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NEWS

Calcium Supplementation and Vascular Disease: A Legitimate New Worry?

Neil A. Andrews

Managing Editor, IBMS BoneKEy

A recent study (1) on calcium supplementation is provoking a good deal of discussion – and controversy – in the bone field. In an article published in the *BMJ* by Ian Reid and colleagues earlier this year, the authors express concern about findings they say demonstrate a potentially troubling link between the use of calcium supplementation and an increased risk of vascular events, including myocardial infarction. Yet several investigators who have data on this topic from their own clinical trials find no reason to worry; they question the quality of the evidence provided in the *BMJ* study and confidently assert that the weight of the evidence, from their own work and other studies, strongly suggests that calcium supplementation has no adverse effects on vascular health.

The *BMJ* study authors, however, are not alone in their stance. In fact, an editorial (2) accompanying the original article expresses support for the study's main conclusions. Furthermore, while some of the study's skeptics dismiss the new research because they see no viable physiological mechanism by which calcium supplementation could cause vascular problems, some experts have no difficulty in identifying a plausible mechanism, and consequently believe the study should not be so easily cast aside on that basis alone. The positions that various experts hold on the new work hinge on whether borderline statistically significant findings concern them and why (or why not); how they interpret related research; and whether treatment effects should be considered genuine only when researchers have pinpointed a feasible mechanism to mediate those effects.

The New Findings

The *BMJ* study presents the results of a secondary analysis of a randomized controlled trial, originally published in 2006 in the *American Journal of Medicine*, that examined the impact of calcium supplementation on the incidence of fractures in healthy postmenopausal women. While the primary endpoint of the original trial was fractures, the authors pre-specified vascular endpoints, including myocardial infarction (MI), stroke, sudden death, or a composite of the three, for the secondary analysis since evidence from previous studies had suggested that calcium supplementation might actually protect against vascular disease, perhaps through effects on blood lipids, blood pressure or body weight.

From the more than 1400 women who took part in the study by receiving either 1 gram per day of calcium citrate or placebo, the *BMJ* research provides three main sets of findings. First, the researchers found that when vascular events were self-reported by study subjects or reported by family members, those receiving calcium supplementation exhibited a statistically significant increase in myocardial infarction (p=.0099), and in the composite endpoint of MI, stroke or sudden death (p=.0075), compared to placebo. Specifically, for MI, there were 45 vascular events in 31 women, compared to 19 events in 14 women, in the calcium group compared to placebo, corresponding to a relative risk of 2.24. For the composite endpoint, there were 101 events in 69 women, compared to 54 events in 42 women, in the calcium group compared to placebo, corresponding to a relative risk of 1.66.

Second, the researchers then had physicians who were blinded to the study results adjudicate the self-reported findings by examining medical records. The relative risk estimates for MI and for the composite endpoint were similar to those seen in the self-reported data, though now statistical significance, of the borderline variety, was observed for MI only (p=.047). Third, concerned by the self-reported and adjudicated findings, the researchers made use of a New Zealand hospital database of hospital admissions to identify additional vascular events among the study participants that might have been overlooked, and assessed whether this approach gave results different from the two previous data sets. Now they found that there were no statistically significant differences between the calcium and placebo groups in the number of women with MI or the composite endpoint. However, when the data were expressed as rate ratios, borderline statistically significant increases were found for MI (rate ratio = 1.67, p=.058) and the composite endpoint (rate ratio = 1.43, p=.043) in the calcium group, compared to placebo.

According to Andrew Grey, a co-author of the study and an associate professor of medicine at the University of Auckland, all of the data point in a similar direction. "The message to us is pretty clear that there is a strong suggestion that there may be a weak but definite effect of calcium to increase vascular event rates," Dr. Grey concludes.

The Skeptics

While the *BMJ* study authors are concerned about their findings, other investigators with relevant data of their own are highly skeptical because of their view of the quality of the evidence presented in the study. First, because many of the study's key findings did not reach statistical significance, and when they did, they reached only borderline statistical significance, these other researchers don't think the *BMJ* work actually provides any evidence of a genuine effect of calcium supplementation, at all. "If this study can't be replicated, the most plausible conclusion is that the finding was due to chance," says Robert P. Heaney, John A. Creighton University Professor at Creighton University in Omaha.

