

## Mini Review

# The role of the calcium intake in the development of cardiovascular calcification

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### Abstract

Calcium covers a wide range of body functions. Adequate calcium intake is critical for skeletal health. Dietary calcium intake is considered safe, while supplemental calcium raises concerns, regarding cardiovascular health. Calcium can be administered alone or in combination with vitamin D. Supplemental calcium can be provided if people cannot meet their dietary needs or as a prescription in patients receiving medication for osteoporosis. The last ten years, a major research debate has been ongoing, regarding the possible relationship between calcium intake and cardiovascular risk. Possible mechanisms have been investigated, concerning the possible effect of calcium supplementation on cardiovascular calcifications. Further analysis is needed regarding levels of calcium intake that could possibly promote calcifications. It is also significant to evaluate the effect of the duration of supplemental calcium administration and the possible protective effect of concomitant administration of vitamin D supplementation. Until there are clinical studies to address those hypotheses, the current recommendations include that calcium (dietary and supplemental) can be given safely, within normal limits, to all healthy people and patients, possibly excluding those with chronic kidney disease.

**Keywords:** Calcium intake, Dietary calcium, Supplemental calcium, Cardiovascular calcification, Cardiovascular disease (CVD) risk

## Introduction

Calcium is a mineral that is crucial for life, necessary for the completion of essential and fundamental functions. In the extracellular environment, calcium behaves as a major protein co-factor assuring the integrity of the plasma membrane. It is also the main ingredient of the inorganic part of bone (hydroxyapatite), ensuring bone strength in an important extent<sup>1</sup>.

Calcium is also essential for intracellular functions, such as muscle contractions and neural stimulation. It also operates as a significant intracellular second messenger, modifying various cellular processes, such as mitosis, gene expression, energy metabolism and cell death<sup>1</sup>.

Moreover, a recent study concluded that calcium ions act as key points in controlling cellular lipid homeostasis, suggesting that  $ERCa^{2+}$  status is an important regulator of basic sensitivity of the sterol detection mechanism<sup>2</sup>. Moreover, research studies suggest the correlation between calcium intake and small reductions of arterial hypertension<sup>3</sup>. Keeping serum calcium within a certain range, through regulatory mechanisms, is vital to the completion of the above functions.

It has been observed that adequate calcium intake is critical for skeletal health. Over the age of 50 years old, for both women and men, the Recommended Nutrient Intakes (RNI) are at least 1.000 mg of calcium and 800 IU of vitamin D per day<sup>4</sup>.

The combination of calcium and vitamin D supplementation is generally recommended for people receiving medication for osteoporosis treatment<sup>4</sup>. According to the European guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis, the dietary calcium intake is recommended. Supplemental calcium (SC) can be provided if people cannot meet their dietary needs<sup>4</sup>.

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Ten years ago, the Auckland Study<sup>5</sup>, with the purpose to identify the effect of supplemental calcium in cardiovascular health, in healthy postmenopausal subjects, (mean age 74 years old), raised a major research debate and controversy that still continues, about the relationship between calcium supplementation and cardiovascular risk. Extensive bibliography has yet been published, investigating the role of increased intake of calcium (dietary and/or supplementary) in the risk of cardiovascular disease (CVD) by describing the role of the different possible mechanisms involved. Various studies have been presented, such as the identification of calcification, as well as the effect of calcium on vascular cell activity.

The purpose of this review is to study the possible role of calcium (dietary and supplementary) in the progression of cardiovascular calcifications. Strong evidence reveals the aggravating role of calcifications in cardiovascular risk, suggesting that calcifications promote rupture of the atherosclerotic plaque and raise blood pressure. Calcification of the coronary arteries is an early marker of coronary arteriopathy and predicts mortality from cardiovascular disease, regardless of age<sup>6</sup>. Cardiovascular (CV) calcification is also a powerful tool for straining the risk of cardiovascular disease. Emerging data shows that even small amounts of Coronary Artery Calcification (CAC) (CAC scores 1-10) have been associated with a significant raise in mortality compared to individuals free of CAC<sup>6</sup>.

## Cardiovascular calcification

Vascular calcification was observed 150 years ago, and until recently it was regarded to be a degenerative, irreversible process that evolves over the aging process. Latest studies suggest that vascular calcification is a protective mechanism designed to mitigate and protect against the chronic inflammatory process in atherosclerosis, but beyond certain limits, calcification becomes harmful for the vascular system<sup>6</sup>.

