Original Article

Conventional antidiabetic agents and bone health: A pilot case–control study

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Abstract

Background and Objectives: The burden of noncommunicable diseases such as diabetes (type 2 diabetes mellitus [T2DM]) and osteoporosis is increasing with increasing longevity. Uncontrolled T2DM is an independent risk factor for osteoporosis explained by the insulin osteocalcin pathway. Due to limited information on the effect of various commonly used antidiabetic agents (ADA) on bone health, our study aims to analyze the association between the two.

Methodology: This is a case–control study, with 100 cases of clinical osteoporosis and 100 age-, sex-, and dietary status-matched controls in whom osteoporosis was ruled out by dual-energy X-ray absorptiometry scan. Prescription details of T2DM, physical activity levels, and disease status were collected using a pretested questionnaire. Exposure to each ADA was compared using the Chi-squared test. Binary logistic regression was performed to adjust the two main confounders, namely glycemic control and physical activity levels, and adjusted risk estimates were calculated.

Results: There were a total of 74 T2DM patients, of whom 45 (60.8%) were cases and 29 (39.2%) were controls. Sulfonylureas (adjusted odds ratio [aOR] = 0.164, $P = 0.004$) and insulin (aOR = 0.248, $P = 0.042$) showed a significant protective effect on bone health. Biguanides (OR = 1.994, $P = 0.029$) and thiazolidinediones (OR: 5.444, $P = 0.033$), which demonstrated that an increased risk of osteoporosis in univariate analysis became insignificant after multivariate analysis.

Conclusion: Sulfonylureas and insulin through the insulin osteocalcin pathway show favorable effect on bone health, but the probability of increased fractures secondary to hypoglycemic falls should be borne in mind. We recommend larger prospective studies to confirm this association.

Keywords: Antidiabetic drugs, bone health, insulin, oral hypoglycemic agents, osteoporosis

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INTRODUCTION

Osteoporosis may be defined as a systemic skeletal disease characterized by a decrease in the bone mineral density (BMD) and/or deterioration of the microarchitecture, resulting in increased bone fragility and susceptibility to fractures.[1] According to the World Health Organization (WHO), osteoporosis affects more than 75 million people in Europe, Japan, and the USA, and the lifetime risk for osteoporotic fractures has been estimated to be approximately 40%, which is similar to that for coronary heart disease.[2] In India, although the exact numbers are not available, 25 million people were thought

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to be affected with osteoporosis in 2007–2008,[3] which has increased many folds now. In 2013, approximately 50 million Indians were thought to be diagnosed with osteoporosis with T-scores <−1.[4] The recent estimate based on small studies suggest that, of the 230 million Indians expected to be over 50 years in 2015, nearly 20% (46 million) are women alone, thought to be suffering from osteoporosis.[5] With increasing longevity due to advancement in medical sciences, the burden of noncommunicable diseases such as osteoporosis and type 2 diabetes mellitus (T2DM) is expected to increase.[6] Diabetes mellitus is a metabolic disease with substantial morbidity and mortality, and patients with diabetes have various skeletal disorders, the most important of which is osteoporosis besides osteopenia or diabetic foot syndrome.[7] A survey of a prospective cohort of 32,089 postmenopausal women in the Iowa Women's Health Study revealed that women with type 1 diabetes mellitus (T1DM) were 12 times more likely to report hip fractures than women without T1DM.[8] Similarly, women with T2DM also had a 1.7-fold higher risk for reporting hip fractures compared with women without T2DM.[8] Ever since the postmarketing surveillance data and data from clinical trials, as early as the year 1999, portrayed thiazolidinediones to increase bone loss and fractures,[9] the zeal to discover the effects of other antidiabetic agents (ADA) on bone health started to increase. A clinical trial with biguanides (metformin) and dipeptidyl peptidase-4 (DPP-4) inhibitor (gliptins) has shown a trend toward the protective effect of both these drugs though not statistically significant due to smaller sample size.[10] On the same note, the effects of sulfonylureas on bone are also limited, but it may improve glycemic effect and cause improved bone health though the risk of fractures secondary to hypoglycemia and fall increases.[11] In the background of such limited information on the effect of various commonly used ADAs on bone health, it is important to analyze the association in an Indian setting and hence this study was conducted.

