

EFFECT ON BONE METABOLISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS OF ORAL HYPOGLYCAEMIC AGENTS

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ABSTRACT

BACKGROUND

This study evaluated the effect of treatment of many oral hypoglycaemic agents on bone metabolism in patients with type 2 diabetes mellitus and occurrence of osteoporosis.

MATERIALS AND METHODS

This cross-sectional study was conducted in Department of General Medicine of Chalmeda Ananda Rao Institute of Medical Sciences, Karimnagar, Telangana, between January 2015 to February 2017.

RESULTS

250 patients were screened for this study. From these, 50 patients with T2DM were included in the study who were satisfying the inclusion criteria. Age in years of patients with T2DM was 50.5 ± 4.8 and in control group, age in years was 50.8 ± 2.5 . BMI in kg/m^2 in patients with T2DM was 25.6 ± 6.9 , in control group, BMI was $28.5 \pm 3.88 \text{ kg/m}^2$. Median duration of menopause was 5 in patients with T2DM and it was 5 in control group. There were more women in both the groups i.e. in patients with T2DM, 36/50; in control group, 35/50. The mean duration of T2DM in the study group was 6.09 ± 1.9 years; mean HbA1C was $8.0 \pm 1\%$. 15 patients were using either TZD alone or in combination with other OHA, the remaining 35 were using other OHA alone or in combination. Overall BMD was in postmenopausal was less significantly at the neck of femur compared to lumbar spine in anterior-posterior view. The BMD in g/cm^2 and z-scores at NOF and LSAP were comparable between the study group and control group. There was no significant difference in the presence of BMD, osteopenia and osteoporosis between both the groups. One-way ANOVA did not show any significant difference between BMD NOF and LSAP, T-scores at level of NOF and LSAP, Z-scores at level of NOF and LSAP on comparing between patients with T2DM treated with TZD, patients with T2DM treated with other OHA and control group.

CONCLUSION

For a period of two years or more, the present study shows that the use of OHA does not significantly affect the BMD in patients with T2DM.

KEYWORDS

Oral Hypoglycaemic Agents, Type 2 Diabetes Mellitus, Bone Mineral Density.

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BACKGROUND

Osteoporosis is a disease where increased bone weakness increases the risk of a broken bone. It is the most common reason for a broken bone among the elderly. Bones that commonly break include the vertebrae in the spine, the bones of the forearm, and the hip. Until a broken bone occurs there are typically no symptoms. Bones may weaken to such a degree that a break may occur with minor stress or spontaneously.¹

Chronic pain and a decreased ability to carry out normal activities may occur following a broken bone. Osteoporosis

may be due to lower than normal bone mass and greater than normal bone loss. Bone loss increases after menopause due to lower levels of oestrogen.² Osteoporosis may also occur due to a number of diseases or treatments including alcoholism, anorexia, hyperthyroidism, kidney disease, and surgical removal of the ovaries. Certain medications increase the rate of bone loss including some antiseizure medications, chemotherapy, proton pump inhibitors, selective serotonin reuptake inhibitors, and glucocorticosteroids.³ Not enough exercise and smoking are also risk factors. Osteoporosis is defined as a bone density of 2.5 standard deviations below that of a young adult. This is typically measured by dual-energy X-ray absorptiometry at the hip. In India, type 2 diabetes mellitus has been one of the most common public health problems.⁴ Patients with type 2 diabetes mellitus, compared to their healthy counterparts, they tend to have most frequent falls in elderly age. In spite of having normal bone mineral density, presence of autonomic and peripheral neuropathy and poor healing properties are present due to a fall.⁵

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On the bone metabolism, the effects of oral hypoglycaemic agents belonging to class thiazolidinediones (TZD), data have emerged. Very few studies have shown the tendency of TZD to cause of osteoporosis. Hence, this study evaluated the effect of many oral hypoglycaemic agents treatment on bone metabolism in patients with type 2 diabetes mellitus and occurrence of osteoporosis.

