Effects of Calcium Supplementation on Cardiovascular Disease in Postmenopausal Women

RAIZEL ROBINSON

INTRODUCTION

In the United States, 53% of the population use dietary supplements. Of the people using supplements, 43% use calcium and 37% use vitamin D. However, 63% of women older than 60 years of age reported using dietary supplements (Park et al., 2009). Calcium supplementation, without co-administered vitamin D, increases the risk of myocardial infarction and cardiovascular-related diseases among postmenopausal women. On the contrary, calcium supplementation with accompanied vitamin D may not produce similar effects.

Postmenopausal women take calcium supplements in an attempt to prevent osteoporosis. This is because postmenopausal women require a larger amount of calcium intake. Throughout a person's life, blood calcium levels continuously decrease due to greater loss of calcium via renal clearance (Tfelt-Hansen and Torring, 2004), reduced intestinal absorption and perhaps other mechanisms. If the amount of calcium lost by the body consistently exceeds the amount absorbed, than a loss of bone results (Hsia et al., 2007). A low calcium intake has been associated with an increased risk of osteoporosis, bone fractures, and falls (Bailey et al., 2010). To compensate, postmenopausal women need up to 20% more calcium per day than their younger counterparts (Prince et al., 2006). If the amount of calcium lost by the body consistently exceeds the amount absorbed, than a loss of bone results (Hsia et al., 2007). Postmenopausal women take calcium supplements in an attempt to prevent osteoporosis. Calcium is a major mineral component of the skeletal system. Bone structure is maintained by the constant remolding of bone as it responds to the normal physiological and pathological skeletal stresses of daily living (Sahota, 2000). A low calcium intake has been associated with an increased risk of osteoporosis, bone fractures, and falls (Bailey et al., 2010).

Since vitamin D plays a role in absorption, these women also require excess vitamin D. Many authoritative doctors and researchers recommend calcium supplements without considering the detrimental side effects that they may cause. Calcium and vitamin D supplements seem ideal. They are pharmacologically active and cost-effective for the treatment of osteoporosis. In addition, they have synergistic effects with antiabsortive agents on bone mass density in relation to fracture prevention (Nieves, 2004). Based on these findings, doctors believed that these supplements can be administered indefinitely without detrimental side effects.

Currently, although researchers have found that calcium and supplements marginally reduce the risk of fractures in elderly women who are deficient in calcium and vitamin D, calcium supplementation increases the risk of myocardial infarctions and heart disease (Bolland et al.,

Raizel Robinson, BS '11 graduated Touro with a major in biology. She will be attending LIU School of Pharmacy in the fall.

2010). Considering the detrimental effects that calcium may have on the cardiovascular system, it is questionable whether calcium supplementation, in an effort to reduce osteoporosis, justified.

Mechanisms for Calcification in the Cardiovascular Vessels

Many mechanisms for calcium absorption have been suggested to explain its effects on the risk of cardiovascular disease and myocardial infarctions. Calcium supplements can acutely elevate serum calcium levels; possibly accelerating calcification in the walls of vascular structures. Vascular calcification lends itself to the occurrence of vascular events such as myocardial infarction and coronary heart disease (Pentti et al., 2009). High calcium uptake has been associated with vascular calcification and mortality in patients with end-stage renal disease (Giachelli, 2004). However, this data may not be representative because of the age of the participants and reduced renal function.

Calcium phosphate deposition, in the form of bioapatite, is the essential characteristic of vascular calcification. This deposition can occur in the blood vessels, myocardium, and cardiac valves. In the coronary arteries, calcification is positively correlated with an increased risk of myocardial infarction and atherosclerotic plaque burden. It is possible that vascular calcification initiates or progresses cardiovascular disease. Vascular calcification, especially calcification in the tunica media of large arteries, leads to increased stiffening, and therefore decreased compliance of the vessels. The resulting loss of important cushioning function of these arteries is a factor that leads to impaired arterial distensibility, increased afterload favoring left ventricular hypertrophy, compromised coronary perfusion, and hypermedial arterial calcification (Giachelli, 2004). Giachelli has suggested four different mechanisms for vascular calcification (refer to figure 1.). First, blood vessel tissues normally express inhibitors of mineralization, such as pyrophosphate and matrix gla protein. The lack of these molecules leads to spontaneous vascular calcification and
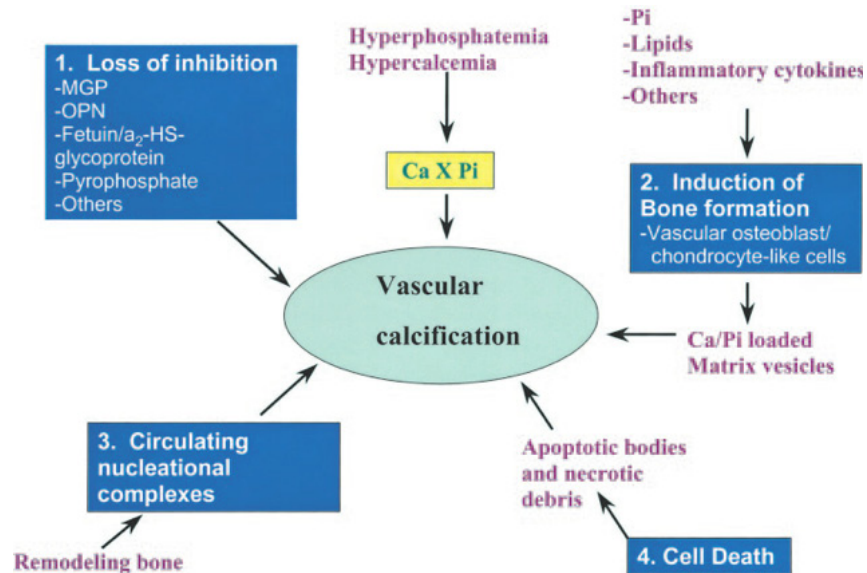
Figure 1. Schematic illustrating four, non–mutually exclusive theories for vascular calcification: (1) loss of inhibition as a result of deficiency of constitutively expressed tissue-derived and circulating mineralization inhibitors leads to default apatite deposition, (2) induction of bone formation resulting from altered differentiation of vascular smooth muscle or stem cells (3), circulating nucleational complexes released from actively remodeling bone, and (4) cell death leading to release of apoptotic bodies and/or necrotic debris that may serve to nucleate apatite at sites of injury.

