Controversy Regarding the Association of High Calcium Intake and Increased Risk for Cardiovascular Disease

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Calcium intake has been shown to be associated with beneficial effects regarding hypertension, coronary heart disease (CHD), vascular disease, and stroke by several prospective cohort studies. However, recent studies have questioned the beneficial cardiovascular effects of calcium intake and instead have shown that high calcium intake is associated with an increased risk for CHD and stroke. These findings have created controversy and concern among physicians, because calcium is consumed by a large number of older men and women to prevent osteoporosis and bone fractures. Based on the methods of patient self-reporting of calcium intake and cardiovascular events, the conclusions drawn from the studies may not be entirely valid. Therefore, until more confirmatory data are available, physicians should not be dissuaded from prescribing calcium supplements to their patients. The best candidates are patients with low calcium intake, but their calcium supplementation should not exceed the recommended 1200 mg/d to 1500 mg/d. *J Clin Hypertens (Greenwich).* 2014;16:545–550.

Calcium is an abundant mineral in the body that plays a pivotal role in bone physiology and the cardiovascular (CV) system. Calcium is also tightly regulated by the calciotropic hormones parathyroid, calcitonin, and vitamin D.[1] Low calcium intake is associated with low bone calcium, osteoporosis, and bone fractures, especially in postmenopausal women and older men. In order to prevent these complications, the Institute of Medicine (IOM) and the National Institutes of Health (NIH) recommend a daily calcium intake of 1200 mg to 1500 mg for women as well as men older than 65 years.[2,3] In addition to high calcium intake preventing bone loss and fractures, it is also associated with beneficial CV effects, as has been demonstrated by several prospective cohort and randomized studies.[4–14] However, 4 recent studies have created a lot of controversy among physicians, because the findings have demonstrated that high calcium intake could be associated with a higher incidence of CV disease (CVD), myocardial infarction (MI), and possible stroke.[15–18] In this commentary, we will present evidence regarding the beneficial or harmful CV effects of high calcium intake and analyze the validity of these findings.

STUDIES DEMONSTRATING SIGNIFICANT AND NONSIGNIFICANT BENEFICIAL CV EFFECTS OF CALCIUM

Several reports including reviews, prospective cohort studies, and one randomized study have demonstrated either a beneficial or no harmful effect of high calcium intake on atherosclerosis, CVD, MI, and stroke.[4–14] The favorable effects of high calcium intake are mediated through several biologic mechanisms, which are summarized in Table I. Experimental studies in albino rats fed a diet high in fat and calcium content was associated with a decrease in blood lipid concentration and an increase in fecal bile acid excretion.[19] In addition, clinical and experimental studies have shown that calcium intake is associated with beneficial CV and blood pressure (BP)–lowering effects.[20,21] The cholesterol-lowering effect of calcium appears to be mediated through its intestinal binding with fatty acids and by decreasing their absorption,[19] whereas its BP-lowering effect is mediated through suppression of plasma renin activity and an amelioration of the BP effects of salt, especially in salt-sensitive hypertensive patients.[20,21] Other studies have shown that high calcium intake improves BP and diabetes through weight loss and an increase in insulin release and sensitivity.[22–24] Other beneficial CV effects of calcium have been attributed to its platelet antiaggregatory and vasodilatory properties.[25,26] The controversy regarding the studies that demonstrate either beneficial or no harmful CV effects of calcium and those that demonstrate harmful CV effects of high calcium intake will be discussed in subsequent sections of this commentary.

PROSPECTIVE COHORT STUDIES DEMONSTRATING BENEFICIAL OR NO HARMFUL EFFECTS OF CALCIUM ON CVD AND STROKE

The findings from prospective cohort and randomized studies that have demonstrated either a beneficial or no harmful CV effect of high calcium intake are summarized in Table II and will be briefly discussed here.

