

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

Huish, Sharon A; Fletcher, Simon; Dunn, Janet A; Hewison, Martin; Bland, Rosemary

DOI:

[10.1016/j.jsbmb.2016.02.009](https://doi.org/10.1016/j.jsbmb.2016.02.009)

License:

Creative Commons: Attribution-NonCommercial-NoDerivs (CC BY-NC-ND)

Document Version

Peer reviewed version

Citation for published version (Harvard):

Huish, SA, Fletcher, S, Dunn, JA, Hewison, M & Bland, R 2016, 'Prevalence and treatment of hypovitaminosis D in the haemodialysis population of Coventry', *The Journal of Steroid Biochemistry and Molecular Biology*.
<https://doi.org/10.1016/j.jsbmb.2016.02.009>

[Link to publication on Research at Birmingham portal](#)

Publisher Rights Statement:

Validated Feb 2016

General rights

Unless a licence is specified above, all rights (including copyright and moral rights) in this document are retained by the authors and/or the copyright holders. The express permission of the copyright holder must be obtained for any use of this material other than for purposes permitted by law.

- Users may freely distribute the URL that is used to identify this publication.
- Users may download and/or print one copy of the publication from the University of Birmingham research portal for the purpose of private study or non-commercial research.
- User may use extracts from the document in line with the concept of 'fair dealing' under the Copyright, Designs and Patents Act 1988 (?)
- Users may not further distribute the material nor use it for the purposes of commercial gain.

Where a licence is displayed above, please note the terms and conditions of the licence govern your use of this document.

When citing, please reference the published version.

Take down policy

While the University of Birmingham exercises care and attention in making items available there are rare occasions when an item has been uploaded in error or has been deemed to be commercially or otherwise sensitive.

If you believe that this is the case for this document, please contact UBIRA@lists.bham.ac.uk providing details and we will remove access to the work immediately and investigate.

Accepted Manuscript

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

Author: Sharon A. Huish Simon Fletcher Janet A. Dunn
Martin Hewison Rosemary Bland



PII: S0960-0760(16)30023-1
DOI: <http://dx.doi.org/doi:10.1016/j.jsbmb.2016.02.009>
Reference: SBMB 4630

To appear in: *Journal of Steroid Biochemistry & Molecular Biology*

Received date: 15-6-2015
Revised date: 7-1-2016
Accepted date: 9-2-2016

Please cite this article as: Sharon A.Huish, Simon Fletcher, Janet A.Dunn, Martin Hewison, Rosemary Bland, Prevalence and treatment of hypovitaminosis D in the haemodialysis population of Coventry, *Journal of Steroid Biochemistry and Molecular Biology* <http://dx.doi.org/10.1016/j.jsbmb.2016.02.009>

This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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

Sharon A Huish^{1,4*} sharon.huish@uhcw.nhs.uk, Simon Fletcher², Janet A Dunn⁴, Martin Hewison³, Rosemary Bland^{2,4}

¹Department of Nutrition and Dietetics, University Hospitals of Coventry and Warwickshire NHS Trust, UK, CV2 2DX

²Department of Nephrology, University Hospitals of Coventry and Warwickshire NHS Trust, UK, CV2 2DX

³Institute of Metabolism and Systems Research, The University of Birmingham, UK, B15 2TT

⁴Warwick Medical School, The University of Warwick, Coventry, UK, CV4 7AL

*Corresponding author at: Dietetics Department, 2nd Floor Rotunda, University Hospitals of Coventry and Warwickshire, Coventry, CV2 2DX, UK.

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)₂D], 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/1.73m². 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 1 α -hydroxylase (CYP27B1; 1 α -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 markers⁶. 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/1.73m² 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 $\geq 75\text{nmol/L}$ in $\geq 90\%$ 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 $\geq 75\text{nmol/L}$? 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 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 ≥ 150 nmol/L. If levels increase to ≥ 150 nmol/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) guidance².

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 (≥ 75 nmol/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 population²⁴ 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.

Acknowledgements

This work is supported in part by a grant from the British Renal Society (SH, RB, JD) and the UK CRN (Study ID numbers: 17213 and 17275).

