Calcium Supplements Tied to Higher MI Risk

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TORONTO – Calcium supplements appear to cause more harm than good, according to a meta-analysis of 28,000 participants in nine trials that include a new analysis of more than 16,000 participants in the Women's Health Initiative, but the re-analysis has raised concerns among the WHI's original investigators.

"We calculate that for every 1,000 people treated with calcium for 5 years, it will lead to four additional myocardial infarctions, four additional strokes, and two additional deaths, while preventing three fractures," Dr. Ian R. Reid said at the meeting.

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Major Finding: People taking a calcium supplement showed a statistically significant 24% excess relative risk for MI, a 15% excess relative risk for stroke, and a 16% excess relative risk for MI or stroke.

Data Source: Meta-analysis of nine studies that compared calcium supplements with placebo in a total of more than 28,000 people.

Disclosures: Dr. Reid said that he had no relevant disclosures.

"I don't prescribe calcium supplements to anyone anymore for preventing bone fractures. People should get calcium from their diet," said Dr. Reid, a professor of medicine at the University of Auckland, New Zealand.

"We believe there is a fundamental difference between dietary calcium and supplemental calcium." He speculated that a calcium supplement, even at a relatively modest dose of 500 mg, produces a "borderline hypercalcemia" that persists for several hours and raises the risk for myocardial infarction or stroke, the same way that people in the highest quartile for normal blood calcium levels have an increased risk for cardiovascular disease events.

But the researchers who ran the Women's Health Initiative (WHI) study questioned the legitimacy of the new analysis beyond a hypothesis-generating exercise.

"The WHI investigators have concerns about the reanalysis and whether omitting the subgroups with favorable results is appropriate," commented Dr. JoAnn E. Manson, professor of medicine at Harvard University and chief of the division of preventive medicine at Brigham and Women's Hospital, both in Boston, and a WHI coinvestigator.

Dr. Reid and his associates initially documented their finding that calcium supplements raise cardiovascular risk in a pair of meta-analyses published online last July (BMJ 2010;341:c3691). They reported that calcium supplement use was linked with a statistically significant 27% and 31% relatively increased risk for myocardial infarction in two separate meta-analyses.

To further explore the impact of calcium supplements on cardiovascular risk, they received permission from the National Heart, Lung, and Blood Institute to reanalyze data collected in a WHI study of more than 36,000 postmenopausal women randomized to receive a daily supplement with 500 mg calcium plus vitamin D or placebo.

The original report from the WHI investigators showed that the calcium plus vitamin D treatment did not significantly increase or decrease coronary or cerebrovascular risk in generally healthy postmenopausal women during 7 years of treatment (Circulation 2007;115:846-54).

But the WHI study design allowed the participants to take more calcium supplements in addition to their study agent, if they wanted to do so. At baseline, more than 19,000 (54%) of the women in the study reported using a calcium supplement on their own, and at the end of the study 69% reported the practice, Dr. Reid said. To address the possible confounding this may have caused, he focused his analysis on the 16,718 women in the WHI study who reported not using a personal calcium supplement at entry into the study.

In this subgroup, the MI rate ran 2.5% in women randomized to calcium supplement treatment, and 2.0% among women in the placebo arm, a 22% relative increased MI rate with the calcium supplement that was statistically significant. The rate of MI or stroke ran a relative 16% higher among the women taking the calcium supplement, which was also statistically significant. The results showed no significant effect of calcium supplementation on stroke rate. "We saw the same effect as in the meta-analysis," Dr. Reid said.

But if Dr. Reid's analysis did not start with a prior hypothesis, this finding can only be considered hypothesis generating, not hypothesis testing, Dr. Manson said in an interview. "Many subgroups were tested in the WHI, and some would be expected to show significant effect modification by chance," she pointed out. In addition, randomization made background levels of calcium use similar in the two treatment arms and thereby neutralized background calcium use as a possible confounder. Dr. Manson also noted that if supplemental calcium posed a risk, the event rates should have been highest among women taking both the study calcium dose and an additional dose on their own.

The evidence for an increased MI risk is stronger than the evidence that supplements prevent bone fractures.

DR. REID

When the Auckland researchers added the results from the WHI subanalysis to their previously reported meta-analysis, they "just reinforced the trends and made them more significant," Dr. Reid said in an interview.

When data from the WHI subgroup that did not use personal calcium supplements at baseline were added to the meta-analysis, the results showed that those who did take supplements had a 24% relative excess of MIs, a 15% relative excess of stroke, and a 16% relative excess of MI or stroke, he reported.

There are concerns about 'whether omitting the subgroups with favorable results is appropriate.'

DR. MANSON

"What we now have is six or seven very large trials, and [the results they show] for myocardial infarction all line up very consistently, without significant heterogeneity. When you look at risk vs. benefit, the evidence for an increased risk of myocardial infarction is stronger than the evidence that calcium supplements prevent bone fractures. It's hard to justify continuing calcium supplements," Dr. Reid said. ■

Bone Changes Precede RA Symptoms

Bone metabolism appears to change before patients show clinical signs of rheumatoid arthritis and could ultimately serve as an early marker of disease, based on a study of 79 patients.

"There appears to be an alteration in bone metabolism parallel to inflammation and autoimmunity in the asymptomatic preclinical phase of RA, which may reflect the beginning of joint destruction," according to Dr. Dirkjan van Schaardenburg, a rheumatologist at Jan van Breemen Institute in Amsterdam, and his coinvestigators.

They found significantly increased average levels of only P1NP (procollagen type I intact N-terminal propeptide) and osteoprotegerin in the group of preclinical RA patients, compared with a control group of healthy individuals. Specifically, P1NP increased by 5 ng/mL and osteoprotegerin increased by 4 pmol/L (Ann. Rheum. Dis. 2010 Oct. 18 [doi:10.1136/ard.2010.135723]).

Three blood samples taken 1, 2, and 5 years prior to the onset of symptoms were identified for 47 patients with RA; two samples were collected from 18 patients and one sample was collected from 14 patients. The individuals had been blood donors prior to developing the disease.

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–Kerri Wachter