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Comparison of dietary and supplemental calcium - a systematic review

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Abstract

Calcium is an essential mineral crucial for several physiological processes. The public has generally perceived its supplementation as beneficial or, at the least, neutral. Additional supplementation has been gaining popularity in recent years, often without professional consultation. This is despite the fact that dietary calcium is mostly sufficient in healthy individuals to meet daily requirements. This review examines studies found on PubMed to contrast dietary calcium intake with supplemental calcium with regard to two specific issues – cardiovascular risk and kidney stone risk.

Research suggests that while dietary calcium protects against cardiovascular disease and nephrolithiasis, supplemental calcium may increase the risk of myocardial infarction and arterial calcification in specific populations.

Therefore, healthcare providers ought to prioritize dietary calcium sources and implement an individualized approach for patients who require such supplementation, such as those at risk of osteoporosis or CVD. The timing and dosage of calcium supplements also require careful consideration. Further research is needed to examine the mechanisms behind these risks and specify clinical guidelines for safe and effective calcium intake.

Introduction

The supplement business has become one of the most profitable market sectors in the world. People are noticeably more interested in their health and now have multiple information sources to inform them about the potential negative consequences of nutrient deficiencies. Therefore, consumers turn to buying supplements, often without professional consultation. This also is an issue with calcium supplementation, as the public widely regards it as a safe and necessary mineral. Pharmaceutical companies often go as far as to recommend additional intake, even though most people will meet their daily needs through diet alone. This review will compare the effect of supplying calcium through diet and supplements.

Methods

The following paper analyzed studies found on PubMed using keywords such as "calcium supplementation," "calcium over supplementation," "dietary calcium," "calcium intake," "cardiovascular mortality," "myocardial infarction," "kidney stones," and "urolithiasis." Articles include randomized controlled trials, meta-analyses, and systematic reviews published from 1995 to the present day, prioritizing resources published after 2000.

Role of calcium in the organism and recommended intake

3

Calcium is an essential mineral involved in several biological processes. Perhaps most importantly, it is the primary structural component of bones and teeth – almost 99% of calcium is found there, and the remaining 1% is found in serum.⁴⁷Apart from its skeletal role, it acts as a signaling molecule taking part in muscle contraction, neurotransmitter release, and hormone secretion.¹ In recent years, calcium's role in blood clotting in the coagulation cascade has also been highlighted, providing a surface for several coagulation factors^{2,48}. Calcium also supports the immune system function by activating T-cells and macrophages and helps regulate pH and electrolyte balance.¹

Dietary reference values differ depending on which reference guidelines are considered. Most notably, the Institute of Medicine's guidelines state that men aged 18 to 70 and women aged 18 to 50 should have a daily calcium intake of 1000mg/d. In contrast, women over 50 and men over 70 should have a calcium intake of 1200 mg/d.

At the same time, it is worth considering the tolerable upper calcium intake proposed by the Institute of Medicine, shown in Figure 1. Its value indicates the amount above which the risk of adverse effects increases. It should not be equated with the recommended intake.

MALES/FEMALES – LIFE STAGE	UPPER INTAKE LEVEL UL
GROUP	
9-13	3,000 mg
14-18	3,000 mg
19-30	2,500 mg
31-50	2,500 mg
51-70	2,000 mg
>70	2,000 mg

Figure 1. Proposed upper intake levels of calcium by the Institute of Medicine.⁶ It should be noted that the UL will be different during pregnancy, lactation, and among younger children under 9 years old.

While it is generally agreed that the appropriate amount of calcium is acquired through dietary means, there are cases in which calcium supplementation is needed. Examples include osteoporosis, osteomalacia, hypocalcemic rickets, hypoparathyroidism, and hypocalcemia in

chronic kidney disease.^{3,4} However, this review does not focus on specific conditions requiring calcium supplementation.

Effects of calcium deficiency

The effects of hypocalcemia can be analyzed in the short term or long term, both leading to severe health consequences. In the short term, hypocalcemia can cause muscle cramps, spasms, paresthesia, and tetany, resulting from a disturbance in nerve function.^{3,5,44} If calcium levels are low enough, it can clinically present through cardiac arrhythmia and life-endangering seizures. Over the long term, however, chronic calcium deficiency is most notably a significant contributor to osteoporosis ^{4,8}. This permanent reduction of bone mass predisposes patients to bone fractures and overall fragility, particularly in postmenopausal women who experience a sharp decrease in estrogen levels ¹⁰

Other long-term effects include cognitive impairment or even behavioral changes⁴⁴. Generally, if an individual develops hypocalcemia gradually, the asymptomatic probability increases.⁴⁴