Van der Vijver and colleagues[6] analyzed the data from a survey of calcium intake on the incidence of CVD from 2605 men and women, Dutch civil servants aged 40 to 65 years, after 28 years of follow-up. The

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TABLE I. Potential Biologic Mechanisms for the Beneficial Cardiovascular Effects of Calcium Intake

Effect	Biologic Mechanism
Decreases cholesterol	Intestinal binding of calcium with fatty acids and bile acids decreases fat absorption[19]
Lowers blood pressure	Down-regulates the renin-angiotensin-aldosterone system. Improves sodium-potassium balance[20,21]
Promotes weight loss	Inhibits fatty acid synthase and activates lipolysis[22]
Improves insulin secretion	Intracellular calcium increases insulin secretion and sensitivity, which stimulates glucose transport[23,24]
Has antithrombotic effects	Inhibits platelet aggregation and prevents intravascular thrombosis[25]
Induces vasorelaxation	Opens calcium-activated potassium channels, increases sensitivity to nitric oxide, and decreases superoxide production[26]

calculated daily calcium intake from dietary recalls ranged from 585 mg to 1245 mg. After multivariate analyses, the adjusted odds ratio (OR) between the lowest vs the highest quintile of calcium intake for CVD and all-cause CV mortality was 1.3 (95% CI, 0.8–1.9) for men and 1.1 (95% CI, 0.6–2.0) for women. They hypothesized that these beneficial CV effects of calcium could have been mediated through its BP-lowering effects. However, a careful analysis of the results found no such association.

Abbott and colleagues[7] analyzed the data from a prospective cohort study of 3150 men aged 40 to 75 years who participated in the Honolulu Heart Program that studied the association of dietary calcium intake and incident stroke. The average calcium intake from dairy foods was 407 mg/d to 3109 mg/d. After a 22-year follow-up, there was an association between the lowest vs the highest quintile of dietary calcium intake and the risk of ischemic stroke (relative risk [RR], 1.8; 95% CI, 1.1–2.9; $P<.001$). Calcium intake from

TABLE II. Prospective Studies Demonstrating Either a Beneficial or No Harmful Effect of Calcium Intake on the Incidence of CVD and Stroke

Author	Study Type	Published, y	Patients, No.	Age, y	Ca^{++} Intake, mg/d	Follow-Up, y	Outcomes
Van der Vijver et al[6]	Survey	1992	2605 men and women	40–65	585–1245	28	Men: OR, 1.3 (95% CI, 0.8–1.9) Women: OR, 1.1 (95% CI, 0.6–2.0) for CVD death for lowest vs highest quintile of calcium intake
Abbott et al[7]	Prospective cohort	1996	3150 men	40–75	407–3109	22	RR, 1.8 (95% CI, 1.1–2.9) for ischemic stroke for lowest vs highest quintile of calcium intake
Bostick et al[8]	Prospective cohort	1999	34,486 women	55–69	543–1110	8	RR, 0.63 (95% CI, 0.40–0.98; $P_{trend}=.09$) for IHD death for highest vs lowest quintile of calcium intake
Iso et al[9]	Prospective cohort	1999	85,764 women	34–59	393–1128	14	RR, 0.69 (95% CI, 0.50–0.95, $P_{trend}=.03$) for ischemic stroke for highest vs lowest quintile of calcium intake
Al-Delaimy et al[10]	Prospective cohort	2003	39,800 men	40–75	497–1190	12	RR, 0.97 (95% CI, 0.81–1.16, $P_{trend}=.64$) for IHD for highest vs lowest quintile of calcium intake
Umesawa et al[11]	Prospective cohort	2008	41,526 men and women	40–59	233–753	13	RR, 0.70 (95% CI, 0.56–0.88; $P_{trend}=.02$) for total stroke for highest vs lowest quintile of calcium intake
Larsson et al[12]	Prospective cohort	2008	26,556 men and women	50–69	876–1916	14	RR, 1.10 (95% CI, 0.98–1.26; $P_{trend}=.09$) for total stroke for highest vs lowest quintile of calcium intake
Kaluza et al[13]	Prospective cohort	2010	23,366 men and women	45–79	1230–1599	9	HR, 0.75 (95% CI, 0.63–0.88; $P_{trend}\leq.001$) for all-cause mortality, and HR, 0.77 (95% CI, 0.58–1.01, $P_{trend}=.64$) for CVD for highest vs lowest quintile of calcium intake
Lewis et al[14]	Randomized	2011	1470 women	75±2.7	0–1200	9.5	RR, 0.92 (95% CI, 0.74–1.15) CVD for calcium intake vs placebo

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazards ratio; IHD, ischemic heart disease; RR, relative risk.

nondairy sources was not associated with a decrease in stroke incidence. Adjustments for age and other risk factors did not influence the results.

