

Review Article:**Effect of oral hypoglycaemic agents on bone metabolism in patients with type 2 diabetes mellitus**

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ABSTRACT

Diabetes mellitus (DM) and osteoporosis are the two important public health problems in India. The burden of both these conditions is expected to increase in the near future in view of changing lifestyle habits and ageing population. Indians are at risk of osteoporosis due to their low body mass index (BMI), genetic predisposition and nutritional factors. The diseases type 1 DM and type 2 DM (T2DM) are associated with increased fracture risk in the disease population, in spite of difference in the bone mineral density (BMD). An increase in fracture risk is also reported among older patients with T2DM despite frequently reported normal or increased BMD. Administration of insulin stimulates osteoblast activity and bone mineral apposition rates. The impact of endogenous insulin production, insulin sensitivity, and exogenous insulin administration as an anabolic agent for bone in T2DM has not been clarified. Biguanides and sulphonylureas do not appear to have adverse effects on BMD. Preclinical evidence suggests that incretin-based drugs may be beneficial for bone, but clinical evidence to support this hypothesis is not yet available. Thiazolidinedione (TZD) group of agents have been implicated in causing osteoporosis in various animal studies and some human studies available till date. The debate regarding this issue is still ongoing. Randomized controlled studies with larger sample size preferably involving multiple centres, multiple ethnicities are required to answer these queries.

Key words: *Oral hypoglycaemic agents, Bone metabolism in bones, Type 2 diabetes mellitus*

Siddhartha Kumar B, Ravi Sankar A, Sachan A, Prabath Kumar D, Katyarmal DT, Sarma KVS. Effect of oral hypoglycaemic agents on bone metabolism in patients with type 2 diabetes mellitus. J Clin Sci Res 2012;1:83-93.

INTRODUCTION

Indians in general are susceptible to obesity and metabolic syndrome. This makes diabetes mellitus (DM) a major health problem in our country. According to Diabetes Atlas 2011 published by International Diabetes Federation there are about 61 million people with DM in India.¹ Various macrovascular and microvascular complications associated with DM are well known. These complications contribute to significant morbidity and mortality in patients with DM. The role of osteoporosis in contributing to the morbidity and mortality is often under stressed. As a result we do not have sufficient data regarding the prevalence of osteoporosis among patients with DM. Another reason for not suspecting osteoporosis among patients with DM is the false notion that type 2 diabetes mellitus (T2DM) are protected against osteoporosis. Various factors such as decreased mobility due to obesity, use of oral hypoglycaemic agents make patients with DM

more susceptible to osteoporosis. Existence of peripheral neuropathy, decreased vision, frequent hypoglycaemic episodes and frequent visits to the slippery bathrooms due to polyuria increases the risk of falls in patients with DM. This increased risk of falls plus the associated osteoporosis makes fractures more common in patients with DM. Among the various factors that increase the risk of fractures in patients with DM, usage of oral hypoglycaemic agents is one factor which is iatrogenic.

These factors put together makes it important to see that osteoporosis is prevented in patients with DM by early initiation of measures to preventive measures.

OSTEOPOROSIS

Osteoporosis is a disease characterized by reduction in the bone mass and disruption of bone architecture leading to impaired skeletal strength and an increased susceptibility of fractures.²

Osteoporosis is one of the major public health problems, especially in the elderly causing

Received: 24 March, 2012.

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considerable socio-economic burden.³ With the increasing proportion of the elderly population all over the world, this problem needs special attention. By increasing the risk of fracture the proportion of dependant among the elderly increases and this in turn causes a great burden on health care system.⁴ Nearly 50% of the world population resides in Asia and significant numbers of Asian population are living in South-East Asia. The phenomenon of increase in the elderly population will place enormous burden on the health care system in the South-East Asia.⁵

