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Research Article

To Determine the Effects of SGLT2 inhibitors on Bone Turnover Markers in Patients of Type 2 Diabetes Mellitus

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ABSTRACT

Background and Objectives: Type 2 Diabetes Mellitus (T2DM) is known to cause microvascular and macrovascular complications, placing a burden on healthcare, with pathophysiology encompassing β-cell dysfunction, insulin resistance, and inflammation. Bone remodelling which provides essential elements of skeletal stability and elasticity is defined by the regulation of adult bone mass and maintenance. Skeletal fragility in diabetes relates to obesity, high blood glucose, oxidative stress, and advanced glycation end products. Long-term exposure to a diabetic environment subtly alters bone remodelling, as suggested by osteoblastic and osteoclastic bone biomarkers in studies. Certain anti-diabetic drugs like pioglitazone, rosiglitazone, and thiazolidinediones may cause bone loss, while metformin and sulfonylureas have neutral or positive effects. Group of SGLT2 inhibitors, may have variable effects on bone biomarkers, e.g. canagliflozin raise concerns related to skeletal structure integrity, but dapagliflozin and empagliflozin haven't show an increased risk of fracture. Therefore, the present study was designed to assess the effect of frequently prescribed SGLT2 inhibitors e.g. dapagliflozin and empagliflozin on bone biomarkers.

Methods: The observational, prospective, open-label study was conducted on 40 newly diagnosed T2DM patients (40-60 years) in Northern India with follow-up of 24 weeks. Those with suboptimal glycemic control were prescribed SGLT2 inhibitors in addition to their existing treatment. Anthropometric measurements, including height, waist circumference, and BMI, were taken at baseline and after 6 months. Blood pressure was recorded using a mercury sphygmomanometer. Biochemical parameters such as fasting/postprandial glucose, HbA1c, serum phosphorus, calcium, vitamin D, parathormone, and various bone markers were analyzed from venous blood samples. Data was analyzed with Microsoft Excel and Prism GraphPad 9.

Interpretation & Conclusion: The 24-week study suggests SGLT2 inhibitor use increases bone resorption markers e.g., FGF23 and parathormone, potentially raising osteoporotic risk. Bone formation markers e.g., BALP and Osteocalcin remain unchanged. Further research on long-term effects of SGLT2 inhibitors is needed. A cautious approach, especially for those with bone health concerns, is recommended when considering antidiabetic drugs.

Results: Statistical analysis showed significant changes ($p<0.05\%$). SGLT2 inhibitors prescribed in T2DM patients have shown significant increase in serum FGF-23 levels, suggesting its potential role as a biomarker for adverse cardiovascular events, secondary impact on bone metabolism and increased risk of fractures. The other bone biomarkers sclerostin and osteocalcin show insignificant changes in serum values over a six month follow up period, while bone-specific markers like BALP remain unaffected, suggesting potential complexities in bone metabolism influenced by weight loss and diabetes-related factors.

Keywords: Diabetes, biomarkers, bone mineral density, sclerostin, FGF23, BALP, osteocalcin

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INTRODUCTION

Globally 530 million adults (age group of 20 to 79 years) are affected with Diabetes, with a prevalence of 10.5% as per IDF Diabetes Atlas 21[1]. Approximately 98% of diabetes cases worldwide are attributed to Type 2 diabetes mellitus (T2DM), with variations observed across different nations. In the United States, diagnosed T2DM prevalence among adults is 8.5%, according to the National Health Interview Survey[2]. India currently has 77 million individuals with diabetes, and this number is projected to surpass 134 million by 2045. Alarmingly, around 57% of these cases go undiagnosed[3].

Type 2 diabetes mellitus (T2DM) can result in various complications, broadly categorized into microvascular and macrovascular which can significantly contribute to increased premature morbidity and mortality in individuals with diabetes. Additionally, the associated financial and other burdens of diabetes impose a substantial economic strain on the healthcare system in India[4].