METHODOLOGY

This was a pilot case–control study conducted in the department of orthopedics among both inpatients and outpatients of a tertiary care teaching hospital in Bengaluru between November 2016 and October 2017. The primary objective of the study was to assess any association between the common ADAs and osteoporosis. Based on a study by Hegazy *et al*.,[10] the mean difference in BMD was assumed to be 0.032 and standard deviation (SD) as 0.070. The sample size thus calculated for a two-tailed test with an alpha error of 5% and power 80% was 77 in each arm. However, considering that there is no data available, to the best of our knowledge, having head on comparison of one ADA over the other, we decided to increase our sample size to 100 patients in each arm. Thus, 100 consenting adults with clinical osteoporosis were included as cases. These patients were either dual-energy X-ray absorptiometry (DEXA) positive for osteoporosis or fulfilled any two of the following three criteria, namely, history of fracture of proximal femur, distal humerus, or distal forearm secondary to trivial trauma as confirmed by the two orthopedicians who are not a part of this study and two radiologists confirmed the osteopenia in any radiological imaging or biochemical derangements such as elevated serum alkaline phosphatase with low or normal calcium levels. Age-, sex-, and dietary status-matched individuals (100 in number) with no osteoporosis confirmed on DEXA scan were chosen as controls in a ratio 1:1. We did not strictly stick to DEXA-confirmed osteoporosis patients as cases because our hospital does not routinely do DEXA scan, for patients who report to us with fractures secondary to trivial trauma due to financial implications on the patient. Patients who were seriously ill unable to answer questions; those with psychiatric illnesses such as dementia with loss of insight; those with malignancies, gastrointestinal disorders, thyroid abnormalities, chronic kidney disease, or other causes known to result in pathologic fractures; and those on other concomitant medications known to have an effect on bone metabolism, namely, steroids, contraceptive pills, proton pump inhibitors, heparin, antiepileptic drugs, and bisphosphonates for at least 3-month duration in the last 1 year were excluded from the study. A pretested semistructured questionnaire was administered which contained the following sections, namely sociodemographic details, prescription details of diabetic agents, and physical activity levels. The physical activity levels were measured using the validated international physical activity questionnaire short version.[12] The examples of moderate and vigorous physical activities were explained using the show cards published by the WHO for global physical activity questionnaire.[13] For this study, patients with at least 6 months of medications for diabetes were taken as adequate exposure to that specific ADA. Those on just lifestyle modifications or recently (<6 months) on medications were not taken as adequately exposed as we assumed that the medicines would at least take so much time to have any effect on BMD. Data entry was done in Epi Info™ Version 7 (Publisher: CDC, Atlanta, Georgia, USA, 2011), and analysis was performed with IBM SPSS Statistics for Windows, Version 20.0 (Publisher: IBM Corp., Armonk, New York, USA, 2011). Demographic characteristics and ADA prescription patterns were summarized using descriptive statistics. Exposure to each

ADA was compared between cases and controls using the Chi-squared test. Binary logistic regression was performed to adjust the two main confounders, namely glycemic control (defined as hemoglobin A1c [HbA1c] >6.5 g %) and physical activity levels, and adjusted risk estimates were calculated. Statistical significance was kept at $P < 0.05$. The study was approved by our institutional ethics committee vide study No. 177/2016.

