Original Article (Under Review: Archives of Osteoperosis)

Impact of type 2 diabetes mellitus and chronic kidney disease on bone mineral density in elderly patients with fragility hip fracture: a cross-sectional study

Introduction

Diabetes mellitus (DM) and chronic kidney disease (CKD) are common medical conditions among the elderly and have been shown to increase the risk of bone fractures due to their negative impact on bone quality. Recent data demonstrates the association of bone mineral density (BMD) measured by using dual-energy X-ray absorptiometry (DXA) scan with fragility fractures in patients with CKD [1].

The effect of Type 1 Diabetes Mellitus (T1DM) and Type 2 Diabetes Mellitus (T2DM) on BMD appear to be discordant [2]. Several studies have found a positive association between HbA1c levels and BMD in T2DM, independent of other factors such as age, sex, body mass index, and diabetes chronicity. The exact mechanisms underlying this relationship are not yet fully understood, but it has been suggested that hyperglycemia may affect bone cells and bone metabolism, leading to decreased bone formation and increased bone resorption [3–5]. In contrast, T1DM is associated with a lower BMD and increased fracture risk. Poorer glycemic control was associated with lower hip BMD in T1DM [6].

When DM and CKD occur in combination, the negative impact on BMD may be greater due to the complex interplay between the two conditions. Considering that a substantial number of patients in renal or geriatric clinics are affected by both, it is important for healthcare providers to be aware of the potential impact of DM and CKD on bone health and to implement appropriate interventions to reduce the risk of bone fractures in this population.

In this study, we investigate potential differences in the impact of T2DM and CKD on BMD in a cohort of elderly patients with fragility hip fracture, when these conditions occur alone versus when they occur in combination. We also investigate the relationship of worsening HbA1c to BMD in the groups with CKD and T2DM versus T2DM alone.

Methods

Study Population: A cross-sectional study was undertaken, encompassing 571 elderly patients aged ≥65 years, who experienced fragility hip fractures and were admitted to Changi General Hospital between June 2014 and June 2016. The study received ethical approval from the Singhealth Institutional Review Board (Approval No: 2017/2962), with informed consent waived by the board. In a previous study utilizing the same dataset, we reported on the outcomes of hip fractures in the elderly [7]. Exclusion criteria were an absence of serum creatinine measurements within 3 months prior to admission, acute kidney injury, history of malignancy, chronic liver disease, and absence of T-score. The study population was stratified into four groups: Group 1 - No CKD or diabetes (n=166), Group 2 - No CKD with diabetes present (n=146), Group 3 - CKD present with no diabetes (n=128), Group 4 - Both CKD and diabetes present (n=131). All patients aged 65 years and above with hip fractures were included as part of the hospital's value care program. Data on patients admitted with hip fractures between June 1, 2014, and June 1, 2016, were extracted from electronic health records. Follow-up extended from the index date to June 1, 2018, or until death.

Laboratory Values and BMD: The estimated glomerular filtration rate (eGFR) was calculated using the 2021 CKD-EPI equation [8]. CKD was defined according to the KDIGO 2021 Clinical Practice Guidelines, including participants with CKD G3-5, corresponding to an eGFR ≤60mL/min/1.73m2 [9]. Biochemical values included 25(OH) vitamin D, serum albumin, serum calcium, and phosphate. Bone mineral density (BMD) was measured using dual-energy X-ray absorptiometry (DXA) at the lumbar spine (L1-L4) and femoral neck (Hologic QDR Discovery Wi, United States). The normative values for assessing BMD are derived from the local Singapore population, which is predominantly Chinese. These values are proprietary and specific to the Hologic densitometer. Studies in the local female population have indicated that BMD is 6-8% lower at the femoral neck and 3-8% lower at the AP spine compared to age matched Americans [10]. Similarly, an Asian male BMD reference database shows values that are 10% lower at the spine and 5% lower at the neck of femur compared to the Caucasian reference database [11]. Low BMD was defined as <2.5 based on the WHO criteria for osteoporosis [12].

Outcomes: We examined the impact of CKD and T2DM on BMD when these conditions were either present alone or in combination. Additionally, we studied the association of worsening HbA1c with BMD in the specified patient groups.

