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Investigations of Chronic Kidney Disease Associations with Hip Fracture Incidence and Mortality in India.

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Abstract

Background: Hip fracture is very common in patients with ESRD. The risk has been estimated to be 4.4 to 14 times greater than that of the general population. KD and hip fracture are important public health problems that share multiple risk factors. Both are more common in older individuals and patients with diabetes. In addition, CKD and low bone mineral density (BMD), a major risk factor for hip fracture, are highly coincident. Therefore, the study aim was to clarify the association of CKD with hip fracture incidence and mortality. **Subjects and Methods:** Present study included 700 participants which were divided into two groups according to kidney disease. Out of 700 subjects, 100 subjects with CKD were included in group I whereas, 600 subjects without CKD were included in group II. We chose femoral neck BMD as the main measurement of hip BMD in our analysis because this region is most predictive for hip fracture. We chose to use the Modification of Diet in Renal Disease (MDRD) formula to calculate the estimated GFR (eGFR). **Results:** It is interesting that when the demographic characteristics of the hip fracture populations were evaluated, there was an association among age, history of hip fracture, and prevalence of CKD. In the participants (aged 50 to 74), the prevalence of CKD was approximately three-fold higher in the group with a history of hip fracture than in the group without a hip fracture (12% versus 4%; P<0.01). However, in older participants (older than 75 yr), the prevalence of CKD was the same regardless of hip fracture history. **Conclusion:** By using different measures of hip fracture incidence and mortality, we have demonstrated why other studies have shown mixed associations between CKD and hip fracture. Hip fracture incidence was higher in individuals with CKD compared with those with normal eGFR particularly where measured with admissions. However, following a hip fracture, CKD did not increase post-hip fracture mortality except in those with CKD of various stages. Nonetheless, a reduction in hip fracture incidence in those with CKD would reduce the number of deaths after hip fracture in the Indian population.

Keywords: CKD, Hip fracture, mortality, Indian.

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Introduction

Hip fracture is very common in patients with ESRD. The risk has been estimated to be 4.4 to 14 times greater than that of the general population.[1,2] Hip fracture is associated with high mortality; up to one-third of people die within a year.3 Although the associations and risk factors for hip fracture in patients with ESRD are widely known,[2–5] considerably less information is available on the risk for hip fracture in patients with less severe chronic kidney disease (CKD). Chronic kidney disease (CKD) is also amajor and growing healthcare challenge, with an estimated global prevalence of 11%–13%, again higher in the elderly and women.[6] CKD and hip fracture are important public health problems that share multiple risk factors. Both are more common in older individuals and patients with diabetes. In addition, CKD and low bone mineral density (BMD), a major risk factor for hip fracture, are highly coincident. A recent study estimated that the prevalence of mild to moderate kidney dysfunction was 60% for women and 45% for men with osteoporosis.[5]

The kidney is an important regulatory organ for the calcium–phosphate homeostasis in the body.[7] The irreversible loss of kidney function is associated with secondary hyperparathyroidism and the lack of synthesis of the active form of vitamin D with resulting metabolic bone disease.[7,8] People with CKD are at increased risk of morbidity, mortality and progressive kidney function decline, leading to renal replacement therapy (RRT).[5–7] A well-recognised complication of RRT is renal bone disease. The association between RRT and risk of hip fracture is well established, with a high incidence of hip fractures.[9] It has been shown that patients on dialysis have approximately an overall four times higher risk of hip fracture than individuals in the general population of the same sex and age.[9,10] On the other hand, in patients with CKD, Hsu et al.[11] reported that low hip BMD was related to traditional risk factors for osteoporosis, principally gender, weight, and age, rather than to kidney function. The evidence of hip fracture risk in CKD is uncertain, particularly at less advanced stages. Some studies report on renal function measured after hip fracture has occurred others restrict to those at high risk of fracture.[12-14] Recent studies reporting hip fracture incidence in those with prior documented CKD

have been conflicting, some showing an association and others not.[15-18] Therefore, the study aim was to clarify the association of CKD with hip fracture incidence and mortality.

