Original Article

A study to predict fracture risk using bone mineral density and FRAX score in patients on chronic maintenance haemodialysis

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Abstract

Introduction: Disturbances in mineral and bone metabolism are prevalent in chronic kidney disease (CKD) and are important causes of morbidity also their diagnosis often delayed and require a spectrum of investigations. The current study attempts to predict and correlate, the fracture risk using simple tools like BMD and FRAX (Fracture Risk Assessment Tool) score in CKD patients. **Methods:** A cross-sectional study among 50 CKD patients age more that 40 years attending OPD (Out Patient Department) at a tertiary care Hospital in north India. **Results:** There is a negative correlation between BMD (NOF) and FRAX score for hip fracture risk and major osteoporotic fracture risk. **Conclusion:** The 10-year fracture risk in these patients, as predicted by FRAX score using FRAX (Indian) calculator, was significantly higher in CKD patients. **Recommendation:** FRAX can be useful tool for early screening of fracture risk in such situations for timely interventions.

Keywords: CKD, FRAX, fracture risk, haemodialysis

Background

Chronic kidney disease (CKD) is now becoming a major public health problem. It affects about one-tenth of the world population, with increasing prevalence and adverse outcomes, including progressive loss of kidney function, cardiovascular disease, and premature death.[1] An Indian population-based study determined the crude and age-adjusted ESRD (end-stage renal disease) incidence rates at 151 and 232 per million population, respectively.[2]

Disorders of mineral and bone metabolism are common in CKDs and are an important cause of morbidity and decreased quality of life. These disturbances include renal osteodystrophy and CKD-mineral and bone disorder (CKD-MBD). Despite the efforts of the CKD Registry of India, which collates data from an estimated 199 affiliated centres, data regarding the characteristics of untreated CKD-MBD in post-dialysis patients and patients on maintenance haemodialysis in India are scarce.[3]

The overall incidence of renal osteodystrophy in patients with advanced renal failure and those treated with maintenance haemodialysis (HD) is 90–100%.[4] Usually, osteodystrophy due to renal cause is diagnosed in patient already undergoing treatment for CKD but sometimes CKD-MBD can be present in early renal disease that can often be missed if not screened early.[5]

BMD (bone mineral density) values correlate with fracture risk and can certainly provide useful information, but it has certain restrictions – the differences in BMD detected by DEXA (dual-energy X-ray absorptiometry) is gradual and a

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period of 1–2 years is usually necessary to recognise significant changes once therapy is started. Moreover, while BMD is important, it is not an exclusive dimension of bone strength. The biggest pitfall of BMD is that it does not consider clinical risk factors for fractures.[6-9]

There are other various biochemical and structural changes that occur in mineral bone disorders that can be assessed for early identification of the problem. However, these parameters, in isolation, do not give an accurate assessment of the fracture risk in CKD patients on haemodialysis. Hence, composite scores that consider both BMD and validated clinical criteria are warranted. One of the composite tools is FRAX (fracture risk assessment tool). FRAX score calculates a 10-year probability of osteoporotic fractures based on clinical risk factors such as body mass index, fracture history, parental fracture history, presence of secondary causes of osteoporosis, use of glucocorticoids as well as smoking status and alcohol consumption with or without BMD measurements.[10]

In patients with CKD on haemodialysis, risk stratification using FRAX score may require fewer DEXA scans with minimal impact in terms of missing high-risk patients and yields a modest reduction in unnecessary treatment.

FRAX can improve the ability of clinicians and researchers to identify individuals at high risk of fragility fractures. However, the application and performance of this tool in specific subpopulations need further evaluation in coming times.[11]

The worst impact of osteoporosis in CKD patients on maintenance haemodialysis lies in that it can result in fragility fractures which can have a significant effect on morbidity, quality of life, and even survival.[12]

According to the studies, the prevalence of fragility fractures in patients on dialysis continues to be high, with reported rates varying between 10% and 40%.[13-15] However, this has not been extensively studied in Indian population.

Keeping the above facts in mind, it is prudent to say that bone disease along with the fracture risk is one of the important determinants of quality of life and survival in patients with CKD on maintenance haemodialysis. Considering the aging dialysis population of today, increasing our knowledge about the nature, early detection tools and treatment of BMD problems in ESRD patients deserve more attention. Thus, there is a need to characterise the disorder early at primary-care level to provide these patients a better quality of life and indeed a better chance of survival.