According to the literature, CV calcification is the calcium deposition process in the extracellular space of the vascular wall. It is classified into 2 different types depending on location:

- a. Intimal calcification which is related to the calcification of the intima. That is the dominant type of calcification observed in the coronary arteries.
- b. Medial calcification primarily affects the peripheral arteries resulting in loss of elasticity. It is usually observed in peripheral vascular disease.

The distribution of calcification is more important than its extent; spotty calcification is associated with a higher risk of atherosclerotic plaque rupture<sup>6</sup>.

Some features that vascular calcification shares with bone formation are osteoblast and chondrocyte differentiation, bone matrix deposition and absorption as well as mineralization. Bone proteins, such as Bone Morphogenetic Protein, BMP-1 and BMP-4, bone sialoprotein, osteocalcin, osteonectin, osteopontin and osteoprotegerin have been found in a calcified artery<sup>6</sup>.

Imbalance between calcification inhibitors and promoters advocates the configuration of osteoblast-like cells in the vascular wall. These cells are derived from trans-differentiation of vascular smooth muscle cells (VSMCs). Some factors, such as oxidative stress, oxidized lipids and Bone Morphogenetic Proteins (BMPs) impact these cells. They are secreted by VSMCs micro-vesicles that are associated with the formation of vascular calcification, building metal calcium nuclei foci<sup>7</sup>. Calcification inhibitors among other include:

1. Matrix gamma-carboxyglutamic acid protein (MGP), an important vascular calcification inhibitor.
2. Osteopontin (OPN), a bone substrate inhibiting matrix preventing mineralisation.
3. RANKL/OPG system, modulator of osteoblastic and osteoclastic activity.
4. Receptor Activator of NF-kB.
5. Fetin.
6. Fibroblast Growth Factor-23, which is produced by osteocytes and inhibits bone mineralisation, while increasing excretion of phosphorus from the distal tubule. It has been proposed as a bioindicator of vascular revaluations<sup>7</sup>.

It has not yet been clarified how the calcium content of atherosclerotic plaques affects the plaques' stability, causing thromboembolic events. In clinical practice, the determination of calcifications is widely used for the assessment of cardiovascular risk, through the CCTA-derived coronary vascular determination. Calcification is considered as the alteration that has more than 130 Hounsfield units in an area of more than 1 to 2 pixels<sup>7</sup>.

## The effect of dietary and supplementary calcium on cardiovascular calcification

During the last few years, the issue of relationship between increased calcium intake and possible aggravating effects on vascular calcification and increased cardiovascular risk has been raised. In addition, there are emerging concerns about the role of calcium sources (dietary and/or supplementary calcium) in vascular calcifications and especially CAC.

There are few studies investigating the relationship between dietary and/or supplementary calcium in cardiovascular calcification. Most of these Studies involve healthy participants, without chronic renal disease or other clinical conditions. Furthermore, most of them do not separate the subgroup of osteoporotic participants from the generally healthy people.

In a large clinical trial of 1471 healthy postmenopausal women with a calcium consumption of 1g/day with 5-year follow-up, and a sample of 323 healthy men with a calcium consumption of 600 or 1200 mg/day with a 2-year follow-up. Results suggested that the intake of calcium (higher in women) was not associated with aortic calcification at baseline and 5 years follow up. Specifically, calcium intake from

either the diet /or supplementation was not associated with alterations in the prevalence of abdominal aortic calcification (AAC) over time. Moreover, supplemental calcium didn't appear to be associated with CAC score in men<sup>8</sup>.

The Framingham study, an observational and prospective study, with a sample of 690 women and 588 men, generally healthy, aged 36 to 83, investigated the relationship between calcium from the diet and use of supplements and coronary artery calcification. Researchers concluded that high calcium intake (the highest quartile of total energy-adjusted calcium intake was 1558-2821 mg/d in women and 1047-3050 mg/d in men) was not associated with increased coronary artery calcification<sup>9</sup>.

A retrospective study with a sample of 2710 men and 1143 women (626 of whom were postmenopausal) examined the association of dietary calcium intake with CAC score. Researchers assessed the 24-hour food diary, and none of volunteers received any calcium supplement. The study did not present any association between dietary calcium intake and CAC score. Furthermore, dietary calcium intake was not related to the fasting glucose levels, blood pressure and insulin resistance. This study also highlighted that dietary calcium intake did not affect levels of calcium or phosphate in the blood<sup>10</sup>.