RESULTS

We approached a total of 114 and 121 prospective cases and controls, respectively, and recruited 100 each. The mean (SD) age of patients considered as cases was 61.68 (8.51) years and that of controls was 61.63 (8.10) years. The sociodemographic characteristics of the participants are given in Table 1. Sixty-three percent of them were women and nearly 60% were from the geriatric age group (age ≥60 years). Correspondingly, a majority of them were either retired or homemakers. The prevalence of low physical activity was 49% (95% confidence interval [95% CI] = 38.9, 59.2) in the case group and 36% (95% CI = 26.6, 46.2) in the control group. The characteristics and prescription patterns of T2DM patients are summarized in Table 2. There were a total of 74 T2DM patients, of whom 45 (45%) were cases and 29 (29%) were controls. Thirty-one cases (68.9% of T2DM in cases) and 8 controls (27.6% of T2DM in controls) were diagnosed to have uncontrolled diabetes based on their glycosylated hemoglobin (HbA1c) cutoffs for their age and associated comorbidities. The most common ADA being prescribed was a biguanide – metformin (36 out of 45 T2DM cases and 22 out of 29 T2DM controls), and the second common ADA was insulin (13 out of 45 T2DM cases and 13 out of 29 T2DM controls). The other common OHAs in use were sulfonylurea (10 out of 45 T2DM cases and 17 out of 29 T2DM controls) and thiazolidinedione (10 out of 45 T2DM cases and 2 out of 29 T2DM controls). With regard to newer ADAs, four patients were on DPP-4 inhibitors, two were on sodium-glucose cotransporter-2 inhibitors, and none on glucagon-like polypeptide 1 (GLP1) analogs or amylin analogs. Due to small numbers, newer ADAs were not considered for subsequent analysis.

Tables 3 and 4 portray the association of various ADA, with the occurrence of osteoporosis using univariate and multivariate analysis, respectively. Biguanides, though seemed to be a significant risk factor initially (odds ratio [OR] = 1.994, $P = 0.029$), it became non-significant after adjusting for confounders. Sulfonylureas showed a significant protective effect on bone health (adjusted odds ratio [aOR] = 0.164, $P = 0.004$). Insulin, on the other hand, showed no significant difference in its action in the univariate analysis, but after regression analysis showed a significant protective effect on bone health (aOR = 0.248, $P = 0.042$). Thiazolidinediones demonstrated an increased

Table 1: Demographic characteristics

Classification	Case (*n*=100)	Controls (*n*=100)
Sex		
Male	37	37
Female	63	63
Age (years)		
40-49	9	7
50-59	31	34
60 and above	60	59
Marital status		
Married	78	75
Never married	4	8
Divorcee	11	17
Spouse expired	7	0
Patient occupation		
Retired/homemaker	65	53
Unskilled laborer	12	14
Semi-skilled laborer	3	2
Skilled laborer	3	4
Farmer, clerk, shop owner	10	17
Semiprofession	3	1
Profession	1	9
Patient education		
Illiterate	35	28
Primary school	9	5
Middle school	5	5
High school	21	17
Post high school diploma	11	12
Graduate/postgraduate	18	23
Professional	1	10
Socioeconomic class		
Upper	48	37
Upper middle	12	7
Lower middle	15	14
Upper lower	24	35
Lower	1	7
Physical activity		
Low	49	36
Moderate	29	33
High	22	31
Diabetic	45	29
Hypertensive	44	27
Cardiovascular diseases	7	4

Table 2: Characteristics of diabetic patients in the study population

Characteristic	Case (*n*=45), *n* (%)	Control (*n*=29), *n* (%)
Uncontrolled DM	31 (68.9)	8 (27.6)
Biguanide use	36 (80.0)	22 (75.9)
Sulfonylurea use	10 (22.2)	17 (58.6)
Thiazolidinedione use	10 (22.2)	2 (6.9)
Insulin use	13 (28.9)	13 (44.8)
Others	2 (4.44)	1 (3.45)
Combination therapy (drugs)		
2	5 (11.1)	5 (17.2)
3	17 (37.8)	14 (34.5)
4	23 (51.1)	10 (34.5)

Percentage corresponds to column percentages. DM=Diabetes mellitus

Table 3: Association of various antidiabetic agents with osteoporosis - univariate analysis