(Reprinted from Giachelli CM, 2004)

increased mortality. Second, osteogenic mechanisms may play a role in vascular calcification. It has been observed that cells derived from the vascular media undergo a bone and cartilage-like phenotypic change and calcification in vitro under various conditions (Giachelli, 2004, Allison et al., 2006). Third, bone turnover leads to the release of circulation nucleational complexes and crystal growth. Lastly, cell death can provide phospholipid rich membranous debris and apoptotic bodies that may nucleate apatite, especially in patients with atherosclerosis, or other diseases where necrosis and apoptosis occur. Elevated calcium and phosphorous levels promote apatite nucleation and crystal growth to a point that would exacerbate vascular calcification initiated by any of the other four previously mentioned conditions.

Effects of Calcium Supplementation

The link between vascular calcification and osteoporosis in postmenopausal women has been associated with the third condition cited by Giachelli (2004), which is bone turnover. Elevated serum calcium levels accelerate vascular calcification and increase mortality in patients (Bolland et al., 2010). Yang et al. (2004) experimented with smooth muscle cell culture systems. He increased the calcium concentration of the media to hypercalcemic levels. The hypercalcemic mixture led to enhanced mineralization and phenotypic transition of vascular smooth muscle cells. The muscular cells underwent a phenotypic change in which they stopped expressing smooth muscle specific genes and simultaneously expressed genes commonly associated with bone differentiation, including osteocalcin, osteopontin and Runx2 (cited in Giachelli 2004). In the a study of Proudfoot et al. (2004) elevated calcium levels (1.8-to 5.0 mM) stimulated human smooth muscle cell calcification in vitro. Calcification is also present in atherosclerotic lesions, thus raising the possibility that increased calcium consumption may increase the risk of cardiovascular disease (Bostick et al., 1999). When women consume calcium supplements, an increase in circulating calcium levels may occur. This increase may possibly lead to myocardial infarctions and cardiovascular disease through the aforementioned mechanisms.

It has been suggested that calcium supplementation may lead to increased aortic valve and coronary artery calcification (Messika-Zeitoun et al., 2006). Aortic valve and coronary artery calcification are associated with cardiovascular risk factors. However, Bhakta et al. (2009) did not find evidence that calcium supplementation would increase calcification in their independent assessments of aortic valve calcification and coronary artery calcification with calcium supplementation among patients older than sixty years old. Their study attempted to confirm whether calcium supplementation increased the rate of aortic valve calcification and coronary artery calcification. In their study of 257 patients, 144 were women. Twenty-five participants, all of them women, reported using calcium supplements. Bhakta et al. (2009) did not observe a statistical increase in aortic valve calcification or coronary artery calcification in the subgroup of women using calcium supplementation. Additionally, there were no significant differences between the two groups regarding baseline serum calcium, renal function, diabetes, hypertension, and cholesterol or body mass index. The presence of oral calcium supplementations was not associated with a statistically accelerated aortic valve calcification or coronary artery calcification progression. However, the results of this study are limited. First, since this study was not a clinical trial, beneficial or harmful effects of therapeutic intervention cannot be ruled out. Second, due to the small sampling size of 25 women using calcium, it is impossible to generalize the study results to the larger population. Yet, one advantage in this study is the use of Electron Beam Computed Tomography (EBCT), which yields more exact results than an echocardiogram.

In contrast, calcium has a lowering effect on the risk of cardiovascular disease and myocardial infarction. Firstly, calcium absorption has a beneficial effect on the high-density lipoprotein cholesterol to low-density lipoprotein ratio in the body (Moyad 2003). The use of calcium supplements have been shown to increase that ratio of by almost 20% in healthy postmenopausal women. Cholesterol changes of this magnitude may be associated with 20-30% reductions in vascular event rates, such as myocardial infarction (Bolland et al., 2007). This increase of high lipoprotein cholesterol results from calcium binding to fatty acids and bile acids in the gut, and leading to a malabsorption of fat, as shown from studies of humans and animals. Calcium, if consumed in quantities greater than the amount needed to maintain homeostasis, binds bile acids in the gut and leads to their excretion. Calcium supplementation is therefore associated with an increased excretion of fecal bile acids. Bile acids-binding resins, such as cholestyramine, lower blood levels of cholesterol, and is found to reduce the risk of ischemic heart disease (Bostick et al., 1999). Supplemental calcium was found to lower serum cholesterol in rats, rabbits, and goats as well, but not young pigs. It may be suggested that that calcium supplementation would have similar effects on humans.