In Type 2 diabetes mellitus (T2DM), pathophysiological changes involving β-cell dysfunction, insulin resistance, and chronic inflammation progressively hamper the regulation of blood glucose levels. These changes contribute to the emergence of microvascular and macrovascular complications. In T2DM, microvascular complications can reduce blood flow to the bone marrow microenvironment, influencing bone remodeling[5].

The underlying mechanisms for skeletal fragility in diabetes are not fully understood but are likely influenced by various factors. These may encompass the effects of obesity, elevated blood sugar levels, oxidative stress, and the accumulation of advanced glycation end products. These factors collectively lead to altered bone metabolism, structure, and strength[6]. Therefore, the medications which are being used to treat the diabetes should be favourable or neutral to the bone as the disease relatively needs a long term approach.

Bone remodelling which provides essential elements of skeletal stability and elasticity is defined by adult bone mass and maintenance. Changes in bone mass result from physiologic and pathophysiologic processes in the bone remodelling cycle, and ultimately this can lead to skeletal fragility[7]. The clinical importance of fragility fractures in patients with T2DM has considerably increased worldwide, as increasing life expectancy in people with T2DM has led to rapid growth in the number of ageing patients with T2DM.

Renal osteodystrophy and secondary hyperparathyroidism, promoting skeletal resorption and mineralization defects may also results as a complications of diabetic nephropathy[8].

Certain antidiabetic drugs from thiazolidienediones group eg. pioglitazone, rosiglitazone, may cause significant bone loss due to impaired osteoblastogenesis leading to increased risk of bone fracture. These drugs divert bone mesenchymal stem cells (MSCs) to form adipocytes rather than osteoblasts. However, the other antidiabetic drugs, metformin and sulfonylureas have a neutral or positive effect on bone health and reduced risk of fracture[9]. While SGLT2 inhibitors, specifically canagliflozin, raise concerns due to potential adverse effects on bone metabolism and an increased risk of fractures in individuals with T2DM, studies involving dapagliflozin and empagliflozin have not indicated a higher likelihood of bone fractures when compared to a placebo. However, some studies have been associated with elevated bone turnover markers and diminished bone mineral density with canagliflozin treatment. Despite these concerns, there is substantial evidence supporting the cardiovascular and renal protective benefits of SGLT2 inhibitors, as highlighted in a study by Jackson et al[10] in 2020. It is noteworthy that SGLTs are proteins located on cell membranes responsible for actively transporting glucose against its concentration gradient. SGLT2 activity promotes glucose conservation and hinders normalization of plasma glucose levels in diabetes mellitus. It is postulated that inhibition of SGLT2 might decrease the threshold for urinary glucose excretion and therefore, prevent the rise in blood glucose level. Therefore, in this six-month observational study, we evaluated the impact of SGLT2 inhibitors on specific markers of bone turnover and examined their overall impact on bone health in individuals with diabetes.

RESULTS

Demographic profile and other baseline parameters have been shown in Table 1. The age of patients varies from 40 years to 65 years. The mean age of patients enrolled is 54.

Table 1 : Demographic profile and other baseline parameters with their mean values

Characters	Mean ± SD
Weight (kg)	66
Height (cm)	163
Body mass index (kg/m^2)	24.94
Systolic Blood pressure (mmHg)	128
Fasting plasma glucose (mg/dL)	170

HbA1C (%)	8.4
Calcium (mmol/L)	2.3
Phosphate (mmol/L)	1.12
25(OH) vitamin D (ng/mL)	15.94
Parathormone (pg/mL)	49.72
Osteocalcin (ng/mL)	3.82
Bone alkaline phosphatase (ng/mL)	3.89
Sclerostin (ng/mL)	1.54
Fibroblast growth factor 23 (pg/mL)	49.41
Urea (mg/dL)	27.69
Creatinine (mg/dL)	0.93

Alterations in BMI, HbA1c, serum glucose, urea, creatinine, calcium, phosphate, and bone markers were measured at 6-month intervals, as illustrated in Table 2. In contrast to the initial measurements, a significant reduction was observed in BMI, HbA1C, and glucose during the initial 6 months. Additionally, total vitamin D, parathyroid hormone, and calcium exhibited a substantial increase in their levels compared to the baseline.