Dr. Heaney's stance results not just from a consideration of the *BMJ* research, but also from an analysis of other studies that have found no effect of calcium supplementation on vascular health. For instance, he points to his own research, a randomized controlled trial of calcium supplementation published in the *American Journal of Clinical Nutrition* in 2007. Like the *BMJ* study, Dr. Heaney's trial had fracture incidence as its primary endpoint, and included similar numbers of women. After learning of the *BMJ* results, Dr. Heaney and a colleague went back to their own trial and looked for evidence of vascular problems and then reported their findings in the *BMJ* (3). They found that, even though their study subjects took about 50% more of the same brand of calcium, from the same company, than the *BMJ* study participants did, they did not find any excess of MI or any other vascular events that were verified with the study subjects' personal physicians. In fact, they observed a trend in the opposite direction: subjects exhibited a slightly lower risk of vascular events, though this trend did not reach statistical significance.

Dr. Heaney highlights not only his own data, but also other studies suggesting the same conclusion, including the Women's Health Initiative (WHI) randomized controlled trial that examined the impact of calcium and vitamin D supplementation on fractures, with cardiovascular disease serving as a pre-specified secondary outcome. The results for the latter analysis, published last year in *Circulation* and including more than 36,000 healthy postmenopausal women aged 50 to 79, showed no effect, positive or negative, of supplementation on vascular events. To Andrea LaCroix, an epidemiologist at the Fred Hutchinson Cancer Research Center in Seattle who is leading the WHI analyses of calcium/vitamin D and mortality, the WHI result is far more believable than the *BMJ* research because the size of the WHI study allowed for the observation of a much larger number of vascular events in both the calcium and placebo groups. For instance,

for verified cardiovascular events, Dr. LaCroix compares the 499 and 475 events (MI or coronary heart disease death) observed in the WHI calcium/vitamin D and placebo groups, respectively, to the 24 and 10 events (MI) in the *BMJ* calcium and placebo groups. "I don't think the *BMJ* study provides strong enough evidence to overturn a null result from a well-designed trial that had twenty times more evidence," Dr. LaCroix stresses. "This is a classic example of a small study with an extreme result getting far more attention and producing far more alarm than it should."

In addition to the small number of events, as well as the lack of statistically significant findings, Dr. LaCroix highlights the *BMJ* study's wide confidence intervals, such as those for the increased relative risk of 2.12 for MI, in the adjudicated data. "The confidence limits go from about 1.0 to 4.5, so this is a very imprecise result," she says. "One can't pin down on the basis of this study whether there is any increased risk," she emphasizes. Dr. LaCroix also notes that the relative risk of 2.12 far exceeds the confidence intervals of 0.92-1.18 observed in the WHI study, where the hazard ratio of MI or coronary heart disease death was 1.04. "Our confidence limits say that if there is any increased risk, it's not above 1.18, and it's highly likely that there isn't any increased risk, because the overall effect is 1.04," Dr. LaCroix concludes.

Richard Prince, an associate professor at the University of Western Australia who has conducted his own clinical trial of the effects of calcium supplementation on fractures, also doubts the *BMJ* study's findings. To Dr. Prince, one of the troubling aspects of the research is that as the quality of evidence to his mind becomes stronger – he regards the self-reported data as the weakest form of evidence, and the data that includes the hospital database as the strongest – the impact of calcium supplementation becomes weaker, with statistical significance vanishing with the strongest evidence, unless results are expressed as rate ratios, but even then, only borderline statistical significance is observed.

Interestingly – and to Dr. Prince's chagrin – the *BMJ* authors cite Dr. Prince's own clinical trial as evidence in support of their main findings. Considering that his results revealed a hazard ratio for ischemic heart disease of 1.12, with a CI of 0.77-1.64, for calcium supplementation compared to placebo, Dr. Prince disagrees that his study provides them with any support. "They claim that a hazard ratio of 1.12, with wide confidence intervals, supports their contention. Well, it doesn't, not if we use conventional estimates of statistical significance," he says.

In addition to the findings from Dr. Prince, Dr. Heaney and the WHI, the other large calcium/vitamin D trial with relevant data, according to the *BMJ* authors, is the RECORD trial, published in *Lancet* in 2005. The *BMJ* authors write that this trial found a trend towards increased death rates (18.5% versus 16.3%) in subjects receiving calcium versus placebo. When asked to comment, RECORD investigators referred any questions on to the *BMJ* authors, since the former are now cooperating with the latter on further analyses.