With this backdrop, the present study was done to assess and compare the detection of the fracture risk using BMD alone and correlating the BMD with FRAX score for estimate fracture risk in CKD patients on maintenance haemodialysis.

Aim and Objectives

- To calculate BMD at three different sites.
- To estimate fracture risk by calculating FRAX score in patients on chronic maintenance haemodialysis.
- To correlate BMD with FRAX score for estimate fracture risk.

Subjects and Methods

This is an analytical cross-sectional study done from November 2015 to March 2017. A total of 50 CKD patients were included in the study. The enrolment was done consecutively for the duration of the study, from all CKD patients, either attending Out patient department (OPD), emergency, or admitted in medicine wards of Dr. RML Hospital, New Delhi, who provide valid consent and fulfil the inclusion and exclusion criteria. This study is a part of thesis research work and was approved by the nine-membered Institutional Ethical Committee, Dr. RML Hospital, New Delhi, on 29 October 2015.

Inclusion criteria

- Age >40 years.
- All the patients of CKD Stage 5[1] (e-GFR less than 15 ml/min) (as per National Kidney Foundation definition) on maintenance haemodialysis for at least 6 months were enrolled into the study after informed consent.

Exclusion criteria

- Patients taking bisphosphonates, teriparatide, calcitonin, and hormonal therapy were excluded.
- Patients who are known case of degenerative sclerotic changes, collapsed compression fractures.
- Patients with skeletal deformities.
- Patients who are known case of chronic liver disease for more than 6 months with documented deranged LFTs.

The patients were evaluated as per the standard protocol specially concentrating on history of the disease including severity, duration of disease, and risk factors with history of previous fragility fracture and family history of fracture if any. Patients' history on any known chronic disease like diabetes, rheumatoid arthritis, and thyroid disorders was also assessed. Patients were also screened for the NCD risk factors like physical inactivity. General physical examination was done, and weight and height measurements were taken using standard scales. Blood investigations like kidney function test and liver function tests and radiological investigation like USG whole abdomen (including KUB) were also done.

1 Criterion for the diagnosis: Chronic kidney disease was diagnosed, according to the eGFR, which was estimated by MDRD formula and USG findings suggestive of medical renal disease. GFR (ml/min/1.73 m^2) = 186 × (PCR) − 1.154 × (age) − 0.203 × (0.742 if female). The GFR is expressed in ml/min/1.73 m^2.

Measurements of BMD

For assessment of BMD, we used DEXA because it is the most widely used tool for assessment of bone mass and fracture risk in the general population.[16]

DEXA scan (manufacturer – Hologic Inc.) was done of the lumbar spine, and distal one-third of radius bone and neck of the femur (hip). *T* and *Z* scores were obtained which reflected the number of standard deviations by which a patient's value differs from the mean of a group of young normal population. The WHO has defined osteoporosis in terms of *T*-score criteria. Osteopenia was defined as a *T* score of between −1.0 and −2.5, and osteoporosis as ≤−2.5.

FRAX score: FRAX score was calculated using the tool with the clinical risk factor responses that were recorded as a yes or a no (http://shef.ac.uk/FRAX/tool.jsp).

Statistical analysis

Data were entered in MS Excel spreadsheet and coded appropriately. Results were given as mean ± SD. Univariate analysis of variables was performed using Mann–Whitney *U* or *t*-tests, depending on the distribution and nature of variables. Bivariate correlations were calculated. Correlation between different bone measurements was assessed by Pearson's correlation coefficients. A stepwise multiple regression analysis was used to investigate relationships between bone measurements and risk factors of bone disease. All tests were performed at 5% level of significance. Analysis was done using advanced Excel, medical calculator (MedCalc) and Epi info version 7.

Observations and Results

This was a cross-sectional observational study involving 50 CKD patients on maintenance haemodialysis for at least 6 months or more in a tertiary care hospital in New Delhi.

Demographic characteristics of the study group

A total of 50 patients were included in this cross-sectional observational study, who met the inclusion and exclusion criteria, and consented to participate. There were 26 males and 24 females. The mean age of the study population was (53.14 ± 9.81) years. The mean height and weight were 154.2 ± 6.8 cm and 49.58 ± 6.37 kg, respectively. The mean BMI of the population was (22.99 ± 2.68) kg/m^2. Majority of patients (66%) belong to lower middle class and 34% of patients belong to upper middle class based on modified Kuppuswamy's scale 2016.