Bostick and colleagues[8] analyzed the association of calcium, vitamin D, and milk products on the incidence of mortality from ischemic heart disease (IHD) in a prospective cohort study of 34,486 postmenopausal women aged 55 to 69 years from Iowa. After a follow-up of 8 years, a multivariate analysis including age showed an inverse relationship between the highest vs the lowest quintile of total calcium intake (dairy+supplemental) and the incidence of IHD mortality (RR, 0.63; 95% CI, 0.40–0.98). There was no association between vitamin D intake and IHD.

Iso and colleagues[9] analyzed the effects of high intakes of calcium, potassium, and magnesium on the incidence of ischemic stroke in a prospective cohort study of 85,764 women aged 34 to 59 years from the Nurse's Health Study. The daily calcium intake varied from 393 mg to 1128 mg. After a follow-up of 14 years, the risk-adjusted multivariate analysis of age, smoking, and history of hypertension showed an independent inverse relationship between the highest vs the lowest quintile calcium intake and the incidence of ischemic stroke (RR, 0.69; 95% CI, 0.50–0.95; P_{trend}=.03).

Al-Delaime and colleagues[10] analyzed the data from a prospective cohort study of 39,800 men aged 40 to 75 years from the Health Professionals Follow-up Study that investigated the association of dietary calcium intake and incidence of IHD. The average dietary calcium consumption varied between 497 mg/d and 1190 mg/d. After a 12-year follow-up and adjusting for risk factors for IHD including age, they found no significant difference in the incidence of IHD between the highest and lowest quintile of total calcium intake (RR, 0.97; 95% CI, 0.81–1.16; P_{trend}=.64). For supplemental calcium intake, the RR was 0.87 (95% CI, 0.64–1.19; P_{trend}=.31) for IHD between the highest vs the lowest quintile of calcium intake.

Umesawa and colleagues[11] analyzed the association of calcium intake and the risk for coronary artery disease and stroke from a prospective cohort study of 41,526 Japanese men and women aged 40 to 59 years with no history of coronary artery disease at baseline. Their total calcium intake varied from 233 mg/d to 753 mg/d. After a 13-year follow-up there was an inverse association between total calcium intake and total stroke (HR, 0.70; 95% CI, 0.56–0.88; P_{trend}=.02) for the highest vs lowest quintile of total calcium intake. A similar association was found between dairy calcium intake and total stroke incidence after a multivariate analysis (HR, 0.69; 95% CI, 0.56–0.85; P_{trend}=.007). In contrast, no association was found between total calcium intake and CVD.

Larsson and colleagues[12] examined the relationship of dietary magnesium, calcium, potassium, and sodium and the risk of stroke in a prospective cohort study of 26,556 Finnish male smokers aged 50 to 69 years. The calcium consumption varied from 876 mg/d to 1916 mg/d. After a 14-year follow-up, there was an inverse relationship for ischemic stroke between the highest vs the lowest quintiles of magnesium intake (RR, 0.85; 95% CI, 0.76–0.97; P_{trend}=.004), which was stronger for men younger than 60 years. There was no significant association between calcium intake and any stroke type (RR, 1.10; 95% CI, 0.98–1.26; P_{trend}=.09). Also, no significant relationship was found between potassium and sodium intake and ischemic stroke incidence.

Kaluza and colleagues[13] examined the association of dietary calcium and magnesium intake with all-cause mortality, CVD mortality, and cancer mortality in a prospective cohort study of 23,366 Swedish men aged 45 to 79 years. Total calcium intake varied from 1230 mg/d to 1599 mg/d. After 10-year follow-up, the adjusted risk for dietary calcium intake was associated with a lower rate of all-cause mortality (HR, 0.75; 95% CI, 0.63–0.88; P_{trend}<.001) and for CVD mortality (RR, 0.77; 95% CI, 0.58–1.01; P_{trend}=.064) but not for cancer mortality. A magnesium intake of 387 mg/d to 523 mg/d was not associated with a decrease in all-cause, CVD, or cancer mortality.

Lewis and colleagues[14] performed a randomized, placebo-controlled study of 1460 Australian women aged 75±2.7 years at baseline from the Calcium Intake Fracture Outcome Study (CAIFOS). These patients were equally randomized to supplemental calcium intake 1200 mg/d or placebo and were followed for 5+4.5 years after completion of the randomized study. The objective of the study was to identify any association of supplemental calcium intake with atherosclerotic vascular disease and death in these patients. After the first 5 years of the trial and the 4.5 years of post-trial follow-up, the multivariate-adjusted risks for the combined endpoint of atherosclerotic vascular mortality or first hospitalization were not increased by calcium supplementation (HR, 0.94; 95% CI, 0.69–1.26) and (HR, 0.92; 95% CI, 0.74–1.15) for the first 5 years and the additional 4.5 years of follow-up, respectively. Also, there was no difference in the primary endpoint in the placebo-treated group. Further analysis of the data showed that calcium supplementation may reduce the risk of hospitalization and mortality in women with preexisting CVD.

