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Research article

The impact of vit-d on survival in hemodialysis patients: A critical appraisal

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ABSTRACT

Vit-D deficiency (20 ng / mL) and deficiency (20-29 ng / mL) are common side effects in people with chronic disease V or End stage Renal Disease on dialysis. In addition to the lack of exposure to nutrients and sun, reduced Vit-D and body composition, obesity, and racial differences also play a role. In addition, due to a deficiency of 25 (OH) D, serum levels of 1, 25 (OH) 2D decreased over time in CKD patients, as well as non-invasive detection of 25 (OH) D by associated renal cells, increased fibroblast factor -23, and a decrease in functional tissue. Vit-D deficiency causes secondary hyperparathyroidism and associated side effects, such as high hyperparathyroidism and hypercalcemia, requiring surgical parathyroidectomy or the use of calcimimetics. This document examines the available evidence and underscores the importance of Vit-D supplementation in hemodialysis patients. To assess the strength and critically review the available evidence on impact of Vit-D in survival of hemodialysis patients. Vit-D has a survival advantage in patients with CKD-MBD, however we need randomized controlled trial in hemodialysis patients with matched controls given placebo, to prove benefits of Vit-D in terms of all cause and cause specific mortality.

Keywords: CKD, MBD, Parathyroid hormone, Vit-D and VDRA

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INTRODUCTION

The term refers to both common forms of renal osteodystrophy, such as SHPT, Vit-D metabolism disorders, hyper phosphatemia, and hypercalcemia, as well as other recently described vascular calcification disorders. CKD-MBD has been identified as a new risk factor for the death of ESRD patients. The guidelines of the National Kidney Foundation's Kidney Diseases Outcomes Quality Initiative (K / DOQI) since 2003 recommended treatment focused on reducing dietary phosphorus, phosphate binders, and the delivery of Vit-D analogue.[1]

Vit-D and Vit-D Receptor Activators have become important therapies for SHPT, due to the steady fall in effective Vit-D levels through the development of CKD, Vit-D and Vit-D Receptor Activators (VDRA).[2] Decreased active Vit-D activity reduces secondary hyperparathyroidism in patients with renal failure [3], and Vit-D deficiency is common in patients with ESRD [4]. Exposure to UVB ultraviolet radiation causes most of the metabolites circulating Vit-D in humans to be produced on the skin from 7-dehydrocholesterol. 25-hydroxylase worsens the conversion to 25-hydroxyVit-D in the liver. 1-hydroxylase then converts 25 (OH) hydroxyl Vit-D into 1, 25- (OH) 2D3, an active form of Vit-D, in the kidneys. Vit-D receptor (VDR) is expressed in both traditional organs and non-primary targets and coordinates 1 functions , 25 (OH) 2D3.[5] SHPT is caused by a combination of factors including a deficiency of 1,25-dihydroxycholecalciferol,[6] reducing the expression of Vit-D receptor and calcium sensing receptor (CSR), hypophosphatemia, hypocalcaemia, and resistance to PTH.[7]

FGF-23, a novel director who plays a key role in the CKD-MBD, recently emerged as a new actor. It has phosphatidic properties similar to PTH, but inhibits 1-a-hydroxylation, resulting in lower levels of activated Vit-D and increased PTH synthesis. FGF 23 can have a direct effect on regenerating parathyroid glands, adding to SHPT continuously. The end result is a decrease in activated Vit-D levels. [8]