Table 2. Biochemical and bone biomarkers assayed at baseline (0 week) and at 24 weeks (6 month) and their mean difference with P value; P value <0.05 is considered significant, <0.001 is considered highly significant

Characteristics	Baseline	At 24 weeks	Mean difference	P value
BMI (Kg/m^2)	24.94 ± 2.42	24.49 ± 2.39	0.45	< 0.001
FBG (mg/dl)	170 ± 53.16	129 ± 32.19	40.48	< 0.001
PPG (mg/dl)	249 ± 74	190 ± 54	58.1	<0.001
HbA1c (mg/dl)	8.4 ± 1.2	7.3 ± .9	1.03	<0.001
S. Urea (mg/dl)	27.69 ± 6.1	27.73 ± .3.8	0.03	<0.96
S. Creatinine (mg/dl)	0.93 ± .3	0.71 ± .25	0.21	<0.001
S. Calcium (mmol/L)	2.3 ± 0.09	2.42 ± 0.09	0.11	<0.001
S. Phosphate (mmol/L)	1.12 ± 0.09	1.26 ± 0.14	0.14	<0.001
S. 25(OH) Vit D (ng/mL)	15.94 ± 2.5	17.18 ± 2.5	1.23	<0.001
S. Parathormone (pg/mL)	49.7 ± 12.91	55.32 ± 10.97	5.6	<0.001

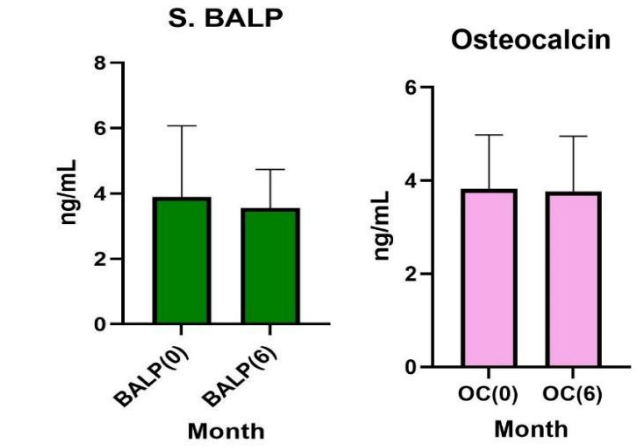
BONE BIOMARKERS

At baseline, serum osteocalcin levels measured 3.82 ng/mL, serum BALP levels were 3.89 ng/mL, and sclerostin levels were 1.54 ng/mL. After 24 weeks, serum osteocalcin levels decreased slightly to 3.76 ng/mL, serum BALP levels decreased to 3.56 ng/mL, and sclerostin levels increased marginally to 1.56 ng/mL. The mean differences between baseline and 24 weeks were 0.05 ng/mL for osteocalcin, 0.32 ng/mL for BALP, and 0.01 ng/mL for sclerostin.

Table 3: Bone Biomarkers values at baseline (ng/ml) and at 24 weeks (ng/ml), their mean difference and p value (significant p-value<0.05)

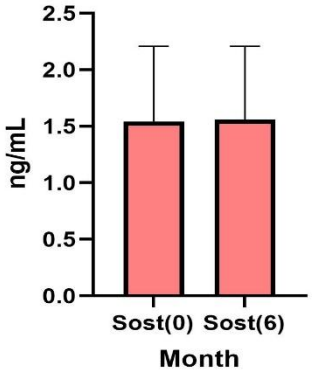
BONE BIOMARKERS	BASELINE (ng/ml)	At 24 weeks (ng/ml)	Mean Difference	p value
S.Osteocalcin (ng/mL)	3.82 ± 1.15	3.76 ± 1.18	0.05	<0.39
BALP (ng/mL)	3.89 ± 2.18	3.56 ± 1.17	0.32	<0.22
Sclerostin (ng/mL)	1.54 ± .66	1.56 ± .64	0.01	<0.31
FGF- 23 (pg/mL)	49.41 ± 18.45	56.90 ± 16.35	7.49	<0.001

Paired t-tests (two-tailed) revealed non-significant p-values ($p>0.05$) for serum osteocalcin, serum BALP, and serum sclerostin. While, mean serum FGF23, values at baseline and 24 weeks were 49.41 pg/mL and 56.90 pg/mL, respectively, indicating a mean difference of 7.49 pg/mL between the groups. The paired t-test (two-tailed) indicated a significant p-value ($p<0.05$) for serum FGF23.

