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Invited Commentary

Comment on Bristow *et al.*: Dietary calcium: adverse or beneficial effects of supplements?

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Adequate Ca nutrition remains a significant issue throughout all stages of life, for bone mineral accrual during growth and maintenance of bone mineral in adulthood. Many individuals do not achieve the recommended daily allowance from their self-selected diets and take Ca supplements[1]. The paper by Bristow *et al.*[2] reports data on effects of Ca both in the form of supplements and in a meal on acute effects on serum Ca and phosphate levels, with most interesting results relevant to the likelihood of Ca supplements increasing serum levels to cause adverse cardiovascular events.

The most recent thorough review of dietary Ca requirements reached remarkable consistency with previous recommendations without controversy[1]. These recommendations were based on physiological outcomes, the level of dietary Ca required to achieve Ca balance, and clinical outcomes, including maintenance of bone mineral density and risk of fracture. The recognition that low Ca intakes are common, has stimulated the medical professionals to promote the use of Ca supplements for over 20 years. Ca is a threshold nutrient, such that an intake sufficient to achieve balance between the intake and excretion is required. No further benefit is achieved by increasing dietary intake above this level as any extra Ca is mainly excreted by the bowel but also by the kidney and through the skin. Within this physiological context, randomised controlled trials (RCT) of Ca supplementation and meta-analyses of their outcomes have demonstrated significant reduction in the risk of fracture among post-menopausal women[3,4]. Such outcomes have prompted strong endorsement for Ca supplements from authorities, including the US National Institutes of Health requiring the outcomes of clinical trials for osteoporosis to be compared with Ca and vitamin D supplementation, as standard of care rather than a true placebo. The uptake of Ca supplements among the general community has been widespread with some 60 % of the US women over 60 years of age taking a Ca supplement in the period 2003–2006, an increase from 28 % in 1988 to 1994[5].

Recent secondary analyses of RCT of Ca and/or vitamin supplementation for fractures have indicated mixed results for cardiovascular events, either increased the risk of adverse events, differential effects between men and women, or had no adverse effects[2,6]. Clearly considerable controversy and confusion remain on this subject. Meta-analyses from RCT are defined as the highest level of evidence, assuming that the design of each study or systematic review has minimised the impact of bias on the results[7]. One has to question whether this assumption is often met particularly in the conduct of RCT involving nutrients. For example, the analysis and re-analyses of data from perhaps the largest and longest RCT in this field, the Women's Health Initiative have provided a variety of results[5]. Of particular interest is that in the original analysis women who were taking their own Ca and vitamin D supplements were not excluded at the commencement of the trial and were allowed to continue this practice, irrespective of whether they were allocated to the active or placebo arms. Re-analyses of these data and inclusion of other subjects based on their baseline-dietary intake demonstrated various health benefits, not indicated by the original analysis for fracture or cardiovascular outcomes[8–10]. Such variation in outcomes would suggest that the basic assumption of an RCT, randomisation of subjects to minimise the impact of bias on the results, has not been met. It is difficult to estimate how many RCT do not meet this criterion.

An interesting and consistent finding is that dietary Ca is apparently not associated with adverse cardiovascular events, the physiological basis of which is not understood. One hypothesis to explain this difference has been that Ca supplements yield higher levels of circulating Ca than when Ca is taken in food. The paper by Bristow *et al.*[2] reports data on serum Ca and phosphate levels, following a variety of forms of dietary Ca. Increases in blood-ionised Ca, serum-total Ca and phosphate were observed with each intervention, although the increased levels of ionised and total Ca following the dairy meal were not as great as with supplements whether fasting or following a meal, providing evidence for this hypothesis.

The central question arising from this study is the physiological significance of such increases whether for bone or cardiovascular health. The major mechanism by which changes in serum Ca levels modulate physiology is through the Ca-sensing receptor (CaSR)[11]. Ionised Ca is the ligand for the CaSR, and the increases of blood ionised Ca demonstrated in the Bristow *et al.* study are sufficient to activate this receptor (0·02–0·05 mmol/l[12]) although the increase following the dairy meal barely achieved this minimum level. For bone health, activation of the CaSR can stimulate bone formation and reduce bone resorption, depending on conditions[12]. For cardiovascular health, activation of CaSR can reduce mineralisation by vascular smooth-muscle cells[11]. Within the context of chronic kidney disease, cardiovascular deaths are most important and the contributions of elevated blood phosphate to this pathology

have been well demonstrated[13]. However, Bristow *et al.* report that the highest phosphate levels are achieved when a meal is involved with the Ca supplement, a condition which one would expect to reduce the risk of adverse outcomes. Finally, although variations of serum Ca of the order demonstrated with Ca supplements have been found in cross-sectional studies to be associated with increased-relative risk of cardiovascular events and coronary artery calcification, the absolute risk of adverse events is very low[14,15], suggesting further interactions are involved.

Clearly, these are highly complex interactions and further research is required into the physiological outcomes of variation of serum Ca and phosphate within the range in healthy people. Designs of the relevant RCT providing data for meta-analyses require careful review, particularly with regard to physiology of nutrients. Ca is a threshold nutrient; insufficient intake is detrimental for health, but too much may also be bad for health. As nutritionists and health practitioners, we are required to emphasise that it is the appropriate level of any nutrient including Ca intake that is important for health.

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