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EDITORIAL

Potential negative cardiovascular effects of calcium supplements

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Calcium supplements have been used for decades in the prevention and, as an adjuvant, for treatment of osteoporosis because low calcium intakes are frequent and have negative effects on bone health. There is an abundant literature showing the beneficial effects of an adequate calcium intake on the maintenance of bone mineral density (BMD) in adults, and on the slowing of the loss of BMD in the elderly. There is even some evidence that it has a moderate effect on fracture risk. In other words, the prescription of calcium supplements in the prevention of osteoporosis has its place, in so far as it causes no harm.

Although a very high intake of 3–4 g per day is not recommended, there is no proof that such intakes are harmful. Hypercalciuria in kidney stone formers and gastrointestinal intolerance are the only well-known contra-indications. Fractional calcium absorption decreases with higher intakes and protects the body from excess intake, at least in part. Indeed, calcium supplementation had no safety restrictions. The negative effects of calcium supplements listed in the recent report of the Institute of Medicine of the US [1] include kidney stones, milk-alkali syndrome and hypercalcemia with its various consequences. But the risk of renal stones is not confirmed [2], that of hypercalcemia is not documented, and as for provoking the rare milk-alkali syndrome, it needs more than just a calcium supplement. If the same strict scientific parameters were applied for assessing the upper tolerable intake level of calcium (or the lowest observed adverse effect level), as for assessing the positive effects of calcium supplements on bone, it would be impossible to define an upper safety limit.

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New information on the possibility of negative cardiovascular effects puts a cloud in the so far quiet sky of calcium supplementation. In the paper by I. Reid et al. in this issue [3], the two studies by the same authors, which provided this troublesome information, are again discussed as a response to the international reaction and criticism which these two papers provoked [4, 5]. The authors defend very carefully their observation that calcium supplements increase cardiovascular risk and discuss the hypothetical mechanisms. As calcium prescribers, one might be tempted to accept this notion, safe in the knowledge that calcium from nutrients is harmless and therefore preferable. However, patients rarely consume the recommended amount of calcium with their food, and for this reason, we should examine carefully the claim for harmful effects of calcium supplements. Without discussing the methodical aspects of the two studies—the authors of the manuscript in this issue do this extensively—a few considerations allow us to question their practical significance.

First, we are entitled to retain from these publications only those results which were statistically significant. Data which are not significant should not be over interpreted. They can be noted as a trend, which should be considered—by definition—as not meaningful, not indicative and not notable, unless the lack of significance is taken as a message in itself. This then excludes the increased risk of stroke and sudden death, which are reported as adverse effects of calcium supplements, and leaves us with the risk of myocardial infarction (MI) as the only significant negative event of calcium supplementation.

The significance stems from a meta-analysis [5]. In the previous trial from the same authors [4], the risk of MI was no longer significantly increased once the data had undergone a quality control audit using the national database of hospital admissions. The meta-analysis of 15 trials demonstrated a significant increase of the risk of MI

induced by calcium supplements, although none of the studies analysed individually resulted in significant results, even not the largest one. In the hierarchy of evidences, the Centre for Evidence-Based Medicine, Oxford, UK puts a meta-analysis with homogenous outcomes above the level of evidence provided by a randomized controlled trial (RCT), but this implies that the outcomes are primary or secondary, and not—as here in many cases—retrospectively defined outcomes. For this reason, this study is not a conventional meta-analysis. Some critics call it a 'review of published trials' [6]. This leads to the following question: will a well-powered RCT with cardiovascular events as primary outcomes not have a comparable weight of evidence? According to Reid and colleagues [3], such trials cannot be envisaged for reasons of practicality and ethical obstacles. But there is one such study, and it showed no negative cardiovascular effects [7].

Even accepting the result of this "meta-analysis", we still should remember its context—namely, in the prevention of osteoporosis. In the treatment of osteoporosis, calcium is prescribed in combination with vitamin D and anti-osteoporotic drugs, and no significant cardiovascular risks were reported. Therefore, the risk of MI would only increase with calcium alone without vitamin D, and is irrelevant for osteoporotic patients.

