Clinical Endocrinology (2010) **73**, 299–304 doi: 10.1111/j.1365-2265.2010.03821.x

ORIGINAL ARTICLE

Association between 25-hydroxyvitamin D, somatic muscle weakness and falls risk in end-stage renal failure

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Summary

Objective Suboptimal levels of 25-hydroxyvitamin D (25OHD) are common in haemodialysis patients (Chronic Kidney disease-5D: CKD-5D) and may be associated with reduced muscle strength and increased falls risk. We tested the hypothesis that 25OHD levels may be independently associated with falls risk in CKD-5D.

Background Supplementation with calcium and cholecalciferol reduces hip and other nonvertebral fractures in elderly individuals, and this effect may in part be attributable to reduction in falls frequency. The relationship between 25OHD and falls risk has not been investigated in CKD-5D.

Design and Patients This is a cross-sectional study of 25 CKD-5D patients with predialysis 25OHD, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$) and intact parathyroid hormone (iPTH) measurement. Falls risk was assessed by quadriceps muscle strength, Falls-Screen© test (FST), Berg Balance Scale (BBS), timed 'up and go' (TUG) test, Modified Barthel Index (MBI) and Falls Efficacy Scale (FES).

Results Mean age was 69·8 ± 12·1 years, and median time on dialysis was 3·1 years. Median 25OHD level was 55·3 nmol/l (range 20·8–125·8 nmol/l). Muscle strength was significantly positively correlated with 25OHD ($P = 0{\cdot}024$) but not with $1,25(OH)_2D$ ($P = 0{\cdot}477$) or PTH ($P = 0{\cdot}461$). Statistically significant correlation between 25OHD levels and FST ($P = 0{\cdot}028$) plus MBI ($P = 0{\cdot}0046$) was noted. No significant correlation was detected between falls risk and $1,25(OH)_2D$ or PTH.

Conclusions Suboptimal levels of 25OHD in CKD-5D are associated with reduced quadriceps muscle strength and increased falls risk. 25OHD may be more important than the active renal metabolite $1,25(OH)_2D$ for muscle strength with implications for vitamin D choice and goals of supplementation. Further investigation is required to examine effectiveness of calciferol supplementation on the incidence of falls in CKD-5D.

(Received 7 December 2009; returned for revision 2 January 2010; finally revised 15 April 2010; accepted 22 April 2010)

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Introduction

Fracture rates are increased in patients with chronic kidney disease undergoing dialysis (CKD-5D), and an increased rate of falls, approaching 40% of patients with CKD-5D per annum, is likely to contribute to this risk.[1–3] Older age, medications, underlying illness, peripheral neuropathy and postural hypotension are all potential contributors to falls risk, and in the general population, low levels of vitamin D are an additional independent risk factor.[4–8] Hip fracture rates in dialysis patients are far higher in all age groups above 45 years and both sexes compared with the general population risk, and this may contribute to the higher mortality noted in ESRF.[4,9] The role of reduced levels of 25OHD in the development of muscle weakness and falls risk in patients on dialysis is unknown.

For patients with CKD 3–4 [estimated glomerular filtration rate (eGFR) of 15–59 ml/min/1·73 m^2], calciferol supplementation is currently recommended for levels of 25-hydroxyvitamin D (25OHD) below 50–75 nmol/l.[10–12] The prevalence of insufficient levels of 25OHD varies depending on the threshold adopted but may indicate up to 85% of these patients should be supplemented. Calciferol supplementation in patients with CKD stages 3–4 does result in a modest reciprocal reduction of parathyroid hormone levels, but biochemical and patient-related data to support such treatment are limited.[13] Calciferol supplementation has also been suggested for low 25OHD levels in patients with CKD-5 (eGFR < 15 ml/min/1·73 m^2) and 5D (on dialysis) by the Kidney Disease: Improving Global Outcomes (KDIGO) work group.[14] For patients on dialysis, (CKD-5D) the benefits of calciferol

supplementation are unknown, and few patients currently receive treatment.

