Journal of Steroid Biochemistry & Molecular Biology 164 (2016) 214–217

Contents lists available at ScienceDirect

Journal of Steroid Biochemistry & Molecular Biology

journal homepage: www.elsevier.com/locate/jsbmb

Review

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

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ARTICLE INFO

Article history:
Received 15 June 2015
Received in revised form 7 January 2016
Accepted 9 February 2016
Available online 11 February 2016

Keywords:
Vitamin D
Hypovitaminosis D
Cholecalciferol
ESRD
Haemodialysis
25 Hydroxyvitamin D

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 30 ml/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 <50 nmol/L and 20,000IU weekly for patients with 25(OH)D 50–75nmol/L; to be continued long term unless levels increase to ≥150 nmol/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 <75 nmol/L (65% deficient, <30 nmol/L; 30% insufficient, 30–74 nmol/L). Only 5% of patients had optimal levels (≥75 nmol/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.

Contents

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http://dx.doi.org/10.1016/j.jsbmb.2016.02.009
0960-0760/

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 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 <30 nmol/l and <75 nmol/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 30 ml/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 ≥75 nmol/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 ≥75 nmol/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 Fig. 1).

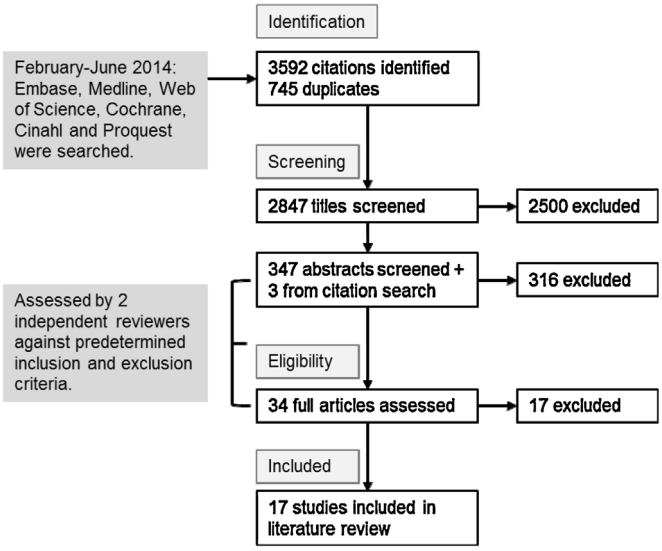

Fig. 1. Flow diagram of literature identification process.
Details of the number of citations identified and excluded at each stage of the search process are indicated. Search strategy was defined by the question; what dose of cholecalciferol is required to replete haemodialysis patients serum 25(OH)D levels to ≥75 nmol/L. The following search terms were used; (i) for intervention; Dietary Sup plements/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.

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

1.1. Cholecalciferol supplementation guideline

A flow diagram of the literature identification process is shown in Fig. 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