

Mini Review

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A perspective on role of calcium and vitamin D in cardiovascular outcomes and lipid profile

Abstract: Recent concerns on increased incidence of myocardial infarction and stroke on administration of calcium and vitamin D supplements have alarmed the physicians about safety of these drugs. Although both calcium and vitamin D have been shown in the past to have beneficial effect on cardiovascular disease status through lowering of harmful lipids, these findings have been contradicted by some recent meta-analysis and randomized controlled trials that have shown no beneficial or in some cases a deteriorating effect of these supplements on lipid levels. In particular, calcium supplementation has been associated more with increased incidence of cardiovascular morbidity than vitamin D, but the convincing proof is still lacking. Here we have highlighted the results of some significant studies that might impact the prescription of these drugs.

Keywords: calcium; cardiovascular disease; lipid; vitamin D.

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Introduction

The role of calcium and vitamin D in maintaining the bone health is well known. Both calcium and vitamin D supplements are frequently prescribed for osteoporosis and fracture prevention. In addition, calcium is prescribed for hypocalcemic tetany, restricting the phosphate absorption in patients with chronic renal failure and hyperkalemia. Vitamin D supplements are also prescribed for treatment of psoriasis, vitiligo, lupus vulgaris, metabolic rickets,

osteomalacia, autoimmune diseases, and cancer (<http://www.webmd.com/vitamins/supplements/ingredient/mono>). The expanding indications of calcium supplements has led to a review of adverse effects, particularly increased cardiovascular morbidity and mortality. Vitamin D deficiency itself has been linked to increased chances of cancer such as colorectal cancer, ischemic heart disease, and hypertension. The main concern with the use of calcium and vitamin D, which has received attention, is whether these drugs have a beneficial or harmful effect on serum lipids and cardiovascular morbidity and mortality. Hence, this brief review was written to collect and update the recent findings which have shown increased chances of cardiovascular outcomes such as ischemic heart disease, stroke, and hypertension in patients being prescribed these supplements. The approach followed for writing this communication was nonsystematic in a way that it included both observational studies and randomized controlled trials and their meta-analysis of calcium and vitamin D supplements and/or their serum concentrations in relation to their effect on cardiovascular disease outcomes and lipid levels. A search was made in Google search engine as well as PUBMED search engine for calcium and/or vitamin D effect on lipids and cardiovascular disease and the results of only clinically and statistically significant studies were included in this communication.

Effect of calcium on lipid levels and cardiovascular disease

Recently, a double-blind placebo-controlled study using calcium supplementation (800 mg/day) in premenopausal and postmenopausal women with dyslipidemia reported an increase in total cholesterol and carotid intima media thickening significantly in postmenopausal dyslipidemic women only, whereas low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were not affected significantly in either premenopausal or postmenopausal women after 2 years of calcium supplementation [1]. In addition,

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meta-analysis of randomized, placebo-controlled trials, popularly known as Women's Health Initiative Calcium and vitamin D (WHI CaD) study which included 36,282 postmenopausal healthy women taking calcium (1 g/day) and vitamin D (400 IU/day) supplementation for 7 years was done for analysis of various cardiovascular disease end points. Meta-analysis suggested that calcium alone or in combination with vitamin D significantly increased the

Table 1: Results of meta-analysis and randomized controlled trials of association of calcium and/or vitamin D with cardiovascular disease and lipid levels.

Year	Study/research using dietary calcium/supplemental calcium/serum calcium	Type of study/study population	Dose/serum levels of calcium	Outcome cardiovascular end points (MI and stroke) and lipid levels	Significance
2013 [1]	Supplemental calcium	Double-blind placebo-controlled study/ premenopausal and postmenopausal women with dyslipidemia (total 395 subjects)	800 mg/day for 2 years	CIMT/lipid levels	↑CIMT (0.7354±0.10–0.7773±0.12 mm ²), ↑Total cholesterol (5.56±0.65–5.87±0.71 mmol/L)
2011 [2]	Supplemental calcium	Meta-analysis (WHI CaD, randomized placebo-controlled trials)/post-menopausal women	1000 mg calcium	MI/composite of MI and stroke	MI (RR:1.24, 1.07–1.45, p=0.004), Composite of MI and stroke (RR:1.15, 1.03–1.27, p=0.009)
2010 [4]	Supplemental calcium	Randomized controlled trial/healthy men (323 in number)	600 mg/day and 1000 mg/day for 2 years	Lipid levels	No change in HDL, LDL, TG or body weight (p>0.28 for all)
2009 [3]	Supplemental calcium	Double-blind randomized controlled trial/ overweight or obese women (44 in number)	1000 mg/day for 30 days	Lipid levels	↑TG (72±28–87±33 mg/dL), ↑LDL (103±27–116±22 mg/dL), ↑VLDL (14±6–17±7 mg/dL) and ↓HDL (56±11–47±11 mg/dL)
2006 [5]	Dairy calcium	Open label/overweight or obese women	600 mg/day and 1000 mg/day	Lipid levels	↓LDL 116.5±46.5–98.4±36.6 mg/dL, p<0.0001, ↑HDL cholesterol 60.0±15.7–63.8±12.2 mg/dL, p<0.05, No change in TG
2002 [6]	Supplemental calcium	Randomized controlled trial/ normal older women (223 postmenopausal women)	1000 mg/day for 1 year	Lipid levels	↑HDL/LDL ratio with mean between-group differences in change from baseline: 0.05 (95% CI: 0.02–0.08; p=0.001), for HDL cholesterol, 0.09 (95% CI: 0.02–0.17; p=0.01); No change in TG
2013 [7]	Serum 25-OH vit D and supplemental vit D	Meta-analysis of 73 cohort studies and 22 RCT (Total 9 lac participants)	Serum 25-OH vit D and supplemental vit D	Cardiovascular mortality	RR 1.50 (1.21–1.87) for serum 25-OH vit D <10 ng/mL, RR 0.89 (0.80–0.99) for vit D ₃ vs RR 1.04 (0.97–1.11) for vit D ₂
2013 [8]	Supplemental vit D	Meta-analysis of 42 RCT	vit D supplementation <800 IU or >800 IU	All-cause mortality	↓All-cause mortality with RR of 0.94 (95% CI, 0.90–0.98) when supplemented for more than 3 years