MATERIALS AND METHODS

This cross-sectional study was conducted in Department of General Medicine of Chalmeda Ananda Rao Institute of Medical Sciences, Karimnagar, Telangana, between January 2015 to February 2017. This study was approved by institutional ethical committee and patients were enrolled in the study after obtaining their informed written consent. 50 patients were selected in this study who were treated for type 2 diabetes mellitus who were aged between 40 and 60 years who were under OHA for at least two years or more were included in this study.

Exclusion criteria included patients who were with T2DM on diet control, patients with T2DM who were on insulin, on treatment of OHA for less than 2 years or patients who were using medications that interfere with the metabolism of calcium such as women who were on oral contraceptive pills, who received hormonal replacement therapy, history of fractures of spine, hip, radius following trivial trauma, ill patients on bed rest, prior to enrolment into the study, before 6 months, hospital stay for more than a month, patients who had a BMI ≤ 18.5 kg/m², alcohol and tobacco smokers and those unwilling to participate in the study were excluded from the study.

A detailed physical examination, clinical history, glycaemic control extent, duration of OHA use was documented. All laboratory investigations were also carried out. The assessment of bone mineral density was done at the lumbar spine (L1 to L4 anteroposterior) and left proximal femur using X-ray absorptiometry. Chi square test was used to calculate the association between two variables. Student t test, ANOVA, Mann-Whitney U test was used to compare continuous variables between the groups.

Aim of the Study- This study evaluated the effect of many oral hypoglycaemic agents treatment on bone metabolism in patients with type 2 diabetes mellitus and occurrence of osteoporosis.

RESULTS

250 patients were screened for this study. From these, 50 patients with T2DM were included in the study who were satisfying the inclusion criteria.

Variables	Patients with T2DM(n=50)	Control Group (n=50)
Men Age (years)	50.5 $\pm$ 4.8	50.8 $\pm$ 2.5
BMI (Kg/m ²)	25.6 $\pm$ 6.9	28.5 $\pm$ 3.88
Median duration of menopause	5 (1-10)	5 (1-12)

Table 1. Demographic Distribution of Patients in both the Groups

Table 1 shows that age in years in patients with T2DM was 50.5 $\pm$ 4.8 and in control group, age in years was 50.8 $\pm$ 2.5. BMI in kg/m² in patients with T2DM was 25.6 $\pm$ 6.9, in control group, BMI was 28.5 $\pm$ 3.88 kg/ m². Median duration of menopause was 5 in patients with T2DM and it was 5 in control group. There were more women in both the groups i.e. in patients with T2DM, 36/50; in control group, 35/50. The mean duration of T2DM in the study group was 6.09 $\pm$ 1.9 years; mean HbA1C was 8.0 $\pm$ 1%. 15 patients were using either TZD alone or in combination with other OHA, the remaining 35 were using other OHA alone or in combination.

Variables	Patients with T2DM(n=50)	Control Group (n=50)
BMD (g/cm ²) Neck of femur	0.658 $\pm$ 0.102	0.688 $\pm$ 0.111
BMD (g/cm ²) Lumbar Spine (Anterior-Posterior View)	0.789 $\pm$ 0.258	0.741 $\pm$ 0.258
Z-score Neck of femur	0.150	-0.250
Z-score Lumbar spine (anterior-posterior view)	-1.250	-1.350

Table 2. Comparison of Bone Mineral Density between both the Groups

Table 2 shows that overall BMD was in postmenopausal was less significantly at the neck of femur compared to lumbar spine in anterior –posterior view. The BMD in g/cm² and z-scores at NOF and LSAP were comparable between the study group and control group. There was no significant difference in the presence of BMD, osteopenia and osteoporosis between both the groups.

