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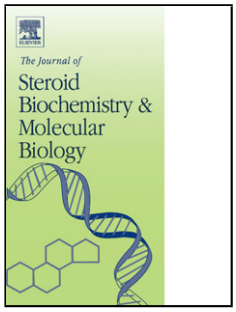

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Prevalence and treatment of hypovitaminosis D in the haemodialysis population of Coventry.

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Highlights

- Hypovitaminosis D is common in the haemodialysis (HD) population in Coventry.
- There is an absence of clear supplementation guidelines for this population.
- We have developed a local guideline for vitamin D supplementation in HD patients.

Abstract

Low serum 25(OH)D and associated bone and non-bone related problems are not well appreciated in end stage renal disease (ESRD). Vitamin D treatment strategies in the UK currently focus almost exclusively on calcitriol [1,25$(OH)_2$D], alfacalcidol or paricalcitol. In ESRD hypovitaminosis D is associated with bone loss, muscle weakness, falls, fractures and increased inflammation. National guidelines changed in 2014 and now recommend the diagnosis and treatment of low serum 25(OH)D in all patients with glomerular filtration rate (GFR) less than 30ml/min/1.73m^2. However as yet there are no standardized guidelines for dosage, frequency and monitoring in ESRD patients. Following a systematic review of the literature we developed a clinical guideline for cholecalciferol supplementation at University Hospitals of Coventry and Warwickshire, UK. The guideline recommends 40,000IU cholecalciferol weekly for patients with 25(OH)D <50nmol/L and 20,000IU weekly for patients with 25(OH)D 50-75nmol/L; to be continued long term unless levels increase to ≥150nmol/L. To date we have measured 25(OH)D levels in 385 in-center haemodialysis patients. Virtually all patients (95%) had serum 25(OH)D levels <75nmol/L (65% deficient, <30nmol/L; 30% insufficient, 30-74nmol/L). Only 5% of patients had optimal levels (≥75nmol/L). Our data indicates that hypovitaminosis D is prevalent in the haemodialysis population in Coventry and Warwickshire and this is likely to reflect UK haemodialysis patients, highlighting the need for a national supplementation guideline.

Keywords: vitamin D; hypovitaminosis D; cholecalciferol; ESRD; haemodialysis; 25 hydroxyvitamin D

1. Introduction

End stage renal disease (ESRD) is characterised by decreased renal expression of 25-hydroxyvitamin D 1α-hydroxylase (CYP27B1; 1α-OHase), the enzyme that catalyses the conversion of 25-hydroxyvitamin D (25(OH)D) the form synthesised in the liver by 25-hydroxylase following production of vitamin D in the skin, to the active form, 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). This is well appreciated in the clinical setting and the majority of haemodialysis patients require treatment with an active vitamin D or an analogue (calcitriol, alfacalcidol or paricalcitol) for the management of calcium and secondary hyperparathyroidism.[1,2] However, recent data have shown that ESRD patients also have low serum 25(OH)D levels with vitamin D deficiency and insufficiency (serum 25(OH)D <30nmol/l and <75nmol/l respectively) seen in up to 95% of haemodialysis patients.[3,4] This is attributed to reduced sunlight exposure, an ethnically diverse and ageing population; both of which have implications on skin synthesis of vitamin D, and the uremic state which hinders hydroxylation of vitamin D in the liver.[5] Anecdotal evidence suggests concurrent cholecalciferol treatment to optimise serum 25(OH)D levels may result in further improvement in mineral bone markers[6]. Non-classical extra-skeletal benefits of 25(OH)D in ESRD are less clear, but recent studies suggest vitamin D deficiency may be associated with resistance to erythropoietin (EPO), reduced health-related quality of life (HRQOL), and increased levels of inflammation and infection.[7-14]

UK guidelines changed in 2014 and now recommend the diagnosis and treatment of low serum 25(OH)D in all people with a glomerular filtration rate (GFR) less than $30ml/min/1.73m^2$ however they make no recommendations for dosage or monitoring and as such recommendations have not widely translated into practice.[15] This, along with a poor understanding of the physiological roles of vitamin D beyond bone mineral homeostasis and a misconception that $1,25(OH)_2D$ therapy alone is sufficient, has meant hypovitaminosis D in ESRD remains prevalent.