The baseline parameters were comparable between the two genders ($P > 0.05$), which facilitate easy comparison between two groups [Table 1]. Presence of various factors like gender, previous history of fracture, parent with history of hip fracture, smoking, alcoholism, and osteoporosis were assessed [Figure 1].

DEXA scan showed that the prevalence of osteopenia (*T*-score −1 to −2.5) and osteoporosis (*T*-score <−2.5) in the patients were 20% and 76%, respectively, with 4% normal BMD.

Variables like age, BMI, duration of CKD, and duration of haemodialysis (in months) were compared in two groups (osteoporosis andosteopenia) [Figure 2]. Out of these, age, duration of CKD, and duration of haemodialysis (in months) were found to be significantly different in the two groups [Table 2]. Mean bone mineral densities (g/cm^2) using DEXA scan at 3 selected sites i.e. at Lumbar Spine, Neck of Femur, Distal 1/3rd of Radius were found to be 0.64±0.07, 0.54±0.04 and 0.48±0.05 respectively. Using Indian FRAX Score the average 10-year probability for major osteoporotic fracture risk in enrolled CKD patients was found to be 10.5% and for hip fracture the risk was 6.96%.

Table 1: Baseline profile of the patients

Particulars	Sex (M/F)	*n*	Mean	Std. deviation	*P*
Age (years)	Male	26	54.46	10.27	0.327
	Female	24	51.71	9.29	
BMI (kg/m^2)	Male	26	23.37	2.53	0.303
	Female	24	22.58	2.84	
Duration of CKD (months)	Male	26	66.81	20.76	0.615
	Female	24	64.04	17.63	

*Significant at $P<0.05$

Table 2: Summary of comparison of variables in two groups (osteoporosis and osteopenia)

Particulars	Severity of osteoporosis	*n*	Mean	Std. deviation	*P*
Age (years)	Osteopenia	10	47.10	4.20	0.02*
	Osteoporosis	38	55.05	10.33	
BMI (kg/m^2)	Osteopenia	10	22.41	2.50	0.30
	Osteoporosis	38	23.36	2.60	
Duration of CKD (in months)	Osteopenia	10	58.50	9.41	0.01*
	Osteoporosis	38	68.47	20.41	
Duration of haemodialysis (in months)	Osteopenia	10	9.10	1.52	0.00*
	Osteoporosis	38	11.42	3.59	

*Significant at $P<0.05$

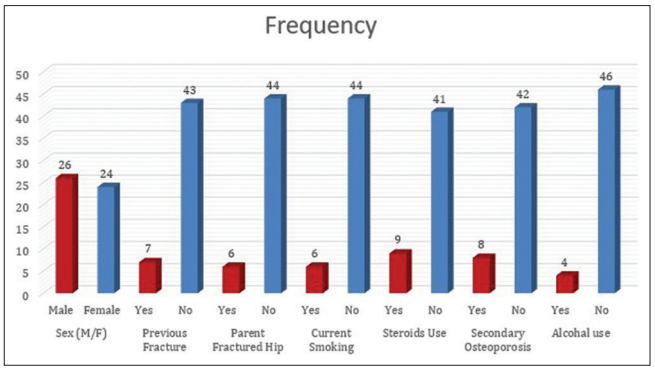

Figure 1: Distribution of the factors for fracture risk in the study participants

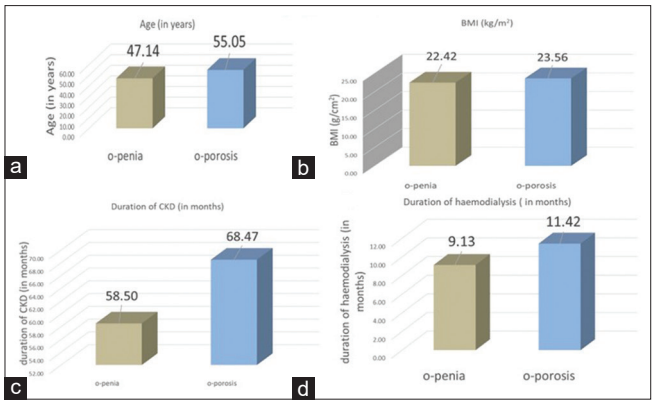

Figure 2: Distribution of severity of osteoporosis with reference to (a) age, (b) BMI, (c) duration of CKD in months, and (d) duration of haemodialysis (months)

