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Vitamin D Status Appears Unrelated to Fractures in Patients with Chronic Kidney Disease

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Author's contribution

The author designed, analyzed, interpreted and prepared the manuscript.

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Short Research Article

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ABSTRACT

Background: Although lack of Vitamin D is widespread in chronic kidney disease, data is scarce in the role Vitamin D may play in fractures in such cases.
Methods: Retrospective analysis of all patients visiting Nephrology outpatients department in 1 UK District General Hospital over 2 years. Chronic kidney disease was categorised by estimated glomerular filtration rate, total Vitamin D and fracture details obtained from Hospital Information Technology system. Total Vitamin D <50nmol/L was considered inadequate. Logistic regression was used to assess the relationships of eGFR and total Vitamin D with fracture incidence. Spearman's correlation coefficient (rs) was used to assess the relationship between continuous variables.
Results: 43/66 patients were Vitamin D deficient - prevalence of Vitamin D deficiency was 65% (95% CI: 52%, 76%). 20/66 patients sustained any form of fracture, incidence of fracture in this chronic kidney disease population was 30% (95% CI: 20%, 43%). There was no association between total Vitamin D level and risk of fracture, OR 0.99 (95% CI: 0.97, 1.01), p = 0.316. The strength of the association between total Vitamin D level and fracture was also unrelated to estimated glomerular filtration level (interaction test, p = 0.971). There was no relationship between estimated glomerular filtration and total Vitamin D level (rs = -0.03, p = 0.8066). Estimated glomerular filtration was found to be negatively associated with risk of fracture, OR 0.96 (0.93,

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1.00), p = 0.028.
Conclusion: Vitamin D deficiency appears widely prevalent in chronic kidney disease with a third of patients sustaining fractures; total Vitamin D levels however are unrelated to fractures. Prospective interventional studies can help answer if earlier replacement of Vitamin D before chronic kidney disease develops will help improve musculoskeletal health and prevent fractures.

Keywords: Bone fractures; CKD; eGFR; vitamin D deficiency.

1. INTRODUCTION

Chronic kidney disease (CKD) affects 5-10% of the world population [1] and is associated with many adverse outcomes including bone disorders and fractures. CKD is characterised into several stages from 1 through to 5 on basis of estimates of glomerular filtration rates (eGFR) [2]. Decreased bone mass and disruption of bone micro-architecture occur early in the course of CKD and worsens with the progressive decline in renal function so that at the time of initiation of dialysis at least 50% of patients have had a fracture [1]. The classic sequence of events begins with a deficit of calcitriol synthesis and retention of phosphorus [3] although more recently an association has been found with the fibroblast growth factor 23 (FGF 23) in response to 'invisible' phosphate retention [4].

In a 2009 survey about 15% of patients in the UK were found to have CKD stages 1-5 [5]. Elderly patient groups are developing end stage renal disease in the UK in record numbers; patients aged over 85 accepted onto the UK dialysis programmes nearly doubled between 2006 and 2011 and the percentage of dialysis patients who are aged greater than 70 years has increased from 19.2% in 2000 to 24.9% in 2012 [6].

The aetiology of fractures in patients with CKD is multifactorial; quantity of bone, osteoporosis with age and alterations in the quality of bone are all suspected factors. While bone quantity and quality can be assessed by laboratory or radiology based techniques, other unmeasured risk factors also likely contributory to fractures in CKD could be poor nutrition, inactivity, medications and increased risk of falling from myopathy or peripheral neuropathy [1]. Elderly and frail patients may have bone disease from age related osteoporosis and therefore are additionally vulnerable to other forms of mineral bone disease associated with the various stages of CKD. The risk of fracture then increases exponentially in this group increasing the burden on stretched NHS resources. Length of stay in an acute care hospital is estimated to be 3 weeks following a hip fracture with a quarter of patients remaining in long-term care institutions for at least a year and a third returning home depend on other people or devices for mobility [7].

As Vitamin D deficiency is known to be widespread in CKD, we hypothesized that increased fracture risk of any kind, fragility related or unrelated, in CKD patients was associated with Vitamin D deficiency.