The aims of this study were to assess the extent of vitamin D insufficiency/deficiency in the haemodialysis population of Coventry and Warwickshire, and to develop a clinical guideline

for cholecalciferol supplementation in haemodialysis patients at the University Hospitals of Coventry and Warwickshire (UHCW) in order to replete serum 25(OH)D levels to ≥75nmol/L in ≥90% patients.

2. Methods

2.1 Guideline development

A structured review of the current literature looking at the safety and efficacy of cholecalciferol supplementation in haemodialysis patients was completed. Search strategy was defined by the question; what dose of cholecalciferol is required to replete haemodialysis patients serum 25(OH)D levels to ≥75nmol/l? The optimal level of 75nmol/L was chosen based on the Endocrinology Society guidelines.[16] Between February and June 2014 the following databases were searched; Embase, Medline, Web of Science, Cochrane, Cinahl and Proquest. The following search terms were used; (i) for intervention; Dietary Supplements/supplement*, drug therapy, vitamin D, vitamin D deficiency, cholecalciferol, colecalciferol, (ii) for population; haemodialysis, haemodialysis, renal dialysis, kidney failure, chronic kidney disease, esrd, end stage renal disease, end stage renal failure, renal insufficiency, (iii) criteria for paper; 'limit to English'. Search results were screened by two reviewers (SH and RB) according to preset inclusion and exclusion criteria; initially by title, then by abstract, and finally by full article *(reported in section 3.1 and figure 1)*.

2.2 Patient recruitment

Routine screening of serum 25(OH)D in all patients having in-center haemodialysis at UHCW NHS trust was introduced from November 2014. If required cholecalciferol is prescribed by the patient's renal consultant within their dialysis prescription book and administration is overseen by nursing staff. Cholecalciferol (Fultium D3) is given according to the guideline outlined in section 3.1 and table 1. NHS ethical approval to study the efficacy and effects of cholecalciferol supplementation was obtained.

2.3 Serum 25(OH)D analysis

Serum 25(OH)D levels were measured in routinely collected blood samples by the hospital biochemistry laboratories using Elecsys Vitamin D Total Assay (Roche). The percentage coefficient of variation varied according to mean serum level and were; 13.6% for 10.2nmol/L, 9.1% for 33.5nmol/L and 6.3% for 73.8nmol/L.

3. Results

3.1 Cholecalciferol supplementation guideline

A flow diagram of the literature identification process is shown in figure 1. The combined search of Embase, Medline, Web of Science, Cochrane, Cinahl and Proquest identified 2847 citations. 2816 were excluded after title and abstract review. Full text assessment of 34 articles identified 17 papers which were reviewed. Although search parameters were not limited by year, these papers were published between 2008 and 2014. Studies varied in the number of participants (7-158), length of study intervention (3-104 weeks) and cholecalciferol dose (weekly equivalent 5,000-100,000IU). The average baseline 25(OH)D level was <50nmol/L in all but one study. Only two studies were carried out over 24 months however adequate repletion was only achieved in 9.2% and 57% of patients.[17,4] Although fourteen studies reported average repletion of 25(OH)D to >75nmol/L, repletion of ≥90% of the population was only achieved in 7 of these.[6,18-23] While these studies varied in supplementation dose and duration, in 6/7 studies the minimum weekly dose of cholecalciferol was 20,000IU for ≥8 weeks. In the remaining study patients were given 200,000IU a week for 3 weeks.[23] Of the combined study population receiving cholecalciferol (n=239) and throughout the duration of these 7 studies only 6 incidents of hypercalcaemia were reported and in many cases patients were receiving concurrent active vitamin D analogue treatment.

