Is Vitamin D an Effective Treatment Method in Reducing Mortality in patients who have Cardiovascular Disease?

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A SELECTIVE EVIDENCE BASED MEDICINE REVIEW

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ABSTRACT

OBJECTIVE: The objective of this selective EBM review is to determine whether or not vitamin D is an effective treatment method in reducing mortality due to cardiovascular disease.

STUDY DESIGN: A review of two double blind, randomized controlled trials (RCTs) and one randomized open-label study published in the English language after 2008. The articles compared oral, intramuscular, or oil drops of vitamin D to a placebo group.

DATA SOURCES: One double-blind randomized controlled trial, one randomized control trial that was not blinded, and one randomized open-label study were found using PubMed, Medline, Embase, or Cochrane. The articles were selected based on their correlation to the specified topic, date of publications, and their evaluation of POEMs.

OUTCOMES MEASURED: The effect of vitamin D supplementation on reducing mortality in patients with cardiovascular disease will be measured. Mortality was measured by main cause of death from death registrations, Rankin scales, repeated contacts with the participants, contact with family physicians, regular review of medical records, and consultation of the respective registration office.

RESULTS: Two studies used in this review showed no significant improvement in vitamin D allocation in the reduction of mortality due to cardiovascular disease while one found clinical significance in the allocation of vitamin D. Avenell et al. and Zittermann et al.'s studies were not able to demonstrate an improvement in vascular mortality or all-cause mortality respectively with vitamin D supplementation. Gupta et al. reported a potential benefit in ischemic stroke survivors with vitamin D insufficiency or deficiency with the supplementation of vitamin D and calcium. This is the only RCT that did not separate calcium and vitamin D supplementation and instead combined both which showed a trend towards reduction in mortality.

CONCLUSIONS: The results of these studies showed no significant improvement in vitamin D allocation alone to reducing cardiovascular death. Although Gupta et al. reported a statistically significant lower mortality rate in the treatment arm compared to the placebo, it did not separate vitamin D allocation from calcium therefore we cannot assume that vitamin D supplementation alone reduced death from cardiovascular disease. Future studies should be conducted when vitamin D supplementation is given before a major cardiovascular event such as a stroke or heart failure.

KEY WORDS: vitamin D, mortality, cardiovascular disease, mortality

INTRODUCTION

Cardiovascular disease (CVD) is a broad term that encompasses different types of diseases. CVD can include diseases such as: hypertension; coronary heart disease, including myocardial infarction, angina pectoris, and heart failure; cerebrovascular disease, including stroke and transient ischemic attack; peripheral artery disease including intermittent claudication; and aortic atherosclerosis and thoracic or abdominal aortic aneurysm. Heart disease is the leading cause of death for both women and men a year, accounting for about 1 in 4 deaths, and with about 610,000 people dying of heart disease in the United States every.[1,2] The incidence of CVD continues to increase as the five leading modifiable risk factors (hypercholesterolemia, diabetes, hypertension, obesity, and smoking) continue to be major risk factors in today's society.[2] It is estimated that these risk factors are responsible for more than half of cardiovascular mortality. Lifetime risk of overall cardiovascular heart disease has begun to approach 50 percent for persons age 30 years and up with no known cardiovascular disease.[1] In 2016, cardiovascular disease cost America $555 billion. By 2035, the cost is estimated to skyrocket to $1.1 trillion.[3]

According to the CDC, 6.7% of office-based physician visits were for coronary artery disease, ischemic heart disease, or history of myocardial infarction.[2] Five and nine tenths percent of visits to the emergency departments included a diagnosis of coronary artery disease, ischemic heart disease, or myocardial infarction.[2]

Cardiovascular disease is caused by underlying atherosclerosis. The dysfunction of the endothelial layer is thought to be the initial step in atherosclerosis and is thought to be caused by loss of endothelium-derived nitric oxide which can cause a loss of vasodilation of the vessels.

Inflammation is also a crucial step of the buildup of atherosclerosis in which macrophages that have been taken up by oxidized LDL, also known as “foam cells,” release inflammatory factors including growth factors, cytokines, and other inflammatory substances. These inflammatory factors can act on smooth muscle cells and other pro-inflammatory cytokines to induce cell proliferation. Intracellular lipids, extracellular deposits and T lymphocytes accumulate early within the intimal layer of the blood vessel forming a fatty streak. As the fatty streak begins to expand, smooth muscle cells accumulate in the intima. As the smooth muscle cells undergo apoptosis within the fatty streak, this begins to increase the amount of macrophage accumulation and micro-vesicles that can calcify and in turn leading to the formation of atherosclerotic plaques.[1] As aging takes place, the lesions begin to progress to plaques in early adulthood and accumulate to thrombotic occlusion acute cardiovascular events in middle age and later adulthood.