The Defense

Dr. Grey and his colleagues are well aware of the critics' objections, many of which have been raised in a slew of Rapid Responses submitted by *BMJ* readers in response to the original article. However, while they concede that their findings could be due to chance, and also admit that definitive conclusions cannot be reached until further studies are in hand, they are not backing down from their findings, and remain concerned, for several reasons.

First, they take less comfort in the other studies, particularly the WHI research, because of differences between the WHI study population and their study population. For instance, they note that the women in WHI were younger than the women in the *BMJ* study by about 15 years on average. In addition, they emphasize that compliance with calcium supplementation was much worse in WHI than in their own trial. Furthermore, they stress that the WHI

subjects received both vitamin D and calcium. "There's some evidence that vitamin D is beneficial in terms of vascular risk, so perhaps that actually attenuates the calcium effect," Dr. Grey says.

Dr. Grey also wonders whether the focus on p values by the study's critics comes at the expense of appreciating a larger picture that he and his colleagues think emerges when all of the data, from all the different data sets, are considered. "People seem to focus, perhaps a little obsessively, about whether the p value is .055 and therefore untrue or .045 and therefore true. I think that the signal from all of these analyses is one that raises the possibility that there is harm here," Dr. Grey says. In addition, the study authors believe that, when considering the potential size of an increase in risk, a larger perspective is needed here as well. "Even if there's only a 20-30% increase in the risk of vascular events in women exposed to calcium supplements, that's a really important finding because of the number of women who were exposed and the prevalence of vascular disease in this age group," Dr. Grey emphasizes.

Furthermore, the investigators believe that the time is ripe for people to question their assumptions about calcium supplementation not only because of the *BMJ* findings, but also because other data in their view suggests that the issue is now more complicated than in the past. For instance, Dr. Grey points to a meta-analysis published last year in the *Lancet* by Benjamin Tang and colleagues suggesting that the use of calcium as monotherapy has quite modest effects on the risk of all osteoporotic fractures of about 10%. He also refers to a meta-analysis that he conducted with his colleagues suggesting that there may in fact be an increase in the risk of hip fractures in those taking calcium as monotherapy. Because of this, Dr. Grey says that the overall message he and his colleagues hope to send is that a much more nuanced and careful approach to the topic of calcium supplementation is in order.

Finally, it should be noted that Dr. Grey and his co-authors are not alone in their position. In an editorial accompanying the *BMJ* article, Graeme Jones and Tania Winzenberg, who have written on calcium supplementation in childhood, express support for the study's main findings. Of most concern to them is the relative risk for MI of 2.12 observed in the adjudicated data, which Dr. Jones views as the strongest evidence because he says it is less prone to error than data coming from national databases. "In the data that I consider the most robust, they saw a doubling of the risk of heart attack, and this effect was statistically significant. If calcium is actually doubling heart attack risk, and only changing fracture risk by a small amount, and if these results are confirmed by other trials, then we shouldn't be using it," says Dr. Jones, a professor of rheumatology and epidemiology at Menzies Research Institute in Hobart, Australia. Like the study authors, Dr. Jones is also less comforted by the WHI research because of the differences in its study population. Finally, while he believes the findings from Dr. Heaney's study are somewhat reassuring, he cautions that this study reported results for the entire group of subjects, and not specifically for patients compliant with treatment.

Is There a Viable Mechanism?

Some critics question the *BMJ* findings because they cannot envision a plausible physiological mechanism by which calcium supplementation could lead to adverse consequences on vascular health. The study authors point to vascular calcification, the deposition of calcium within the body's blood vessels, as a possible mechanism, since there is evidence of vascular calcification in patients with chronic renal failure taking calcium supplements. While the subjects in the *BMJ* study were not suffering from that condition, Dr. Grey notes that because of their advanced age, their renal functioning levels will have already declined in comparison to younger individuals. Those who doubt the vascular calcification hypothesis counter by saying that serum levels of calcium would not rise high enough during calcium supplementation to cause vascular calcification. They also argue that because damaged tissue calcifies, vascular

calcification could simply be a marker of tissue damage; calcium supplementation need not have caused that damage. Observers say that measuring the calcium levels in the blood achieved with calcium supplementation, as well as assessing the degree of vascular calcification, would help address these concerns.