2. METHODS

This retrospectively analysed study was undertaken at a UK District General Hospital, Countess of Chester NHS Trust that caters to ~250000 population in West Cheshire, North West UK. We retrospectively analysed all total Vitamin D levels measured in patients visiting the Nephrology OP between July 2011 - May 2013 by accessing records via the Hospital laboratory information technology system, MEDITECH™. Dates when total Vitamin D was measured were available in all cases from MEDITECH™. Total Vitamin D was the sum of Vitamin D2 and D3; all results for total Vitamin D were obtained from Birmingham Children's Hospital UK. Total Vitamin D results were then matched to each patient's kidney disease status via their serum creatinine and the eGFR. We also obtained serum albumin, calcium and phosphate and the parathyroid hormone (PTH) level for each patient. Any fracture, fragility related or unrelated that was recorded on MEDITECH™ were then obtained for each patient along with dates of occurrence. A total of 8 fractures occurred between 2001-2009, 1 additional fracture did not have a date of incidence, 11 fractures occurred between 2010-2013. For purposes of this study we analysed all fracture incidences. Sex and age of each patient was recorded. Severe deficiency of total Vitamin D was defined as less than 25nmol/L. Inadequate status of vitamin D was considered to be at a level less than 50nmols/L whereas anything higher than 50nmol/L was assumed to be adequate Vitamin D status. 19 total Vitamin D measurements in this study were during May to September and defined as

Summer and the rest during October to April, defined as Winter. As data was irreversibly anonymised we did not seek patient consent or ethics approval for this study.

2.1 Statistical Analysis

Continuous patient demographic characteristics – including eGFR and Vitamin D - were recorded as mean (standard deviation) or median (inter-quartile range) depending on their distribution. Categorical variables were recorded as frequency (percentage). Spearman's correlation coefficient (r_s) was used to assess the relationship between continuous variables. Univariate logistic regression was used to assess the relationship between each variable and incidence of fracture (yes/no). A stepwise multivariable model selection procedure, based on Akaike's information criterion (AIC), was employed in order to find a final multivariable model. The sensitivity of the final model to the inclusion and exclusion and covariates and relevant two-way interactions was also assessed using AIC. The Hosmer-Lemeshow goodness-of-fit test was used to assess the adequacy of model fit. All point estimates are reported with accompanying 95% confidence intervals (CI). All statistical analyses were conducted using Stata 13 (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

3. RESULTS

Table 1 qualifies the study population. 66 patients had Vitamin D levels measured between 2011-13. 48 of these had a raised PTH level >7pmol/L median 14.5 (IQR 20, 10). The aetiology of renal impairment in this group was diabetes in 21%, glomerular disease in 33% and vascular or hypertension in 14%. 18% did not have an identifiable cause for CKD. Of 66 patients 68% were females, mean age was 61 (SD 19), median GFR 32 (IQR 21, 49) with median total Vitamin D level 38 (24, 54) nmol/L. Population median PTH levels were 11.4 (6.8, 17.1) pmol/L.

43 out of 66 patients were Vitamin D deficient giving an estimated prevalence of Vitamin D deficiency in this population of 65% (95% CI: 52%, 76%). 20 out of 66 patients suffered any form of fracture, giving an estimated incidence of fracture in this population of 30% (95% CI: 20%, 43%). 11/20 fractures occurred between 2010 and 2013. There were 7 hip, 3 scaphoid, 4 vertebral, 3 ribs and 5 radial/fibular/metatarsal/malleolar fractures. 15/66 in this cohort overall were on either calcium binders or active Vitamin D and 6/20 patients with fractures were on either active Vitamin D or calcium containing binders. 45/66 patients had their Vitamin D measurements during the months of UK Winter time, 6 of these 45 suffered a fracture with 5 sustaining no fractures.

There was no evidence of an association between total Vitamin D levels and risk of fracture, OR 0.99 (95% CI:0.97, 1.01), p=0.316 (Table 2, Fig. 1). This result persisted irrespective of eGFR (interaction test, p=0.971), i.e. there is no evidence that relationship between total Vitamin D level and risk of fracture is affected by eGFR. eGFR was however found to be negatively associated with risk of fracture, OR 0.96 (0.93, 1.00), p = 0.028 (Fig. 1). More intuitively this gives a risk of fracture for patients with an eGFR of 20, 40, 60 and 80 as 42%, 26%, 14% and 7% respectively.

There was no evidence of a relationship between eGFR and total Vitamin D levels (r_s = -0.03, p = 0.8066, Fig. 2). No other variables were found to be univariately associated with fracture (Table 2) although sex was close to being statistically significant, OR 0.27 (95% CI: 0.07, 1.07) p = 0.063, with 3 out of 21 males (14%) and 17 out of 45 females (38%) experiencing a fracture. Although sex and eGFR were selected in the final multivariable model, sex offered a negligible improvement in model fit according to Akaike's information criterion (AIC) and therefore only eGFR was retained.

4. DISCUSSION

This small retrospective study demonstrates that in the North West of UK in patients with CKD, Vitamin D levels are unassociated with fractures; other than a low eGFR there are no other factors in the chemical biochemistry profile that appear to influence this outcome.

The most recent UK national diet and nutrition survey showed 20% suffer from severe Vitamin D deficiency with 60% insufficient of Vitamin D – in both adults and children [8]. Vitamin D supplementation can potentially reduce falls and non-vertebral fractures, including those at the hip. This benefit is dose-dependent with doses of 700 to 1000 IU Vitamin D per day reducing falls by 19% and doses of 482 to 770 IU Vitamin D per day reducing non-vertebral fractures by 20% and hip fractures by 18% [9].