The guideline was developed by the renal multidisciplinary team consisting of dietitians, renal consultants and specialist renal pharmacist, and a summary of the information from the review was discussed with two vitamin D experts. Based on the review data and taking

account of local clinical guidelines for the general population the guideline we developed for haemodialysis patients (table 1) recommends 40,000IU cholecalciferol weekly for patients with 25(OH)D <50nmol/L (to be reviewed at 3 months) and 20,000IU weekly for patients with 25(OH)D 50-75nmol/L; to be continued long term unless levels increase to ≥150nmol/L. If levels increase to ≥150nmol/L cholecalciferol should be stopped and 25(OH)D levels rechecked in 3 months. Although cholecalciferol supplementation is considered safe, hypercalcaemia is considered a marker of toxicity and as such must be monitored. Serum calcium is routinely measured each month in haemodialysis patients and should be maintained between 2.10-2.58mmol/L (based on the local laboratory reference range and corrected for serum albumin). If hypercalcaemia occurs the following calcium therapies should be reviewed; calcium supplements, calcium based phosphate binders, alfacalcidol, calcitriol and paricalcitol. Where required calcium therapies should be discontinued. Cholecalciferol should not be discontinued unless hypercalcaemia remains after the above calcium therapies are stopped. In the event that cholecalciferol needs to be discontinued the patients' vitamin D level should be checked in order to assess for toxicity. Serum intact parathyroid hormone should be maintained at 8-38pmol/L (2-9 times the upper laboratory target). Cholecalciferol should be given concurrently with current treatment regimens for hyperparathyroidism; as per by current UHCW and NICE (National Institute for Health and Care Excellence) guidance[2].

3.2 Prevalence of hypovitaminosis D

To date we have measured serum 25(OH)D levels in 385 haemodialysis patients. Virtually all patients (95%) had serum 25D levels <75nmol/L (65% deficient, <30nmol/L; 30% insufficient, 30-74nmol/L). Only 21 patients (5%) had optimal levels (≥75nmol/L) (figure 2).

4. Discussion

Data from this study supports other studies that suggest hypovitaminosis D is common in the haemodialysis population. Deficiency is multifactorial and in addition to the issues highlighted

earlier, increased 24-hydroxylase activity (induced by the use of active vitamin D analogues) and increased levels of FGF23 (fibroblast growth factor 23) seen in ESRD, could also be key.

We have produced a local guideline to ensure deficiency is identified and appropriately treated in our patients. Serum 25(OH)D levels are measured initially every 3-4 months in all haemodialysis patients at UHCW (to enable monitoring of effectiveness, safety and adherence), but this will be reviewed in the longer term once the efficacy and maintenance data over an 18 month prospective period has been appraised. Whilst the maintenance dose of cholecalciferol recommended in our guideline (20,000IU weekly) is higher than the current national guidelines recommend for the general population[24] it is well within the recommended safe upper limits.[25,26] The sample size of our haemodialysis cohort (n=385) is unmatched by any comparable previous or currently ongoing research. This provides a unique opportunity, not only to collect repletion data, but also to collect biochemical and qualitative data in order to investigate classical and non-classical effects of vitamin D; something that can only be studied in the ESRD population, due to the reduced renal synthesis of $1,25(OH)_2D$. Currently an optimal serum 25(OH)D level remains controversial; we anticipate that our current and future studies together with other emerging evidence will help better determine a target serum 25(OH)D in relation to health outcomes in the haemodialysis population.

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Figure Captions

Figure 1. Flow diagram of literature identification process. Details of the number of citations identified and excluded at each stage of the search process are indicated. Search strategy was defined by the question; what dose of cholecalciferol is required to replete haemodialysis patients serum 25(OH)D levels to ≥75nmol/l. The following search terms were used; (i) for intervention; Dietary Supplements/supplement*, drug therapy, vitamin D, vitamin D deficiency, cholecalciferol, colecalciferol, (ii) for population; haemodialysis, haemodialysis, renal dialysis, kidney failure, chronic kidney disease, esrd, end stage renal disease, end stage renal failure, renal insufficiency, (iii) criteria for paper; 'limit to English'. Search results were screened by two reviewers (SH and RB) according to preset inclusion and exclusion criteria; initially by title, then by abstract, and finally by full article.