Subjects and Methods

The cross sectional study was conducted in the orthopaedics department of Rohilkhand medical college and hospital, Bareilly. Present study included 700 participants which were divided into two groups according to kidney disease. Out of 700 subjects, 100 subjects with CKD were included in group I whereas, 600 subjects without CKD were included in group II. All the subjects were from 18 to 70 years age group and both sexes. Present study was conducted from July 2018 to January 2019 in the department of orthopaedics.

A history of hip fracture was assessed through the administration of a questionnaire by trained field staff. Participants were asked the question, "Has a doctor ever said you had a broken/fractured hip?" BMD of the proximal femur was determined by dual-energy x-ray absorptiometry (DXA) scan at five regions: Femoral neck, trochanter, intertrochanter, total femur, and Ward's triangle. We chose femoral neck BMD as the main measurement of hip BMD in our analysis because this region is most predictive for hip fracture.[13,14] Femoral neck BMD was classified according to the World Health Organization (WHO) criteria for the diagnosis of osteoporosis in postmenopausal white women (<2.5 SD below the gender-specific age 20 to 29 reference mean) and osteopenia (1 to 2.5 SD below the gender-specific age 20 to 29 reference mean).[15] For women, osteoporosis was considered present at a BMD <0.64 g/cm2 and osteopenia at a BMD between 0.64 and 0.82 g/cm2; BMD <0.82 g/cm2 was considered normal. For men, osteoporosis was considered present when the BMD was _0.68 g/cm2 and osteopenia at a BMD between 0.68 and 0.90 g/cm2; BMD <0.90 g/cm2 was considered normal.

We chose to use the Modification of Diet in Renal Disease (MDRD) formula to calculate the estimated GFR (eGFR), the primary measure of kidney function in this analysis, because it is a more accurate measure of kidney function than other formulas:[16]

GFR (ml/min) =186.3 x serum creatinine-1.154
x age-0.203 x -0.742 (if female) (1)

Patients with ESRD, defined as an eGFR <15 ml/min, were excluded from this analysis because they were not the primary focus of this study. Because our primary goal was to investigate the association between CKD and hip fracture in study population in whom osteoporosis and CKD are highly co-prevalent, no exploratory analyses were performed for individuals who were younger than 18 year.

Vitamin D samples were obtained from fresh or frozen serum. Frozen serum was stored at - 20°C. This was a two-step procedure in which 25-OHD and other hydroxylated metabolites first are extracted from the serum or plasma with acetonitrile. After extraction, the treated sample is assayed for 25-OHD by RIA. Vitamin A level was measured in fasting serum samples that were protected from exposure to light. Samples were frozen at _70°C and it was measured by isocratic HPLC.[8]

This study was designed to measure the association of kidney function with hip fracture prevalence rates in older adults. Abnormal kidney function was defined as having an eGFR between 15 and 60 ml/min. The baseline covariates that are independent predictors of hip fracture were unevenly distributed between the groups with and without CKD. We therefore developed a model to balance these differences in the covariate structure of the primary independent predictor of interest to derive an unbiased estimate of the effect of kidney dysfunction on hip fracture prevalence rates. A logistic regression model was created with abnormal kidney function as the outcome variable. Independent variables that were entered into the model included established risk factors for osteoporosis: Age, history of type 2 diabetes, menopausal status (last period _1 yr ago), personal history of osteoporosis, current estrogen usage (oral or transdermal), diuretic usage (thiazide and nonthiazide), dietary calcium intake, serum vitamin A level, tobacco use and a history of maternal hip fracture.

Results

A total of 300 participants who were older than 50 yr both gender had sufficient information to calculate an eGFR and had responded to the hip fracture questionnaire. This group included participants with a history of hip fracture. CKD, as defined by an eGFR 15 to 60 ml/min, was present in 875 (14.0%) of the participants. Serum creatinine ranged between 0.7 and 2.9 mg/dl in the participants who reported a hip fracture; 42 of these participants had an eGFR <60 ml/min. There were no hip fractures in the group of participants with an eGFR <20 ml/min.