A large Korean Study with a sample of 23.652 volunteers without chronic kidney disease or clinically apparent cardiovascular disease assessed the relationship between dietary calcium and phosphorus and CAC score levels. It was noted that elevated levels of serum calcium, phosphorus and calcium-phosphorus derivatives are associated with increased CAC score levels, yet no direct relationship was made between dietary calcium and phosphorus intake with the CAC score<sup>11</sup>.

Another study, with a sample of 7553 healthy people, concluded that elevated levels of calcium, phosphorus and calcium phosphorus derivatives in the blood are significantly associated with the calcification of atherosclerotic plaque. The causal link was not clear<sup>12</sup>.

A cross-sectional study in a sample of 720 diabetic patients from the Diabetes Heart Study examined the effect of the dietary and supplemental calcium intake in patients with subclinical elements of CVD, such as the calcification in the carotid, coronary artery, abdominal aorta and the mortality. The study found no correlation of dietary and supplemental calcium with plaque calcification or with higher mortality because of the increased calcium intake. On the other hand, calcium supplements intake of up to 500 mg were associated with reduced mortality from all causes in women (HR: 0.62, 95% CI: 0.42, 0.92)<sup>13</sup>.

A 5-year clinical trial from Auckland, investigated the relationship between bone density and fractures' incidence, in a sample of 1471 healthy postmenopausal women who were divided into two groups: one group received a supplement of 1000 mg/day calcium citrate and the other group received placebo. The re-analysis of the Study detected

a statistically significant raise in the incidence of myocardial infarction (MI) for the supplemental calcium users in comparison with the placebo group. Those data were based on a self-report that was verified by doctors<sup>5</sup>. The analysis of the registered hospital patients in the national database and the re-examination of the death certificates proved that the statistical raise on strokes or sudden deaths was negligible.

A Finnish observational study on a sample of 10.000 healthy women of average age 57 years, without Coronary Heart Disease, during a 6-year follow-up, proved that SC intake with or without vitamin D administration showed a 24% elevated risk of developing Coronary Heart Disease, in comparison with volunteers who did not receive supplements, after adjustment for baseline covariates in two groups<sup>14</sup>.

Multi Ethnic Study of Atherosclerosis (MESA) with a sample of 2742 volunteers, aged 45-84 years old, free of cardiovascular disease and renal abnormalities, evaluated the cv effects of calcium dietary intake, as well as supplemental calcium. The categories of calcium intake per day were: 313.3, 540.3, 783, 1168.9 and 2157.4 mg/day. The coronary artery calcification (CAC) was calculated by tomography, with a follow-up of ten years. The researchers concluded that increased calcium intake from the diet was associated to a reduced risk of developing atherosclerosis. However, the use of calcium supplements may increase the risk for CAC. Findings suggested that the supplemental calcium may increase the risk of myocardial infarction, possibly through the atherosclerosis mechanism, since the CAC score is a strong indicator of atherosclerosis prognosis<sup>15</sup>.

Large clinical trials<sup>16-18</sup>, with older participants (>70 years old) examined the association of the supplemental calcium (with or without vitamin D) with the fractures' incidence. Researchers found no significant association from using calcium supplements on cardiovascular risk or mortality in secondary analyses.

Results from the RECORD Study with a sample of 5000 elderly people (85% women) at high risk of fractures after 2-5 years of follow up did not reveal any association between supplemental calcium and significant effects on cardiovascular mortality<sup>17</sup>.

Another five-year, double-blind, randomized trial, with a sample of 1400 women of average 75 years of age, received 1200 mg supplemental calcium (calcium carbonate) per day or placebo. The analysis showed that supplemental calcium was related to a reduction in the hospitalization and mortality in women with pre-existing cardiovascular morbidity<sup>18</sup>.

A sub-study of the Women's Health Initiative Calcium and Vitamin D trial (WHI CaD), after 7 years of follow-up, did not detect a difference in the CAC score, between women who received 1000 mg of elementary calcium and 400 IU of vitamin D, per day, compared to the placebo group<sup>19</sup>.

Two meta-analyses suggested a 25% raise in the relative risk of MI among calcium supplement users, with or without vitamin D, compared to placebo group<sup>20,21</sup>. In more detail,

the WHI CaD analysis aimed to further research of the role of supplemental calcium, with and without vitamin D, on cardiovascular risk<sup>21</sup>. Bolland assumed that the “personal use” of calcium supplements may mask the impact of calcium in cardiovascular risk. For this reason, possible synergistic effects between the “personal use” of supplementary calcium and the vitamin D plus calcium administration for cardiovascular risk were assessed. A hypothesis was made that volunteers with elevated calcium intake at baseline could be at a higher risk of exposure to supplemental calcium<sup>22</sup>. Researchers mentioned that volunteers who consumed calcium and vitamin D, had increased risk of cardiovascular events, particularly MI. Another issue was that the occurrence of MI was based on self-referencing of the volunteers who received calcium supplements. However, self-referencing is more likely to result in wrong results<sup>23</sup>.