CIMT, carotid intima media thickening; WHI CaD, Women's Health Initiative Calcium and vitamin D; MI, myocardial infarction; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; VLDL, very-low-density lipoprotein; RCT, randomized controlled trials; RR, risk ratio.

risk of myocardial infarction [relative risk 1.24 (1.07–1.45), $p=0.004$] and the composite of myocardial infarction and stroke [1.15 (1.03–1.27), $p=0.009$] [2]. In a similar double-blind randomized controlled trial of calcium supplementation (1000 mg/day) for 30 days in overweight or obese women, there was a significant increase in the triglyceride, LDL cholesterol, very low-density lipoprotein (VLDL) cholesterol and decrease in HDL cholesterol in women administered calcium supplement [3]. Together, the results cited suggest that administration of calcium is an independent risk factor for cardiovascular disease which is probably mediated by increase in carotid intima media thickening, total cholesterol, LDL-cholesterol, VLDL-cholesterol, triglycerides, and decrease in HDL-cholesterol irrespective of the dose and duration of therapy administered, underlying pre-existing lipid levels and comorbid conditions (Table 1). On the contrary, several studies in the past had shown a beneficial effect of calcium supplementation on plasma lipids. In one such study, Reid et al. reported that the calcium supplementation (1 g/day for 1 year) in normal older women led to significant increase in HDL/LDL cholesterol ratio with insignificant decline in LDL levels and no change in triglyceride levels [6]. In another study done to evaluate the effect of dairy calcium (low calcium – 600 mg/day and high calcium – 1400 mg/day) on plasma lipids in overweight or obese women, there

was a significant decrease ($p<0.0001$) in LDL cholesterol from 116.5 ± 46.5 to 98.4 ± 36.6 mg/dL for all participants in both the groups, whereas HDL cholesterol was raised from 60.0 ± 15.7 to 63.8 ± 12.2 mg/dL ($p<0.05$) in both the groups following the intervention. Plasma triglycerides did not change significantly in any of the participant [5]. Another randomized controlled trial in healthy men analyzed the effect of calcium supplementation (600 mg/day or 1200 mg/day) on plasma lipids over a period of 2 years. Results of the study showed that there was no significant treatment effect of calcium supplementation in either doses on the ratio of HDL to LDL cholesterol ($p=0.47$), triglycerides, LDL cholesterol, or HDL cholesterol ($p>0.28$ for all) [4]. Above findings were in sharp contrast to some recent studies which have shown a harmful effect of calcium supplementation on plasma lipids (Table 2).

Effect of vitamin D on lipid levels and cardiovascular disease

In a similar manner, the effect of vitamin D alone on lipid levels and cardiovascular disease has been investigated in several randomized controlled trials. In a study done to evaluate the effect of vitamin D on lipid levels in type 2

Table 2: Results of observational studies of association of calcium and/or vitamin D with cardiovascular disease and lipid levels.