More pronounced long-term effects are seen among children, where insufficient calcium intake can also severely impair bone development. It can lead to overall stunted growth and an increased risk of rickets ^{45,46.} This is a condition where the growth plate cartilage is defectively mineralized due to abnormalities in chondrocyte function, resulting in bone deformities ^{45,46.} Calcipenic rickets, however, is more frequent among developing countries such as South Africa, Nigeria, or Bangladesh, although research suggests that the problem has started to reappear in richer countries.⁴⁵

Potential cardiovascular risk

Multiple factors can contribute to the acceleration of vascular diseases by supplementing calcium. The starting point is increased serum calcium, which promotes arterial calcification ^{11,28}. This could be by calcium simply depositing in the arterial wall, but in recent years, an alternative, more precise mechanism has been proposed. It involves the process in which the elevated ionized calcium concentration disrupts the regulation of calcification modulators - particularly pyrophosphate, with which it creates complexes. ¹¹

Another way that elevated serum calcium promotes calcification is through its binding to receptors expressed on smooth muscle cells. While the exact mechanism is still debated,

studies suggest that it has to do with the down-regulation of the receptor.¹¹ Additionally, calcium overload is reported to obstruct the balance between the muscle contraction and relaxation of vascular smooth tissue. High levels additionally cause oxidative stress and inflammation, contributing to endothelial dysfunction ^{5,11}. All these factors combined promote elevated blood pressure and atherosclerosis and add workload on the heart, leading to an increased risk of cardiovascular events ^{11,26}. This will be the focus of the next section of this review.

What does research suggest?

A study in 2010 by Bolland et al. examined the potential effect of calcium supplements on the overall risk of cardiovascular effects, including myocardial infarction. This meta-analysis considered randomized, placebo-controlled trials of calcium supplements, 500mg or more. It was concluded that supplementation is linked to an increased probability of MI.¹²

Another prospective cohort study compared dietary calcium intake with its supplementation. It extracted data from 23,980 participants of the European Prospective Investigation into Cancer and Nutrition study with an average follow-up time of 11 years. Not only was there no association between dietary calcium and increased CV risk, but a higher intake was linked to a lower MI risk.¹⁴

Interestingly enough, there was a statistically significant increase in the myocardial infarction risk among people who supplement calcium, though data on the exact dosage of calcium was not collected. The possible explanation for the different outcomes can be attributed to a different response in serum calcium. Research shows that serum calcium is more elevated after taking supplements rather than through dietary means.¹³

Another study worth examining was conducted by Wang et al., a meta-analysis of prospective cohort studies examining dietary calcium intake and mortality risk from cardiovascular diseases. No evidence supported the claim that calcium supplements increase the risk of CV mortality. However, the researchers admit to not considering magnesium intake, which multiple studies have shown to decrease mortality from CVD.¹⁷ Dietary calcium intake and the risk of V mortality appear to form a U-shaped relationship, a conclusion supported by another Swedish study. ¹⁶ The researchers' baseline reference: a daily intake of 800 to 1000mg calcium showed the lowest CV mortality. A 500 mg daily intake – 8 percent increase in

mortality, 1200 mg daily intake -5 percent increase in mortality, 1400mg daily intake -10 percent increase in mortality. These findings point to the conclusion that both low and high calcium intake have specific side effects.

Differences between men and women

A large prospective cohort study by Xiao et al. (2013) involving over 388,000 participants examined the effect of both supplemental and dietary calcium on cardiovascular incidents. Firstly, there was a lack of connection between dietary calcium and CV incidents, a recurring conclusion in most studies. On the other hand, supplemental calcium - over 1000mg a day, was associated with CVD mortality only among men - the risk was almost 20 percent higher.¹⁸

A very similar outcome was observed by Yang et al. in 2016. Thirty-two thousand eight hundred twenty-three participants in the Cancer Prevention Study II Nutrition Cohort were examined with a mean follow-up of 17.5 years. It turned out that men who took 1000mg calcium a day showed a statistically significant elevated risk of all-cause mortality, which the researchers primarily linked to CVD-specific incidents. Simultaneously, the correlation was inverse for women - both total and supplemental calcium were tied to lower mortality.¹⁹

Nephrolithiasis - the role of calcium and research analysis

For decades, patients were advised to follow a low-calcium diet to minimize the risk of kidney stone formation. A recommendation stemming from the notion that higher calcium intake would raise urinary calcium. This was questioned by the Nurses' Health Study I in 1997, a prospective cohort study where a higher calcium intake through diet decreased the risk of kidney stones.²² Moreover, supplemental calcium elevated the risk, particularly among older women. On the other hand, a follow-up study conducted in 2004 showed slightly different results, confirming that dietary sources decrease the risk while not associating supplemental sources with any particular outcome. ²¹ Despite the two studies slightly varying, they changed how the medical field approached the subject of kidney stone prevention.