Another positive reason to supplement with calcium, despite the consequences is that people living in calcium rich water areas have lower cardiovascular disease mortality than people utilizing soft water. Additionally, evidence suggests that calcium supplementation causes reduction in blood pressure, although these reductions are small and transient. This may suggest that calcium, through other mechanisms, generates a positive effect on the human cardiovascular system (Bolland et al., 2007).

Effect of Calcium Supplementation on the Risk of Cardiovascular Disease

Several large clinical studies were conducted to verify the effects of calcium supplements on the cardiovascular system. The Women's Health Initiative did the first and largest clinical experiment (LaCroix et al., 2009). They conducted a randomized control study of 36,282 postmenopausal women. Eligible postmenopausal women, ages 51-82, were randomly assigned to calcium and vitamin D supplementation (calcium carbonate, 500 mg, with vitamin D3 200 IU, twice daily, for a total of 1,000 mg calcium and 400 IU vitamin D3 per day) or to a placebo (Wactawski-Wende et al., 2006). Concurrent calcium and vitamin D supplementation were permitted. The Women's Health Initiative concluded that amongst women younger than 70 years, calcium and vitamin D supplementation appears to reduce risks of cardiovascular disease. However, the detection of the benefits of calcium with vitamin D in this experiment is distorted. Sixty four percent of the women in the placebo group had an intake of least 800 mg calcium per day and 42% had a daily vitamin D intake of at least 400 IU from concurrent diet and supplementation allowed outside the study. The low dose of 400 IU vitamin D per day may not be large enough to affect a change. Trials that have previously demonstrated benefits of calcium with vitamin D supplementation have administered at least 700 IU per day to the patients (Hsia et al., 2007). Furthermore, more than half of the participants in both groups were receiving hormone-replacement therapy (Finkelstein, 2006).

Adherence to the study drug was not complete, as only 60% of the study participants took at least 80% of their study medication for the duration of an average of six years. Death caused by myocardial infarction or coronary heart disease was confirmed in 499 women assigned to active calcium/vitamin D and 475 assigned to a placebo (refer to table 1. on page 15). According to this study, the risk of coronary heart disease, because of the use of active calcium/calcium and vita-

min D, is inversely related to bone mass index (BMI) (LaCroix et al,. 2009). Women with higher BMI are at lower risk for coronary heart disease with active calcium/vitamin D supplementation, whereas those with lower BMI were at higher risk. This aspect of the Women's Health Initiative observation is in line with that of The Kuopio Osteoporosis Risk Factor and Prevention Study (2009), who also found that women with a higher BMI are at lower risk for cardiovascular disease.

However, after evaluating the risk of coronary cerebrovascular events in the Women's Health Initiative randomized trial of calcium plus vitamin D supplementation, Hsia et al. (2007), did not find significant correlation between the risk of cardiovascular heart disease and calcium supplementation. Temporal trends do not indicate a significant increase in the risk of coronary heart disease over seven year's time with calcium supplementation (Hsia et al., 2007).

There are several explanations to clarify the basis for the lack of difference observed between the calcium-supplemented group and the placebo group in Women's Health Initiative study on the risk of coronary heart disease. First, the use of personal supplements, as well as the poor adherence to the study medication may have blurred the researchers from identifying the effect of the study treatment. Second, the Women's Health Initiative protocol led to only a small increase in median plasma 25-hydroxyviamin D levels from 42.3 nmol/liter to 54.1nmol/liter. This is because the dose of vitamin D was inadequate to affect substantial change. In order to prove whether vitamin D supplements affect cardiovascular disease, the women would require supplementation of at least 1,000 IU vitamin D, thereby achieving the recommended level of 75 nmol/liter. By extrapolating this data, it can be inferred that Vitamin D supplementation at moderate to high doses may have beneficial effects in reducing the risk for coronary heart disease (Hsia et al., 2007). In contrast, calcium supplementation seems to have no apparent affect on the risk of cardiovascular disease. A third explanation as to why the data of the Women's Health Initiative is not valid is that concurrent postmenopausal hormone therapy interfered with treatment effects. Most of all, cardiovascular heart disease was not the primary design of the study; the primary goal of the Women's Health Initiative trial was to determine the calcium and vitamin D component in causing hip fractures (McGowan and Pottern, 2000).

	Calcium/Vitamin D (N=18, 176), n (Annualized %)	Placebo (N=18,106) n (Annualized %)	Hazard Ratio (95% CI)	P=
Myocardial infarction or CHD death	499(0.39)	475(0.37)	1.04(0.92-1.18)	0.50
Myocardial infarction	411(0.32)	390(0.31)	1.05((0.91-1.2)	0.52
CHD Death	130 (0.10)	128(0.10)	1.01 (0.79-1.29)	0.92

Table 1. Cardiovascular Events by Treatment Group Assignment (cardiovascular event includes coronary heart disease (CHD), and myocardial infarction.)