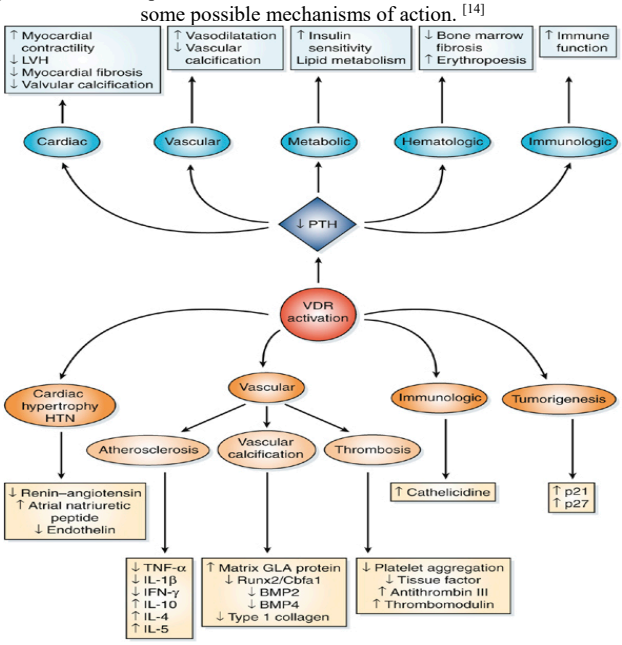
Vit-D supplementation instead of body fat levels seems to be a sensible strategy for treating SHPT. The use of Vit-D in body doses often fails to regulate SHPT, in part due to a decrease in the production of Vit-D in the parathyroid gland. This can be overcome by the administration of high doses of activated Vit-D, but such doses can cause side effects, which are less common in hypercalcemia and hypophosphatemia, which are also associated with higher mortality in hemodialysis patients. To reduce these side effects, the newly developed agents have a selective effect on reducing PTH production, which has a small effect on the gut and bone mass of calcium and phosphorus. [9, 10]

Vit-D Receptor Activator (VDRA): Mechanisms of Actions -

VDRA has benefits especially in lowering the level of parathyroid hormone (PTH). PTH lowers heart volume, metabolic (reduces insulin sensitivity and problems with lipid metabolism), hematological (bone marrow and erythropoiesis) and erythropoiesis) physical impairment. [11]

Vit-D receptors are found throughout the body. Its stimulus, along with its effects on the cardiovascular system, can be explained by altering cardiac hypertrophy, reducing renin-angiotensin system function, inhibiting the production of proteins involved in the census, inhibiting the production of Vit-D-blocking cytokines, and preventing pneumonia. Increased cathelicidine and anticancer effects are two non-cardiac effects of VDR stimulation. [12, 13]

Figure 1: Vit-D receptor activation is linked to a decreased death rate. Here are some possible mechanisms of action. [14]



Vdra and Survival in Esrd/ Ckd

Possible explanation for association of lower mortality in observational studies of hemodialysis patients with the use of Vit-D seems to be effect of VDR activation on lowering PTH and on various cardiovascular and metabolic processes.

Hypovitaminosis D is common in general medical patients even in those with intake exceeding recommended daily intake and without apparent risk factor for Vit-D deficiency.

Also important is Vit-D deficiency, which is a rare, non-traditional risk factor for heart disease. Vit-D can protect the cardiovascular system through a variety of mechanisms, including 1) anti-inflammatory, anti-thermogenesis, and protection against blood vessel damage; 2) reducing cardiac hypertrophy and mycotic enlargement; and 3) renin-angiotensin modulation system.

Clinical Application of Vit-D Level

Wolf et al found lower 25(OH) Vit-D levels to be associated with significantly higher mortality in incident hemodialysis patients and subsequent treatment with active Vit-D nullified this association, although supplementation with 25(OH) Vit-D was not done. Also, serum levels of calcium, phosphorus and PTH correlate poorly with Vit-D levels. It is a possible that benefit from 25 (OH) Vit-D replacements is partially independent of active Vit-D. As per Coen et al adequate 25-hydroxy levels may also be important for the pleiotropic effects attributed to Vit-D, including potential cardiovascular and immunomodulatory benefits important in preventing cardiovascular diseases, cancers, autoimmune disorders and infectious diseases.[15,16]

Vit-D Analogues

Native VDRA, calcitriol, effectively suppresses SHPT, but can have less salutary effects by inducing hypercalcemia and hypophosphatemia.

The newer Vit-D analogs can suppress PTH production with a lesser concomitant hypercalcemia and hyperphosphatemic effect. These differential actions have been attributed to the differential gene activation profile with them. Another interesting aspect is angiotensin converting enzyme (ACE) gene polymorphism seen in hemodialysis patients which requires angiotensin converting enzyme inhibitor (ACEI) therapy for those with resistant hyperparathyroidism.