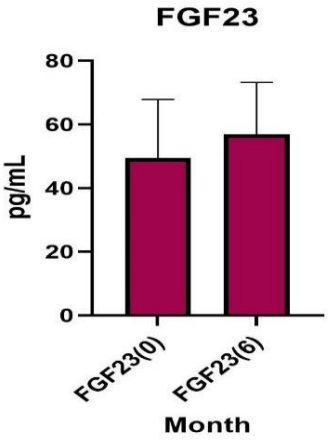


1 (A)

1 (B)



1 (C)



1 (D)

Figure 1: 1 (A), 1 (B), 1 (C), 1 (D) showing values of serum osteocalcin, serum BALP, serum sclerostin, serum FGF23 values at baseline and after 6 months of follow up respectively

DISCUSSION

Complications of type 2 diabetes mellitus (T2DM), like retinopathy and autonomic dysfunction, can increase the risk of bone fractures by raising the likelihood of falls. Nephropathy may lead to renal osteodystrophy, and altered bone properties which can contribute to an elevated fracture risk in T2DM, independent of bone mineral density (BMD). The marrow microenvironment is increasingly recognized as crucial for efficient bone remodeling. Evidence indicates that elderly individuals with T2DM face a 50%–80% higher extremity fracture risk, with a meta-analysis reporting a 1.7 relative risk for hip fractures [11]. Medications, including thiazolidinediones, may affect bone remodeling, and systemic changes in inflammation and oxidative stress may contribute to bone fragility in T2DM. According to the 2023 publication of the Indian Council of Medical Research – India Diabetes (ICMR INDIAB) study, the prevalence of diabetes is reported to be 101 million. Despite the rise in diabetes prevalence globally, particularly in Asia, identifying T2DM patients at increased fracture risk remains challenging. Lifestyle modifications are crucial for T2DM management, considering its association with cardiovascular disease (CVD), a major comorbidity, affecting about one-third of people with diabetes. Joint management of CVD and T2DM has gained attention, with SGLT2 inhibitors showing positive effects on CVD outcomes. However, safety and efficacy data related to bone health with SGLT2 inhibitors remain uncertain. Long-term exposure to a diabetic environment subtly alters bone remodeling, as suggested by osteoblastic and osteoclastic markers in studies.

A meta-analysis of major trials including ACCORD, ADVANCE, UKPDS, and VADT (27,049 participants) revealed a 16% reduction in cardiovascular disease (CVD) with intensive glucose control, particularly beneficial for those without a history of macrovascular disease. Following FDA attention on cardiovascular safety, SGLT2 inhibitors gained prominence. The EMPAREG OUTCOME trial[12] on empagliflozin demonstrated significant superiority in reducing CVD-related mortality, heart failure hospitalization, and all-cause death. Similarly, the CANVAS Program and CANVAS–Renal [13] for canagliflozin, and the DECLARE–TIMI 58 trial[14] for dapagliflozin, indicated positive effects on CVD outcomes in patients with type 2 diabetes mellitus (T2DM). Despite the rising use of SGLT2 inhibitors, concerns persist about their safety and efficacy related to bone health due to conflicting results.

Extended exposure to a diabetic environment induces subtle alterations in bone remodeling and turnover markers. A cross-sectional study involving 40 patients with type 2 diabetes mellitus (T2DM) at the Rajiv Gandhi Centre for Diabetes and Endocrinology aimed to explore the impact of SGLT2 inhibitors on bone turnover markers and their potential correlation. The study encompassed osteoblastic and osteoclastic markers and various biochemical assays.