(Taken from Hsia, et al., 2007)

A second study, the Iowa Women's Health Study, was a cohort study of cancer incidence in a sample of Iowa women. In 1986, 99,826 women aged 55-69 were invited to participate in an observational trial. A secondary study was conducted to determine the result of calcium supplementation. These women were mailed a questionnaire about sociodemographics, body measurements,

physical activity level, smoking and alcohol consumption, gynecologic history, dietary intake and supplement use. A 127-Food-Item Harvard Food Frequency questionnaire was utilized to assess these women's usual food and nutrient intake. Forty-two percent of the women completed the baseline questionnaire. The average age of the participants at baseline was 60.6 years, and 78.6 at follow up. The Iowa Women's Health Study confirms that many more women use calcium supplementation alone than calcium and vitamin D simultaneously (Refer to Table 2).

	Baseline (1984)		Follow-up (2004)	
	% of women using supplements	Number of women using supplements	% of women using supplements	Number of women using supplements
Calcium	46.2	8,474	60.4	11,078
Vitamin D	10.9	1,995	11.9	2.185

Table 2. This table shows the increase in the use of calcium/vitamin D supplements over the twenty years and that many more women use calcium, than Vitamin D.

One disadvantage of this study is that the questions on the follow-up questionnaire varied from the initial assessment. For example, on the baseline questionnaire, vitamin D intake was inquired as an individual question. In contrast, the follow-up questioned the use of vitamin D supplements in a combined question of miscellaneous supplements. Although there were questions about use ofvitamin supplements , the questionnaire did not ask about over-the-counter-medications or herbal use. Certain non-food products, for example, Tums, contain nutrients that were not taken into account.

The evidence of Park et al. (2009) demonstrates that women within the highest quartile of calcium intake can reduce their risk of myocardial infarction by approximately 35%. They found that calcium intake would reduce the risk, regardless of whether it is of dietary or supplementary source or if taken together with vitamin D (reviewed in Bostick et al., 1999).

In contrast, the researchers of the Kupio Osteoporosis Risk Factor and Prevention Study observed that calcium or calcium with vitamin D supplementation increases the risk of coronary heart disease. Within a cohort of 10,555 women ages 52-62, over 25% reported use of calcium or calcium plus vitamin D supplementation. Eight thousand, four hundred and twenty seven (8,427) women, without a preexisting condition of coronary heart disease, were categorized as postmenopausal (Pentti et al., 2009). The criteria for coronary heart disease included: obvious symptoms of angina pectoris, myocardial infarction, coronary artery bypass graft surgery, percutaneous balloon angioplasty, chest pain, and significant coronary artery stenosis on a coronary angiography. During the course of seven follow-up years, 513 cases of coronary heart disease were reported in the cohort of 10,555 women. Of the 513 cases, 424 were from the postmenopausal subgroup (n=8,424). Three hundred and two cases of coronary heart disease occurred in postmenopausal women not using calcium or vitamin D supplements; only 122 women who were using supplements developed a condition. Many more nonusers of calcium supplements were diagnosed with coronary heart disease than users of calcium or calcium and vitamin D. Interestingly, calcium-supplement users in this study who had a lower BMI, with a mean of 26.3 kg/m²; were non-smokers or former smokers than calcium supplement non-users; and had fewer childbirths than nonusers had. These differences provide an alternate explanation as to why more nonusers of calcium supplements developed coronary heart disease, rather than concluding that it was specifically calcium/calcium plus vita-

min D that triggered these results. After considering all the variables that can affect the risk of heart disease, the relative risk of developing coronary heart disease was 1.0 vs. 1.26, nonusers of supplements to users of supplements respectively. This statistical evidence demonstrates that the use of calcium or calcium with vitamin D increased the risk of coronary heart disease in the subgroup of postmenopausal women. It should be noted, however, that for women slightly after menopause, calcium supplements did have a reducing affect on the risk of coronary heart disease. However, as the years past menopause increased, so did the risk of a heart condition. The risk of cardiovascular heart disease increased in women ages 60-62 by 61% with the use of calcium supplements (Pentti et al., 2009). In addition to other drawbacks, this study could not determine coronary heart disease morbidity, to the varied doses of calcium supplementation as the participants used products that contained a wide range of doses of calcium. Again, this makes it impossible to verify whether the increased coronary heart disease risk was solely related to calcium, or calcium and vitamin D (Pentti et al., 2009).

Bolland et al. (2007) conducted a five-year randomized placebo-controlled study in New Zealand to determine the effect of calcium supplementation on myocardial infarction, stroke, and sudden death in healthy postmenopausal women. One thousand, four hundred and seventy one (1,471) postmenopausal women (mean age 74) participated. Of those women 732 received calcium supplementation and 739 received placebos. Myocardial infarction occurred more often in the calcium group than in the placebo group (45 events in 31 women vs. 19 events in 14 women). Study participants were aged 55 or more, had been postmenopausal for a minimum of five years, and had a life expectance of at least five more years. This study excluded women who were receiving treatment for osteoporosis, those with any major disease and women with serum 25-hydroxyvitamin D levels less than 25 nmol/l. Participants received 1,000 mg of elemental calcium daily as citrate or an identical placebo. Ninety-percent of the women had a follow-up every six months for five years. Cardiovascular events were self reported or reported by family members and then verified.