To complicate matters further in the quest for a mechanism is the potential role of vitamin D and parathyroid hormone (PTH). According to Michael Holick, a vitamin D expert and professor of medicine, physiology and biophysics at Boston University Medical Center, subjects in the *BMJ* study are likely to have been deficient in vitamin D and also to have secondary hyperparathyroidism. "To me, the most important thing is the vitamin D status, and the PTH status, since we think those may very well affect the risk of soft tissue calcification, including calcification of the arteries," Dr. Holick explains. Measuring levels of both would help clarify whether calcium itself is truly the culprit.

However, researchers may be too focused on vascular calcification at the expense of overlooking other potential mechanisms by which calcium supplementation could cause vascular events, according to Dwight Towler, an expert on vascular calcification. "To think that all of the potential problems with calcium supplementation in vascular function have to be related to vascular calcium deposition is a knee-jerk reflex that ignores a lot of other physiology. Vascular calcification matters, but it's not the only thing," Dr. Towler, a professor of medicine at Washington University in St. Louis, stresses. For instance, he notes that alterations in PTH signaling are associated with impaired vascular responses, such as abnormalities in the response of blood vessels to blood flow, and an increased risk of cardiovascular mortality. As another example, he points to recent genetic evidence showing that polymorphisms in the calcium-sensing receptor that affect calcium and PTH levels are associated with coronary heart disease, MI, and cardiovascular mortality. That many reflexively think of vascular calcification as the potential mechanism may stem from the fact that knowledge in this area is still young and emerging. "I think it points to shortcomings in our understanding of the effects of calciotropic hormones both directly and indirectly on physiological function in the vasculature, including calcification, but not just calcification," Dr. Towler says.

Furthermore, Dr. Towler notes that the younger age of the women in the WHI study might explain why vascular problems were not an issue there. Indeed, he emphasizes that major changes in renal function occur as people age from their 60s into their 70s. In fact, he observes that the baseline renal functioning of subjects in the *BMJ* study was at approximately the level at which kidney problems begin to have significant vascular consequences, an issue that experts are only starting to understand. "We're beginning to learn that major perturbations in renal function do matter in terms of cardiovascular risk," Dr. Towler emphasizes, noting that it is estimated that a change in kidney function from the normal range to that seen in the *BMJ* study results in a 2.5 to 3-fold increase in cardiovascular mortality. For these reasons, Dr. Towler thinks it would be useful to stratify the vascular events observed in the *BMJ* work with respect to kidney function.

Finally, in noting the uncertainty that some have voiced about a possible mechanism of action, Dr. Jones stresses that a lack of understanding in this regard need not imply that an effect of calcium supplementation must not be genuine. "You don't always have to have a mechanism for something to be real," he says, noting that in his field of rheumatology, many examples exist of treatments that have been proven to work in clinical trials yet whose mechanism of action remains uncertain.

Salvation in a Meta-Analysis? But What About Now?

The *BMJ* study authors believe that a meta-analysis of calcium trials with data on vascular events will clarify whether there is truth to their findings or not. In fact, Dr. Grey and his colleagues are now working with an international group of collaborators who

have been involved with other major calcium studies for just this purpose. This is an approach to settling unresolved research issues that may not thrill investigators who caution that meta-analyses are only as good as the studies composing them.

Until then, are any changes in current recommendations for calcium intake in order? In the conclusion to their article, the *BMJ* authors write that the "potentially detrimental effect [of calcium supplementation on vascular events] should be balanced against the likely benefits of calcium on bone, particularly in elderly women." This language has particularly inflamed critics who feel that detrimental effects should actually be demonstrated with evidence before investigators make statements that might affect clinical practice. Dr. Heaney says that the benefits of calcium supplementation are proven and that there is simply no reason to modify current recommendations based on the *BMJ* findings. In the end, critics have been concerned that the new research has caused and may continue to foster unwarranted anxiety. Dr. Grey says that though he and his colleagues certainly did not intend for this outcome, they also felt they couldn't withhold publishing their findings from the research community. "I hope we haven't caused too much alarm, but we really didn't have any choice. It's a very important issue that needs to be discussed and presented."

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