In the general population, low levels of 25OHD are associated with muscle weakness and an increased risk of falling, and, in a prospective study of elderly people, low 25OHD levels were reported to predict loss of muscle strength and sarcopenia.[15–17] A recent meta-analysis demonstrated that, in comparison to patients treated with calcium or placebo, patients administered cholecalciferol supplementation experience a 20% lower incidence of falls.[18] As supplementation with calciferol is inexpensive with minimal side effects, this finding could translate into reduced fractures, morbidity, mortality and health costs.[19,20] Although target levels of 25OHD for fracture reduction are debatable, current data suggest that levels over 50 nmol/l are associated with reduced risk of hip fracture in nonuraemic populations.[21,22]

Megalin receptors for the complex of 25OHD and its vitamin D–binding protein have been identified in both animal and human skeletal muscle supporting a direct role for circulating 25OHD.[23–26] So, in addition to the traditional endocrine role for vitamin D that requires renal conversion of $1,25(OH)_2D$, circulating levels of 25OHD may play a more important auto/paracrine role in muscle metabolism, in both people with normal renal function and those on dialysis. This study aimed to test the hypothesis that circulating 25OHD levels may be independently associated with falls risk in CKD-5D. The study was designed to examine whether there is an association between falls risk scores in CKD-5D and circulating level of 25OHD above or below 50 nmol/l.

Methods

This cross-sectional study was performed within the haemodialysis unit of a tertiary care hospital in Perth, Western Australia. Inclusion criteria for the study included age greater than 45 years and duration on dialysis more than 3 months. Exclusion criteria were conditions causing irreversible impairment to mobility or which rendered the patient unable to co-operate with testing. These included leg amputation, significant medical illness that interfered with muscle strength testing (stroke, symptomatic cardiac or respiratory disease, but not renal disease), arthropathy affecting mobility, visual impairment and significant cognitive impairment (mini-mental state examination score <22/30). Consequently, we excluded most well-recognized causes of falls risk, apart from renal disease in our study cohort. Patients were also excluded who were unable to give informed consent. Out of 104 patients with CKD-5D, 61 fulfilled the inclusion and exclusion criteria. The first 25 patients who volunteered for the study were recruited. Two patients were from the Indian subcontinent, one was Asian, one African and the remainder were Caucasian. The study was approved by the Sir Charles Gairdner Human Ethics Committee.

Demographic data were collected, and any history of previous falls and fractures was recorded (Table 1). All medications were documented, including those that might affect bone metabolism such as calcium, vitamin D (cholecalciferol, ergocalciferol and calcitriol) or those medications that may affect the incidence of falls, including antihypertensive and psychoactive agents.

Laboratory tests were performed, studies were conducted on the day of and prior to dialysis, and samples were collected during the southern hemisphere winter months (June-August). All participants received 4 h of dialysis, three times per week, with a high flux dialyser (FX6). The ionized calcium level in the dialysate was 1·3 mmol/l, which generally does not cause significant shifts in levels of serum calcium. All participants in the trial attained adequate small solute clearance with Kt/V >1·2; 80% were dialysed through an arteriovenous fistula, and the rest dialysed via a central Hickman catheter.

Intact parathyroid hormone (PTH) was measured in EDTA plasma by immunochemiluminescence on the Immulite 2000 platform, ensuring complete sample filling of the collection vessel.[27,28] Interassay CV for intact PTH was 9% at 3·2 pmol/l, 5·6% at 30·3 pmol/l and 5% at 104 pmol/l. 25OHD was measured by radioimmunoassay (RIA) using the DiaSorin RIA method with interassay CV of <10% at 14 and 33 nmol/l.[29,30] $1,25(OH)_2D$ was