3a. Number of women (number of events) self reported by patients or family members.

Vascular Event	Calcium Group	Placebo Group
Myocardial Infarction	31(45)	14(19)

3b. Number of women (number of events) self reported or reported by family members and verified.

Vascular Event	Calcium Group	Placebo Group
Myocardial Infarction	21(24)	10(10)

3c. Number of women (number of events) self reported, reported by family members and verified or not reported but confirmed by the national database of hospitals admissions in New Zealand.

Vascular Event	Calcium Group	Placebo Group
Myocardial Infarction	31(36)	21(22)

Table 3. This table depicts the difference between the number of women who experienced myocardial infarctions and the number of total events between the calcium-supplemented group and the placebo group (taken from Bolland et al., 2007).

Initially, there seems to be a statistically significant increased number of myocardial infarctions in the calcium group compared to the number of infarctions in the placebo group. However, after adjusting the data to include cardiovascular events not reported by participants or family members, the increase was not substantial (refer to Table 3c.). When the data was evaluated as event rates, the rate ratios for myocardial infarction were minimally significant. A notable difference was detected when the data for myocardial infarction was plotted over time. The numbers of recorded cardiovascular events between the two groups began to diverge after about twenty-four months, and thereafter continued to separate, although statistical significance was not attained.

In Bolland et al.'s 2007 study, the postmenopausal women had serum 25-hydroxyvitamin D levels greater than 25 nmol/l. Participants received either 400 mg of elemental calcium as a citrate, or a placebo. Results of this experiment show that although cardiovascular events, such as angina and chest pain, did not differentiate greatly between groups, myocardial infarction and transient ischemic attacks did have a significant statistical increase (refer to Table 3.c). There were 36 events of myocardial infarction in the calcium group, in contrast to 22 events of myocardial infarction from women non-using calcium supplements.

Three years later, in 2010, Bolland et al. conducted a meta-analysis to reassess whether calcium supplements increase the risk of cardiovascular events in all patients; not specifically women. After analyzing approximately 12,000 participants from 11 trials, seven of which were comprised solely of females, the researchers concluded once again that calcium supplements, without co-administered vitamin D, increases the chances of cardiovascular events. Their research excluded studies that incorporated vitamin D as a variable between the control group and calcium- supplemented group. Bolland et al. (2010) detected a 31% increase in the risk of incident myocardial infarction in the calcium-supplemented group. Calcium treatment was associated with an increased risk of myocardial infarction in people with dietary calcium intake above the median of 805 mg/day, but no increase was associated with participants with dietary intakes lower than the median. Additionally, recurrent cardiovascular events were more common in the calcium-supplemented group; 19 versus 13 cases of calcium supplemented women to non-supplemented women respectively had more than one cardiovascular event.

However, the trials considered in the study of Bolland et al. (2010) excluded trials in which calcium and vitamin D were administered together against a placebo comparator, trials were only eligible if vitamin D was given to both intervention and control groups, or to neither. Furthermore, any trial in which calcium was administered in the form of dietary modification or a complex nutritional supplement was excluded from the study (Bolland et al., 2007). Since vitamin D supplementation has been associated with decreased mortality, the research of Bolland et al. (2007) does not necessarily reflect the risk of cardiovascular disease among postmenopausal women taking calcium supplementation alongside vitamin D.

The experimental data of Bolland et al. (2010) shows that if 69 people are administered calcium, without co-administered vitamin D, one myocardial infarction will result. The risk of myocardial infarction tended to be greater in those with dietary calcium intake above the median, but independent of age, sex, and type of supplement. The finding of this study is consistent with the conclusion of most of the trials analyzed by Bolland et al. (2010).

Bolland et al.'s (2007 and 2010) study results and conclusions differ from those of the Women's Health Initiative. Despite the great improvements observed in the ratio of high-density lipoprotein cholesterol to low-density lipoprotein cholesterol, Bolland et al.'s studies (2007 and 2010) do not show any evidence that calcium supplementation may decrease the incidences of

vascular events. On the contrary, an increased risk for myocardial infarction is most noticeable in those with high compliance with the study drug. Although this study does not completely prove that calcium supplements can be detrimental to the cardiovascular system, it does suggest that administering calcium supplements is not a matter to be taken lightly.

There are several ways to explain the differing results of Bolland et al. and the Women's Health Initiative. Of the 1,471 participants in the study of Bolland et al. (2007), 105 women were older than 80 years of age at baseline. Many other factors may have caused a myocardial infarction in an elderly population other than calcium supplementation. Women participating in the Women's Health Initiative study were younger, with a mean age of 62, were heavier and had higher calcium intakes on average. More importantly, the women in the Women's Health Initiative took vitamin D with calcium, and a majority of the women were undergoing hormone replacement therapy. The women in Bolland et al.'s (2007) study did not use vitamin D supplements or oestrogen. Additionally, Bolland et al. (2007) conducted a randomized control study by dispensing large dose of calcium citrate, a highly bioavailable calcium supplement that has already proven affects on bone turnover and bone density. In contrast, the Women's Health Initiative that used a low bioavailable drug, calcium carbonate, had a lower compliance with the study drug, and their test results had to compete with the effects of the use of oestrogen and non-trial supplements (Hsia et al., 2007).