Bone Markers

Fibroblast growth factor (FGF-23)

FGF-23, produced by osteocytes, acts as a phosphaturic hormone, influencing bone and mineral metabolism. The present study found a significant increase in mean serum FGF23 levels ($p<0.05$) with SGLT2 inhibitors (56.90 ± 16.35 pg/mL) usage in T2DM patients compared to the baseline group (49.41 ± 18.45 pg/mL), aligning with previous reports on SGLT2 inhibitors[15]. Monitoring of serum FGF-23 could be crucial during SGLT2 inhibitor treatment as a potential biomarker for adverse cardiovascular events primarily and bone metabolism secondarily.

Sclerostin

A key regulator of the Wnt pathway, sclerostin, expressed mainly in osteocytes, influences bone mass. Serum sclerostin tends to increase with age, and several other determinants which affect serum sclerostin levels including, parathyroid hormone (PTH), estradiol (E2), follicle-stimulating hormone (FSH) and kidney function. In a cross-sectional study involving postmenopausal women and men aged over 50 years with T2DM, elevated levels of sclerostin were associated with the presence of vertebral fractures[16]. Higher circulating levels of sclerostin have been detected in T2DM patients, potentially contributing to diminished bone turnover and an increased susceptibility to fractures within this population. Although no direct SGLT2 inhibitor effect on sclerostin was identified, weight loss induced by SGLT-2 inhibitors might impact bone mineral density and turnover. In our study, the mean serum values between the groups were found to be non-significant ($p>0.05$). No existing studies have demonstrated the impact of SGLT2 inhibition on sclerostin. However, weight loss resulting from SGLT-2 inhibition may influence both bone mineral density (BMD) and bone turnover. The increase in adiponectin, an anti-inflammatory cytokine, following fat loss activates adiponectin receptors in osteoblasts. This activation hinders sclerostin, an inhibitor of the Wnt pathway, and promotes the differentiation and maturation of osteoblasts.

Osteocalcin (OC)

Synthesized by osteoblasts, osteocalcin plays a role in bone health. In T2DM, osteocalcin levels exhibit an inverse relationship with glycemic control, fasting insulin concentrations and HbA1C. The only marker that seems to be consistently decreased in T2DM is Osteocalcin. A reduction in OC is linked to vertebral fractures, and a lower ratio of OC to BALP signifies an elevated risk of fractures, regardless of BMD. The present study observed nonsignificant mean serum values between groups ($p>0.05$). Similar findings were also observed in a placebo-controlled, randomized, double-blind study involving individuals with type 2 diabetes (T2D). In another study, empagliflozin did not induce significant changes in osteocalcin levels after both 3 days and 3 months of treatment, as reported by M Rau and colleagues in 2022[17]. Conversely, the bone formation marker osteocalcin and the bone resorption marker β-CTX were both raised simultaneously. This implies that weight loss might stimulate bone turnover, potentially resulting in adverse bone regulation, as indicated by Shah and colleagues in 2011.

Bone-Specific Alkaline Phosphatase (BALP)

BALP, a bone-specific enzyme, reflects osteoblast activity. A subgroup analysis was conducted within a randomized controlled study to assess the impact of ipragliflozin on bone in Japanese individuals diagnosed with T2DM and the levels of bone-specific alkaline phosphatase (BALP) were not significantly changed. Similarly, we found that in our study the mean serum values between the groups was found to be non-significant ($p>0.05$). In type 2 diabetes patients with NAFLD, using Canagliflozin (100 mg/ day) for 24 weeks BALP levels didn't change [18].

Other Parameters

Parathormone (PTH)

The majority of studies on type 2 diabetes mellitus (T2DM) indicate normal or even low levels of PTH. However, some reports have shown elevated circulating PTH. The inconsistency in data is partly attributed to variations in the assays used for PTH measurement, which may detect either active or inactive fragments of the hormone molecule[19].

In our study, usage of SGLT2 inhibitors in T2DM patients has increased the mean serum parathormone levels (55.32 ± 10.97 pg/mL) significantly ($p<0.05$) when compared to baseline group (49.7 ± 12.91 pg/mL). Elevations in parathyroid hormone (PTH) levels have been observed in several studies involving the use of SGLT2 inhibitors. This increase in PTH levels could be attributed to the indirect activation of the FGF23–1,25-dihydroxyvitamin D–parathyroid hormone axis through SGLT2 inhibition[20].