Another consideration concerning the practical importance of these observations is the uncertainty about the total calcium intake of the subjects. In RCTs of medical treatments of osteoporosis, the total calcium intake is usually assessed by simplified questionnaires. A precise assessment would be very cumbersome and expensive and needs a detailed quantification of the food intake by a Food Frequency Questionnaire (FFQ), or equivalent, which determines the calcium content and the amount consumed of each nutrient. Such a detailed investigation leads to higher numbers of calcium intake than the simplified questionnaires. Indeed, FFQ analysis showed that calcium from dairy products represents not more than 50% of the total nutritional intake [8], at least in Switzerland. Therefore, it can be supposed that in certain subjects taking supplements of 1,000 mg or more, the total calcium intake would be very high.

One also can question if the increased risk of MI is meaningful, independently of its statistical significance. In this context, health authorities, and by this the lay press, tend to exaggeration. For instance, the antidiabetic drug rosiglitazone had to be withdrawn from the market, because it was reported to increase the odds ratio for MI by 80% [9]. But the absolute risk was not mentioned in the relevant paper [9]. It is the absolute increase in risk, and not only the relative risk, which allows us to determine the importance of the finding. In an earlier publication from the same author [10], it appears that the combined outcome of MI or cardiovascular death or stroke occurred in 0.73% of the patients on rosiglitazone, and in 0.67% of placebo-treated patients, a difference of only 0.06%. In other words, these adverse effects occurred as the eventual consequence of rosiglitazone in 1 out of 1,666 patients treated. Is it reasonable that such a weak effect results in the unavailability of this agent with the established benefit for the majority of patients? The risk of MI induced with rosiglitazone is not much higher than the risk of mortality by driving a car in Switzerland (about 1 per 10,000 cars per year) and negligible when compared with the 40,000 persons killed in car accidents each year in the USA. Returning to calcium, Reid et al. [3] report a 30% increased risk of MI is associated with calcium supplements. This sounds impressive. But according to Table 3 of their 'meta-analysis' [5], MI occurred in 2.714% of the patients on calcium, and in 2.239% in those on placebo, a difference of 0.475%, which might affect 1 out of 210 patients treated over 5 years, not more. Although this risk would still be higher than that we normally accept in daily life, it is based on an analysis with questionable evidence.

Another concern about the validity of these studies relates the amount of calcium prescribed. The calcium supplements contained 1 g or more, and could have been taken in the fasting state. As mentioned by the authors, this may give rise to transient hypercalcemia for several hours, which—when repeated every day over several years—might increase the risk of coronary heart disease. Indeed, no increased cardiovascular risks were observed with calcium from food which is absorbed more slowly. Even the administration of a calcium supplement in the form of bone powder does not increase the plasma calcium level above normal [11]. In the same way, calcium supplements increase slightly the risk of renal stones in some studies, whereas calcium from food decreases this risk [2]. It might be assumed, therefore, in the light of the studies of Bolland et al. [4, 5], that supplements of only 500 mg of calcium taken after a meal are harmless, even when taken twice a day.

The question remains if a supplement of 500 mg per day is enough. One could argue that a supplement of 500 mg of calcium does not meet the requirements, which were redefined recently by the Institute of Medicine in the USA (IOM) [1]. The report states that 1,000 mg of calcium is the estimated average requirement for women over 50 years, and 1,200 mg/day is the recommended daily allowance. But these figures are derived from studies in populations whose bone health was not optimal. These studies were not titrated against the blood level of 25-hydroxyvitamin D. They were performed in populations that probably were—as we now know to be—vitamin D deficient. Vitamin D deficiency is prevalent worldwide [12] and it is reasonable to assume, therefore, that the recommendations of the IOM are

unnecessarily high. If human beings were exposed to sunlight regularly, not only would they have higher 25-hydroxyvitamin D levels, they might also need less calcium for optimal bone health. It is, by the way, surprising, how low the recommendations of the IOM report are for vitamin D. They were considered by experts like R.P. Heaney and M. Holick as to 'fail on three grounds: logic, science and guidance' [13]. This allows us to suppose that calcium supplements of 500 mg are effective, so long as the vitamin D level is optimal. Indeed, high 25-hydroxyvitamin D levels seemed to compensate for the otherwise negative effects of a low calcium intake (<716 mg/day) on BMD [14].

In conclusion, if the reported increased risk of MI induced by calcium supplements of 1,000–1,200 mg were the result of a meta-analysis of studies with MI as primary outcomes, it still would not challenge the clinical practice free of cardiovascular dangers, which favours supplements of 500 mg to be taken after meals, combined with vitamin D when the nutritional intake of calcium does not sum up to 800 mg.

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