Cardiovascular disease of different origins can present in patients in many different aspects. Generalized symptoms for cardiovascular disease can include chest pain and tightness, shortness of breath, pain and numbness in distal extremities, lightheadedness, irregular heartbeats, dizziness, edema in the hands, ankles, or feet, and headaches. Although cardiovascular disease continues to be prevalent in today’s society, there are many non-pharmaceutical and pharmaceutical methods that could assist with the management of cardiovascular disease. Lifestyle and diet modifications such as exercising regularly, smoking cessation, and decreasing fatty and processed foods intake with an increase in fruits and vegetables are the initial steps in management. Pharmacological agents such as diuretics, ACE inhibitors, angiotensin II receptor blockers, calcium channel blockers, beta blockers, and statin therapy can all assist in managing cardiovascular disease.[1] Currently, there is no definitive cure

for cardiovascular disease however the medications listed as well as lifestyle modifications and controlling underlying conditions have improved symptoms in individuals with cardiovascular disease. Vitamin D may assist in reducing mortality among these patients although many systematic reviews have not been done to prove any correlation**.** Vitamin D is able to decrease prostaglandins, COX-2, and pro-inflammatory cytokines to reduce inflammation decrease calcium cellular influx while increasing matrix Gla protein, which inhibits vascular calcification and smooth muscle proliferation. It is also able to decrease renin in turn regulating blood pressure and volume homeostasis.[8] Reduction in the formation of atherosclerotic plaques and smooth muscle proliferation leading to endothelial damage can lead to a decrease in all forms of cardiovascular disease. More recent studies have been investigating if vitamin D supplementation may be used as an oral, intramuscular (IM), or in the form of oil drops supplementation to decrease morbidity and mortality associated with cardiovascular disease.

OBJECTIVE

The objective of this selective EBM review is to determine whether or not vitamin D is an effective treatment method in reducing mortality in patients who have cardiovascular disease.

METHODS

All three articles were researched using PubMed, Medline, Embase, or Cochrane and were chosen based on their clinical relevance to the research question and their patient-oriented outcomes. The key words used to research these articles included “vitamin D”, “cardiovascular diseases”, and “mortality.” All of the articles included in this review are published in the English language after 2008. Inclusion criteria included human studies that were randomized and controlled, in the English language, and on the subject of humans while studies published more than 10 years ago and articles on other species were excluded. The summary of statistics

included numbers needed to treat (NNT), RBI, CER, EER, ABI, and P-values. Three randomized controlled trial studies on the use of vitamin D supplementation (orally, IM, or oil drops) on adults aged 18 and over with ischemic stroke, fractures, vascular diseases, and heart failure were studied in this analysis (Table 1). All three trials compared a treatment group receiving vitamin D supplementation to the experimental group who received no vitamin D supplementation or usual care for their underlying disease. The outcomes of these articles focused on decrease in mortality in cardiovascular disease patients with vitamin D supplementation. The results were measured by main cause of death from death registrations, Rankin scales, repeated contacts with the participants, contact with family physicians, regular review of medical records, and consultation of the respective registration office.

OUTCOMES MEASURED

The outcomes that were measured were based on a Patient Oriented Evidence that Matters (POEM). This EBM review measured the effect of vitamin D supplementation on reducing mortality in patients with cardiovascular disease.

Avenell et al. used vascular disease mortality from data that was derived only from main cause of death from death registrations that were collected through the national United Kingdom databases of the General Register of Scotland and the National Health Service Medical Research Information Service.[5] Zitterman et al. tested for all-cause mortality as well, which was measured by repeated contacts with the participants, contact with family physicians, regular review of medical records, and consultation of the respective registration office.[6] Gupta et al. used the Modified Rankin scale Scale (mRS) at 3 months and 6 months post stroke.[7] The mRS

Table 1. Demographics and Characteristics of Included Studies

Study	Type	# pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Avenell,[5] (2011)	RCT	5292	70 and above	Fragility fracture within the last 10 years and aged at least 70 years old.	UK residents with cancer likely to metastasize, bedbound before fracture, mental test below 7 (total=16), life expectancy less than 6 months, not taking more than 200 IU of vitamin D treatment, or any vitamin D metabolite in the last 5 years	0	2 tablets daily with meals containing a total of 800 IU (20 micrograms) of vitamin D3
Zittermann,[6] (2017)	RCT	400	18-79	18-79 years of age, HF patients classified as having New York Heart Association Functional Class II or higher who were in a long-term program for heart transplantation	"High urgent" listing for heart transplantation, supplemental vitamin D intake >800 IU/d, and baseline 25-hydroxyvitamin D levels greater than or equal to 75 nmol/L.	0	4000 IU vitamin D3 daily
Gupta[7](2016)	RCT	73	60.4 +/- 11.3 yrs	Within 7 days of onset of first stroke, prestroke modified Rankin score of <2, age >/= 35	Patients already on vitamin D and calcium supplements, renal and hepatic impairment, those who underwent thrombolysis	12	Single IM injection of 600,000 IU cholecalciferol followed by oral cholecalciferol 60,000 IU once a month