However, other meta-analyses (with clinical trials or observational studies) presented different results, finding no consistent evidence in relating calcium supplements and increased risk for cardiovascular events<sup>24-26</sup>. Specifically, in Chung’s analysis, with 27 observational studies, a linear and non-linear analysis method were applied. Results did not prove a correlation between the dietary or total calcium intakes and risks for stroke or cardiovascular mortality. Clinical trials have not been presented in this meta-analysis due to results’ heterogeneity. However, 4 trials are included in the summary. The analysis of WHI Study didn’t reveal a positive correlation between SC, vitamin D and the incidence for coronary artery disease or stroke in the study sample. The other 3 trials did not show significant correlations for CVD outcome<sup>26</sup>.

Despite the large number of the available data (the largest meta-analysis concluded 18 studies with 64.000 participants), researchers reported many limitations. Particularly, it has been reported that none of the trials had the main purpose of assessing how the calcium supplements affect cardiovascular or coronary artery disease. This can result in increased probability for false positives, especially when many secondary outcomes were evaluated as part of subgroup analysis. There are also many unpublished data on cardiovascular outcomes that were gathered and taken into account retrospectively.

It is also important to notice that research field is focusing on the relationship between dietary and/or supplementary calcium in cardiovascular disease risk. Fewer trials are dealing with the mechanism of cardiovascular calcification in healthy elderly people. Most of these studies do not have the criterion of separation between the osteoporotic participants possibly using also other medication such as bisphosphonates and healthy people. Other criteria to be used for future analysis could include selecting homogenous groups of subjects in order to examine the direct effects of calcium supplementation on cardiovascular calcifications (normal healthy individuals versus patients with osteoporosis or other disorders).

Concerning vitamin D, prospective studies demonstrate that low levels of vitamin D may be related to cardiovascular disease. Some studies suggest that vitamin D may decrease the CVD risk<sup>22</sup>. Furthermore, Vitamin D is related to the reduction of different causes mortality. Data shows that lower levels of vitamin D in serum have been correlated to elevated risk of cardiovascular disease<sup>27</sup>.

Till now, available bibliography gives raises important questions, like what are the levels over which the calcium is related to calcification, and how exactly are the calcium sources linked to calcifications. It has been observed that dietary calcium is safe, while supplemental calcium raises concerns to the researchers. Further analysis is needed about the high calcium intake, over 2000-2500 mg/day, in particular the levels that cause toxicity and possibly promote calcifications. However, it is mentioned that most people cannot reach those levels. Moreover, until now the available bibliography supports that calcium intake up to 1200 mg/day cannot offer further health benefits. There are few studies conducted on healthy elderly people with the main purpose to research the effect of higher calcium intake to the rate of advancement of the vascular calcification<sup>28</sup>. In addition, it is significant to evaluate the duration of supplemental calcium administration and the protective effects of vitamin D.

Although, this work does not analyze the impact of calcium intake in patients with chronic kidney disease, it is important to mention that most of available data presents that caution is required for patients with impaired kidney function taking supplementary calcium towards the risk of vascular recurrences<sup>29</sup>. Over the last 20 years there is evidence that long-term administration of SC in Chronic Kidney Disease (CKD) promotes vascular calcification resulting in raised risk of cardiovascular morbidity, due to the coexistence of hyperphosphatemia<sup>29</sup>.

In animal models the results are diverse. Two studies showed that low levels of calcium intake appeared to promote calcification in the aorta and kidneys. On the other hand, elevated intake levels were not generally related to cardiovascular calcification<sup>30,31</sup>. In Another study done on a sample of rats with chronic renal disease and secondary hyperparathyroidism, calcium supplementation was associated with arterial calcification<sup>32</sup>.

In summary, the available literature agrees that dietary calcium does not affect vascular calcifications, while concerns are raised for the association of supplemental calcium intake and cardiovascular calcification. It is noteworthy that data suggest the maintenance of serum calcium levels within certain narrow limits, so the calcium intake is rarely associated with serum levels.