The estimated lifetime risk of osteoporotic fracture is as high as 50 % in Asian women. Osteoporotic fractures occur one to two decades earlier in the Asian women when compared to their western counterparts. The factors which influence the risk of osteoporosis in the later life includes predominantly peak bone density along with other factors such as genetic factors, ethnicity, race, environment, lifestyle.⁶⁻¹⁰ The factors such as nutrition, body weight,^{11,12} exposure to sex hormones at puberty^{13,14} and level of physical activity¹⁵ are not only important for the acquisition of maximal bone mass but also for its maintenance throughout life.^{16,17}

The important underlying mechanism in all cases of osteoporosis is an imbalance between process of bone resorption and bone formation. Up to 10% of the total bone is actively involved in the process of remodelling at any point of time and this process takes place in the bone multicellular units. The process of bone remodelling is first described by Frost.¹⁸

Bone is resorbed by osteoclast cells (derived from the bone marrow), after which new bone is deposited by osteoblast cells. The three main mechanisms by which osteoporosis develop are inadequate peak bone mass, excessive bone resorption and inadequate formation of new bone during remodelling. Interplay of these three mechanisms underlies the development of fragile bone tissue.¹⁹

Hormonal factors strongly determine the rate of bone resorption. Lack of oestrogen (e.g., as a result of menopause) increases bone resorption

as well as decreasing the deposition of new bone that normally takes place in weight-bearing bones. The amount of oestrogen needed to suppress this process is lower than that normally needed to stimulate the uterus and breast gland. The α -form of the oestrogen receptor appears to be the most important in regulating bone turnover.¹⁹ In addition to oestrogen, calcium metabolism plays a significant role in bone turnover, and deficiency of calcium and vitamin D leads to impaired bone deposition; in addition, the parathyroid glands react to low calcium levels by secreting parathyroid hormone (PTH), which increases bone resorption to ensure sufficient calcium in the blood.

Various molecular signals like receptor activator for nuclear factor κ ligand (RANKL) regulate the activation of the osteoclast. This molecule is produced by osteoblasts and other cells (e.g. lymphocytes). RANKL stimulates receptor activator of nuclear factor κ (RANK). Osteoprotegerin (OPG) binds RANKL before it has an opportunity to bind to RANK, and hence suppresses its ability to increase bone resorption. RANKL, RANK and OPG are related to tumour necrosis factor (TNF) and its receptors in their chemical structure. The role of the wnt signalling pathway is recognized but less well understood. Local production of eicosanoids and interleukins plays role in regulation of bone turnover, and excess or reduced production of these mediators may lead to the development of osteoporosis.¹⁹ Trabecular bone is more active because of the inhabitation of the osteoblasts and osteoclasts near the bone surface. Trabecular bone is more subject to bone turnover and to remodelling. Both the bone density and bone microarchitecture are disrupted. The weaker spicules of trabecular bone break lead to formation of “microcracks” and are replaced by weaker bone. Common osteoporotic fracture sites, the wrist, the hip and the spine, have a relatively high trabecular bone to cortical bone ratio.

Risk factors

Risk factors for osteoporotic fracture can be non-modifiable and potentially modifiable.

Non-modifiable risk factors

The most important risk factors for osteoporosis are advanced age (in both men and women) and female sex; oestrogen deficiency following menopause is correlated with a rapid reduction in bone mineral density (BMD), while in men a decrease in testosterone levels has a comparable (but less pronounced) effect. European or Asian ancestry predisposes for osteoporosis, although it occurs in all ethnic groups.²⁰ Family history increases the risk of fracture; the heritability of the fracture as well as low BMD is relatively high, ranging from 25% to 80%. At least 30 genes are associated with the development of osteoporosis.¹⁹ Those who have already had a fracture are prone for osteoporotic fracture twice more commonly than people of the same age and sex.²¹

Potentially modifiable risk factors

Excess alcohol: chronic heavy drinking [alcohol intake greater than 3 units/day (a unit is defined as 14 g of alcohol)] especially at younger age increases risk of osteoporotic fracture significantly,²² whereas, small amounts of alcohol do not increase osteoporosis risk and may even be beneficial.²³