STUDIES SHOWING AN ASSOCIATION BETWEEN HIGH TOTAL CALCIUM INTAKE AND INCREASED RISK FOR CVD AND STROKE

The CV beneficial effects of calcium intake have been challenged by three recent cohort studies and one randomized study, which showed that high calcium intake was associated with an increased incidence of CVD, MI, and possibly stroke.[15–18] The findings from these studies are summarized in Table III.

The study by Pentti and colleagues[15] was a prospective cohort study of 10,555 Finnish women aged 52 to 62 years from the Kuopio Osteoporosis Risk Factor and Prevention Study (KORFPS). The objectives of the study

were to obtain information on the effects of calcium supplementation on the risk of coronary heart disease (CHD) and disease morbidity and mortality in older women who used calcium supplements vs those who did not and who did not have CHD at baseline. After a 6.6-year follow-up, a multivariate-adjusted risk analysis showed an increased incidence of CHD (HR, 1.26; 95% CI, 1.01–1.57) in women who used calcium supplements in addition to their dietary calcium intake vs those who did not use calcium supplements. The amount of dietary and supplemental calcium intake is not provided in this study.

A study by Bolland and colleagues[16] was a randomized, placebo-controlled trial of 1471 postmenopausal women with a mean age of 74.0 years from New Zealand. These patients were randomized to calcium supplementation of 1000 mg/d (n=732) or placebo (n=739) and were followed for 5 years. During the follow-up period, 31 of 732 women in the calcium supplementation group developed MI vs 14 of 739 in the placebo group (RR, 2.24; 95% CI, 1.20–4.17; *P*=.01). Also, 69 of 732 women in the calcium supplementation group developed the combined end point of MI, chest pain, stroke, or sudden death vs 42 of 739 in the placebo group (RR, 1.66; 95% CI, 1.15–2.40; *P*=.008). The association did not change after adjustments for age and history of hypertension, IHD, stroke, dyslipidemia, diabetes, or compliance with the study drug. It should be stated here that these events were reported by either the patients themselves or their relatives. The verified events were slightly lower but still statistically significant.

A study by Michealsson and colleagues[17] was a prospective cohort observational study of 61,433 Swedish women aged 53.3 to 54.9 years. The objective of this study was to investigate the long-term association of dietary and supplemental calcium intake with CVD and all-cause mortality. After a 19-year follow-up, there was a higher incidence of all-cause mortality between the highest quintile of total calcium intake (>1400 mg/d) vs the lowest quintile of (600–1000 mg/d) (HR, 1.40; 95% CI, 1.17–1.67). Similar effects were demonstrated for CVD mortality (HR, 1.49; 95% CI, 1.09–2.02) and for IHD mortality (HR, 2.14; 95% CI, 1.48–3.09). After multivariable adjustments there was a U-shaped association between both dietary and total calcium intake and deaths from CVD and IHD but not for stroke (HR, 0.73; 95% CI, 1.33–1.65).

A study by Xiao and colleagues[18] was also a prospective cohort study of 388,229 men and women aged 50 to 71 years from the NIH-AARP Diet and Health Study. The objective of this study was to investigate whether dietary and supplemental calcium intake was associated with CVD and stroke. Supplemental calcium was used by 51% of men and 70% of women. After a 12-year follow-up, supplemental calcium intake (>1000 mg/d vs placebo) was associated with a higher risk of CVD mortality (RR, 1.20; 95% CI, 1.05–1.36) in men but not stroke (RR, 1.14; 95% CI, 0.81–1.61). In women, supplemental calcium intake was not associated with CVD deaths (RR, 1.06; 95% CI, 0.96–1.18) or heart disease deaths (RR, 1.05; 95% CI, 0.93–1.80). In addition, supplemental calcium intake was also not associated with a higher risk of

TABLE III. Studies Demonstrating an Association Between High Calcium Intake and Increased Risk of CVD and Stroke