25(OH) vitamin D

In individuals with T2DM, vitamin D impacts both rate of insulin secretion and sensitivity. An inverse relationship between T2DM and vitamin D is postulated from cross-sectional and prospective studies. In our study, usage of SGLT2 inhibitors in T2DM patients has increased the mean serum 25(OH) vitamin d levels (17.18 ± 2.5 ng/mL) significantly ($p<0.05$) when compared to baseline group (15.94 ± 2.5 ng/mL). Our study was in contrast to other studies which showed a decrease in $1,25(OH)_2$ vitamin D possibly due to intervention by the treating physician[21].

Phosphate

Patients with type 2 diabetes mellitus commonly experience disruptions in serum electrolyte levels, which may stem from osmotic fluid shifts induced by hyperglycemia or result from total-body deficits due to osmotic diuresis. Past research, such as the study conducted by Billington and colleagues in 2017[22], has indicated an inverse association between serum phosphate levels and bone mineral density in both postmenopausal women and men. However, a retrospective and cross-sectional

investigation by Y Yang et al. in 2020[23] did not reveal a linear correlation between serum phosphate levels and BMD in individuals with type 2 diabetes.

In our study, the administration of SGLT2 inhibitors to T2DM patients resulted in a significant ($p<0.05$) increase in mean phosphate levels (1.26 ± 0.14 mmol/L), as compared to the baseline group (1.12 ± 0.09 mmol/L). These findings align with other studies that confirm similar outcomes. In a single-blind, randomized crossover study involving 25 healthy volunteers, the use of canagliflozin led to elevated serum phosphorus levels. Similarly, the administration of dapagliflozin was associated with increased serum phosphorus levels and significant rises in parathyroid hormone (PTH) levels, as reported by de Jong and colleagues in 2019[24].

Calcium

In prospective studies, a consistent inverse relationship is observed between low calcium intake and the occurrence of type 2 diabetes mellitus (T2DM). Additionally, in men diagnosed with type 2 DM, serum calcium levels are positively linked to impaired glucose metabolism, irrespective of parathyroid hormone (PTH) or bone metabolism, as indicated by Yamaguchi and colleagues in 2011[25].

In our study, usage of SGLT2 inhibitors in T2DM patients has increased the mean calcium levels (2.42 ± 0.09 mmol/L) significantly ($p<0.05$) when compared to the baseline group (2.3 ± 0.09 mmol/L). In contrary to our results most of the studies have shown to have negligible effects on serum calcium, possibly due to intervention by the treating physician[26].

METHODS

Study Population

The 40 patients of newly diagnosed T2DM of age group 40-60 years from northern India were diagnosed based on clinical symptoms and American Diabetes Association (2020) criteria. Patients were managed based on present diabetic care standards and guidelines for clinical practices. The standard regimen for treatment included modification of diet, regular physical activity and oral anti-diabetic medications. The doses of glucose-lowering drugs were adjusted during the study to achieve optimal metabolic control of diabetes, consistent with a routine clinical practice.

The study conducted was an observational, prospective and open labelled. The patients who were prescribed metformin or metformin with glimepiride and experiencing sub-optimal glycaemic control were added with SGLT2 inhibitors, included in the study. The patients with type 1 diabetes mellitus, those on insulin or other injectable agents or systemic corticosteroids and other drugs which may affect the glycaemic parameters, patients with history of diabetic ketoacidosis (DKA), significant diabetic nephropathy and patients with significant liver disease, congestive heart failure (CHF), significant lung disease, septicaemia, psychotic patient, pregnant women, known cases of HIV / HBsAg / Anti-HCV and immunocompromised patients were excluded from the study. Patients for analysis were divided into two groups: Group 1 patients were prescribed Metformin (500mg-1000mg) with or without Glimepiride (2mg) and Group 2 patients were added with SGLT2 inhibitors (Dapagliflozin 5/10mg or Empagliflozin 10/25mg) along with Metformin with or without Glimepiride (2mg), followed up after 24 weeks.