Table 1. Description of patient characteristics

Variable	No fracture	Fracture	Overall
N	46 (70%)	20 (30%)	66
Sex			
F	28 (62%)	17 (38%)	45 (68%)
M	18 (86%)	3 (14%)	21 (32%)
Age, mean (SD)	59 (19)	66 (20)	61 (19)
Diabetes			
No	37 (71%)	15 (29%)	52 (79%
Yes	9 (64%)	5 (36%)	9 (21%)
eGFR (ml/min), median (IQR)	35 (25, 55)	27 (18, 32)	32 (21, 49)
Vitamin D (nmol/L), median (IQR)	38 (28, 55)	33 (22, 52)	38 (24, 54)
Creatinine (umol/L), median (IQR)	146 (105, 200)	190 (145, 277)	159 (129, 218)
Albumin (g/L), median (IQR)	38 (36, 40)	36 (34, 39)	37 (35, 40)
Phosphate (mmols/L), median (IQR)	1.1 (1.0, 1.3)	1.2 (1.1, 1.4)	1.1 (1.0, 1.3)
Adjusted calcium (mmols/L), median (IQR)	2.3 (1.2, 2.4)	2.4 (1.6, 2.4)	2.4 (2.3, 2.5)
Parathormone (pmols/L), median (IQR)	6.8 (0.7, 10.9)	6.5 (0.8, 13.8)	11.4 (6.8, 17.1)

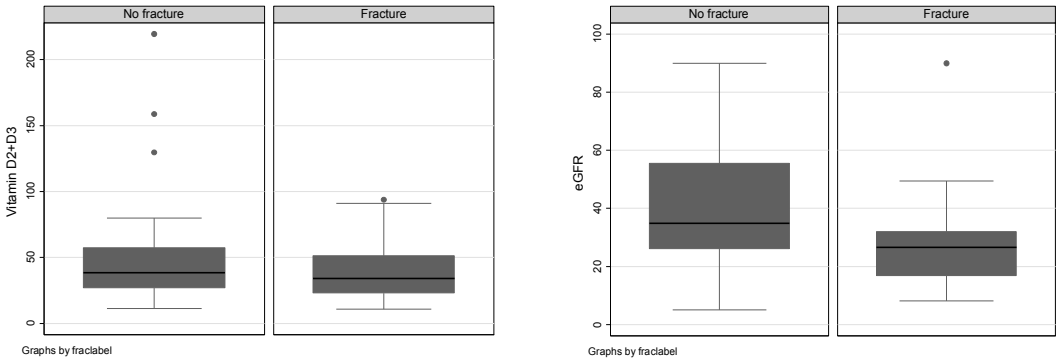

Fig. 1. Vitamin D and EGFR comparison between fracture groups

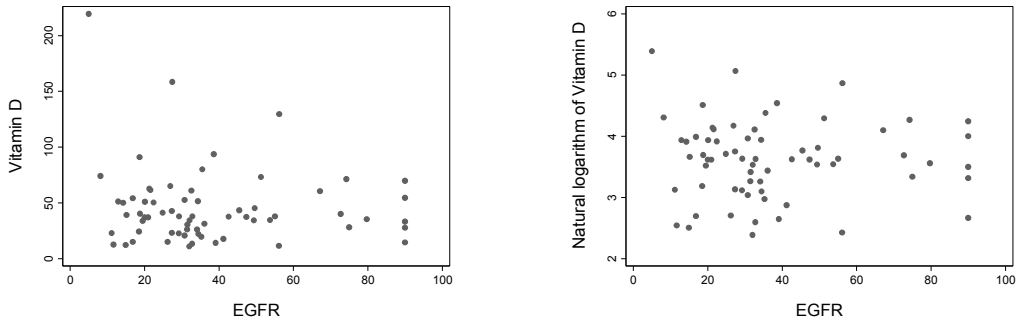

Fig. 2. There is no evidence on an association between EGFR and Vitamin D (rs = -0.03, p = 0.8066)

65% of patients in this study demonstrated Vitamin D deficiency. This Vitamin D deficient state was unrelated to their CKD status. Such high degrees of Vitamin D deficiency could amount to a serious Public Health issue in the UK. As the UK is estimated to have the highest rates of fractures in the general population in the EU with one in two women and one in five men aged over 50 years in the UK suffering a fracture [10] and as 15% of the UK population is estimated to have CKD, we felt it was important to assess the scale of Vitamin D deficiency in the CKD population and the possible role of this modifiable risk factor in fractures in those with

CKD. Previous systematic reviews and meta-analyses failed to show a convincing evidence of a clear role of vitamin D for any outcome although selective outcomes are still probable with Vitamin D deficiencies [11].