Vitamin D and its Effect on Cardiovascular Disease

Oestrogen levels of postmenopausal women are constantly decreasing. Consequently, these women are predisposed to osteoporosis. Vitamin D enhances intestinal absorption of calcium and influences bone metabolism. Because Vitamin D supplementation is helpful in increasing bone mineral density, it is beneficial to ingest vitamin D along with calcium. Therefore, postmenopausal women are a primary concern for vitamin D deficiency (Gaugris et al., 2005). The question now is whether co-administered vitamin D with calcium supplementation affects the risk of myocardial infarction or heart disease. Various researchers have studied this subject and come to different conclusions.

Stages of vitamin D status	25(OH)D concentrations (nmol/l)	Biochemical/clinical symptoms
Deficiency	0-25	Severe hyperparathyroidism
Insufficiency	>25-50	Elevated PTH levels, low intestinal calcium absorption rates, reduced bone mineral density, subclinical sympathy
Hypovitaminosis D	>50-70 to 100	Low body stores of Vitamin D, slightly elevated PTH
Adequacy	70-100 to 250	No disturbance of vitamin D-dependent functions
Toxicity	>250	Intestinal calcium hyperabsorption, hypercalcemia

Table 4. This table demonstrates that a deficiency of vitamin D leads to elevated parathyroid hormone (PTH) levels and low intestinal calcium absorption
(Taken from Zittermann. 2006)

Parathyroid hormone maintains the short-term homeostasis of extracellular ionized plasma calcium (ECF-Ca 2+) by increasing calcium re-absorption and mobilizing calcium from the labile bone pool. The major control of ECF-Ca 2+ is through the renal production of 25(OH)2D. The homeostasis of calcium ions is complex due to the influence of the gastrointestinal tract, the bones

and the kidneys. Once vitamin D is absorbed from one's diet or produced by the skin from the presence of sun exposure, it is metabolized in the liver to 25-hydroxyvitamin D. The kidney then serves as the endocrine gland to produce the biologically active form of vitamin D. This active form of vitamin D, 1-α,25-dihydroxyvitamin D3, is synthesized in the proximal tubule by the renal cytochrome P450 enzyme 25- hydroxyvitamin D3-1-α-hydroxylase. Additionally, the kidney regulates the concentration of vitamin D through determining the final excretion of calcium ions in the urine.

Homeostatic levels of calcium ions are necessary in order to insure normal bone mineralization (Hoenderop and Bindels, 2005). According to Hoenderop and Bindels (2005), The vitamin D endocrine system is crucial for the proper development and maintenance of this Ca2+ homeostatic system. The homeostasis of extracellular ionized plasma calcium (ECF-Ca 2+) is tightly regulated by a number of hormones, including Vitamin D. Vitamin D is transported to the liver, binding to a specific α-globulin and to a small extent, albumin and lipoproteins. The vitamin is then hydroxylated to calcidiol, 25-hydorxylated vitamin D- 25(OH)D. Afterwards, the vitamin D passes to the kidney where it is further hydroxylated to 1,25-dihydorxylated vitamin D- 1,25(OH)2D. This active metabolite increases ECFCa2+ by increasing calcium and phosphate absorption from the gut and mobilizing calcium from the bone (Sahota 2000).

Because 25(OH) D is the substrate for the renal enzyme that produces 1,25(OH)2D3, it may have a direct and indirect effect on calcium absorption. A deficiency of vitamin D will reduce the intestinal absorption of calcium (Diaz-Lopez and Cannata-Andia, 2006). Inadequate vitamin D levels contribute to high levels of parathyroid hormone which lead to excessive bone remodeling and ultimately to bone weakening (Wang et al., 2010). Moreover, excess parathyroid hormone levels increase blood pressure and cardiac contractility and leads to cardiomyocyte hypertrophy and interstitial fibrosis of the heart. Thus, excess parathyroid hormone contributes to cardiovascular disease. According to Jean et al. (2008), 25 (OH) D deficiencies may lead to mineralization and bone formation defects. Vitamin D inhibits thrombosis and arterial calcification. It is therefore essential for calcium homeostasis and cardiovascular health.

It has been shown that women who use vitamin D supplements have a lower mortality from cardiovascular disease than those that do not. For example, in a large cohort of 51,037 U.S. patients receiving hemodialysis, those who received activated injectable vitamin D had lower cardiovascular disease mortality (7.6 per hundred-person years) than those who did not receive the therapy (14.6 per hundred person-years) (Wang et al., 2010). The investigation of Bostick, et al. (1999) on the Iowa Women's Health Study showed similar results. However, although Bostick, et al.'s (1999) study assessed nutrient intake by using questionnaires, and assessed the risk of cardiovascular disease by using predetermined endpoints, their study did not evaluate participants' sun exposure and duration of supplement use. Additionally, an Australian study of elderly women that compared the risk of ischemic heart disease between women assigned vitamin D placebo plus calcium supplementation to those assigned to both vitamin D and calcium supplementation found similar results (Wang et al. 2010).