Table 1. Demographic and biochemical data

Factor	25OHD ≤ 50 nmol/l (n = 9)	25OHD > 50 nmol/l (n = 16)	P-value	Total (n = 25)
Age (years)	72·0 ± 10·3	68·5 ± 3·3	0·50	69·5 ± 12·1
Duration of ESRD (years)	5·0 ± 3·1	3·6 ± 3·9	0·37	4·1 ± 3·6
Male gender	67%	88%	0·21	80%
Diabetes mellitus	56%	13%	0·021	28%
Body mass index (kg/m^2)	28·9 ± 6·5	25·9 ± 6·0	0·29	27·0 ± 6·2
Beck Depression Index	16 (15–18)	17·5 (16–23)	0·20	18·4 ± 3·7*
Mini-mental state examination	28 (27–29)	29 (28–29)	0·31	28 (27–29)*
Calcium supplements	7	10	0·43	17
Calcitriol therapy	8	8	1·0	16
Calcium (mmol/l)	2·40 ± 0·22	2·43 ± 0·15	0·44	2·42 ± 0·18
Phosphate (mmol/l)	1·71 ± 0·53	1·83 ± 0·66	0·80	1·79 ± 0·61
PTH (pmol/l)	52·5 (10·5 to 55·4)	18·15 (13·4 to 58·75)	0·65	21·5 (12·6 to 55·4)*
25OHD (nmol/l)	38·0 ± 8·8	80·9 ± 28·2	–	55·3 (45·9 to 79·2)*
1,25(OH)2D (pmol/l)	15 (12 to 22)	40 (17 to 60·5)	0·04	25 (13–57)*

*Median (interquartile range)

measured following C18 column extraction by RIA, with interassay CV of 11% at a mean of 64 and 173 pmol/l.

The prespecified primary outcome of the study was the association between 25OHD and $1,25(OH)_2D$ with quadriceps muscle strength, which has been demonstrated to predict falls in nonuraemic individuals.[31–33] Secondary outcomes included mean scores for muscle strength testing above and below 50 nmol/l and comparing both groups using Student's *t*-test (after ensuring normality of data distribution).

All subjects were right-handed, so strength was measured using the right quadriceps, with subjects seated in a high chair, hips flexed at 90 degrees and knees positioned at 70–80 degrees with a strap, connected to a horizontally directed spring gauge, attached 10 cm above the lateral malleolus. Subjects were instructed to extend the knee forcefully. The maximal isometric muscle force representing the highest result from three separate knee extensions was recorded by the same researcher, and measurements were reported in kilograms.[34,35]

Subjects were tested using the Mini-Mental State Examination (MMSE) and the Beck Depression Index (BDI). Subjects were screened using tools that have been validated as reliable predictors of falls in the elderly general population: the FallsScreen© test (FST; a falls risk calculator that includes measurement of visual edge contrast, proprioception, reaction time, quadriceps strength and balance that are then standardized for age), Berg Balance Scale (BBS; a scale that determines patients' balance), timed 'up and go' (TUAG; a measure of balance and muscle strength) test, modified Barthel Index (MBI; a measure of physical function associated with falls risk) and the Falls Efficacy Scale (FES).[36–41] All physical testing was performed with the investigators blinded to levels of 25OHD and $1,25(OH)_2D$.

Numerical results were expressed as mean ± standard deviation, unless otherwise specified. Normality of variables was assessed, and transformation was applied to improve normality if required. Subjects were separated into two groups defined by 25OHD ≤50 nmol/l or >50 nmol/l to assess differences in quadriceps strength and scores on falls risk assessment tools. Results were compared using student *t*-test if variables were normally distributed or Kruskal–Wallis rank test if not normally distributed. Categorical variables were analysed by chi-squared test and normally distributed continuous variables by linear regression analysis with Spearman's rank correlation reserved for variables unevenly distributed. Analyses were performed using STATA 8·2 (StataCorp, College Station, TX, USA). A 50-N difference in quadriceps strength between groups has been previously associated with an increased risk of falls, and prior research showed that the standard deviation for quadriceps strength is 75N. Consequently, assuming an alpha of 5% and 80% power, we prespecified that a sample size of approximately 30 subjects would be required for this study.

Results

The mean age of subjects was 69·8 ± 12·1 years, and the median time on dialysis was 3·1 years (range 0·5–15·3 years) (Table 1). Diabetes mellitus was present in 28% of patients. The aetiology of kidney failure was diabetic nephropathy in 24%, glomerulonephritis in 20%, hypertensive nephrosclerosis in 20%, polycystic kidney disease in 4% and related to other disease processes in 32%. All of the patients with diabetes suffered from type 2 diabetes, and none had significant impairment of visual acuity, symptomatic peripheral neuropathy or suffered from postural hypotension. Sixteen of the 25 subjects were taking calcitriol therapy with nine using daily dosing and seven were taking calcitriol three times weekly or less. No subjects were taking cholecalciferol therapy, and unlike other areas of the world, vitamin D fortification of food or drink is not