Antidiabetic agent	case (*n*=100)	Control (*n*=100)	OR	*P*
Biguanides				
Yes	36	22	1.994	0.029
No	64	78		
Sulfonylureas				
Yes	10	17	0.542	0.147
No	90	83		
Thiazolidinediones				
Yes	10	2	5.444	0.033
No	90	98		
Insulin				
Yes	13	13	1.000	1.000
No	87	87		

OR=Odds ratio

Table 4: Association of various antidiabetic agents with osteoporosis - multivariate analysis

Antidiabetic agent	aOR	95% CI	*P*
Biguanides	1.821	0.702, 4.721	0.218
Sulfonylureas	0.164	0.048, 0.566	0.004
Thiazolidinediones	4.335	0.640, 29.347	0.133
Insulin	0.248	0.065, 0.951	0.042

The analysis has been adjusted for two main confounders, namely physical activity and whether diabetes was under control or not.
aOR=Adjusted odds ratio, CI=Confidence interval

risk of osteoporosis (OR = 5.444, P = 0.033), which became insignificant after multivariate analysis.

DISCUSSION

We report that treatment of T2DM with insulin and sulfonylurea, an insulin secretagogue, shows a protective effect from the development of osteoporosis. Sulfonylureas reduce the risk of osteoporosis by around 84% and insulin decreases the risk of osteoporosis by 75%. This could easily be explained by the osteocalcin– insulin endocrine feed-forward loop.[14] Osteoblasts have a functional insulin receptor (IR), and thus when treated with insulin, it stimulates the proliferation and differentiation of osteoblasts. On interaction with IR, insulin transmits its signal by inhibiting FoxO1, which, in turn, inhibits Runx2-dependent transcriptional activity.[15] Insulin stimulates osteoblast to secrete osteocalcin, and, in turn, osteocalcin enhances the insulin sensitivity in osteoblasts, thereby establishing a positive feedback mechanism.[14] There are two forms of osteocalcin, namely, the carboxylated (cOC) and uncarboxylated (ucOC) forms, the latter being considered the active from stimulating the expression of insulin in the islet cells of pancreas.[16] cOC, on the other hand, increased the sensitivity of insulin.[17] Thus, under the influence of insulin, osteocalcin is produced by the osteoblasts, which is cOC by Vitamin K-dependent mechanism, and cOC accumulated in the bone matrix, thereby enhancing BMD.[14] Besides osteoblast differentiation, insulin also activates osteoclast-mediated bone resorption, which releases the ucOC that helps maintaining the blood glucose levels.[18] Although osteoclasts are activated, the net response with insulin in the bone is to enhance the BMD as new osteocalcin is produced and conjugated.[14] Besides the direct stimulation of insulin, osteocalcin also indirectly enhances the production of GLP-1 from the intestinal cells[18] and adiponectin from the adipose tissue both of which again reduces glucose concentration in the blood.[19]

Although, in our study, we report that sulfonylureas and insulin reduce the risk of osteoporosis, it is important to note that both of these agents did not achieve statistical significance in univariate analysis. This is explained by the fact that uncontrolled diabetes played a key role for this result. This could be theoretically explained by the fact that, when there is poor glycemic control, there is an increase in the production of advanced glycosylated end products, which gets deposited in the bone matrix, causing an increase in interleukin-6 production, which in turn favors bone resorption.[20] Although a favorable effect is demonstrated with sulfonylureas in increasing the BMD, the risk of fractures increases as sulfonylureas have increased the risk of hypoglycemia and falls resulting in fractures.[11] The same could be true with insulin, as well as they also have the propensity to cause hypoglycemia.