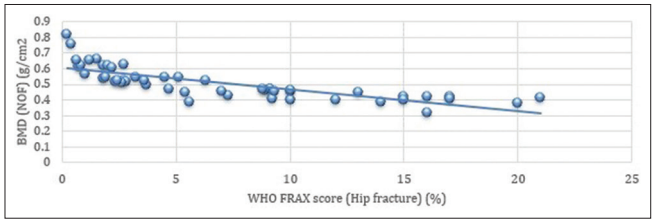

Figure 3: Correlation between BMD (NOF) and FRAX score (hip fracture risk)

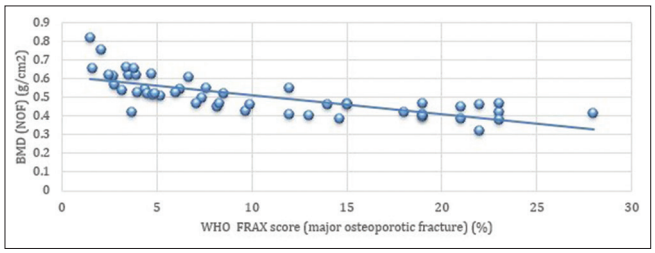

Figure 4: Correlation between BMD (NOF) and FRAX score (major osteoporotic fracture risk)

There was a negative correlation between BMD (NOF) and WHO FRAX score (hip fracture risk) ($r = -0.78$), which was statistically significant ($P < 0.001$) [Figure 3]. Similar negative correlation was seen between BMD (NOF) and FRAX score (major osteoporotic fracture risk) ($r = -0.74$), which was statistically significant ($P < 0.001$) [Figure 4].

Discussion

Present study was a cross-sectional study. In this study, total 50 diagnosed cases of CKD, on maintenance haemodialysis, were enrolled after taking informed consent. Detailed history was obtained, and examination and investigations done. The mean age of the population was 53.14 ± 9.81 years with range between 41 and 74 years. The patients' data were analysed for various clinical risk factors of FRAX score and BMD. FRAX score was calculated using the WHO guidelines.

BMD in CKD

Mean BMD in our study was 0.506 ± 0.101 g/cm^2 which was very lower as compared to other studies. Most of the above data from studies involved CKD patients not on haemodialysis.[12,17-22] This might be one of the reasons in addition to ageing and other confounding factors like steroid use, malnutrition, smoking, history of previous fracture etc., for this discrepancy.

Fracture risk in CKD

In our study, 20% of CKD patients had osteopenia and 76% patients had osteoporosis. Not enough Indian studies are available on prevalence of fracture risk in CKD patients on haemodialysis. The prevalence of osteopenia in our study is similar to the study by Govindarajan *et al.*[19] The results are not like other previous reports; prevalence of osteoporosis was much higher in our study population.[12,22,23] The cause for this difference may be different population characteristics, higher age group, malnutrition, and other confounding factors. Little is known about the fracture risk in haemodialysis patients with reduced BMD. Gupta *et al.*[24] showed 3–4 times increased risk of hip fracture among end-stage renal failure patients. In the general population, the risk of fracture increases 1.5–3 times for each standard deviation of decrease in BMD.[25]

Fracture risk in Indian population

In our study, there was a difference in mean in BMD of males (0.496 ± 0.096) g/cm^2 and females (0.571 ± 0.108) g/cm^2 but the difference was not statistically significant ($P = 0.469$). In India, the precise prevalence of osteoporosis is not known because of lack of registries and under-reporting of the same. However, in study of Joshi *et al.*[26], it is estimated that more than 61 million Indians have osteoporosis and 80% of these patients are females. Agrawal *et al.*[27] in a study on 200 healthy Indian men above 50 years of age reported the prevalence of osteoporosis and osteopenia to be 8.5% and 42%, respectively, when BMD was measured at the femoral neck. Aggarwal *et al.*[28] reported osteopenia and osteoporosis in 53% of women above 45 years of age in Chandigarh.