In [Table 1], we compare various characteristics between the two groups of participants: Those with CKD, as defined by an eGFR between 15 and 60 ml/min and those without CKD, as defined by an eGFR _60 ml/min. As a group, participants with CKD differed significantly in several respects from those without CKD. With regard to demographic characteristics, the CKD group was significantly older and included more women.

Table 1: Demographic pattern of the study population

Variable	Kidney Disease		No Kidney disease		p value
	n/N	SE	n/N	SE	
Age (Yr)	57	9.8	52	10.3	>0.05
Male	40/100	4.3	280/600	4.7	<0.01
Female	60/100	3.9	320/600	5.2	<0.01

Table 2: Medication and nutrition

Variable	Kidney Disease		No Kidney disease		p value
	n/N	SE	n/N	SE	
Oestrogen use	12/100	1.8	58/600	3.1	<0.01
Diuretic use	42/88	3.9	40/600	4.9	<0.01
Dietary calcium	17/88	4.5	568/600	8.4	<0.01
Dietary vitamin A	17/88	2.8	568/600	5.7	<0.01

[Table 2] shows that a significantly high population was on oestrogen replacement therapy, diuretic use, calcium and vitamin A

There was a significant difference between serum vitamin A, D, calcium, phosphate and alkaline phosphate in CKD group compare to no CKD group. [Table 3]

Table 3: Biochemical parameters

Variable	Kidney Disease		No Kidney disease		p value
	n/N	SE	n/N	SE	
Serum vitamin A	14/100	3.6	569/600	7.4	<0.01
Serum vitamin D	14/100	2.9	572/600	5.8	<0.01
Serum calcium	15/100	4.2	550/600	6.1	<0.01
Serum phosphate	15/100	1.8	562/600	3.9	<0.01
Serum alkaline phosphate	15/100	3.1	554/600	5.6	<0.01

[Table 4] shows that CKD patients had significantly high incidence history of diabetes, osteoporosis, hip fracture and women of postmenopausal status. Other differences between the groups included tobacco use which was insignificant. Renal function, whether analyzed as a continuous variable (serum creatinine in mg/dl or eGFR in ml/min) or a categorical variable (eGFR 60 ml/min), was strongly associated with an increased prevalence of hip fracture. Other variables that were associated with increased prevalence of hip fracture included several traditional risk factors for osteoporotic fractures, such as increasing age, female gender, a history of maternal hip fracture, a history of osteoporosis, femoral neck BMD that met WHO criteria for osteoporosis, and low activity levels. Increasing propensity score was associated with an increasing association with hip fracture, indicating that the likelihood of being a hip fracture case increased as the likelihood of being a CKD case increased. We also created bivariate models to evaluate potential modifying effects of risk factors for hip fracture on CKD (data not shown). Our results confirmed the positive association between CKD and hip fracture prevalence. Only age, weight, a history of osteoporosis, and low BMD on the basis of WHO criteria reduced the association between CKD and hip fracture. However, even when these factors were considered, CKD remained strongly associated with hip fracture in these models.

Table 4: Medical history

Variable	Kidney Disease		No Kidney disease		p value
	n/N	SE	n/N	SE	
Diabetes	25/100	2.2	94/553	2.9	<0.01
Osteoporosis	5/98	1.2	18/534	3.4	<0.01
Post menopausal status	46/50	4.3	248/270	3.9	<0.01
Tobacco use	50/78	5.4	98/178	3.9	>0.05
History of hip fracture in mother	9/100	1.3	18/600	2.3	<0.01

It is evident from figure 1 that femoral neck BMD also was significantly lower in CKD group (0.66±0.08 gm/cm2) compare without CKD group (0.75±0.09 gm/cm2) with p value <0.01.

It is interesting that when the demographic characteristics of the hip fracture populations were evaluated, there was an association among age, history of hip fracture, and prevalence of CKD (Figure 2). In the participants (aged 50 to 74), the prevalence of CKD was approximately three-fold higher in the group with a history of hip fracture than in the group without a hip fracture (12% versus 4%; P<0.01). However, in older participants (older than 75 yr), the prevalence of CKD was the same regardless of hip fracture history.