Tobacco smoking : Tobacco smoking inhibits the activity of osteoblasts and is an independent risk factor for osteoporosis. Smoking results in lower body weight, increased breakdown of exogenous oestrogen and earlier menopause, this can contribute to lower BMD.²⁴

Vitamin D deficiency: Vitamin D deficiency has also emerged as a potentially modifiable risk factor for osteoporotic fractures.²⁵

Malnutrition: Low dietary calcium and/or phosphorus, magnesium, zinc, boron, iron, fluoride, copper, vitamins A, K, E and C (in addition to vitamin D). Excess sodium along with acidosis are known to inhibit bone formation.²⁶

Physical activity: Bone remodelling occurs in response to physical stress, and weight bearing. Exercise can increase peak bone mass achieved in adolescence. In adults, physical activity helps maintain bone mass and physical inactivity can lead to significant bone loss.²⁴ Incidence of osteoporosis is lower in overweight people.²⁷

Hormonal status: Oestrogen deficiency is known to cause osteoporosis. Even though oestrogen therapy can prevent osteoporosis, its use is advisable in patients with other compelling indications for hormonal replacement. Pregnancy is associated with bone losses of approximately 3% to 5% at the spine and hip in some studies,²⁸⁻³⁰ while other studies have found that bone density remains stable during this period of increased calcium demand,³¹ or declines significantly only at the trochanter.³²

In contrast, lactation has more consistent and profound effects on bone density. Bone loss of 3% to 10% at the spine and hip are seen over three to six months of lactation.³³ Bone loss is related to duration of lactation and duration of amenorrhoea and calcium supplementation has not shown to prevent this bone loss.³⁴⁻³⁶

PTH-related protein, which is secreted by the lactating mammary gland, plays a role in the control of calcium mobilization during lactation.^{37, 38} Circulating calcitonin³⁹ and the oestrogen deficiency that is characteristic of lactation may also be involved in the control of bone loss during this time.

Bone loss reverses during and after weaning, but the regulators mediating bone recovery in this setting have not been clearly defined.⁴⁰ Recovery from lactation-associated bone loss may continue for 18 months or longer and studies in both humans and animal models suggest that the pattern and extent of bone recovery may be site specific with complete reversal at the spine and incomplete or slower recovery at other sites.^{41,42} Most studies have not found an association between either parity or lactation and osteoporosis or increased fracture risk in postmenopausal women.^{43,44}

Secondary osteoporosis

Medical conditions or treatments⁴⁵ that interfere with the attainment of peak bone mass and may cause secondary osteoporosis are listed in the Table 1. During secondary osteoporosis, an increased rate of bone remodelling or an increase in the quantity of bone being remodelled causes an overall increase in the rate of bone loss. Osteoporosis can also be the result of disorders

where bone marrow cavity expands at the expense of trabecular bone leading to decreased strength of the bone.

Diagnosis of osteoporosis

The measurement of BMD by dual-energy x-ray absorptiometry (DEXA) as an index of bone strength and fracture risk, has been used in postmenopausal women predominantly. The distribution of BMD follows a Gaussian distribution in young healthy adults until the peak bone mass is reached. The BMD values in the individuals can be expressed as standard deviation (SD) units in relation to the reference population. This help in reduction of difficulties associated with differences in calibration between various instruments. When the SD units are used in relation to the young healthy adult population, the measurement is referred to as T-score. When the SD units are used in relation to the age-matched norms, the measurement is referred to as Z-score.^{46,47}

The T-score is calculated using the following formula:^{46,47}

$$T\text{-score} = (\text{observed BMD} - \text{young normal mean}) / \text{standard deviation of young normal mean}$$

In postmenopausal women, normal bone has been defined as BMD greater than 1 SD below the young adult female reference mean (T-score ≥ -1 SD). Osteopenia has been defined as BMD greater than 1 SD below the young adult female

mean, but less than 2.5 SD below this value (T-score < -1 and > -2.5 SD). Osteoporosis has been defined as BMD 2.5 SD or more below the young adult female mean (T-score ≤ -2.5 SD) with or without the presence of a fragility fracture according to World Health Organization (WHO).⁴⁷