The analogs differ significantly in the ancillary effects. The effects on calcium, phosphorus, vascular calcification and capillary density are favored by analogs. More severe perivascular fibrosis is seen with calcitriol. This pre-clinical result however needs clinical correlation.

Currently, the approved indication for use of active Vit-D is only SHPT and choice of agent is decided by the patient tolerance, individual side effect profiles and cost considerations. Paricalcitol and doxercalciferol are the approved agents in US on the basis of their favorable profile compared to calcitriol, but they have different pharmacological characteristics; side effect profile is better for Paricalcitol and doxercalciferol has longer half-life.

Black and Hispanic individuals demonstrate longer survival on dialysis than non-Hispanic white individuals, which may be attributed to their more favorable clinical characteristics however this gets partially attenuated after adjustment for these clinical

characteristics. More studies are needed to establish the role of Vit-D for patients of different ethnicities. [17, 18]

Objective and hypothesis

Hypothesis

Vit-D has a strong association with survival in haemodialysis patients.

Objective

To assess the strength and critically review the available evidence on impact of Vit-D in survival of haemodialysis patients

Methodology

Pub med database and Cochrane library were searched for this thesis work with the following search terms: Vit-D, haemodialysis and survival. Additional search was sought through manual search in some relevant journals. Several studies were identified and reviewed with limitation of the search on English language published studies. Reviewed KDOQI recommendations

Articles included:

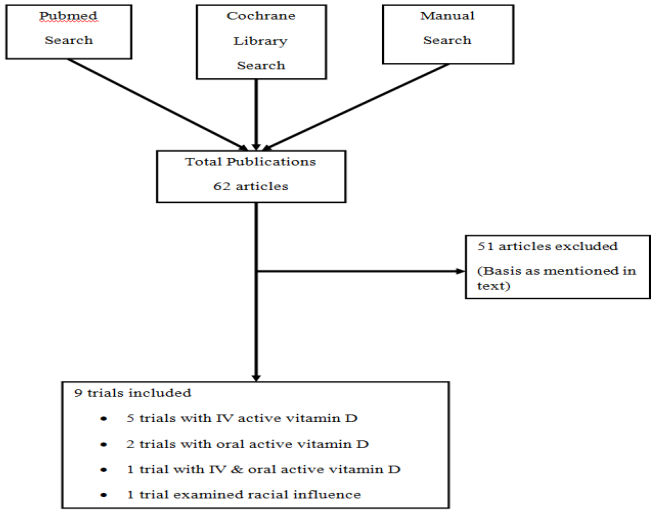
- Published studies examined impact on survival of haemodialysis patients with Vit-D, either oral or IV formulations
- Studies compared haemodialysis survival in various races and Vit-D.

Articles excluded:

- The published articles were expert opinion
- The articles were not published in English
- The full articles were not accessible
- Articles used Vit-D in experimental studies
- Articles used animals for the study
- Participants were children
- Articles used Vit-D levels and survival
- Articles used patients on peritoneal dialysis
- Articles used chronic kidney disease patients not started on dialysis.

All the studies have been scored on the scale of 1 to 10 based on the questionnaire by critical appraisal skills Programme (CASP), making sense of evidence.

Figure 2: Flow chart indicating the number of articles retrieved by search and final number of studies included in this work