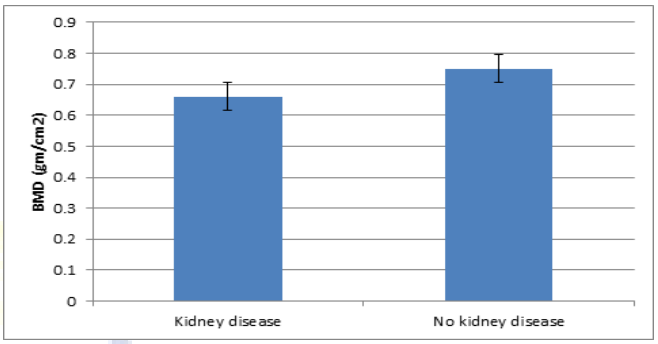

Figure 1: BMD at femoral neck

[Figure 2] shows that incidence of fracture was significantly high in CKD group (9%) compare to no CKD group (3%) with p value <0.01.

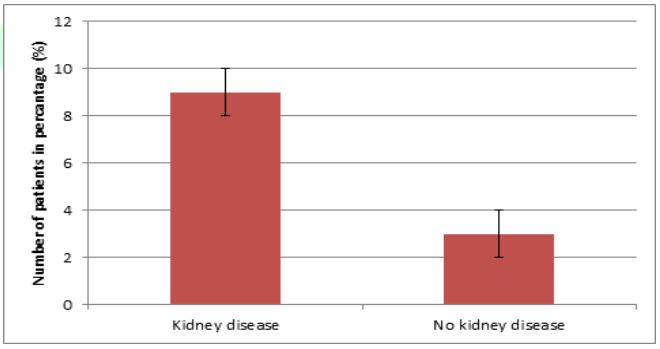

Figure 2: prevalence of hip fracture in both groups

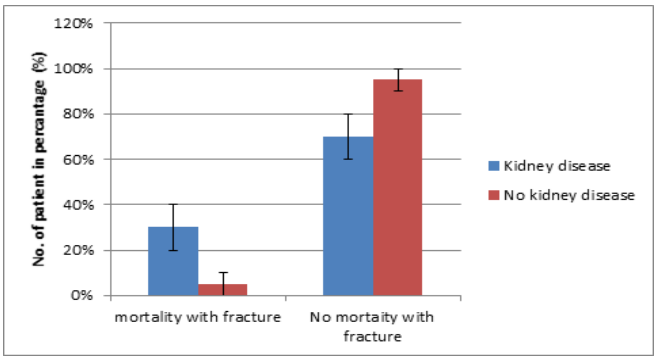

Figure 3: Post-hip fracture admission mortality in CKD, both (a) all-cause mortality and (b) hip fracture-related mortality

Discussion

In this study of 700 participants were included among them 100 patients suffering with CKD were under group I; while 600 subjects without CKS recorded results under group II. We found that the prevalence of CKD was increased in those who reported a hip fracture. Furthermore, the co-prevalence of CKD and hip fracture was even more remarkable in participants who were aged 50 to 74 yr than it was in those who were older than 74 yr. In the younger group, the prevalence of CKD was approximately three-fold higher in those with than in those without a history of hip fracture. The association between hip fracture and CKD was strengthened further by the use of a balancing variable in the logistic model to control for differences in important risk factors for hip fracture between the CKD and non-CKD groups.

The high prevalence of kidney dysfunction in the hip fracture population is consistent with recently published data indicating high prevalence rates of kidney dysfunction in patients who meet WHO criteria for both osteoporosis and osteopenia at the femoral neck. Klawansky et al.[5] reported that the prevalence of mild to moderate kidney failure (GFR of 35 to 60 ml/min) was 33.5% for women and 16.4% for men with osteopenia. Similarly, the prevalence of mild to moderate kidney failure was even higher in participants with osteoporosis, 61.3% for women and 46.5% for men.

