Is calcium supplementation a risk factor for cardiovascular diseases in older women?

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Low intake of dietary calcium is related to bone loss and fragility fracture in older adults, especially postmenopausal women. Contradictory findings have been reported from studies that investigated the association between calcium supplementation and hypertension and the risk of stroke and cardiovascular disease. Misinterpretation of findings from studies that are not primarily designed to address these issues might overshadow the benefits of dietary calcium. Until well-designed studies address the current uncertainties, the possible detrimental effect (e.g., hypercalcemia and its complications) of higher-than-recommended calcium intake should be balanced against the likely benefits of calcium on bone, particularly in elderly women.

INTRODUCTION

Calcium is the most abundant mineral in the human body, contributing to 1–2% of adult human body weight.1,2 Over 99% of calcium is located in bones and teeth. In bone, calcium exists primarily as hydroxyapatite \([\text{Ca}_{10} (\text{PO}_4)_6(\text{OH})_2]\) and bone mineral is almost 40% of the weight of bone.2 Hence, calcium plays an essential structural role in the skeleton. Further, the skeleton serves as reservoir for calcium.2 Blood, extracellular fluid, muscle, and other tissues contain calcium as well.

Because of important roles of calcium in mediating vascular contraction and dilatation, muscle contraction, nerve transmission, and glandular secretion, serum calcium is tightly defended in the face of changes in dietary calcium intake and is only affected by prolonged and severe calcium deficiency. A transient drop in serum calcium will activate endocrine pathways that release calcium from bone, which can harm bone, especially in the elderly, if persistent. The association between low calcium intake and risk of osteoporosis and fragility fracture in postmenopausal women has been well documented.2,3 The Standing Committee on the Scientific Evaluation of Dietary Reference Intakes (DRI) of the Institute of Medicine has established recommendations, defined as adequate intake (AI) and tolerable upper limit intake (UL), for calcium intake across the lifespan.2 For individuals aged 51 and over, including postmenopausal women, the AI for calcium is 1200 mg/day and the UL is 2500 mg/day.2

Endogenous estrogen has a favorable effect on blood lipid profile and bone mass and structure in women. However, after menopause, the blood lipid profile changes with increases in atherogenic lipids.2,4 Moreover, in postmenopausal women, there is a tendency for a progressive increase in body weight and central adiposity.2 Studies suggest that an increase in intra-abdominal fat mass is responsible for the elevated atherogenic lipid profile after menopause.6 Hence, postmenopausal women are at greater risk of cardiovascular diseases than younger women and need to be monitored for gain in fat mass and changes in blood lipid profile.

CALCIUM SUPPLEMENTATION AND CARDIOVASCULAR DISEASE

Many epidemiologic, experimental, and clinical studies concerning the relationship between calcium intake and morbidity and mortality from hypertension,2,6 coronary...
heart diseases,9,10 and cerebrovascular diseases9,10 have
been reported, but they have failed to find consistent
results. Recently, Bolland etal.11 published a worrisome
report concerning the relationship between dietary
calcium supplement intake and the risk of heart attacks,
strokes, and/or other vascular events in postmenopausal
women participating in a clinical calcium supplementa-
tion trial (the New Zealand Study).

Bolland etal.11 conducted a randomized, placebo-
controlled, calcium supplementation trial among 1471
postmenopausal women (mean age, 74 ± 4.3 years) for 5
years. Study participants were randomized into two
groups, those who received a calcium citrate supplement
(supplying 1000 mg/day elemental calcium) (n = 732)
and a placebo group (n = 739). This study was primarily
designed to assess the effect of calcium supplementation
on bone mineral density and risk of fracture over 5 years
in postmenopausal women.12 The current report from
this study is a secondary analysis to determine the effect
of calcium supplementation on myocardial infarction,
stroke, and sudden death. Subjects were excluded from
participating in the study if they were: under treatment
for osteoporosis; taking calcium supplements; vitamin D
deficient (i.e., had serum 25-hydroxy vitamin D levels
lower than 25 nmol/L); or had major renal, thyroid,
cancer, and bone diseases. Risk of cardiovascular disease
was assessed by comparing the frequency of events in the
two groups. The first group of events included: death,
sudden death, myocardial infarction (MI), angina, other
chest pain, stroke, and transient ischemic attack. The
second group of events analyzed was a composite cardio-
vascular endpoint that consisted of sudden death, myo-
cardial infarction, angina, or chest pain.

Baseline characteristics were similar between the
two groups and compliance was not different after 5
years (58% in the placebo group and 55% in the calcium
group). Calcium supplementation was associated with
beneficial trends in increasing high-density lipoprotein
and decreasing low-density lipoproteins. Although self-
reported possible MI and composite cardiovascular
endpoint was significantly higher in the calcium sup-
plementation group, only MI was significantly higher
in the calcium supplementation group when self-
reported data were verified through an adjudication
process.

In the adjudication process, the researchers evaluated
the self-reported data along with data from the national
database of hospital admissions. When the authors
included unreported data (obtained from the adjudica-
tion process) to the verified reported data, the previous
findings were no longer significant (Table 1).

Additional statistical data analyses, including
Kaplan-Meier survival analysis and time course analyses,
demonstrated a pattern of higher MI in the calcium
supplementation group; however, these apparent differ-
ences were not statistically significant. Rate ratio analyses
showed borderline significance for a higher rate of MI
(P = 0.058) and composite cardiovascular endpoint
(P = 0.043) in the calcium supplementation group. Event
rate of the composite cardiovascular endpoint was higher
in compliant subjects (>60% compliance) in the calcium
supplementation group (2.1, P = 0.03). Poisson regression
analyses, adjusting for possible confounder and effect
modifiers, revealed that previous ischemic heart disease
and high compliance were independent risk factors for a
negative outcome.