Variables	Patients with T2DM treated with TZD(n=15)	Patients with T2DM treated with other OHA(n=35)	Control Group (n=50)
BMD NOF	0.721 $\pm$ 0.222	0.756 $\pm$ 0.258	0.789 $\pm$ 0.124
BMD LSAF	0.829 $\pm$ 0.147	0.874 $\pm$ 0.365	0.895 $\pm$ 0.587
T-Score NOF	-0.763 $\pm$ 1.470	-0.952 $\pm$ 0.897	-0.925 $\pm$ 0.687
T-score LSAF	-1.587 $\pm$ 1.287	-1.968 $\pm$ 0.854	-1.886 $\pm$ 1.472
Z-score NOF	-0.150	0.150	-0.250
Z-score LSAF	-0.955	-1.250	-1.350

Table 3: Comparison Of BMD between Patients with T2DM Treated with TZD, T2DM Treated with other OHA and Control Group

Table 3 shows that one-way ANOVA did not show any significant difference between BMD NOF and LSAP, T-scores at level of NOF and LSAP, Z-scores at level of NOF and LSAP on comparing between patients with T2DM treated with TZD, patients with T2DM treated with other OHA and control group.

DISCUSSION

This cross-sectional study was conducted in Department of General Medicine for a period of 2015 to 2017, 250 patients were screened for this study. From these, 50 patients with T2DM were included in the study who were satisfying the inclusion criteria. Our result is correlates to studies done by Siddhartha Kumar et al⁶ conducted a study on 41 patients (study group) with T2DM (mean age 51.9 ± 5.5 year; 31 females) who received treatment with oral hypoglycaemic agents (OHA) [thiazolidinediones alone (n=14) or in combination with other OHA (n=27)] for a time period of at least 3 years and 41 aged patients and their gender matched healthy controls (mean age 51.4 ± 5.1 year) were inclusion criteria in the study. Physical examination was conducted in all patients and a detailed clinical history was taken from all patients and recording of anthropometric data. For both patients and controls, BMD was assessed. The mean body mass index (kg/m^2) (26.5 ± 4.90 vs 27.3 ± 5.33) and median [inter-quartile range (IQR)] duration of menopause (year) among women [6(2-12) vs 6(1-13)] were comparable between both groups. In study and control groups, the bone mineral density (BMD; g/cm^2) at the level of neck of femur (NOF) (0.761 ± 0.112 vs 0.762 ± 0.110), lumbar spine antero-posterior view (LSAP) (0.849 ± 0.127 vs 0.854 ± 0.135); median Z-score NOF {0.100[(-0.850)-(0.550)] vs -0.200[(-0.800)-(0.600)]}, LSAP {-1.200[(-1.700)-(-0.200)] vs -1.300 [(-1.85)-(-0.400)]} were similar. Normal BMD (9/41 vs 8/41), osteopenia (16/41 vs 18/41) and osteoporosis (16/41 vs 15/41) was present which were comparable between the study and control groups. In those treated with other OHA and controls, in the BMD, no significant difference was observed, T-scores and Z-scores at NOF and LSAP among T2DM patients treated with thiazolidinediones.

In the present study, one-way ANOVA did not show any significant difference between BMD NOF and LSAP, T-scores at level of NOF and LSAP, Z-scores at level of NOF and LSAP on comparing between patients with T2DM treated with TZD, patients with T2DM treated with other OHA and control group.

In a study conducted by L. Ma et al⁷ bone metabolism was influenced by type 2 diabetes mellitus (T2DM), but across studies, the relation of T2DM with bone mineral density (BMD) remains inconsistent. Those where the association between T2DM and BMD measured by dual energy X-ray absorptiometry were considered eligible and evaluation was done using a cross-sectional, cohort or case-control design, including both healthy controls and subjects with T2DM. 15 observational studies (3,437 diabetics and 19,139 controls) were analysed. BMD in diabetics was significantly higher which was shown by meta analysis, with

pooled mean differences of 0.04 (95% CI: 0.02, 0.05) at the femoral neck, 0.06 (95% CI: 0.04, 0.08) at the hip and 0.06 (95% CI: 0.04, 0.07) at the spine. Between diabetics and non-diabetics, the differences for forearm BMD were not significantly different. In both genders, sex-stratified analyses showed similar results. From differences in study design and possibly diabetes definition, substantial heterogeneity was originated.