Result: Table 1: Results - Characteristics of Studies

Study ID	Study design	Setting SC/ MC	No. of Participants	Form of Vit-D	Follow-up period	Survival Benefit/RR (CI) in Vit-D group	Study Score
M Teng et al[19], 2005	Prospective cohort study	MC	51,037	Any VDRA vs no treatment	2 years	20%, HR 0.80(0.76-0.83) ↓CV mortality (P<0.001)	9
M Teng et al[20], 2003	Prospective cohort study	MC	67,399	Paricalcitol vscalcitriol	1999-2001	16% (P<0.001) Benefit observed in 28/42 strata	8
Tentori et al[21], 2006	Cohort study	MC	14,586	Any VDRA vs no treatment	1999-2004 (37 weeks)	Paricalcitol over calcitriol (P<0.0001) Identical for paricalcitol&doxercalciferol	8.5
Kalatar-Zadeh et al[9], 2006	Prospective cohort study	MC	50,058	Paricalcitol vs no treatment	July 2001-June 2003 (2 year)	Any dose of paricalcitol, HR 0.5-0.8 in time dependent models	9
Peter et al[22], 2009	Retrospective cohort	MC	193,830	IV vs no treatment	5.25 years	7-17%, HD duration <1year (P<0.0001)	8.5
T Shoji et al[23], 2004	Cohort study	SC	242	PO vs no treatment	61 ± 23 months	Reduced CV mortality (P=0.003), all cause mortality similar	6
N. Diaz et al[24], 2008	Cohort study	MC	16,004	PO vs no treatment	16 months	45% all cause mortality, 45-48% cause specific mortality	7.5
M Wolf et al[26], 2008	Prospective cohort study	MC	9303	IV vs no treatment	July 1, 2004 to June 30, 2005	Better survival of Black & Hispanic than white patients (P<0.01)	8.5
Tentori et al[26], 2009	Prospective cohort study	MC	38066	Vit-D (IV+ PO) vs no treatment	16 months	No survival benefit 0.98 (0.93-1.02)	9

DISCUSSION

- In conclusion, most studies have indicated a strong association of Vit-D with better survival in haemodialysis patients. Consistent results have been obtained in incident and prevalent haemodialysis patients and in patients from different countries.
- Therefore the evidence to support the hypothesis that Vit-D has association with survival in haemodialysis patients is strong.
- There isabout 7 to 50% reduction in all-cause mortality and reduction in cause-specific mortality with Vit-D (IV and oral active Vit-D). However, more studies have been done with IV compared to oral Vit-D.
- There is no data comparing oral with IV active Vit-D and hence which form is superior needs to be established. Also, when oral has to be replaced by intravenous or vice versa, the conversion factor for different analogue substitutions needs to be established.
- Active Vit-D is beneficial in Black and Hispanic patients compared to white patients. Untreated blacks have very high mortality. Randomized, controlled trials Vit-D is needed to establish its role considering the racial impact.
- Further clarification is needed for impact of time duration, regularity and dose of Vit-D on all cause and cause specific mortality

- Paricalcitol, doxercalciferol and calcitriol are the IV active Vit-D analogues being used in practice. Paricalcitol treated patients have survival advantage over calcitriol, attributed to its differential effects; paricalcitol and doxercalciferol have shown almost identical survival benefits; which needs further evaluation.
- There is inconsistency in observations about doses of Vit-D, some studies have shown survival benefit with any dose and some other study has shown an inverse relation with the dose of the active Vit-D. Average weekly dose used for each Vit-D analogue is calcitriol 1.6 µg, paricalcitol 7.5 µg and doxercalciferol 5.7 µg. Calcitriol equivalent doses are variable with ratio for Paricalcitol: calcitriol from 4:1 to 4.6:1 and for doxercalciferol: calcitriol from 2:1 to 3.1:1.
- Statistical analyses when performed independent of unmeasured confounding have shown no survival benefit of Vit-D. This is in agreement with a recent meta-analysis of randomized controlled trials in chronic kidney disease. In view of these findings, ethical issues related to the randomized controlled trial of Vit-D in MHD population can be reconsidered.

CONCLUSION

Vit-D has a survival advantage in patients with CKD-MBD, however we need randomised controlled trial in haemodialysis patients with matched controls given placebo, to prove benefits of Vit-D in terms of all cause and cause specific mortality. Study should answer what type, how much to give, how to approach in patients belonging to different races and whether this approach is safe especially with low levels of PTH or elevated levels of calcium and phosphorus so that the known resistance to Vit-D in uraemia is overcome and simultaneously the apparent survival benefit that has been observed is capitalized.

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