DM are deficient in amylin (IAPP); a hormone co-secreted with insulin by pancreatic beta cells. In rodent models of T1DM, amylin has been shown to increase osteoblastic and chondrocyte proliferation activity, while suppressing osteoclastic proliferation and activity.<sup>[61]</sup> [Figure 1]

T1DM is associated with other autoimmune syndromes like celiac disease. In a study from North India, the prevalence of celiac disease in patients with T1DM is 11.1%.<sup>[62]</sup> Celiac disease via various mechanisms like vitamin D deficiency, malabsorption, weight loss and reduction in IGF-1 results into low BMD and osteoporosis in children.<sup>[63]</sup>

## DIAGNOSIS OF OSTEOPOROSIS IN T1DM

Although diagnostic modalities for osteoporosis are similar in individuals with or without diabetes, some additional considerations should be applied to patients with diabetes.<sup>[21]</sup> DXA is the standard bone imaging method for children, adolescents and adults because of its availability, reproducibility, speed and low exposure to ionizing radiation.<sup>[64,65]</sup> There are no guidelines available to clinicians on how and when to measure the BMD in children with T1DM. The International Society of Clinical Densitometry (ISCD) recommends that bone mass measured by DXA should be reported as BMC or areal BMD which can be compared with reference values from children of similar age, gender and if possible race/ethnicity to calculate Z-score.<sup>[66]</sup> However, this recommendation is based mainly on expert opinion rather than evidence. The challenges currently for the measurement of BMD in children are; (1) there is no standardized reference BMD using DXA technology (2) there is no normative data across different ethnic children standardized as per age, race, BMI and height. However, attempts are going on towards making a normative curve for BMD in children.<sup>[67]</sup> Recently, American academy of pediatrics has published guidelines for the measurement of BMD in children and adolescent. These guidelines focus mainly on children with cystic fibrosis and cancer, but lack focus on T1DM.<sup>[68]</sup> One potential drawback of DXA when used for patients with T1DM is that it does not take into account the bone size and geometry because children with T1DM have small bones.<sup>[24]</sup> Another bone assessment technique, peripheral quantitative computed tomography (pQCT), might overcome this limitation. It measures volumetric apparent BMD, cross sectional area (CSA) and also differentiates between cortical and trabecular bone.<sup>[69]</sup> Finding from clinical assessment and BMD should be considered together to calculate the 10-year risk of sustaining an osteoporotic fracture. The FRAX<sup>®</sup> tool from the WHO is available to facilitate the calculation of fracture risk.<sup>[70]</sup> This tool was initially used

in 12 countries, but recently data from Indians living in Singapore has also been added to it. Many Endocrinologists suggest the use of FRAX using the Singapore data to predict the fracture risk among Indians.<sup>[71]</sup> This tool has many limitations including its utility in children and adolescents with T1DM, which is currently unknown.<sup>[72]</sup>

## PREVENTION OF OSTEOPOROSIS IN T1DM

Since the data indicates that bone accrual decreases from the diagnosis of T1DM, the preventive strategies should be considered from the beginning and incorporated along with the diabetes management. Physical activity is the best way to promote the bone accrual and bone strength during childhood and adolescence. The discussion of type of exercise, mechanism by which exercise helps, is beyond the scope of this review.<sup>[73]</sup> In one study, regular weight-bearing physical activity (180 min/wk, including ball games, jumping activities, and gymnastics) improved total and lumbar bone mineral accretion in children with T1DM, in a similar magnitude to healthy subjects.<sup>[74]</sup> Therefore, children with T1DM should be encouraged to have regular physical activity. As we discussed previously, vitamin D deficiency is rampant in these children. Replacement of vitamin D along with calcium has been found to improve the BMD in children with T1DM. Therefore, all children with T1DM should be recommended to have adequate calcium intake (1200 mg/day) and replacement of vitamin D, if they are deficient. Diabetic complications like retinopathy and nephropathy can increase the risk of osteoporosis and fracture. Prevention and early treatment of these complications benefit patients with T1DM. Diabetes Control and Complications Trial (DCCT) clearly showed that intensive insulin treatment reduces the risk of these microvascular complications by 35-60%.<sup>[75]</sup> Hence, the physicians should try to achieve the goal A1c without causing hypoglycemia in patients with T1DM. Certain medications like glitazone and diuretics should be avoided in high risk patients.<sup>[36,46,47]</sup> Furthermore, the treatment of associated autoimmune disease may prevent osteoporosis. For example, gluten free diet in patients with celiac disease increases the BMD.<sup>[76,77]</sup>

## TREATMENT OF OSTEOPOROSIS IN PATIENTS WITH T1DM

The management of osteoporosis in patients with T1DM is not evidence based. Vestergaard and colleagues studied whether the reduction in bone turnover by use of antiresorptive drugs is detrimental in patients with diabetes. They studied a nationwide cohort from Denmark who used antiresorptive therapy and compared the benefit in



terms of fracture prevention in those with diabetes and those without diabetes. They concluded that diabetes does not seem to affect the fracture-preventive potential of bisphosphonates or raloxifene.<sup>[78]</sup> In absence of randomized control trials, this study at least reassures clinicians to use antiresorptive therapy in patients with T1DM with osteoporosis. The newer agent, denosumab has been used in many osteoporotic conditions, but there is lack of data on its use in patients with T1DM.

The main defect in the genesis of osteoporosis in patients with T1DM is osteoblastic dysfunction rather than osteoclastic overfunction. Hence, it is logical that PTH therapy should be superior in comparison to antiresorptive therapy in patients with T1DM. Motyl and colleagues recently published the effect of different doses of PTH in the T1DM mice model and found that high dose of PTH significantly increased tibial trabecular bone density parameters in both control and diabetic mice models, and the lower dose elevated trabecular bone parameters in diabetic mice. The increased bone density was due to increased mineral apposition and osteoblast surface, all of which are defective in T1DM.<sup>[79]</sup> Therefore, PTH may be a more promising agent to treat osteoporosis in patients with T1DM; however it needs to be proven in the human study.

In recent years, it has been found that pancreas-kidney transplant improves adverse clinical outcomes and lowers fracture risk in patients with T1DM and end stage renal disease. Nikkel *et al.*, showed that pancreas-kidney transplant was associated with 31% reduction of fracture risk in men.<sup>[80]</sup> Still long term studies are required in this field to implement this as one of the methods for fracture prevention in T1DM.

## FUTURE DIRECTIONS

There are more questions than answers as far as osteoporosis is concerned in patients with T1DM. There is no clear epidemiological data from India on prevalence of osteoporosis in T1DM. There is no evidence to say which diagnostic modality is best for diagnosing osteoporosis and predicting fracture risk in adolescent and adult patients with T1DM. Moreover, there is a need for more randomized trial in the therapeutic area to know as to which drug is the best for treatment of osteoporosis in patients with T1DM. We hope that in future, there will be evidence-based answers to all these questions.

## CONCLUSION

Patients with T1DM are at high risk for osteopenia and osteoporosis in later life. There is clear epidemiological

evidence that prevalence of osteoporosis and fracture is higher in patients with T1DM than general population. There are number of factors which influence BMD in such individuals. Physicians involved in care of patients with T1DM should carefully evaluate the risk factors for osteoporosis. Promotion of physical activities since the diagnosis of disease, adequate calcium and vitamin D supplementation are corner stone for prevention of osteoporosis in T1DM. The treatment of osteoporosis in T1DM is similar to osteoporosis in general. However, more studies are needed to say which treatment modality is better in patients with T1DM.

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