Figure 2. Prevalence of hypovitaminosis D in haemodialysis patients Graph illustrating the serum 25(OH)D concentrations of 385 haemodialysis patients screened at University Hospitals of Coventry and Warwickshire (UK). Virtually all patients (95%) had serum 25D levels <75nmol/L (65% deficient, <30nmol/L; 30% insufficient, 30-74nmol/L). Only 21 patients (5%) had optimal levels (≥75nmol/L). Data represents individual patient values grouped into deficient (<30nmol/L), insufficient (30-74nmol/L) and optimal (≥75nmol/L) *(median)*.

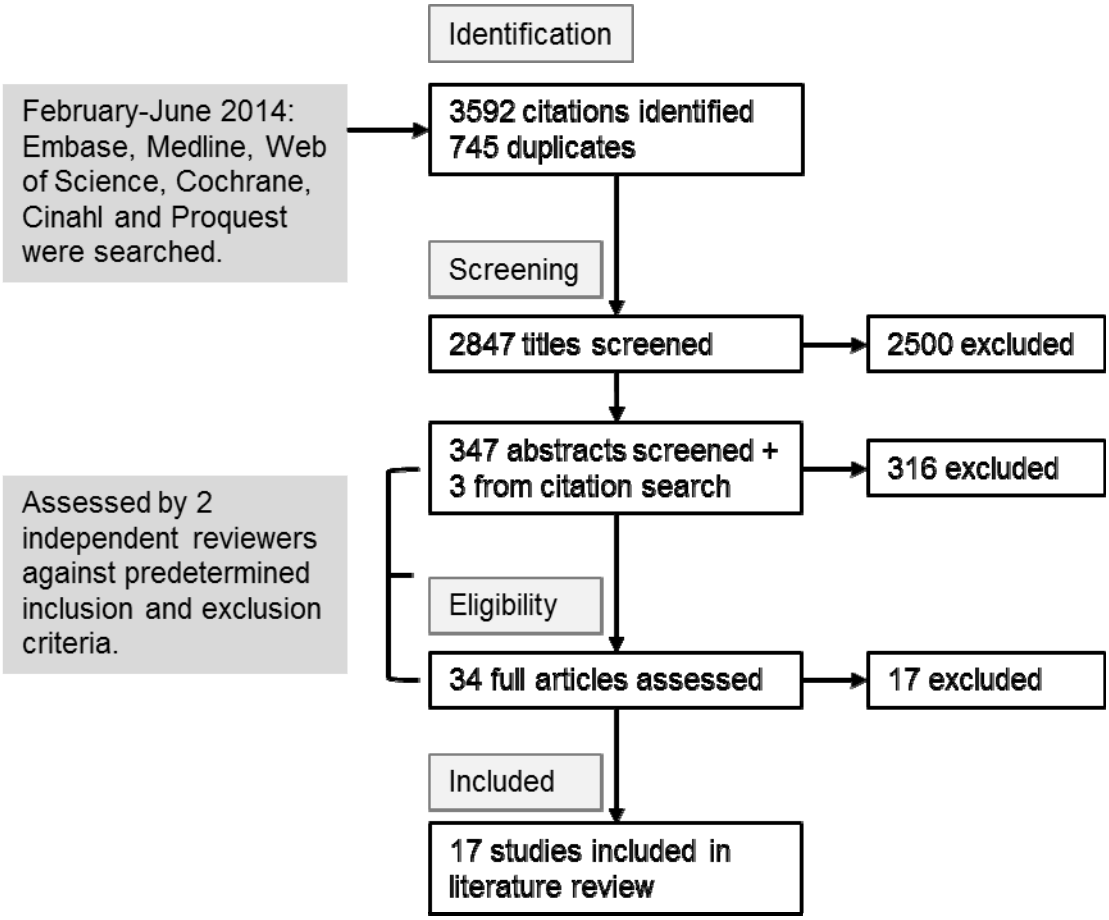

Figure 1.