In premenopausal women, the population with fracture is much lower when compared with postmenopausal women, and the relationship between BMD and fracture risk is not the same. Therefore, the diagnostic guidelines and the treatment practices based on bone density measurements in postmenopausal women can apply to this population. The International Society for Clinical Densitometry (ISCD) recommends use of BMD Z-scores at the lumbar spine, total hip, femoral neck, and distal radius, rather than T-scores in premenopausal women and men less than 50 years age.^{47,48} The BMD assessment in the T-scores can be applied to the men aged more than 50 years.⁴⁷⁻⁴⁹ International Osteoporosis Foundation and WHO recommends the National Health and Nutrition Examination Survey (NHANES) reference database from women belonging to the age group 20–29 years as the reference range.⁴⁶

In women, bone loss occurs predominantly after the menopause. In the young healthy population, 15% of women have a T-score of less than -1 and thus have low bone mass or osteopenia.⁴⁶ Because of the normal distribution for BMD, about 0.5% of women fall into the osteoporotic range,

Table 1: Various conditions leading to secondary osteoporosis

Chronic kidney disease
Cushing’s disease
Hepatic dysfunction
Anorexia nervosa and bulimia
Rheumatoid arthritis
Malabsorption syndromes (e.g., coeliac disease, tropical sprue, blind loop syndromes)
Multiple sclerosis
Chronic obstructive pulmonary disease
Scurvy
Endocrinological diseases (hyperparathyroidism, hyperthyroidism, hypercortisolism)
Haematological diseases (thalassemia, multiple myeloma, leukaemia)
Metastatic bone diseases
Medications or chemicals (cigarette smoking , corticosteroid therapy, alcohol abuse, lithium, aluminium, barbiturates, antacids containing aluminium etc.)

Source: reference 45

with a T score of -2.5 or less. Furthermore, the proportion of women osteoporosis at any one anatomical site increases greatly with age in much the same way as fracture risk increases with age.⁴⁶ The ISCD recommends avoidance of the term osteopenia. Instead, the term “below the expected range for age” has been considered appropriate when Z-scores < -2.0 SD are observed.^{48,49}

A young woman with low BMD for age and with risk factors for fracture or secondary causes of osteoporosis (such as glucocorticoid therapy, hypogonadism, or hyperparathyroidism) may be defined as having premenopausal osteoporosis in addition to the BMD score criteria obtained by DEXA as described above.

Fragility fracture

Despite this dichotomy, new bone formation as well as bone micro-architectural integrity is altered in the diabetic state, leading to an increased risk for fragility fracture and inadequate bone regeneration following injury. T2DM was associated with 2% - 8% higher regional and whole body BMD (both areal and volumetric measures) even with adjustment for body composition variables of lean mass, fat mass, and abdominal visceral fat and other confounding factors in a study.⁵⁰ The unique finding of lower spine bone volume was observed in this study. Another study⁵¹ demonstrated that at lower bone volumes the structural integrity of cancellous bone is rapidly compromised. Lower spinal bone volumes in patients with T2DM can account for increased incidence of fractures in these patients.

The aetiology of the increased BMD in T2DM remains unclear, as evidence of decreased bone formation, increased bone resorption and increased bone formation have all been reported in studies on subjects with T2DM.⁵²⁻⁵⁴ These studies frequently do not specify and/or analyze results on the basis of treatment type (diet vs. oral hypoglycaemic agent Vs. insulin), which could also account for the inconsistencies in studies of bone density in T2DM. Animal studies illustrate these differences. Specifically, in mice, rosiglitazone administration was observed to have significant decrease in BMD, bone volume, and bone

formation rate associated with a decrease in osteoblast specific gene expression,⁵⁶ and increased apoptotic death of osteoblasts.⁵⁶

In contrast, administration of insulin to the point of hyperinsulinaemia stimulates osteoblast activity and mineral apposition rates.⁵⁷ Treatment administered can also imply the differences that exist in disease severity further confounding the outcome of such studies.