As the precise mechanism of renal calculi formation has not been discovered, sources generally cite a mix of genetic and environmental factors ^{24,23}. Nonetheless, the leading pathogenic background is linked to the disturbance of balance between substances, promoting and inhibiting their formation. Promoters are substances such as calcium, oxalate, uric acid,

cystine, and inhibitors substances like citrate and magnesium. A typical patient with no underlying conditions will absorb up to 20 percent of dietary calcium, about 800-1000mg^{23,24}. Calcium ions create complexes with oxalate or phosphate - promoters of urinary calculi, reducing the bioavailability and thus absorption, this being a specific protective mechanism against kidney stones. This does not occur when ingesting supplemental calcium alone, which manifests through an increase in the urinary excretion of calcium, oxalate, and phosphate. ^{22,25} This explanation is aligned with a study conducted by Domrongkitchaiporn et al., in which the importance of the timing of taking calcium supplements was highlighted. Three groups were formed – subjects took either 1g of calcium carbonate with a meal 3 times a day or 3g at bedtime. After a specific period, the activity of calcium oxalate from urinary samples was collected - it served as a predictor of stone formation. When taking calcium with food, calcium oxalate activity remained relatively unchanged, whereas the activity increased significantly when supplements were taken at bedtime ²⁰. Therefore, it is necessary to consider an appropriate schedule when adjusting calcium supplementation among patients. Patients who lack adequate calcium intake should be mindful of their oxalate-rich food intake, e.g., various teas, spinach, and chocolate ²⁵.

This review does not evaluate studies examining the joint effect of supplementing additional substances to calcium, but magnesium should be mentioned regarding urolithiasis. It has been shown that magnesium supplementation inhibits crystal formation.²⁹ Therefore, additional research should be conducted on the cumulative effect of both magnesium and calcium on kidney stone prevention.

Discussion and opportunities for future research

Although some of the findings are inconclusive, this review highlights the importance of prioritizing dietary calcium above supplementation. This review did not take into consideration studies that examined the joint effect of supplementing additional substances such as magnesium or vitamin D. These nutrients can also modulate calcium's impact on the body and should also be considered when evaluating calcium supplementation. Moreover, some studies mentioned in this article did not specify the amount of calcium patients took, making it difficult to form a uniform baseline reference.

Conclusion and clinical implications

This review focuses on the complex relationship between calcium intake and cardiovascular health with kidney stone risk. Even though dietary calcium remains a safe and beneficial way to meet daily requirements, calcium supplementation poses potential health risks, especially in excess doses or taken outside of meals. Sex-specific differences further highlight the need for adjusted supplementation plans. Men appear more vulnerable to adverse cardiovascular outcomes from supplemental calcium, whereas women may experience protective effects under specific conditions. Additionally, when consumed independently of meals, supplemental calcium may elevate the risk of kidney stone formation by disrupting calcium metabolism and urinary excretion.

To optimize patient outcomes, healthcare professionals ought to advocate for dietary calcium as the leading approach and implement a cautious, individualized approach to supplementation. Further research is necessary to understand better the mechanisms driving the risks associated with supplemental calcium and to refine clinical guidelines. By weighing out the benefits of calcium for bone health with its potential risks, particularly for cardiovascular safety and kidney stone prevention, doctors can promote optimal health outcomes for different patient populations.

Disclosure

Author's contribution

Conceptualization, Karolina Siembab; Julia Białeta **methodology**, Michalina Jurkiewicz; **software**, Agnieszka Napieralska; **check**, Wiktoria Pysiewicz, Wiktor Garbarczyk and Alicja Cernohorska; **formal analysis**, Albert Kapla; **investigation**, Daria Bednarczyk; **resources**, Michalina Jurkiewicz; **data curation**, Agnieszka Napieralska; **writing** - rough preparation, Julia Białeta, Karolina Siembab **writing - review and editing**, Karolina Siembab, Katarzyna Rowińska; **visualization**, Katarzyna Rowińska; **supervision**, Julia Białeta; **project administration**, Karolina Siembab.

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The authors used ChatGPT to improve language and readability, after which the content was reviewed and edited. The authors accept full responsibility for the substantive content of the publication.

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