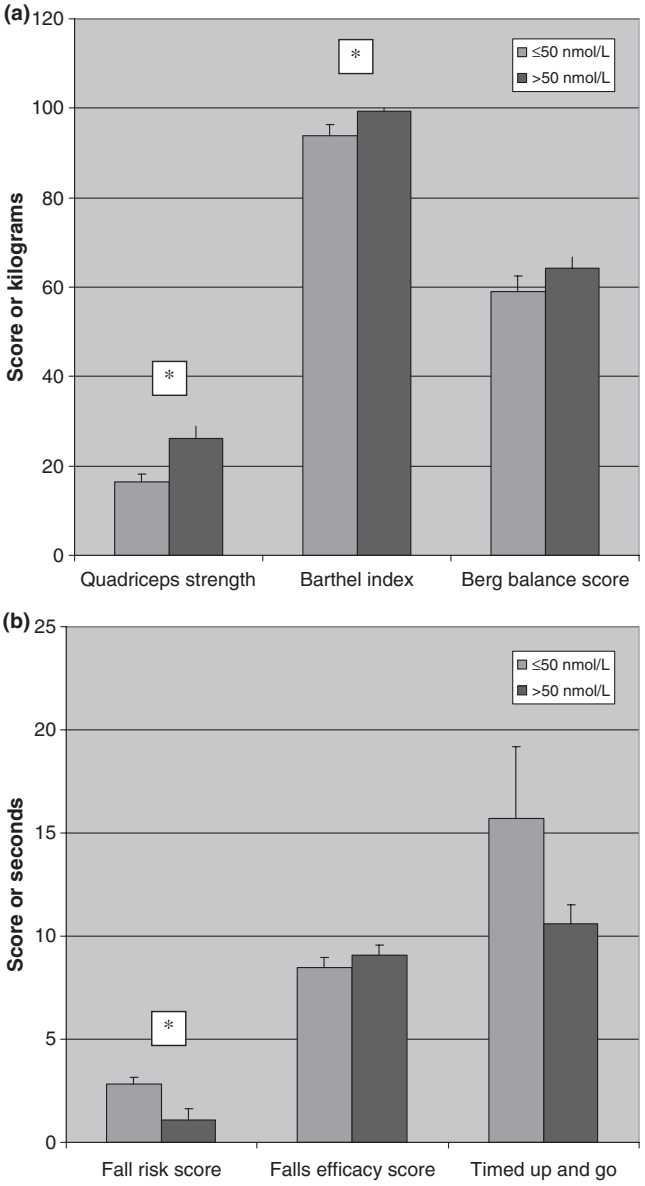

Fig. 1 (a) Mean differences with standard deviation scores in quadriceps strength, Barthel index and Berg balance score between groups defined by 25OHD above and below 50 nmol/L. *Statistically significant difference between groups, $P = 0.027$ for quadriceps strength, $P = 0.045$ for Barthel index. (b) Mean differences with standard deviation scores in falls risk score, falls efficacy scale and timed up and go between groups defined by 25OHD above and below 50 nmol/L. *Statistically significant difference between groups, $P = 0.032$ for falls risk score.

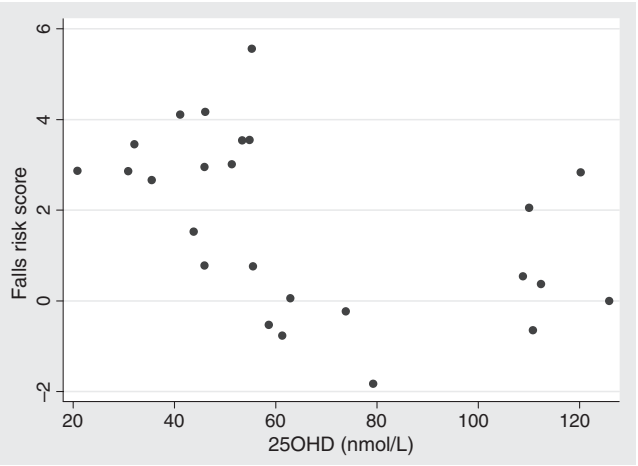

Fig. 2 Scatterplot of 25OHD and falls risk score, demonstrating inverse relationship between each variable. Rho = −0·44, P = 0·028.

present in Australia. No data on casual sunlight exposure were collected.