The Institutional Ethics Committee (IEC) of J.N. Medical College and hospital, AMU, Aligarh approved the study protocol and written informed consent was obtained from all the participants.

Anthropometric measurements

Anthropometric measurements were conducted at the initial assessment and after 6 months of treatment. Height and waist circumference were measured with a precision of 0.5 cm. Body Mass Index (BMI) was determined by dividing weight (in kg) by the square of height (in m2). Blood pressure (in mmHg) was recorded using a mercury sphygmomanometer while the participant was seated, following a rest period of approximately 5 minutes.

Assays

Biochemical parameters, including fasting and postprandial serum glucose, HbA1c, serum phosphorus, calcium, vitamin D, parathormone, osteocalcin, bone-specific alkaline phosphatase, FGF23, sclerostin, etc., were measured. To estimate the bone biomarkers, venous blood samples were collected from each participant on first visit and after 6-months study period. The blood samples were centrifuged at 1000 rpm for 20 minutes at 4°C. The resulting serum samples were then separated, portioned into aliquots, and stored frozen at -70°C. Serum glucose was measured by the glucose oxidase method. Method opted for determining HbA1c is boronate affinity High Performance Liquid Chromatography (HPLC) and the instrument used was Trinity Biotech Premier Hb9210 Automated HPLC System. Calcium and Phosphate were analysed using Beckman Coulter AU480 chemical analyser. Based on Chemiluminescence Immunoassay technique Vitamin D was analysed by Beckman Coulter Access 2. Parathormone was analysed by Access Intact PTH assay which is a two-site immunoenzymatic ("sandwich") assay. Similarly other bone markers including FGF23, Sclerostin, Bone specific alkaline phosphatase (BALP), Osteocalcin were analysed using immunoenzymatic ('sandwich') assay procured from Realgene labs (Ghaziabad, UP, India; Catalog numbers 3011764, 3012799, 3018560, 3012390)

Statistical analysis

Data are presented as mean ± standard deviation (SD). Differences among the groups were evaluated by paired Student's t-test. The alterations in parameters were determined by subtracting the initial values from the measurements obtained after 6 months of treatment. A p-value of less than 0.05% was considered as statistically significant. The charts for Statistical analysis were prepared using Microsoft Excel and data were interpreted using Prism Graph pad 9.

CONCLUSION

In conclusion, the present study suggests that the usage of SGLT2 over the periods of 24 weeks inhibitors is associated with a significant increase in bone resorption markers such as FGF23 and parathormone, however the serum levels of bone formation markers BALP and Osteocalcin didn't change significantly. This could potentially elevate the risk of bone resorption and contribute to osteoporotic effects. While serum 25(OH) vitamin D and serum calcium have shown significant

increases, contrary to previous studies. To validate these observations, a large cohort-based randomised controlled trial in the Indian population is imperative, considering the substantial regional variations in reference values for bone markers. Additionally, further research should investigate the long-term effects of SGLT2 inhibitors, and we recommend a cautious approach, especially for individuals with concerns related to bone health, when considering the use of antidiabetic drugs. Follow-up studies extending over 6 months could provide valuable insights into the prolonged impact of SGLT2 inhibitors on bone metabolism.

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Author's contributions

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1. Sumedh GK	Conceptualization, Literature search, Data Acquisition, Statistical Analysis, Manuscript editing, Manuscript review
2. Jameel Ahmad	Supervision, Conceptualization, protocol writing, Manuscript Editing, Manuscript review
3. Waseem Rizvi	Supervision, Conceptualization, Manuscript writing, Manuscript editing, Manuscript review
4. Sheelu Shafiq Siddiqui	Supervision, Conceptualization, Manuscript writing, Manuscript editing
5. Vibhu Pandey	Literature reviewing, statistical analysis, Manuscript Editing
6. Mahendra Rathour	Literature reviewing, Manuscript Editing

Conflict of interest
The authors declare no conflict of interest.

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Ethical Approval
The study protocol was approved by the Institutional Ethics Committee (IEC), A.M.U., Aligarh on 02-11-2021 (Registration No. IECJNMC/537 dated 28-11-2020).

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