References

1. Kidney Disease Improving Global Outcomes (KDIGO) Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney International* (2009); 76 (113)
2. National Institute for Health and Care Excellence (NICE): Cinacalcet for the treatment of secondary hyperparathyroidism in patients with end-stage renal disease on maintenance dialysis therapy: NICE technology appraisal guidance 117 available from: <http://www.nice.org.uk/nicemedia/live/11608/33857/33857.pdf>
3. Saab G, Young DO, Gincherman Y et al. Prevalence of vitamin D deficiency and the safety and effectiveness of monthly ergocalciferol in hemodialysis patients. *Nephron Clinical Practice* (2007): 105:132-138
4. Tokmak F, Quack I, Schieren G, et al. High-dose cholecalciferol to correct vitamin D deficiency in haemodialysis patients. *Nephrology Dialysis Transplantation* (2008); 23(12): 4016-4020
5. Michaud J, Naud J, Ouimet D, et al. Reduced Hepatic Synthesis of Calcidiol in Uremia. *Journal of the American Society of Nephrology* (2010); 21(9): 1488–1497
6. Jean G, Souberbielle J-C and Chazot C. Monthly cholecalciferol administration in haemodialysis patients: a simple and efficient strategy for vitamin D supplementation; *Nephrology Dialysis Transplantation*; 2009; 24: 3799–3805
7. Ferreira AC, Matias P, Jorge C et al. Vitamin D, inflammation and malnutrition in prevalent haemodialysis patients – is there a link? *Portuguese Journal of Nephrology and Hypertension* (2008); 4: 305-312
8. Kiss Z, Ambrus C, Almasi C et al. Serum 25(OH)-Cholecalciferol Concentration Is Associated with Hemoglobin Level and Erythropoietin Resistance in Patients on Maintenance Hemodialysis. *Nephron Clinical Practice* (2011); 117 (4):373-378
9. Stenvinkel P. The role of Inflammation in the Anaemia of End Stage Renal Disease. *Nephrology, Dialysis, Transplantation* (2001); 16(7): 36-40
10. Srisakul U, Gilmartin C, Akkina S, Porter A. Effects of vitamin D repletion on

haemoglobin and the dose of an erythropoiesis stimulating agent, National Kidney Foundation poster abstract (2011) Chicago

11. Lac P T, Choi K, Liu I A et al. The effects of changing vitamin D levels on anaemia in chronic kidney disease patients: a retrospective cohort review. *Clinical Nephrology* (2010); 74 (1): 25-32
12. Icardi A, Paoletti E, De Nicola L et al. Renal anaemia and EPO hyporesponsiveness associated with vitamin D deficiency: the potential role of inflammation. *Nephrol Dial Transplant*. 2013; 28(7):1672-9
13. Sim JJ, Lac P T, Liu I L A, Meguerditchian S O, et al. Vitamin D deficiency and anemia: a cross-sectional study. *Annals of Hematology* (2010); 89:447–452
14. Kumar V A, Kujubu D A, Sim J J et al. Vitamin D Supplementation and recombinant human erythropoietin utilization in vitamin D-deficient hemodialysis patients. *Journal of Nephrology* (2011); 24 (supplement 1) 98-105
15. National Institute for Health and Care Excellence (NICE): Chronic Kidney Disease: early identification and management of chronic kidney disease in adults in primary and secondary care - CG182 2014; Available from: <https://www.nice.org.uk/guidance/CG182>
Accessed on 21/10/14
16. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011; 96 (7):1911-30
17. Jakopin E, Balon B P, Ekart R et al. High-dose Cholecalciferol Supplementation for Vitamin D Deficiency in Haemodialysis Patients. *The Journal of International Medical Research* (2011); 39: 1099-1106
18. Marckmann P Agerskov H, Thineshkumar S, Randomized controlled trial of cholecalciferol supplementation in chronic kidney disease patients with hypovitaminosis D. *Nephrology Dialysis Transplantation* (2012); 27 (9): 3523-31