In the present study, overall BMD was in postmenopausal was less significantly at the neck of femur compared to lumbar spine in anterior –posterior view. The BMD in g/cm^2 and z-scores at NOF and LSAP were comparable between the study group and control group. There was no significant difference in the presence of BMD, osteopenia and osteoporosis between both the groups.

Anafroglu I et al⁸ reported that at the hip, lumbar spine, and radius, there was no difference in BMDs and T scores. Patients with radial or lumbar or hip osteoporosis had a longer duration of diabetes ($P=.000$), were older ($P=.000$), and had a lower BMI ($P=.000$). Between osteopenia or osteoporosis and haemoglobin A1c level, presence of microalbuminuria, retinopathy, neuropathy, peripheral artery disease, cerebrovascular event, and coronary artery disease, no correlation was found. BMD at the hip was positively correlated with BMI ($P=.000$) but negatively correlated with age ($P=.000$) and duration of diabetes ($P=.000$) among the three sites. A negative correlation with BMD at the femoral neck ($P=.042$) revealed the presence of micro-albuminuria.

Al-maatouq MA et al⁹ reported that the mean spine BMD was $0.928 \text{ gm}/\text{cm}^2$ (T-score = -2.28 SD) and for femoral neck the mean BMD was $0.817 \text{ gm}/\text{cm}^2$ (T-score = -1.21 SD) in the diabetic group. The mean spine BMD was $1.036 \text{ gm}/\text{cm}^2$ (T-score = -1.2) and mean femoral neck BMD was $0.914 \text{ gm}/\text{cm}^2$ (T-score = -0.608) in control group. There was 16 (16.64%) patients with normal BMD of the spine, 42 patients (43.68%) with osteopenia (mean T-score = -1.8 SD) and 45 (46.8%) with osteoporosis (mean T-score = -3.3 SD) in the diabetic group. In the present study, BMI in kg/m^2 in patients with T2DM was 25.6 ± 6.9 , in control group, BMI was $28.5 \pm 3.88 \text{ kg}/\text{m}^2$. Median duration of menopause was 5 in patients with T2DM and it was 5 in control group. There were more women in both the groups i.e. in patients with T2DM, 36/50; in control group, 35/50. The mean duration of T2DM in the study group was 6.09 ± 1.9 years; mean HbA1C was $8.0 \pm 1\%$. 15 patients were using either TZD alone or in combination with other OHA, the remaining 35 were using other OHA alone or in combination.

Zhou Y et al¹⁰ reported that BMDs, T- and Z-scores at the total hip, femoral neck and ward's triangle were significantly lower in non-obese diabetic women than those in BMI-matched control subjects ($P < 0.038$). Obese diabetic patients and control subjects had similar BMDs and T- and Z-scores at various skeletal regions. Osteopenia/osteoporosis was more common at the hip and femoral neck in non-obese diabetic women than in obese diabetic women and control subjects ($P = 0.026$). On multiple linear regression analysis, which was adjusted for the sex hormone concentration, BMI, fasting insulin level, and serum osteocalcin were positively

associated with BMDs at the hip and lumbar spine. Age, mean HbA_{1c} levels, and NTx/Cr showed negative correlation ($P < 0.0284$) with BMD at the lumbar spine and femoral neck.

CONCLUSION

This study concludes that compared to lumbar spine in antero-posterior view, the overall BMD in postmenopausal women was less significant at the neck of femur. In both study group and control group, the BMD in g/cm² and z-scores at NOF and LSAP were comparable. In the presence of BMD, there was no significant difference in osteopenia and osteoporosis between both the groups. Thus, the present study shows that the use of OHA does not significantly affect the BMD in patients with T2DM.

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