BMD is a strong predictor of hip fracture in the general population; therefore, the absence of an association between hip fracture and BMD in the multivariate model is noteworthy. However, although measurement of BMD by DXA provides an assessment of the amount of bone mass, it does not provide information on bone remodeling activity or bone quality or distinguish among the various possible metabolic processes that could affect the structural integrity of the skeleton in patients with CKD.[20,21] Therefore DXA is not a robust predictor of risk for hip fracture in patients with CKD. Moreover, our data are in agreement with the observations of Hsu et al.[11] Using NHANES III, these investigators found that patients with renal dysfunction had significantly lower femoral BMD. However, after adjustment for age, weight, and gender, the negative association between renal function and BMD was extinguished. In contrast, Yendt et al.[22,23] observed that BMD at both the one-third radius and lumbar spine was asso-ciated with decreased creatinine clearance, assessed on a 24-h urine collection, and not with age. Because these investigators did not measure femoral BMD, it is not possible to compare their findings directly with those of Hsu et al.[11] However, their findings may be explained, in part, by the greater predominance of cortical bone at the one-third radius site than the femoral neck site and the particular susceptibility of cortical bone to the catabolic effects of excess parathyroid hormone secretion, even at minimally elevated levels.[24] When more severe degrees of renal dysfunction (GFR <35 ml/min) were included in the prevalence estimates, approximately 85% of women and 57% of men with osteoporosis had some degree of renal dysfunction. In both men and women, the prevalence of renal dysfunction was low in younger age groups and rose precipitously with advancing age.[5] Because low femoral neck BMD is an important risk factor for hip fracture and BMD decreases with increasing age, it is not surprising that we also observed a relationship between renal dysfunction and hip fracture. However, we also noted that in participants with a history of hip fracture, there was a greater association between hip fracture and CKD in the younger age group. This observation may suggest that CKD plays a greater role in altering bone architecture and reducing bone strength in younger than in older age groups, when other traditional risk factors for hip fracture become more prevalent. Longitudinal studies on the role of CKD in the pathogenesis of hip fracture are needed to confirm this hypothesis.

The mechanisms underlying the association between CKD and fractures are likely to be at the metabolic level, due to abnormalities in the parathyroid–calcium– phosphate axis as a result of reduced kidney function.[25] In addition, CKD may be a marker for frailty, leading to falls and an increased risk of fracture. In keeping with some but not all,[15,17,18] reports, we have shown that hip fracture incidence is increased in individuals with CKD. We showed this effect is best demonstrated when hip fracture incidence is measured with admissions but also present when measured with deaths. We demonstrated that this increased risk was present across all ages; few previous studies included all age ranges and many only included the elderly.[16,17,26–29]

Further, we found that post-hip fracture mortality, among those who had a hip fracture admission, was little affected by CKD stages 3–5 overall, except stage 4. Studies in general (30) and RRT populations 39 have reported elevated subsequent mortality in individuals who suffer a hip fracture compared with their age-matched non-fractured peers. However, to our knowledge, few studies have investigated the effect of CKD on mortality post-hip fracture.[19,21,31–33] Three reported increased mortality risk with worse renal function, either eGFR20 or creatinine,[31,32] and one found no mortality risk with worse creatinine after adjusting for confounders.[29] All of these studies, however, only included older patients and were based on single admission creatinine or eGFR, thus, deranged creatinine could be due to acute kidney injury (AKI). A further study relied on hospital admission coding for hip fractures with surgical repair, and a concurrent code for CKD or otherwise,[18] thus limiting CKD ascertainment.

Conclusion

By using different measures of hip fracture incidence and mortality, we have demonstrated why other studies have shown mixed associations between CKD and hip fracture. Hip fracture incidence was higher in individuals with CKD compared with those with normal eGFR particularly where measured with admissions. However, following a hip fracture, CKD did not increase post-hip fracture mortality except in those with CKD of various stages. Nonetheless, a

reduction in hip fracture incidence in those with CKD would reduce the number of deaths after hip fracture in the Indian population.

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