19. Ozkurt S and Musmul A, The effects of cholecalciferol treatment on mineral metabolism and inflammation markers in Turkish hemodialysis patients; Saudi Medical Journal: (2013); 34 (5); 497-502
20. Stubbs JR, Idiculla A, Slusser J et al. Cholecalciferol supplementation alters calcitriol-responsive monocyte proteins and decreases inflammatory cytokines in ESRD; Journal of the American Society of Nephrology; (2010); 21; 353-361
21. Armas LA, Zena M, Lund R et al. Calcium absorption response to cholecalciferol supplementation in hemodialysis; Clinical Journal of The American Society of Nephrology: CJASN; (2013); 8: 1003–1008
22. Burchard S, Barberato SH, Stingham A. EN et al. Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in hemodialysis patients without hyperparathyroidism; Journal of Renal Nutrition (2012); 22 (2): 284-291
23. Wasse H, Huang R, Long Q et al. Efficacy and safety of a short course of very-high-dose cholecalciferol in hemodialysis; American Journal of Clinical Nutrition; (2012); 95; 522-528
24. Department of Health: Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. (1991) Report on Health and Social Subjects No. 41. HSMO, London
25. Ross C A, Taylor C L, Yaktine A L, and Del Valle H B, Editors; Committee to Review Dietary Reference Intakes for Vitamin D and Calcium; Institute of Medicine (2011) The National Academies Press. Washington DC
26. European Food Safety Authority. Scientific Opinion on the Tolerable Upper Intake Level of vitamin D. EFSA Journal (2012);10(7):2813

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 $\geq 75\text{nmol/l}$. 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 $< 75\text{nmol/L}$ (65% deficient, $< 30\text{nmol/L}$; 30% insufficient, $30\text{-}74\text{nmol/L}$). Only 21 patients (5%) had optimal levels ($\geq 75\text{nmol/L}$). Data represents individual patient values grouped into deficient ($< 30\text{nmol/L}$), insufficient ($30\text{-}74\text{nmol/L}$) and optimal ($\geq 75\text{nmol/L}$) (*median*).