<table>
<thead>
<tr>
<th>Vascular events</th>
<th>Data accuracy*</th>
<th>Calcium group (n = 732)</th>
<th>Placebo group (n = 739)</th>
<th>P value†</th>
<th>Relative risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>Reported</td>
<td>31 (45)</td>
<td>14 (19)</td>
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<td></td>
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<td>10 (10)</td>
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<td></td>
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<td>31 (36)</td>
<td>21 (22)</td>
<td>0.23</td>
<td>1.49</td>
</tr>
<tr>
<td>Stroke</td>
<td>Reported</td>
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<td>28 (34)</td>
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<td>1.44</td>
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<td>22 (23)</td>
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<tr>
<td></td>
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<td>25 (26)</td>
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<td>Sudden death</td>
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<td>1 (1)</td>
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<td></td>
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<td>6 (6)</td>
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<td>0.51</td>
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<td>Myocardial infarction, stroke, or sudden death</td>
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<td>42 (54)</td>
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<td>Confirmed</td>
<td>60 (76)</td>
<td>50 (54)</td>
<td>0.32</td>
<td>1.21</td>
</tr>
</tbody>
</table>

*Reported: Possible cardiovascular events reported by patient or a family member. Verified: Reported events that were verified by
adjudication process. Confirmed: Includes verified reported events and events not reported (obtained from the New Zealand national
database on hospital admissions).

†Values are numbers of women (numbers of events). Results are based on Fisher's exact test.

Data adopted and summarized from tables 2–4, Bolland et al.11

Table 1 Summary of analysis on vascular events in postmenopausal women in calcium supplementation and
placebo groups.
NOTE OF CAUTION

This is the first study that reports a probable negative effect of calcium supplementation on the risk of cardiovascular disease. However, some caution should be exercised in the interpretation of these findings because a careful review of the New Zealand Study reveals no explicit adverse cardiovascular events in the calcium supplementation group when the accuracy of the analyzed data was increased by using only data that could be verified by hospital records (Table 1). The findings do indicate a possible need for caution in prescribing very high doses of calcium supplements to the elderly, who may already be predisposed to chronic life-threatening cardiovascular disease. The participants in the calcium supplementation group consumed 1000 mg/day elemental calcium from a highly bioavailable calcium supplement (calcium citrate) in addition to their mean habitual calcium intake of about 900 mg/day, resulting in an overall mean calcium intake of 1900 mg/day. This mean level of daily calcium intake in the calcium supplementation group was higher than the current AI recommendation of 1200 mg calcium/day from the IOM. It was also higher than the 1500 mg calcium/day recommended by Osteoporosis Canada to protect bone in individuals older than 50 years, and it was lower than the 2500 mg/day tolerable upper limit set by the IOM. However, some participants in the calcium supplementation group who had a higher level of habitual calcium intake may have exceeded the 2500 mg/day upper-level calcium recommendation and would be at risk of hypercalcemia and its complications, including vascular calcification when lesion(s) are already present in the vascular endothelium. The beneficial effect of calcium supplementation on blood lipids reported in this study rules out possible mechanisms related to changes in blood lipid profile.

This study by Bolland et al. has important limitations. First, the original study was not primarily designed to evaluate the effect of calcium supplementation on cardiovascular diseases; hence, the sample size is small for cardiovascular endpoints. Second, the use of a composite cardiovascular endpoint creates difficulties in assessing the real impact of calcium supplementation on the relative risk of myocardial infarction. Third, some findings, such as those with borderline significance (Table 1), were misrepresented and overemphasized. Fourth, all subjects were white and about 10% of subjects were over 80 years of age, which makes it difficult to generalize the findings of this study to all postmenopausal females. Fifth, during the study, the authors did not monitor other possible confounders that could affect cardiovascular events, including serum 25-hydroxyvitamin D, analgesic usage, smoking, and hormone replacement therapy.

Most calcium supplementation studies have not evaluated cardiovascular events. A similar, but more reliable, study in terms of sample size is the Women’s Health Initiative. Participants included 36,282 postmenopausal women aged 50–79 years who were randomized into two groups—the calcium and vitamin D group (n = 18,176), which received calcium carbonate (500 mg) with vitamin D (200 IU) twice daily (elemental calcium of 400 mg/day), and the placebo group (n = 18,106). Although cardiovascular disease was not the primary outcome measure of this study, calcium and vitamin D supplementation did not increase the risk for myocardial infarction, death from coronary heart disease, stroke, hospitalized angina, heart failure, transient ischemic attack, and coronary revascularization. It should be noted that even though women were allowed to continue their calcium supplement intake, the total calcium intake in the intervention group did not exceed 1500 mg/day.

CONCLUSION

Data available from current studies, including the New Zealand Study and the Women’s Health Initiative, do not permit definitive conclusions to be reached with regard to calcium supplementation and the risk of cardiovascular diseases. In future studies, the cardiovascular effects of calcium supplementation should be assessed more carefully. The calcium supplementation studies reviewed here needed to be specifically designed to evaluate the risk of cardiovascular diseases as the primary outcome to address the current uncertainties. The possible detrimental effect (e.g., hypercalcemia and its complications) of higher-than-recommended calcium intake should be balanced against the likely benefits of calcium on bone, particularly in elderly women. To do this, women over 50 years of age are encouraged to meet the current IOM or Osteoporosis Canada calcium intake recommendations of 1200 or 1500 mg/day, respectively.

REFERENCES


