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Genetic Study Supports Link Between Serum Calcium and CAD Risk

The findings strengthen concerns about the use of calcium supplementation, one expert says.

By Todd Neale July 26, 2017

People who are genetically predisposed to having higher serum calcium levels seem to have an elevated coronary risk, a mendelian randomization study shows.

Every 0.5-mg/dL increase in serum calcium levels estimated on the basis of information about six single-nucleotide polymorphisms (SNPs) was associated with greater chances of both overall CAD (OR 1.25; 95% CI 1.08-1.45) and MI (OR 1.24; 95% CI 1.05-1.46), Susanna Larsson, PhD (Karolinska Institute, Stockholm, Sweden), and colleagues report in a study published in the July 25, 2017, issue of the Journal of the American Medical Association.

Those findings, Larsson told TCTMD, are consistent with relationships seen in prior observational studies and secondary results of randomized trials of calcium supplementation. Thus, this study offers "more confirmation that the association between calcium and cardiovascular disease could be causal, that it is a true association," she said.

The totality of the evidence suggests that high serum calcium levels might be harmful, so clinicians should be more cautious about prescribing calcium supplements, which have been shown to have only a modest impact on lowering fracture risk, Larsson said.

She pointed out, however, the exposure in this study was to higher lifelong, genetically determined serum calcium levels. "We don't know if short-to-medium-term calcium supplementation also increases the risk or if you need to take calcium supplementation for a very long time to cause harm," she said.

More research is needed to clarify the issue.

Erin Michos, MD (Johns Hopkins University School of Medicine, Baltimore, MD), who was not involved in the study, called it "a very important and timely paper given the recent

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controversy about the safety of calcium supplements."

Prior studies have shown that higher serum calcium levels are associated with greater risks of incident diabetes, stroke, MI, CVD mortality, and all-cause mortality. But because those studies have been observational, they likely were subject to residual confounding and confounding by indication, Michos wrote in an email to TCTMD. Additionally, clinical trials of calcium supplementation have yielded mixed results.

"Mendelian randomization genetic studies can overcome these concerns about confounding and provide support for biological (causal) associations," said Michos.

Six SNPs Linked to Serum Calcium

For this analysis, the researchers identified six SNPs directly associated with serum calcium but no other risk factors from a meta-analysis of genome-wide association studies. They then estimated the magnitude of the relationships between the SNPs and coronary disease using an additional meta-analysis that included a total of 184,305 people, one-third of whom had CAD (about 70% with MI). By their estimation, the SNPs explained about 0.8% of the overall variation in serum calcium levels observed in that group.

None of the individual SNPs were associated with CAD, but the relationship became significant when estimates of the effects of the six SNPs were combined.

To TCTMD, Michos said she has "long advocated for caution with calcium supplement use," pointing to evidence that consuming more calcium than recommended

may contribute to various health problems, including kidney stones, constipation, and possibly MI.

"These genetic studies give more credence to the concerns raised by the . . . observational studies and can help inform the calcium debate," she said. "This paper by Larsson et al has certainly strengthened my concerns."

If the association is causal, there could be several potential mechanisms to explain it, according to Michos.

"This excess serum calcium could deposit in soft tissues such as the vasculature. Additionally, as calcium is an important component of the coagulopathy cascade, acute rises in serum calcium levels can trigger a hypercoagulable state," she explained. "Elevated serum calcium levels may also lead to diabetes and endothelial dysfunction."

Citing the importance of calcium for many bodily functions, Michos advised getting the recommended daily allowance of the mineral from dietary sources, which do not confer excess risk. Such foods include leafy green vegetables and low-fat dairy products.

"When calcium is taken in through diet, it is taken in in smaller doses spread throughout the day and taken in with other nutrients," Michos said. "But in a supplemental form, it is often consumed in a large bolus all at once that can transiently raise the serum levels of calcium. If one is reaching the recommended daily allowance, then supplementation is probably not needed."

Sources

Larsson SC, Burgess S, Michaëlsson K. Association of genetic variants related to serum calcium levels with coronary artery disease and myocardial infarction. JAMA. 2017;318:371-380.

Disclosures

The study was supported by a Junior Researcher Award grant to Larsson from the Strategic Research Area in Epidemiology at Karolinska Institute.

Larsson reports no relevant conflicts of interest.

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