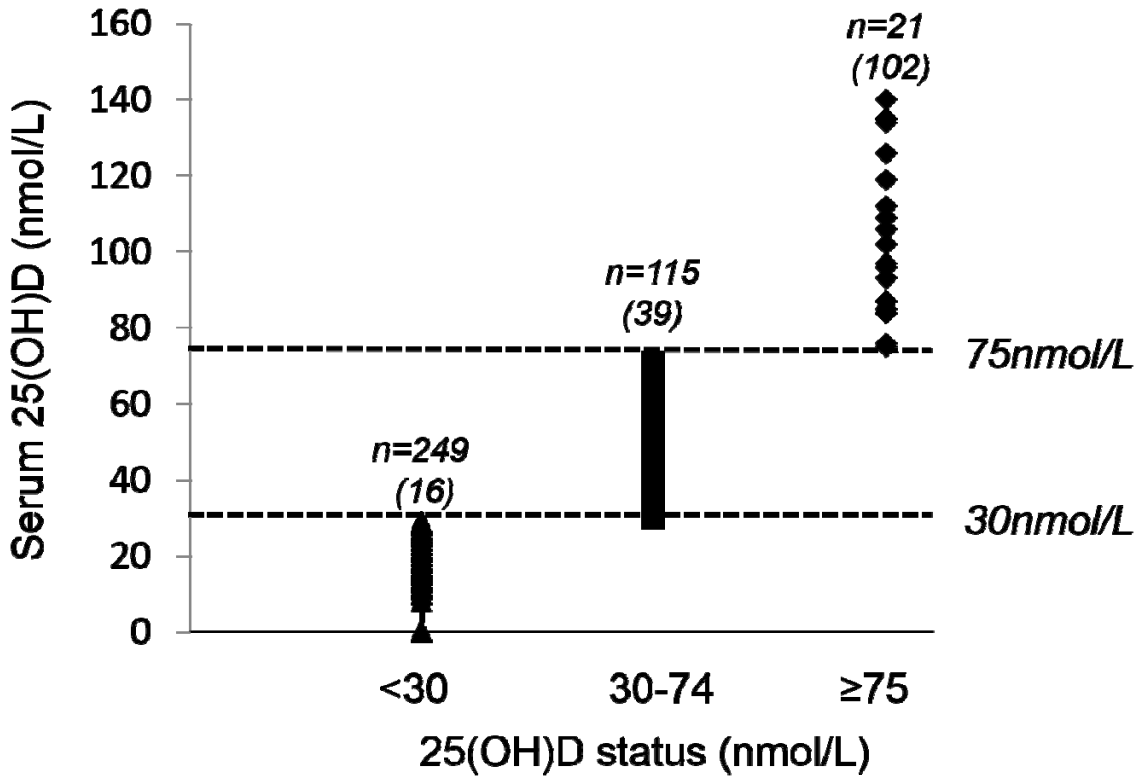

Figure .2.

Tables

Table 1. Clinical guideline for cholecalciferol supplementation in haemodialysis patients at University Hospitals of Coventry and Warwickshire, UK.

Serum 25(OH)D	Cholecalciferol Dose
<50nmol/L	40,000IU weekly. Review at 3 months.
50-74nmol/L	20,000IU weekly. Review at 3 months.
75-150nmol/L	If not already taking cholecalciferol - no indication to start. If taking cholecalciferol already maintain levels on maintenance dose of 20,000IU weekly. Review at 3 months.
<150nmol/L	STOP cholecalciferol, recheck level in 3 months and provided <150nmol/L restart maintenance dose of 20,000IU weekly.