Biguanides, based on our study, could be considered as bone neutral, though a large number of *in vitro* studies have shown that metformin is osteogenic. Metformin can induce MC3T3-E1 osteoblastic cell differentiation and bone matrix synthesis through adenosine 5'-monophosphate-activated protein kinase activation and induction of endothelial nitric oxide synthase and bone morphogenetic protein-2 (BMP-2) expression.[21] It can also regulate small heterodimer partner in MC3T3-E1 cells, an orphan nuclear receptor which stimulates osteoblastic bone formation by interacting with the transcription factor Runx2.[22] Metformin also increased osteoblast proliferation, alkaline phosphatase activity, and the number of mineralized nodules formed in rat primary osteoblasts through insulin-like growth factor-1 production.[23] The action of metformin on bone marrow mesenchymal progenitor cells (BMPCs) was that it caused an osteogenic effect, suggesting a possible action of metformin in promoting a shift of BMPCs toward osteoblastic differentiation though a high concentration of metformin inhibited osteoblast differentiation.[24] Despite such large pool of evidence based on *in vitro* studies, *in vivo* human studies reveal ambiguity toward its effect on bone health. A large case–control study from Denmark with 124,655 patients with fractures and 373,962 age- and

sex-matched healthy volunteers revealed that metformin's effect on fracture risk was insignificant at the three common sites of osteoporotic fractures, namely, hip (OR = 0.76; 95% CI = 0.55, 1.04), forearm (OR = 0.72; 95% CI = 0.49, 1.06), and spine (OR = 0.92; 95% CI = 0.45, 1.87) at a defined daily dosage ≥500 mg.[25]

Thiazolidinedione in our study initially showed an increased odds ratio of osteoporosis by ≥5 times. However, in the multivariate analysis, this risk became insignificant. This could be due to smaller number of patients receiving these drugs. An increased risk in osteoporosis could well be explained by the fact that osteoblasts and adipocytes having a common progenitor mesenchymal stem cell. Peroxisome proliferator-activated receptor gamma (PPAR-γ) overexpression (as in the use of PPAR-γ activators like thiazolidinediones), trade-off adipocytes for osteoblasts resulting in decreased bone mass.[26] However, there are varying clinical evidence on the effect of these agents on fracture risk. A recent meta-analysis incorporating 22 randomized control trials involving 24,544 patients with 896 fractures concluded that there was a significantly increased risk of fractures in women (OR = 1.94; 95% CI: 1.60, 2.35; $P < 0.001$), but not in men (OR = 1.02; 95% CI: 0.83, 1.27; $P = 0.83$).[27]

The strengths of our study include that it being a case–control study provides much stronger evidence on the actual association between ADA and osteoporosis when compared to cross-sectional studies. To the best of our knowledge, this study is first of its kind in an Indian scenario. On the other hand, some of our limitations include our inability to accurately gauge the amount of exposure to these drugs in terms of their dosage and duration as these particular data were retrospective. We feel that this limitation could be overcome only by doing a cohort study. We were also not able to analyze the effect of the newer ADAs due to smaller sample sizes. Finally, among cases, only 56% had DEXA scan, which is the gold standard diagnostic modality, though all efforts were made to ensure that the patients were clinically diagnosed warranting treatment for osteoporosis. Due to financial constraints, bone turnover markers were also not assayed.

CONCLUSION

Based on our study results, we would like to state that sulfonylureas and insulin through the insulin osteocalcin pathway may show favorable effect on bone health. However, based on previous studies, the increased risk of fractures secondary to hypoglycemic falls has to be borne in mind, and we recommend that, if carefully chosen keeping in mind the patient's profile ruling out increased risk for fall, these agents could probably be preferred in T2DM patients with suspected osteoporosis or osteopenia over other conventional ADAs assessed in this study. Metformin, on the other hand, shows neither favorable nor adverse effect on the bone, despite multiple *in vitro* studies confirming the bone-forming activity. We further recommend that larger prospective studies with biochemical parameters be planned to decipher and confirm the association of various ADAs, especially the newer ones with bone health as it becomes very important due to the increasing numbers of both T2DM and osteoporosis patients globally.

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Conflicts of interest

There are no conflicts of interest.

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