Statistical Analysis

Patients were stratified into 4 groups: Group 1 -No CKD or diabetes, Group 2 -No CKD with diabetes present, Group 3 -CKD present with no diabetes, Group 4 -both CKD and diabetes present. Continuous variables were summarized as mean ± standard deviation (SD) or median (interquartile range) and categorical variables as proportions. *p*-values represent differences in characteristics based on ANOVA for continuous variables, and Chi-square test for categorical variables. A p-value <0.05 was considered significant. All statistical analyses were performed using SAS v9.4 (SAS Institute Inc., NC, USA).

Statistical significance for p-values in the case of multiple comparisons was pre-specified as 0.05/n using Bonferroni correction.

Results

Baseline Characteristics:

A total of 571 elderly patients with hip fractures were included in the study and divided into four groups based on the presence or absence of chronic kidney disease (CKD) and diabetes mellitus (DM). The groups were defined as follows:

Group 1: CKD-/DM- (n=166)

Group 2: CKD-/DM+ (n=146)

Group 3: CKD+/DM- (n=128)

Group 4: CKD+/DM+ (n=131)

The baseline characteristics of patients stratified by CKD and DM status are summarized in Table 1. The mean age of the study population was 79.5 ± 7.3 years, with 70.6% being female.

Bone Health:

The mean T-score at the femoral neck was -3.1 ± 0.94. Notably, Group 2 (CKD-/DM+) exhibited a higher T-score compared to Group 1 (CKD-/DM-), with an increase of 0.20 in BMD, as shown in Table 1. Group 4 (CKD+/DM+) similarly demonstrated a better T-score than Group 1(CKD-/DM-) (P=0.04), as shown in Table 2.

Relationship of HbA1c to T-Score:

Figure 1 illustrates the association between HbA1c and T-score in Groups 2 and 4. Although a positive linear relationship was observed between higher HbA1c levels and T-score, this relationship did not reach statistical significance. Notably, this positive association was absent in Group 4 (CKD+/DM+).

Clinical Outcomes:

Patients in Group 4 had a longer length of stay compared to the other groups, with a mean of 10.1 days (p=0.002). However, there was no significant difference in survival during the index admission between the groups.

Discussion

In this retrospective study of 571 elderly patients with fragility hip fractures, we examined the impact of chronic kidney disease (CKD) and diabetes mellitus (DM) on bone mineral density (BMD) in elderly patients with fragility hip fractures. Specifically, we explored the effects of CKD and DM when occurring alone or in combination, as well as the influence of worsening glycemic control, as measured by HbA1c, on BMD.

Our findings revealed that patients with DM alone exhibited a slightly higher T-score (0.20) compared to those without DM or CKD. Interestingly, when DM and CKD coexisted, there was no detrimental effect on BMD, as assessed by T-scores. However, in patients with type 2 diabetes mellitus, we observed a positive association between worsening HbA1c levels and T-score. Notably, this association disappeared in the presence of concurrent CKD. Given the important role of serum phosphate and 25(OH) vitamin D levels in bone mineralization and formation, we have included this data alongside the T-scores in Table 1. An inverse

relationship between serum phosphate and BMD is well documented in both aging men and postmenopausal women [13,14]. Hyperphosphatemia in CKD is known to contribute to bone fragility [15]. Similarly, vitamin D deficiency is often associated with or can exacerbate osteoporosis [16].

It is important to acknowledge that bone health is adversely affected by the presence of DM and CKD, yet conventional risk assessment tools often overlook these conditions [17, 18]. Our study adds to the existing literature by highlighting the differential effects of type 1 and type 2 diabetes on BMD, with type 2 diabetes being associated with higher BMD. This aligns with previous research indicating an increased BMD in patients with abnormal glucose metabolism [19, 20].