The median 25OHD level was 55·3 nmol/l (range 20·8–125·8 nmol/l); nine subjects had levels <50 nmol/l and one <25 nmol/l. The median $1,25(OH)_2D$ level was 25 pmol/l (range 4–109 pmol/l; reference limit 30–120 pmol/l) with 23 patients having levels below the median of the reference limit. A statistically significant correlation was present between levels of 25OHD and $1,25(OH)_2D$ (rho = 0·54 and P = 0·005). Levels of 25OHD <50 nmol/l were more commonly associated with diabetes mellitus (Table 1).

The median quadriceps strength for the complete group was 19 kg (range 5–46 kg), which was below the expected range for healthy nonuraemic subjects (range 35–58 kg) but comparable to the range identified in nonuraemic 70–74-year-old men (range 25–46 kg; unpublished in-house data). Muscle strength correlated positively with levels of 25OHD levels (Spearman's rho = 0·45, P = 0·024). There was also a statistically significant difference in quadriceps strength between the group with 25OHD ≤ 50 nmol/l and the group with 25OHD >50 nmol/l (P = 0·027; see Fig. 1).

There was a significant negative correlation between levels of 25OHD and FSI plus MBI (Spearman's rho = −0·44, P = 0·028 and Spearman's rho = 0·55, P = 0·0046, respectively; Fig. 2). Although not significant, there was a trend to worse FES, BBS and TUAG in the group with 25OHD ≤ 50 nmol/l. For subjects with levels of 25OHD ≤ 50 nmol/l, the median score on the FST was 2·87, which indicates a higher future risk of falls, compared to subjects with 25OHD levels >50 nmol/l who had a median score of 0·46. No statistically significant correlation was detected between any of the falls risk assessment tools and either $1,25(OH)_2D$ or PTH.

Discussion

In patients with CKD-5D, there is a significant direct relationship between levels of 25OHD and our primary end-point of quadriceps strength, as well as differences in secondary outcome measures including FST and MBI according to 25OHD levels above and below 50 nmol/l. However, no statistically significant association was detected between levels of 25OHD and TUG, FES or BBS. This was likely to be related to study numbers and differences in the functions measured by each of these tests. Levels of $1,25(OH)_2D$ were not associated with falls risk as assessed by any of these instruments.

In nonuraemic elderly populations, deficiency of 25OHD has been associated with an increased falls risk, and supplementation with cholecalciferol has resulted in significant reduction in this risk.[16,18] We found levels of 25OHD to be <50 nmol/l in 36% of this dialysis population located in Perth, Western Australia, at latitude 31°S, similar to Durban or, in the northern hemisphere, Houston and Kuwait. This was consistent with previous estimates in the general Australian population.[42] We also noted an association between type 2 diabetes and 25OHD levels <50 nmol/l. Although factors including disturbed bowel motility, fat malabsorption and the known association with coeliac disease may contribute to lower levels of 25OHD levels in patients with diabetes, reduced sun exposure is likely to be the major factor, because most 25OHD is derived from UVB radiation exposure. A recent study also reported that patients with CKD stage 5 and diabetes had lower mean 25OHD levels than other patients (54 ± 30 *vs* 75 ± 33 nM; P < 0·0001) and that 29% of patients with diabetes (types 1 and 2) had 25OHD levels below 37 nmol/l in comparison to a prevalence of 13% in those patients without diabetes.[43] The interaction between 25OHD and falls risk reported here is comparable to that seen in the general population, in which quadriceps strength is a powerful predictor of falls. Therefore, although not validated in a dialysis setting, it is reasonable to hypothesize that muscle strength may also influence falls risk in patients on dialysis.[33,44]

Falls in CKD-5D are common, result in significant morbidity and have been independently associated with an increased risk of death in community-dwelling haemodialysis patients.[3] Surprisingly, few studies have investigated their aetiology. Factors that have been associated with an increased risk of falls include older age and diabetes, a higher number of prescribed drugs including antidepressants, a greater number of comorbidities, inability to walk more than 10 m and a history of falls.[45,46] The results of our study suggest that suboptimal levels of 25OHD may also contribute.