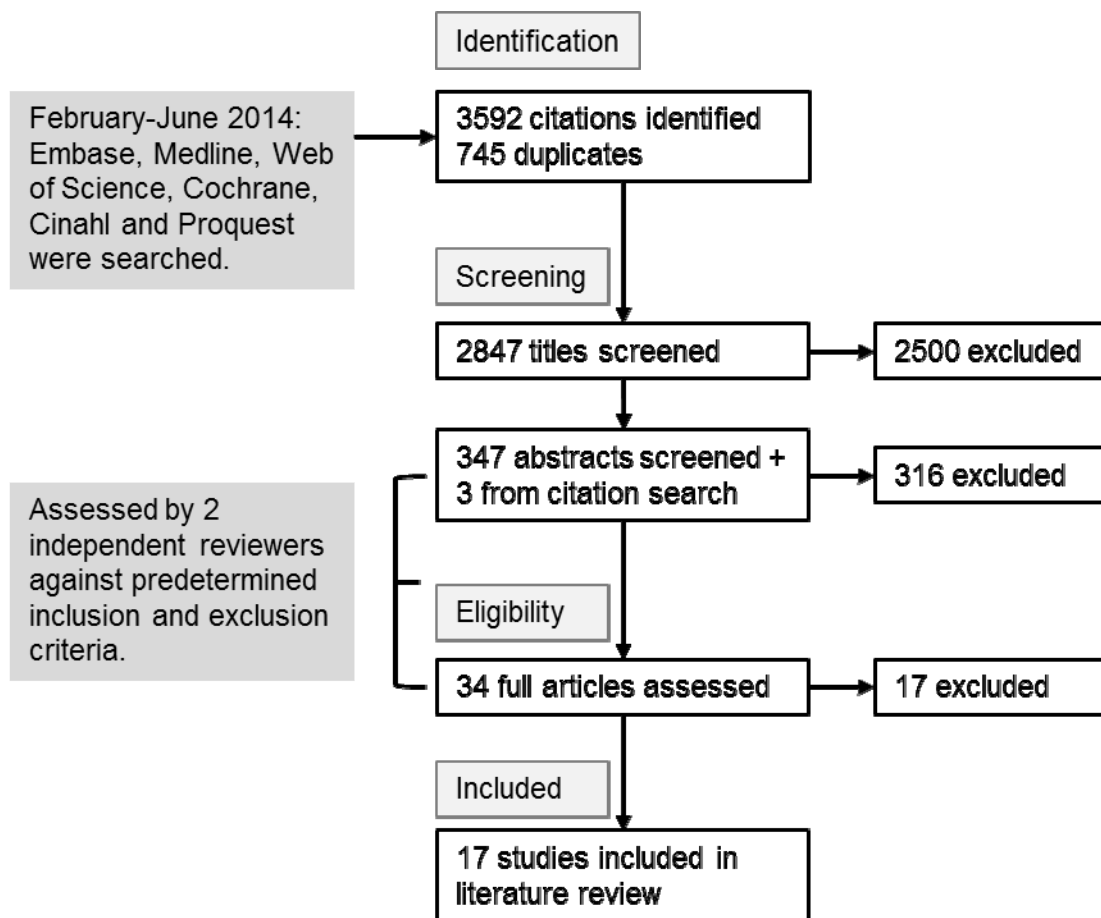


Figure 1.

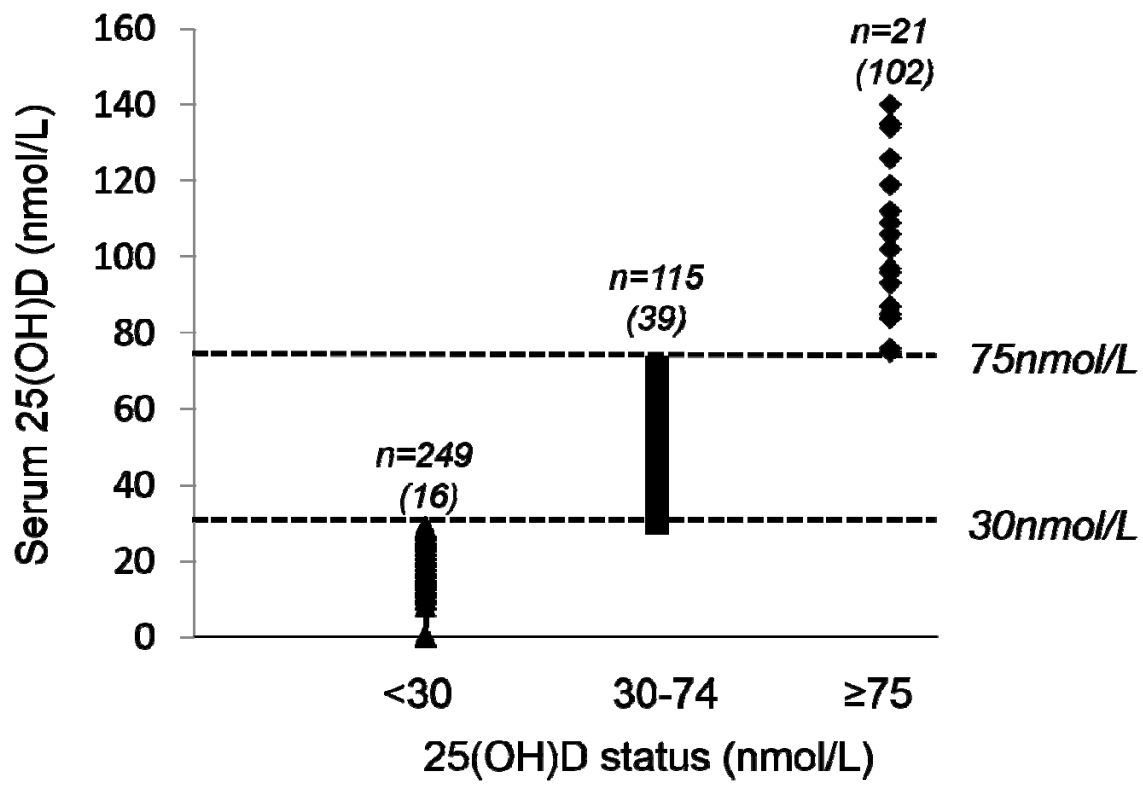


Figure .2.

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.