measures the degree of dependence or disability in the daily activities of people who have suffered a stroke or other causes of neurological disability. For this systematic review, the Modified Rankin scale score of 6 was used as a validating measure signifying death in these stroke patients.

RESULTS

This review included 3 randomized control trials to assess the effect of vitamin D supplementation on cardiovascular mortality. The inclusion and exclusion criteria for all three trials can be found in Table 1 above.

Avenell et. al selected 5,292 people with a mean age of 77 of whom 2,649 received vitamin D3 supplementation and 2,643 were in the control group. Majority of the candidates in the vitamin D and placebo groups had similar descriptions including being Caucasian female, 32% having a high risk for vitamin D deficiency, 12% being smokers, and equal percentages having proximal femur, leg and pelvic or distal forearm fractures. Randomization was computer generated, assigned into groups and minimized by age.[5]

Participants were randomized into 2 groups with one group receiving two tablets daily with meals containing a total of 800 IU vitamin D3 and one receiving the placebo. The study reported follow-up mortality data that had been notified through the trial and the 3-year follow-up period. During the trial and 3 years of follow-up, it was found that 32.4% (1,717) of the 5,292 died with the main cause of death being vascular disease for 42.3% (726) of the 1,717 participants. Vitamin D supplementation showed to only slightly reduce vascular death as 836 participants (31.6%) of the 2,649 participants allocated vitamin D died, compared with the 881 of the 2,643 (33.3%) participants not allocated vitamin D dying from vascular causes. The reduction in mortality showed a confidence interval between 0.79 and 1.05 for the comparison of

vitamin D administration vs. placebo in vascular death specifically with a p-value of 0.175. This indicated there was not a statistically significant difference shown by a treatment effect with a wide and imprecise confidence interval. The NNT calculated in this study was 100 making the treatment effect very large. Table 2 of this review shows the CER, EER, RBI, ABI, and NNT values. Compliance proved to be an issue in the study in which those returning questionnaires showed the rate of pill takers had decreased to 67% at 12 months and 63% at 24 months.[4] No adverse health effects were noted in this RCT.

Table 2. Rate of Death Due to Vascular Disease in Placebo vs. Treatment Arms

CER	EER	RBI	ABI	NNT
0.142	0.132	-0.0704	0.01	100

Note: CER= Control Event Rate; EER= Experimental Event Rate; RBI= Relative Benefit Increase; ABI= Absolute Benefit Increase; NNT= Numbers Needed to Treat

The double-blind randomized control study conducted by Zittermann et al. included patients 18-79 years old that were classified as having New York Heart Association functional class II or higher. These candidates were either listed as "elective" for heart transplantation or were in a long-term program for heart transplantation. Of the 400 randomized candidates, 199 were allocated to receive 4000 IU vitamin D3 daily in the form of eight drops of an oily vitamin D preparation known as Vigantol oil.[6] The 201 candidates that were randomized to receive placebo received a matching vitamin D- free oil daily (Migliol oil) during a meal. Concealment in both parties was achieved by sequentially numbered drug containers.

Eighty-five candidates of the treatment arm and 84 candidates of the placebo arm discontinued intervention due to center transfer, poor health condition, no pleasure to participate, hypercalcemia, home-based care, and "other reasons."[6] Majority of the patients selected in the study included males who suffered from dilated or ischemic cardiomyopathy with 80% having a pacemaker and 41% having a baseline 25(OH)D level. The hazard ratio for the vitamin D

versus placebo group was 1.09, which signifies a very slight difference in survival between the two groups. The p-value found was 0.726 which proved to be statistically insignificant. Table 3 shows the change in all-cause mortality noted in both the placebo and vitamin D arms.