Thus, the impact of endogenous insulin production, insulin sensitivity, and exogenous insulin administration as an anabolic agent for bone in T2DM has not been clarified.

Fracture risk

Both T1DM and T2DM are associated with increased fracture risk in spite of differences in the BMD.⁵⁸ Age-adjusted relative risk ratios (RR) for fracture among individuals with ranged from 1.4 to 2.9 and frequently demonstrated an increasing RR with longer duration of disease.

This would suggest that factors independent of BMD might also contribute to the increased RR for fractures. Falls and traumatic injuries that are associated with various other factors in the patients with DM can account for increased incidence of fractures in them. Specifically, hypoglycaemia unawareness and hypoglycemic seizures, visual impairment, peripheral neuropathy, and nocturnal polyuria are some of the important factors that can contribute to a higher risk of fall.⁵⁹⁻⁶¹ Prolonged fracture union time and prolonged healing are also seen in patients with T2DM.⁶² Specifically, the presence of DM is associated with an increased risk of wound complications following surgical treatment of fractures and non-union or malunion of healing fracture sites.

Oral hypoglycaemic agents and osteoporosis

Effects of drugs used for DM should be considered along with the effect of DM on bone mineral metabolism.⁶³⁻⁷³ The effect of thiazolidinediones (TZD) observed in various clinical studies⁶⁶⁻⁶⁸ is given in the Table 2. The prevalence of osteoporosis in patients with T2DM in various studies is given in Table 3.⁶⁹⁻⁷³ TZD group of agents have been

Table 2: Effect of thiazolidinediones on bone mineral density in various clinical studies

Author (year), Place	Sample size	Results	Observations	Merits and limitations
Watanabe (2003), Japan ⁶⁶	T2DM (n=25)	T2DM patients after 1 year of continuous treatment with TZD showed improvement In BMD	Levels of urine type 1 collagen N-telopeptide and serum bone alkaline phosphatase were reduced after the first month of treatment but returned to baseline levels by 12 months	Serum leptin levels, type I collagen N-telopeptide, bone alkaline phosphatase have been measured. Only 14 women in the total of 25 subjects
Schwartz (2006), United States ⁶⁸	T2DM (n=666) TZD (n=69)	Each year of TZD use was associated with greater bone loss of BMD in women not in men	TZD use was associated with loss of BMD in women only	Patients were also on insulin in the TZD group. Smokers and alcoholics also included.
Kanazawa (2010), Japan ⁶⁷	T2DM on pioglitazone (n=22) T2DM on metformin (n=23)	BMD at femur, radius significantly showed reduction after 1 year of pioglitazone use compared with metformin group	BMD at femur, radius significantly showed reduction after 1 year of pioglitazone use	No disease free control group

T2DM = type 2 diabetes mellitus; TZD = thiazolidinediones; BMD = bone mineral density

Table 3: Prevalence of osteoporosis in patients with diabetes mellitus in various published studies