Table 2. Univariate logistic regression

Variable	Odds ratio (95% CI)	p
Vitamin D	0.99 (0.97, 1.01)	0.316
EGFR	0.96 (0.93, 1.00)	0.028
Age	1.02 (0.99, 1.05)	0.177
Sex (Males relative to females)	0.27 (0.07, 1.07)	0.063
Albumin	0.95 (0.87, 1.04)	0.294
Creatinine	1.00 (1.00, 1.00)	0.417
Phosphate	0.91 (0.55, 1.50)	0.708
Adjusted calcium	0.87 (0.08, 9.15)	0.911
Parathormone	1.02 (0.99, 1.06)	0.4114
Diabetes mellitus	1.37 (0.39, 4.77)	0.620

The largest observational study of an unselected cohort of patients with varying levels of kidney dysfunction, prevalence of abnormalities of vitamin D metabolites, iPTH, and Ca and P was published in 2007 [12]. Other studies in the field were from USA [13,14,15]. Levin's study [12] demonstrated low 1, 25 OH2 D3 in 13% in those with eGFR >80 ml/min, >60% in those with eGFR <30 ml/min. In this study a Vitamin D deficiency or replete state appeared unassociated with eGFR levels.

Whilst the association between fractures and patients with end stage renal disease has been explored to some extent [16] studies around associations of fractures in earlier stages of CKD and Vitamin D are very few. Although 30% of the CKD population sustained a fracture in this study there seems to be no association with Vitamin D levels and fractures. Whilst this appeared to be a surprising outcome, fractures in CKD are multi-factorial and bone health with adequate levels of systemic Vitamin D is perhaps important far earlier even before patients go onto develop CKD. With 2/3 of patients in this study being Vitamin D deficient, one can speculate early replacement of this metabolite could have helped improve musculoskeletal health and prevented the 30% of fractures seen in the study [17]. Our study indicates only the stage of kidney disease can predict the incident risk of fractures with an eGFR of 20, 40, 60 and 80 predicting a risk of fractures as 42%, 26%, 14% and 7% respectively.

Over a period of 2 years Vitamin D levels appear to have been requested in 73% of patients (48/66) with a raised PTH level. Guidelines issued by National Kidney organisations in USA or UK (KDOQI/NICE) suggest being selective in checking for bone biochemical disorders in those with low GFR [2,18]. NKF-KDOQI does suggest checking PTH levels in patients with eGFR <60ml/min but only then check Vitamin D levels if abnormal in this group. The lack of a relationship between Vitamin D deficiency and fractures or eGFR in this study makes measuring this metabolite routinely in CKD patients an intriguing issue. In addition, although seasonal variations if Vitamin D is well established, low Vitamin D levels during Winter in North West UK would not appear to be causal in fractures in patients with CKD in this study.

Whether general Vitamin D replacement would transpire into fruitful musculoskeletal health continues to remain unclear; in one meta-analysis in this field the authors conclude skeletal effects of vitamin D supplementation have not been studied [19]. Urgent interventional/longitudinal studies are required to see if early Vitamin D replacement before onset of disease states alters musculoskeletal health both in the wider population but also in those that are destined to develop CKD over time.

As all retrospective studies do this too has several drawbacks. This was a single centre study with few patients. As this study was undertaken retrospectively there was no sample size estimate – we also believe post-hoc sample size calculations are inappropriate. We did however limit the number of variables permitted into the multivariable analysis in order to satisfy the 10 events per variable rule of thumb. Total Vitamin D levels were only available in a few patients and it is possible the patient sample in the final analysis may not be fully representative of other Renal Out Patient Departments. Laboratory results were obtained at single time points and CKD status or Vitamin D status could have been unrelated to their Orthopaedic

incidents. All fractures were included for analysis; although 9/20 fractures occurred earlier than 2010, excluding these 9 fractures that occurred before 2010 did not affect the interpretation of the results. As undiagnosed Vitamin D deficiency or CKD are chronic long term conditions and may have been present before presentation to Nephrology Out Patients we justified including all fractures into the study. We did not specifically study the types of fracture, fragility related or unrelated as numbers of patients were too small to achieve statistical significance.

5. CONCLUSION

Although widespread, Vitamin D deficiency does not appear to be associated with fractures in patients with CKD; Vitamin D deficiency is also unrelated to stages of underlying CKD. Almost a third of CKD patients sustain fractures and only the stage of renal disease appears to be predictive of fractures in patients with CKD. If fractures are unrelated to Vitamin D levels in patients with CKD can Vitamin D replacement in the wider population help improve musculoskeletal health to a degree that will then prevent fractures in elderly or in those that are predestined to develop CKD over time? Only long term prospective population based interventional Vitamin D studies could help answer such a question.

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COMPETING INTERESTS

Author has declared that no competing interests exist.

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