One way to explain the lowered risk of cardiovascular disease among women using vitamin D supplements in addition to calcium is that 1,25-vitamin D directly inhibits vascular calcification (Zittermann, 2006). 1,25-vitamin D levels are inversely correlated with the extent of vascular calcification; the higher the intake of vitamin D, the less vascular calcification there will be (Watson et al, 1997). Without sufficient vitamin D, women may not be able to absorb ample amounts of calcium. Heaney et al. (2003) observed in their study of 34 postmenopausal women that the mean

20

calcium absorption under vitamin D repletion was 35.3% (+/-11.8) of the load and without supplemental vitamin D, 22.5% (+/-12.0) of the load. It is clear from their study that without sufficient vitamin D, women will absorb a minimal amount of calcium.

Inadequate vitamin D intake seems to be associated with an increased risk for cardiovascular diseases. Should the hypothesis that vitamin D deficency contributes to cardiovascular disease be true, perhaps cardiovascular mortality would be higher in countries of higher geographic latitude and vice versa.

CONCLUSION

Many researchers, such as those who conducted the Women's Health Initiative and the Iowa Women's Health study, have concluded that calcium supplementation reduces the risk of coronary heart disease, myocardial infarction and other cardiovascular related conditions. Others did not observe a statistically important difference between the placebo and supplemented groups. Finally, other researchers observed detrimental effects of calcium supplements on myocardial infarction rates, such as the study of Bolland et al. (2007 and 2010). However, even in the case study of Bolland et al. (2010), the increased risk for myocardial infarction, in the calcium-supplemented group was not statistically significant, once the values of myocardial infarction events were verified from the national database. Additionally, this study did not consider the effect of vitamin D as a variable.

It may be suggested that calcium supplementation with co-administered vitamin D can reduce the risk of cardiovascular disease. On the contrary, calcium supplementation, without co-administered vitamin D appears to have deleterious effects on cardiovascular disease. Further research is required to understand better the mechanisms of calcification and the role of vitamin D in calcium absorption, as it relates to lowering the risk of cardiovascular disease.

In conclusion, when women are treated with calcium, more instances of myocardial infarction will be caused than the number of symptomatic fractures that will be prevented (Bolland et al., 2007). This statistical data brings to the forefront the idea that calcium supplementation in effort to prevent osteoporosis, may not be an appropriate choice.

REFERENCES

Allison MA, Cheung P, Criqui MH, Langer R D, Wright CM. 2006. Mitral and aortic annular calcification are highly associated with systemic calcified atherosclerosis. Circulation 113:861-866.

Bailey RL, Dodd KW, Goldman JA, Gahche JJ, Dwyer J T, Moshfegh AJ, Picciano M F. 2010. Estimation of total usual calcium and vitamin D intakes in the United States. J Nutrit 140:817-821.

Bhakta M, Bruce C, Messika-Zeitoun D, Bielak L, Sheedy P F, Peyser P, Sarano M. 2009. Oral calcium supplements do not affect progression of aortic valve calcification or coronary artery calcification. JABFM 22:610-616.

Bolland MJ, Barber PA, Doughty RN, Mason B, Horne A, Ames R, Gamble GD, Grey A, Reid IR. 2007. Vascular events in healthy older women receiving calcium supplementation: Randomized controlled trial. BMJ 1-8. (Online first).

Bolland MJ, Avenell A, Baron JA, Grey A, MacLennan GS, Gamble GD, Reid IR. 2010. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: Meta-analysis. BMJ 1-9. (Online first).

Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR. 1999. Relation of calcium, vitamin D, and dairy food intake to ischemic heart disease mortality among postmenopausal women. Am J Epid 149:151-161.

Diaz-Lopez B, Cannata-Andia JB. 2006. Supplementation of vitamin D and calcium: Advantages and risks. Nephrol Dial Tranplantation 21:2375-2377.

Finkelstein JS. 2006. Calcium plus vitamin D for postmenopausal women- bon appétit? The New Eng J Med 354:750-752.

Gaugris S, Heaney RP, Boonen S, Kurth H, Bentkover JD, Sen SS. 2005. Vitamin D inadequacy among postmenopausal women: A systematic review. QJM: An International Journal of Medicine 98:667-676.

Giachelli CM. 2004. Vascular calcification mechanisms. J Amer Soc Nephrol 15:2959-2964.

Heaney RP, Dowell MS, Hale CA, Bendich A. 2003. Calcium Absorption Varies within the reference range for serum 25-H droxyvitamin D. J Amer College of Nutrit 22:142-146.

Hoenderop JGJ, Bindels RJM. 2005. Is vitamin D indispensable for Ca2+ homeostasis: lessons from knockout mouse models? Nephrol Dial Transplant 20:864-867.

Hsia J, Heiss G, Ren H, Allison M, Dolan NC, Greenland P, Heckbert SR, Johnson KC, Manson JE, Trevisan M, and Women's Health Initiative Instigators. 2007. Calcium/vitamin D supplementation and cardiovascular events. Circulation 115:846-854.