Year	Study/research using dietary calcium/supplemental calcium/serum calcium/serum 25-OH vit D/vit D supplement	Type of study/study population	Dose/serum levels of calcium/serum levels of 25-OH vit D	Outcome cardiovascular end points (ischemic heart disease and stroke)/lipid levels	Significance
2014 [9]	Serum 25-OH vit D	Cross-sectional observational study/type 2 DM (108 participants)	Serum levels of 25-OH vit D	Lipid profile	↑TG in vit D insufficient patients 145.91 ± 79 mg/dL as compared to vit D sufficient patients with TG 122.95 ± 55.82 mg/dL
2014 [10]	Serum 25-OH vit D	Observational study/11 independent clinical studies	Serum levels of 25-OH vit D	Cardiovascular disease risk	RR=1.03 (95% CI 1.00–1.06) per 25 nmol/L decrement in serum 25-OH vit D
2013 [11]	Serum 25-OH vit D	Cross-sectional observational study/177 healthy subjects	Serum levels of 25-OH vit D	Lipid profile	Serum 25-OH vit D levels correlated negatively with total cholesterol concentrations ($r=-0.196$; $p=0.01$). Adjusted OR with 25-OH vit D <15 ng/mL for total cholesterol >200 mg/dL was 2.83 (95% CI, 1.06–7.51). Subjects with serum 25-OH vit D <15 ng/mL had higher LDL cholesterol levels (138 ± 39 mg/dL vs 125 ± 28 as compared to subjects with higher serum 25-OH vit D levels, $p=0.04$)

diabetic patients, serum 25-OH vitamin D levels were found to correlate inversely with triglyceride levels only, whereas there was no significant correlation between serum 25-OH vitamin D levels and LDL cholesterol, VLDL cholesterol, and HDL cholesterol [9]. The association between serum 25-OH vitamin D and cardiovascular disease was also studied in high-risk subjects which showed that serum 25-OH vitamin D levels were inversely associated with cardiovascular disease [10]. Another recent systematic review and meta-analysis of observational and randomized controlled trials of serum 25-OH vitamin D concentrations and vitamin D supplementation, respectively, showed that the relative risk of cardiovascular diseases increased with decreasing serum concentrations of 25-OH vitamin D and vitamin D₃ supplementation had more beneficial effect on all-cause mortality than vitamin D₂ supplementation [7]. A very significant meta-analysis of long-term vitamin D supplementation on all-cause mortality showed that all-cause mortality was reduced significantly with a RR of 0.94 (95% CI, 0.90–0.98) when vitamin D was supplemented for more than 3 years, whereas a shorter administration for <3 years had no significant benefit with a RR of 1.04 (95% CI, 0.97–1.12) [8]. Beneficial effect of vitamin D on harmful lipids was also seen in a study by Cutillas-Marco which showed a negative correlation with total cholesterol ($p=0.01$) and LDL-cholesterol ($p=0.04$) [11]. An umbrella review of observational studies and meta-analysis of vitamin D supplementation for its relationship with various clinical outcomes including cardiovascular outcomes and lipid profile revealed that there was a nominal statistical significance of vitamin D supplementation and decreased risk of various cardiovascular outcomes such as ischemic stroke, hypertension, and ischemic heart disease. In addition, total cholesterol concentrations were found to correlate inversely with vitamin D supplementation [12]. Taken together, evidence seems to be more convincing for vitamin D supplementation in reducing harmful lipids and cardiovascular morbidity. A number of trials are also underway that are assessing the role of vitamin D supplementation for prevention of cardiovascular diseases. One such trial, Vitamin D and Omega-3 Trial (VITAL), is an ongoing effort in this regard that is being conducted in USA for primary prevention of cancer and cardiovascular disease using vitamin D₃ supplementation in 20,000 men and women aged more than 50 years [13]. A similar trial, FIND trial, is being conducted in Finland for primary preventive role of vitamin D₃ supplementation in cancer and cardiovascular disease. The underlying mechanisms for beneficial effect of vitamin D have been explained by the presence of vitamin D receptors in various tissues viz. endothelial cell, cardiomyocytes, smooth muscle cell, dendritic cell, T

cell and macrophages. Vitamin D has been shown to cause endothelial dilation and decrease cardiac remodeling by modulation of proliferation, migration and matrix turnover of cardiomyocytes. In addition, vitamin D has been found to possess anti-inflammatory effects by modulating the cytokine expression ($\downarrow T_H1/\uparrow T_H2$) and decreasing the renin-angiotensin system (RAS) activation [10].

Conclusions

There is more convincing evidence for beneficial effect of vitamin D supplementation on lipid levels and cardiovascular mortality as compared to calcium supplementation which seems to enhance the risk of cardiovascular diseases. Nonetheless, its prescription should be done with care when it is co-administered with calcium particularly in high-risk subjects who are prone to cardiovascular diseases. One such trial has found co-supplementation of calcium and vitamin D to be beneficial in reducing the risk of heart failure in postmenopausal women without heart failure risk, whereas there were no such benefits in women with pre-existing heart failure risks [14]. Hopefully, more such trials will be conducted in near future that will give a clearer picture in diverse populations with different comorbid conditions as these two supplements are frequently administered together in clinical setup. Another important thing that should be borne in mind is that there might be some confounding factors such as smoking, diabetes, hypertension, lack of exercise, and dietary habits which themselves are an independent contributor to cardiovascular disease and can have clinical impact during the administration of these supplements.

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