Study (year)	Place	Type of study	No. of subjects	Method of BMD assessment	Key results	Comments
Chakrabarthi et al (2004) ⁷³	Kolkata, India	Hospital based prospective study	DM (n=138) T1DM (n=32) T2DM (n=106) Controls (n=212)	Bone ultrasound attenuation study of calcaneous analyzed using WHO criteria	No statistically significant difference in bone ultrasound attenuation between patients with T2DM and normal controls. BMD was significantly low in subjects with T1DM compared with control subjects	No mention regarding the prevalence of osteoporosis
Anaforoglu et al (2007) ⁶⁹	Ankara, Turkey	Hospital based prospective study	T2DM (n=206) Controls (n=61)	DEXA analyzed according to WHO criteria	The groups did not differ on BMDs and T scores at the hip, LS, and radius. Patients with radial and/or LS and/or hip osteoporosis had a longer duration of T2DM, were older and had a lower BMI	Patients on glitazones excluded. Only post-menopausal women included
Yijun Zhou et al (2010) ⁷⁰	Shenyang, China	Hospital based prospective study	T2DM (n=890) Controls (n=689)	DEXA analyzed according to WHO criteria	BMD, T- and Z-scores at the total hip, femoral neck and ward's triangle were significantly lower in non-obese women with T2DM than those in BMI-matched control subjects (p < 0.038). Obese women with T2DM and control subjects had similar BMDs and T- and Z scores at various skeletal regions	Only post-menopausal women included. Patients on thiazolidinediones excluded
Viégas et al (2011) ⁷²	Alagoas, Brazil	Hospital based prospective study For assessment of risk of fractures	T2DM only (n=148)	DEXA analyzed according to WHO criteria	The prevalence of vertebral fractures was 23% , mostly mild and located at the thoracic spine. Patients with fractures were older, had longer menopause had lower creatinine clearance (p=0.026)	No control group . patients on glitazones excluded. Patients with CKD and previous history of fracture included
Al-Maatouq et al (2011) ⁷¹	Riyadh, Saudi Arabia	Hospital based prospective study	T2DM (n=104) Controls (n=101)	DEXA analyzed according to WHO criteria	Osteoporosis is more common among patients with T2DM postmenopausal females in this ethnic	Only post-menopausal women included

BMD = bone mineral density; BMI = body mass index; DM = diabetes mellitus; T2DM = type 2 diabetes mellitus; T1DM = type 1 diabetes mellitus; DEXA = dual energy x-ray absorptiometry; WHO = World Health Organization; CKD = chronic kidney disease

implicated in causing osteoporosis in various animal studies and some human studies available till date.⁷⁸⁻⁸⁰ One study has shown that these agents through their action on leptin metabolism have improved BMD.⁸¹ Biguanides and sulphonylureas do not appear to have adverse effects on bone. Preclinical evidence suggests that incretin-based drugs may be beneficial for bone, but clinical evidence to support this hypothesis is not yet available.⁸⁰

Thiazolidinediones and bone metabolism

Treatment with TZD class of antidiabetic drugs, causes bone loss and further increases fracture risk. In vitro and *in-vivo* animal studies have demonstrated that TZD-mediated PPAR γ activation increases bone resorption and reduces the formation of new bone. A shift in marrow cells from osteoblast lineage to adipocyte formation due to PPAR γ activation can result in reduced bone formation.⁶³ Ageing and oestrogen deficiency are sensitizing factors to bone loss as a result of TZD therapy.⁶⁴

In the RECORD trial,⁶⁵ the incidence of fractures was higher in the rosiglitazone group. Fractures occurred mainly in the upper and distal lower limbs and were more common in women than in men. However, the primary objective of this study was to observe the effect of rosiglitazone in cardiovascular outcomes in oral agent combination therapy for T2DM.

Prevalence of osteoporosis in patients with T2DM

The study population considered for these studies constitute of predominantly postmenopausal women. Studies from Turkey and China^{69,70} suggest that the prevalence of osteoporosis in patients with T2DM were comparable to the control subjects. In a study from Saudi Arabia⁷¹ the patients with T2DM were observed to have higher prevalence of osteoporosis when compared with the study subjects. Contrary to the popular belief that patients with T2DM may have lesser risk of developing osteoporosis these studies show that the risk of osteoporosis in T2DM is comparable to the general population.

Similar to the patients with T1DM, patients with T2DM, who were once thought to be protected from osteoporosis due to higher BMD and obesity, are also at a higher risk for developing osteoporosis. Use of oral hypoglycaemic drugs (especially the TZD group) has been associated with risk of osteoporosis. Therapeutic interventions by increasing the bone density and decreasing the risk of falls are the key to prevent fractures. Further work toward understanding the particular bone response to diabetes is important for disease-specific tailored prevention and therapeutic strategies. In the meanwhile care of patients with diabetes should include an assessment of bone health.

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