Table 3. Comparison in All-Cause Mortality in Vitamin D vs. Placebo[6]

	Baseline							Mortality Rate
Vitamin D group	199	194	188	180	174	166	166	19.6%
Placebo	201	194	185	180	174	166	160	17.9%

Gupta et al. conducted a randomized controlled open-label trial at a tertiary hospital that included 53 patients that were equal or over the age of 35 of who presented within 7 days of onset of first ever ischemic stroke and a pre-stroke modified Rankin score of less than 2. Randomization was done by a random number generator on the computer. While the control group received "usual post-stroke care alone," which was not specified in the article, the intervention group received a single intramuscular injection of 600,000 IU cholecalciferol followed by 60,000 IU of oral cholecalciferol once a month with one-gram elemental calcium daily along with usual poststroke care.[7]

Of the 53 randomized candidates, all of the candidates had a baseline vitamin D level less than 75 nmol/L. The intervention arm began with 25 candidates while 4 were lost to follow-up by 6 months. In comparison, the usual care arm began with 28 candidates while 5 were lost to follow-up by 6 months. By 6 months, the intervention group had a total of 4 deaths as opposed to 11 total deaths in the usual post-stroke care alone group. Gupta et al. used an intention to treat basis at the final follow-up with 11 patients (44%) having a "good outcome", classified as a modified Rankin score of 0-2[8], in the intervention arm; while 11 patients (39.3%) had a good outcome in the usual care arm. The outcome analysis showed a decrease in mortality with

vitamin D and calcium showed by Table 3. No adverse health effects were noted in this study that directly correlated with vitamin D administration alone. Low calcium levels that were said to be caused by vitamin D deficiency stimulated an excessive amount of parathyroid hormone releasing resulting in a secondary hyperparathyroidism.[7]

Table 4. Outcome Comparisons in the Vitamin D plus Calcium Group vs. Treatment by Usual Care Alone Group[7]

Outcome	Vit. D and Calcium	Usual care	Difference in % (95% CI)	Unadjusted OR/HR with 95% CI	P- value	Adjusted OR/HR with (95% CI)	P value
Intention to treat	N=25	N=28					
Mortality outcome	N=25	N=28	-	-	-	-	-
Death	4 (16%)	11 (39.3%)	-	0.34 (0.1-1.1)	.06	0.26 (0.08-0.9)	.03

DISCUSSION

The results from Avenell et al.'s study was not able to demonstrate an improvement in vascular mortality with vitamin D supplementation. Although, Avenell et al.'s experimental group proved to be the largest of the RCTs, the population was limited to Caucasian females with a mean age of 77 who had a previous fracture 3 months or longer from enrollment. Although there was no significant reduction in the mortality of the specified population used, Avenell et al. stated that it is not known if these results would apply in younger people, older people without a history of a fragility fracture, or high-risk populations in nursing homes. Other limitations included variation in size and shape of the vitamin D and placebo tablets and lack of concealment as a part of randomization in the trial which could lead to lack of validity in the trial. On the other hand, Zittermann et al. had a strong representation of middle-aged males with New York Heart Association Functional Class II heart failure. However, Zittermann et al. admits

that enrollment did not reach the planned number of study participants and the annual mortality was lower than originally expected therefore showing a low statistical power to assess an actual significant difference between the experimental arm and placebo.[5] Although both studies' results met the requirement for this systematic review, the specificity of each studies' population could be accounted as a limitation in both studies.

Gupta et al. reported a potential benefit in ischemic stroke survivors with vitamin D insufficiency or deficiency with the supplementation of vitamin D and calcium. This is the only RCT that did not separate calcium and vitamin D supplementation and instead combined both which showed a trend towards improvement in disability. However, it is noted in the study that the baseline differences in serum cholesterol because the supplemental arm had higher baseline levels, dietary habits and level of outdoor physical activity, and prevalence of atherosclerosis, which was not evaluated in detail in the study, were not considered and cannot be ruled out when discussing trends towards disability in this article specifically. The randomization and allocation were done by a single investigator and was not blinded which could have led to bias or other study limitations.

The National Institute of Health recommended dietary allowances of vitamin D to be 600 IU in males and females aged 14-70 years old and 800 IU in males and females over the age of 70. Although rare, vitamin D toxicity can to hypercalcemia and other non-specific signs such as weight loss, polyuria, anorexia, and heart arrhythmias.[9]

CONCLUSION

Based on the results of this systematic review, there is no significant improvement in reducing mortality due to cardiovascular disease with vitamin D supplementation. Gupta et al.

showed a potential benefit of vitamin D supplementation along with calcium supplementation in reducing all-cause mortality in stroke victims.

Future studies should be conducted when vitamin D supplementation is given before a major cardiovascular event such as a stroke or heart failure. Vitamin D supplementation in early stages of cardiovascular disease such as hypertension should be studied to assess all cause-mortality with vitamin D supplementation over years rather than short time durations. Future studies are warranted in a more diverse group of candidates and including ultraviolet light as a possible supplement with dietary, intramuscular, or oral vitamin D supplementation. The use of vitamin D early in cardiovascular disease can reduce cardiovascular complications and costs in the long run for these patients.

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