Despite the interaction between 25OHD, falls risk and muscle strength, we did not detect any association between falls risk or muscle strength and either $1,25(OH)_2D$ or PTH. A number of mechanisms may explain an effect of 25OHD in patients with minimal residual renal function. These include the possible uptake of 25OHD by skeletal myocytes with local conversion to $1,25(OH)_2D$ by locally expressed 1-alpha hydroxylase. Binding of 25OHD directly to the vitamin D receptor (VDR) may also explain these findings. While VDR in skeletal myocytes has a 500-1000-fold greater affinity for $1,25(OH)_2D$ in comparison to 25OHD, the 500-fold higher serum concentration of 25OHD may indicate a biological role for this vitamin D metabolite.[47,48] Although the PTH method used in our studies has been shown to have a positive bias relative to other methods including the Nichols Allegro, which many regard as a reference method, the agreement between these methods is high with a correlation of >0·975.[49] We did not use a threshold of PTH in our analysis but looked at the correlation

between PTH and falls risk. Consequently, we do not believe that method differences would lead to appreciable differences in our conclusions. Sixteen patients received calcitriol, seven of whom received doses three times weekly or less. Calcitriol treatment may have influenced levels of $1,25(OH)_2D$, but with an elimination half-life of 3–6 h, levels taken the day after dosing should largely reflect endogenous production. The low median $1,25(OH)_2D$ level and correlation of 25OHD with $1,25(OH)_2D$ also support endogenous production as the major contributor.

In the nonuraemic population, optimal levels of 25OHD required to reduce the risk of falls and or fractures have not been clearly established but are likely to fall between 50 and 75 nmol/l. In patients on dialysis, the optimal lower and upper limits of 25OHD levels are still not clear. In general, toxicity from cholecalciferol supplementation is very uncommon. Nevertheless, there are suggestions that 25OHD levels above 100 nmol/l may be associated with reduced bone turnover in patients on dialysis and it would seem prudent to aim for levels up to, but not exceeding this limit until additional evidence is available.[50]

Our study has several limitations. The small sample size limits the power of our study and limits multivariate or subgroup analysis to independently assess whether male sex or diabetes have independent effects on falls risk. Our study subjects are a heterogenous subpopulation with multiple comorbidities so that additional factors may be involved in falls risk. However, the finding of significant associations with relatively low patient numbers, in a similar direction to that observed in the general population, supports the possibility of a significant role for 25OHD in falls risk and muscle strength in CKD-5D. Although the majority of $1,25(OH)_2D$ results were low, the levels were above the limit of detection of our assay, and consequently, the lack of association between muscle strength and $1,25(OH)_2D$ cannot be solely explained by results clustering below the level of detection. Because the majority of our subjects were men, their risk of a first osteoporotic fracture is likely to be lower that that of women. Nevertheless, their risk of subsequent fracture is higher than in females, so that demonstrating this effect in men has important epidemiological significance.[4,51] The interpretation of our findings may also be complicated by factors such as the presence of diabetes. A larger study would permit adjustment of such variables. Finally, the falls risk assessment tools used in our study require further validation in CKD-5D.

The association between 25OHD, muscle strength and falls risk supports the concept that vitamin D actions in patients with CKD-5D are not entirely dependent on conversion of 25OHD to $1,25(OH)_2D$. While calcitriol therapy may be significantly more potent for PTH suppression, calcium and phosphate transport, $1,25(OH)_2D$ levels appear less important than 25OHD levels for maintaining muscle function and reducing falls risk. This finding has implications for the use in CKD-5D of the unactivated vitamin D sterols: cholecalciferol and ergocalciferol, which are inexpensive, well tolerated and have minimal side effects.[52] This study supports a rationale to proceed with randomized controlled trials to investigate the role of calciferol on falls risk and muscle strength. These are important patient-level outcomes because of their impact on mobility, independence, fracture risk and mortality in patients suffering from CKD-5D.

Conflict of interest and/or financial disclosures

The authors have no conflict of interest to declare.

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