However, despite the apparent increase in BMD, individuals with diabetes are at a substantially higher risk (40-70%) of fragility fractures compared to non-diabetic counterparts [21, 22]. This increased fracture risk in type 2 diabetes is attributed to altered bone metabolism, leading to compromised bone microarchitecture, as evidenced by thicker femoral cortices and narrower bones, which predispose to microcrack accumulation and cortical porosity [4, 23]. Diabetes could affect bone through several mechanisms, some of which may have contradictory effects. Obesity which is widespread in T2DM is strongly associated with higher BMD, probably through mechanical loading and hormonal factors, including insulin, estrogen, and leptin [24, 25]. High-resolution peripheral quantitative computed tomography (HRpQCT) has demonstrated a 10% higher trabecular BMD with an increase in intracortical porosity. An increased fraction of fat has also been reported in the bone marrow of patients with diabetes. Thus, these patients showing increased cortical porosity and have significantly lower bone strength than healthy controls [26].

CKD, characterized by a markedly elevated fracture risk, is also known to negatively impact bone health through various mechanisms, including increased parathyroid hormone levels, reduced vitamin D levels, metabolic acidosis, and malnutrition. Unfortunately, established

risk assessment tools like FRAX do not currently account for DM or CKD, which have significant implications for bone health [18].

Furthermore, therapeutic options for osteoporosis prevention in advanced CKD remain limited, highlighting an unmet need in this population [27]. Despite the expected detrimental effects of DM and CKD on BMD, our study did not find a compounding negative impact when these conditions coexisted.

There are various proposed mechanisms for increased BMD in patients with diabetes mellitus, one being the association with the deposition of glycosylated protein [21]. We found a positive correlation between higher HBA1C and T-score, though it did not reach statistical significance. These findings are in line with a study from China reporting on the positive association of BMD with HBA1C when values exceeded 7.5% [28]. This association however was absent in the concurrent presence of CKD.

It is worth mentioning that our study has several limitations, including its cross-sectional design, which precludes causal inference, and its restriction to elderly patients with fragility hip fractures. Our study did not include measures like trabecular bone score (TBS) or assessment by HR-pQCT which can predict hip and major osteoporotic fracture at least partly independent of BMD [29]. We also did not address the issue of falls which is an important contributor to fracture risk in patients with T2DM. Our cohort of patients with CKD had an eGFR which was mildly decreased hence it would not be possible to comment on the effects of CKD on BMD in those with severe CKD or dialysis dependent. However, our findings underscore the importance of considering T2DM and CKD in the interpretation of BMD and clinical decision-making regarding osteoporotic therapy initiation.

The interplay between T2DM and CKD on BMD underscores the complexity of bone health in these populations and highlights the need for comprehensive risk assessment strategies and targeted interventions to mitigate fracture risk in vulnerable individuals.

Conclusion

Our study among elderly patients who underwent hip fracture surgery revealed that Group 2 (CKD-/DM+) exhibited a significantly higher bone mineral density (BMD) compared to Group 1 (CKD-/DM-), with an increase of 0.20 in T-score. This underscores the potential influence of diabetes mellitus on bone health in this population.

Contrary to expectations, the presence of both chronic kidney disease (CKD) and diabetes mellitus (DM) did not contribute to a worsened BMD. This suggests that the effect of T2DM on the BMD was overwhelming at least in a cohort of patients with mild CKD.

Our findings indicate a positive association between higher HbA1c levels and BMD in Group 2 (CKD-/DM+), suggesting a potential protective effect of elevated HbA1c on bone health. However, this correlation is not particularly robust, indicating that other factors may also influence BMD in this group. Interestingly, this positive association disappears in Group 4 (CKD+/DM+), suggesting a different mechanism affecting bone health in individuals with both CKD and DM.

Furthermore, we observed a significant difference in postoperative length of stay (LOS) between Group 1 (CKD-/DM-) and Group 4 (CKD+/DM+), with Group 4 experiencing a longer LOS (median 10.1 days vs. 8.6 days, $p=0.002$). This highlights the potential impact of CKD and DM comorbidity on postoperative recovery and hospitalization duration in elderly hip fracture patients.

Implications:

These findings underscore the importance of early detection and management of diabetes mellitus and chronic kidney disease in elderly patients to mitigate the risk of fragility hip fractures and improve bone health. Future research should delve deeper into the mechanisms underlying the observed associations and explore targeted interventions to optimize bone health outcomes in this vulnerable population.

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