Author	Study Type	Publication, y	Patients, No.	Age, y	Ca^{++} Intake, mg/d	Follow-Up, y	Outcomes
Pentti et al[15]	Prospective cohort	2009	2723 women	47–56	NA	7	HR, 1.24 (95% CI, 1.02–1.52) for CVD for calcium users vs nonusers
Bolland et al[16]	Randomized	2009	732 women	50–59	800–1200	5	RR, 2.12 (95% CI, 1.01–4.47) for MI for highest vs lowest quintile of calcium intake RR, 1.40 (95% CI, 0.83–2.43) for stroke
Michaelsson et al[17]	Prospective cohort	2013	38,984 women	53–54	600–1400	19	HR, 1.40 (95% CI, 1.17–1.67) for all-cause death HR, 1.49 (95% CI, 1.09–2.02) for CVD HR, 2.14 (95% CI, 1.48–3.09) for IHD death for highest vs lowest quintiles of calcium intake
Xiao et al[18]	Prospective cohort	2013	388,229 men and women	50–71	590–904	12	RR, 1.12 (95% CI, 1.14–1.20) for all-cause death for highest vs lowest calcium intake RR, 1.12 (95% CI, 1.04–1.20) for CVD death for supplemental calcium intake >1500 mg/d

Abbreviations: CI, confidence interval; CVD, cardiovascular disease; HR, hazards ratio; IHD, ischemic heart disease; MI, myocardial infarction; NA, not available; RR, relative risk.

stroke for men (RR, 1.14; 95% CI, 0.81–1.61) or women (RR, 1.08; 95% CI, 0.87–1.33).

DISCUSSION

The presented data show that dietary calcium intake with or without supplemental calcium has a protective effect on preventing CVD and stroke and of lowering BP, as has been demonstrated by several prospective cohort studies and reviews.[4–14] However, these beneficial CV effects of calcium have been challenged by recent prospective cohort and randomized studies.[15–18] These recent studies showed that high calcium intake (dietary+supplemental) was associated with an increased risk of CVD and stroke morbidity and mortality in the participants in these studies. Consequently, these results have created major concerns among physicians and patients alike, since more than 54% of older men and more than 64% of older women are taking calcium supplements to prevent osteoporosis and bone fractures.[27–29] However, the problem with these studies is that the information on dietary and supplemental calcium intake was provided by the patients themselves and the accuracy could not be verified. Also, the information concerning the adverse events from the intake of calcium was provided by either the patients themselves or their relatives, and the information could not be verified in the majority of cases. In addition, misinformation and misclassification of CV events such as MI, angina pectoris, stroke, heart failure, and vascular disease is quite possible in such cases, and several investigators have reported a poor concordance between self-reported CV events and adjudicated or record-verified events.[30–32] Besides, the level of accuracy varies according to participant educational characteristics and the methods of questionnaire administration.[32] Supporting these assumptions are the data from a randomized clinical trial reported by Lewis and colleagues,[13] who used hospital admission records to verify the events reported by the study participants. These investigators found no association between supplemental calcium intake and increased risk of CVD morbidity and mortality after 9.5 years of total follow-up.[14] In addition, the observational prospective cohort Framingham Offspring Study of 690 women and 588 men with a mean age of 60 years did not find any association between calcium intake (dietary+supplemental) and coronary artery calcification after 4 years of follow-up.[33] In this study, the coronary artery calcification was measured by a multidetector computed tomographic scanner and was expressed in Agatston scores. The Agatston scores are highly correlated with the severity of coronary artery calcification, which is an established risk factor for coronary artery disease.[34]

CONCLUSIONS

There is currently controversy regarding the beneficial or harmful CV and stroke effects of high calcium intake. The findings of the 4 recent studies associating high calcium intake with an increased risk for CHD and stroke have created great anxiety and concern among physicians and patients alike, since calcium is being taken by a large number of older women and men to prevent osteoporosis and bone fractures. However, the studies reporting an association between high calcium intake and increased CV and stroke risk have used less-than-ideal methods of data collection and verification, which could have led the investigators to the wrong conclusions. These data have been refuted by a recent well-executed randomized placebo-controlled study. Therefore, until more information on this matter is available, physicians should not be dissuaded from prescribing calcium supplements±vitamin D to older men and women, since this treatment is effective in preventing bone calcium loss and bone fractures. However, since low calcium intake is associated with an increased risk for CV and stroke, patients with low calcium intake should be encouraged to increase their calcium intake through dietary or supplemental means to a daily dose of 1200 mg to 1500 mg as recommended by the IOM and NIH until more information is available.

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