Jean G, Terrat, J-C, Vanel T, Hurot J-M., Lorriaux C, Mayor B, Chazot C. 2008. Daily oral 25-hydroxycholecalciferol supplementation for vitamin D deficiency in haemodialysis patients: Effects of mineral metabolism and bone markers. Nephrol Dial Transplantation 23:3670-3676.

LaCroix AZ, Kotchen J, Anderson G, Brzyski R, Cauley JA, Cummings SR, Gass M, Johnson KC, Ko M, Larson J, Manson JA, Stefanick ML, Wactawski-Wende J. 2009. Calcium plus vitamin D supplementation and mortality in postmenopausal women: The Women's Health Initiative Calcium-Vitamin D Randomized Controlled Trial. J Geront A Biol Sci Med Sci 64A:559-567.

McGowan JA, Pottern L. 2000. Commentary on the Women's Health Initiative. Maturitas 34:109-112.

Messika-Zeitoun D, Bielak LF, Peyser PA, Sheedy PF, Turner ST, Nkomo VT, Breen JF, Maalouf J, Scott C, Tajik AJ, Enriquez-Sarano M. 2007. Aortic valve calcification: Determinants and progression in the population. Arteriosclerosis, Thrombosis, and Vascular Biology 27: 642-648.

Moyad MA. 2003. The potential benefits of dietary and/or supplemental calcium and vitamin D. Urologic Oncology: Seminars and Original Investigations 21:384-391.

Nieves JW. 2004. Calcium and vitamin D: Current developments in the prevention of osteoporosis and osteomalacia. Curren Orthopedic Practice 15:383-388.

Park K, Harnack L, David JR, Jr. 2009. Trends in Dietary Supplement Use in a Cohort of Postmenopausal Women from Iowa. Am J Epidemiol 169:887–892.

Pentti K, Tuppurainen MT, Honkanen R, Sandini L, Kroger H, Alhava E, Saarikoski S. 2009. Use of calcium supplements and the risk of coronary heart disease in 52-62-year-old women: The Kuopio Osteoporosis Risk Factor and Prevention Study. Maturitas 63:73-78.

Prince RL, Devine A, Dhaliwal, SS, Dick IM. 2006. Effects of calcium supplementation on clinical fracture and bone structure: Results of a 5- year, double-blind, placebo-controlled trial in elderly women. Archives of Internal Medicine 166: 869 875.

Proudfoot D, Skepper JN, McNair R, Johannides A, Weissberg PL Shanahan CM. 2004. Mineral ion-induced release of mineralization-competent matrix vesicles from human vascular muscle cells. Cardiovasc Path 13[3 Suppl]: S186.

Sahota O. 2000.Osteoporosis and the role of vitamin D and calcium-vitamin D deficiency, vitamin D insufficiency and vitamin D sufficiency. Age and Ageing 29:301-304.

Tandon VR, Sharma S, Mahajan A. 2010. Calcium Supplementation and cardiovascular risk. JK Science 12:1-2.

Tfelt-Hansen J, Torring O. 2004. Calcium and Vitamin D3 supplements in calcium and vitamin D3 sufficient early postmenopausal healthy women. European Journal of Clinical Nutrit 58:1420-1424.

The Women's Health Initiative Study Group. 1998. Design of the Women's Health Initiative Clinical Trial and observational Study. Controlled Clinical Trials 19:61-109.

Wactawski-Wende J, Kotchen JM, Anderson GL, Assaf AR, Brunner RL, O'Sullivan MJ, Margolis KL, Ockene JK, Phillips L, Pottern L, Prentice RL, Robbins J, Rohan TE, Sarto GE, Sharma S, Stefanick ML, Van Horn L, Wallace RB, Whitlock E, Bassford T, Beresford SAA, Black HR, Bonds DE, Brzyski RG, Caan B, Chlebowski RT, Cochrane B, Garland C, Gass M, Hays J, Heiss G, Hendrix SL, Howard BV, Hsia J, Hubbell FA, Jackson RD, Johnson KC, Judd H, Kooperberg CL, Kuller LH, LaCroix AZ, Lane DS, Langer RD, Lasser NL, Lewis CE, Limacher MC, Manson JE. 2006. Calcium plus vitamin D supplementation and the risk of colorectal cancer. The New England Journal of Medicine 354:684-896.

Wang L, Manson JE, Song Y, Sesso HD. 2010. Systematic Review: Vitamin D and calcium supplementation in prevention of cardiovascular events. Ann Int Med 152:315-323.

Watson KE, Abrolat ML, Malone LL, Hoeg JM, Doherty T, Betrano R, Demer LL. 1997. Active serum vitamin D levels are inversely correlated with coronary calcification. Circulation 96: 1755-1760.

Yang H, Curinga G, Giachelli CM. 2004. Elevated extracellular calcium levels induce smooth muscle cell matrix mineralization in vitro. Kidney Int 66: 2293-2299.

Zittermann A. 2006. Vitamin D and disease prevention with special reference to cardiovascular disease. Progress in Biophysics and Molecular Biology 92:39-48.