Fracture risk in CKD population

There are limited data on osteoporosis in Indian patients of CKD, especially on haemodialysis. In the study by Akkupalli *et al.*,[29] at Sri Venkateshwara Institute of Medical Sciences SVIMS University, Tirupati, AP, India, prevalence of osteopenia and osteoporosis in CKD patients was found 33.3% and 33%, respectively. In another study by Jabbar *et al.*,[17] at Postgraduate Institute of Medical Education and Research, Chandigarh, India, prevalence of osteopenia and osteoporosis in CKD patients was found 37% and 12%, respectively. In the study by Govindarajan *et al.*,[19] at Postgraduate Institute of Medical Education and Research, Chandigarh, India, prevalence of osteopenia and osteoporosis in CKD patients was found 23.2% and 8.3%.

Studies across the world have shown a variable incidence of osteopenia and osteoporosis. In a study by Taal *et al.*,[21] at

Renal Division, Brigham and Women's Hospital, Boston, USA, prevalence of osteopenia and osteoporosis in CKD patients was found 48.9% and 19.3%, respectively.

In our study, mean BMD in our study was (0.506 ± 0.101) g/cm^2 which was way lower as compared to other studies (Rix *et al.*, Grzegorzewska *et al.*, Avramovsk *et al.*).[12,18,22] Most of the above data from studies involved CKD patients not on haemodialysis. This might be one of the reasons in addition to ageing and other confounding factors like steroid use, malnutrition, smoking, history of previous fracture etc., for this discrepancy. About 76% patients had osteoporosis. Not enough Indian studies are available on prevalence of fracture risk in CKD patients on haemodialysis.[18,20]

In our present study on using the INDIAN FRAX calculator, the average 10-year probability for major osteoporotic fractures in CKD stage 5D was 10.5%. The 10-year probability for hip fracture risk in CKD stage 5D was 6.96%.

Anburajan *et al.* used the FRAX calculator to screen for osteoporotic fracture risk in South Indian rural population of Tamil Nadu above 50 years of age. When clinical risk factors were used together with BMD, the mean 10-year probability for major osteoporotic fracture in normal and osteoporotic males were 4.19% and 6.3%, respectively, whereas, in normal and osteoporotic females, the probabilities were 4.71% and 11.4%, respectively. With respect to gender, the mean 10-year probability of hip fracture was two times more among osteoporotic males than the normal males (3.55% vs. 1.73%), whereas this difference was around 6 times more among females.[30]

Kuruvilla *et al.*[31] used femoral neck BMD together with clinical risk factors to calculate the FRAX score in 44 Asian Indian men living in the United States. A percentage of 29.5 of the population had normal *T* scores while 63.6% had osteopenia and 6.8% had osteoporosis. FRAX score for major osteoporotic fracture was 6.2% and for hip fracture 1.5%. This study too was limited using a non-Indian (Caucasian American) FRAX calculator.

Study by de Bruin *et al.*[32] estimated fracture risk with severity of CKD and found that the risk of a subsequent fracture in a patient with a history of hip fracture was similar in patients with higher severity CKD when compared with to eGFR >60 ml/min.

The values of FRAX score in our study were much higher as compared to other studies, because of the following factors:

- Different FRAX calculator
- Different study population
- Different risk factors and confounding factors

Despite an extensive search, we could find only a few data on FRAX score and CKD.

This study is limited in terms of focusing only few CKD-related factors, whereas there can be multiple factors associated with osteoporosis apart from those directly related to CKD[33] which may confound the results so in-depth analysis is needed to confirm this association.

Summary and Conclusion

1. In this study done at a tertiary care hospital, we tried to predict 10-year future fracture risk using FRAX score.
2. Our study confirmed the high incidence of low BMD in patients of CKD on maintenance haemodialysis.
3. About one-fifth participants had osteopenia and three-fourth had osteoporosis which was very high.
4. BMD was negatively correlated with FRAX score for all fracture risks which suggest it can be explored as a tool for quick assessment of fracture risk.

Recommendations

The 10-year fracture risk in these patients as predicted by FRAX score was significantly higher in CKD patients, by the FRAX (Indian) calculator, and hence, it may be useful tool for early screening of fracture risk in such situations for timely interventions. As this is a simple and easy to estimate tool, it can be used by primary care physicians to early identify the fracture risk in susceptible patients. Further, studies especially trials, on large number of participants, must be done to ascertain the usefulness of the tool.

Ethical approval

This study is a part of thesis research work and was approved by the nine-membered Institutional Ethical Committee, Dr. RML Hospital, New Delhi, on 29 October 2015.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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