### Possible mechanisms of calcium intake and Cardiovascular Calcification

Research has described possible mechanisms linking supplemental calcium with increased cardiovascular risk, but results are yet unclear. Some observational studies suggest

that supplemental calcium, but not dietary, was related to increased cardiovascular risk. That suggestion has led to the hypothesis that the rapid and prolonged elevations in serum calcium may play a central role<sup>14</sup>.

It's reported that osteoporosis and vascular calcification occur simultaneously, but in opposite directions in the elderly people. Phosphate and crystals are passively placed on the vessel wall and myocardium<sup>33</sup>. It is recently suggested that calcium ions contribute to PiT1 stimulation, a sodium co-transporter type III phosphate, from vascular smooth muscle cells (VSMCs), which can permit phosphate ions to concentrate intracellularly. It is suggested that phosphate ions activate the growth of VSMC in an osteochondral phenotype<sup>33</sup>. At the same time, calcium causes the release of structures resembling matrix vesicles from sustainable VSMCs and apoptotic bodies from VSMC apoptoids that behave as nuclei for the precipitation of extracellular calcium phosphate<sup>34</sup>. Finally, calcium leads to lower expression of calcification inhibitors by VSMCs<sup>35</sup>.

## Present recommendations

The Institute of Medicine (IOM) recommends for men and women 19-50 years old, the consumption of 1000 mg of calcium per day, while for women over 50 and men over the age of 70, these levels are raised and reaching 1200 mg/day. It is mentioned that higher doses do not have additional health benefits<sup>36</sup>.

The American Society for Bone and Mineral Research Professional Practice Committee on calcium supplements and cardiovascular events, emphasizes that the available data cannot lead to the conclusion that supplemental calcium is associated with cardiovascular events<sup>37</sup>. In addition, the position of the American Society for Preventive Cardiology with the National Osteoporosis Foundation was "there is moderate-quality evidence (B level) that calcium with or without vitamin D intake from food or supplements has no relationship (beneficial or harmful) to the risk for cardiovascular and cerebrovascular disease, mortality, or all-cause mortality in generally healthy adults at this time". Extending their position, the available evidence suggests a range between 2000-2500 mg of calcium per day is considered safe<sup>38</sup>. Moreover, the US Preventive Services Task Force, in a recent report concludes that "the current evidence is insufficient to assess the balance of the benefits and harms of daily supplementation with doses greater than 400 IU of vitamin D and greater than 1000 mg of calcium for the primary prevention of fractures in community-dwelling, postmenopausal women"<sup>39</sup>.

It has been reported that calcium supplementation leads to coverage or over-coverage of daily needs. More specifically, 65% of women over the age of 71 and up to 40% of the total US population take supplementary calcium. Some reports show that calcium supplements contribute to higher calcium intakes. In addition, there is no further benefit of increased calcium intake in skeletal health, while

the average intake of calcium through diet, in all age groups, for adults is 700-1000 mg/day<sup>23</sup>. This quantity can be ensured by providing two to three servings of rich in calcium food sources such as dairies: yogurt, milk, cheese and other food groups including oily fish, and vegetables with green leaves<sup>23</sup>. It is mentioned that most people do not need more than 500 mg daily administration of SC to meet their daily needs, if they are not only covered by dietary sources<sup>23</sup>. Finally, it is important to cover the recommended intake of vitamin D, with 600 IU/day until the age of 70 and 800 IU/day for people over the age of 70<sup>23</sup>.

## Conclusion

Calcium is a valuable nutrient, and covering calcium needs through life stages, for all age groups, is considered essential for a variety of body functions. Research has not yet led to conclusions about the relationship between calcium intake and the cardiovascular calcification, due to studies' limitations. It appears that elevated calcium intake, beyond 2000-2500 mg/day, especially from supplements, may be associated with the onset and/or progression of cardiovascular calcification, but this level is difficult for someone to reach. Dietary calcium is the proposal way to cover calcium needs. A balanced diet with 3 servings of rich in calcium food sources, such as dairies (yogurt, milk, cheese), in combination with other nutritious food groups such as oily fish, vegetables with green leaves, nuts (almonds) can cover the calcium needs. However, if those needs are not only covered by dietary sources, most people can use SC, but it has been referred that they do not need more than 500 mg daily administration of SC to meet their daily needs. Further prospective studies, particularly randomized clinical trials, should investigate the direct relationship between calcium intake and calcifications, especially in people with high calcium intakes that are close to or beyond tolerable upper intake levels, are clearly necessary. Until there are clinical studies to address those hypotheses, the current recommendations include that calcium (dietary and supplemental) can be given safely, within normal limits, to all healthy people and patients, possibly excluding those with chronic kidney disease.

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