Oral calcium, sevelamer and vascular calcification in uraemic patients

Sir,

We have greatly appreciated the excellent, challenging review by Coladonato et al. [1] of the issue relating oral calcium load to artery calcifications and cardiovascular complications. We would like to add scientific works, which do not support this link, and stress shortcomings of the protocol design of the recently published ‘Treat to goal’ study [2] aimed at proving a causal relationship between oral calcium load and cardiovascular damage.

As Coladonato et al. [1] already have stressed the weaknesses of cross-sectional studies, we wish to focus on three longitudinal, observational studies. Renaud et al. [3] assessed for 3 years the extension of calcifications in the abdominal aorta and iliac arteries. They showed that it was independently associated primarily with age, male gender, blood pressure, and plasma triglyceride and glucose levels whereas the link with plasma concentrations of calcium and phosphate was borderline and not at all significant with the dose of CaCO₃. In the study by Goldsmith et al. [4] progression of vascular calcification was also related primarily to age and blood pressure, and also to plasma phosphate, calcitriol and ferritin levels, but paradoxically there was a negative correlation with plasma calcium. Furthermore this study showed that surgical treatment of hyperparathyroidism was followed by less extensive vascular calcification than medical parathyroidectomy by more aggressive calcitriol therapy. The third study by Bonifacio et al. [5] challenges the bad prognostic significance of coronary calcifications in haemodialysis patients after percutaneous dilatation of coronary artery stenosis. Long-term morbidity and mortality were actually better in patients with calcifications, the apparent paradox being explained by a more severe dyslipidaemia in those without calcifications.

As regards the shortcomings of the ‘Treat to goal’ study design, it is important to stress that the plasma parathyroid hormone (PTH) levels actually obtained were in the targeted range (150–300 pg/ml) for the Renagel™ group, but below this range for the patients in the calcium group, this PTH oversuppression possibly contributed to the higher incidence of hypercalcaemia (33 vs 7%) and therefore to a higher risk of soft tissue calcification [6]. It is interesting to point out that the 7% incidence of hypercalcaemia observed with Renagel™ + 1αOH vitamin D was comparable with that observed in our trial comparing CaCO₃ with calcium acetate in patients not taking 1αOH vitamin D, as this latter was only 8%. Furthermore, this incidence was comparable with both calcium salts [7] and not lower with calcium acetate (in contrast to the suggestion of Coladonato et al. [1]), in spite of its twice-lower dose when expressed in calcium element.

With regard the oversuppression of PTH in the calcium group of the ‘Treat to goal’ study, it questions the necessity of administering 1αOH vitamin D to this group. In such patients with moderate hyperparathyroidism, Indridason and Quarles [8] clearly demonstrated that increasing oral CaCO₃ intake from 5 to 15 g daily was as effective as daily oral or intermittent intravenous (i.v.) calcitriol in maintaining PTH between 200 and 100 pg/ml at a comparable serum calcium of 9.0–9.5 mg/dl, with the distinct advantage of maintaining serum phosphate at 3.5 mg/dl instead of 5.0 mg/dl in the calcitriol group, while aluminum hydroxide was needed in the two calcitriol groups, exposing both to long-term aluminum toxicity and higher risk of soft tissue calcifications.

As dyslipidaemia is a recognized risk factor for coronary artery calcification [9] the fact that sevelamer significantly improved uraemic dyslipidaemia [10] gives a distinct advantage to this phosphate binder over CaCO₃ in the prevention of vascular calcium overload. However the results of the
'Treat to goal' study cannot be readily used to demonstrate the claimed vascular toxicity of oral calcium per se. To solve this issue, which has an obvious economic impact for public health expenditures, a cost-effectiveness study of the prevention not only of vascular calcifications but of all-cause cardiovascular events should therefore be performed to prove the claimed superiority of sevelamer + 1xOH vitamin D derivatives over high doses of CaCO₃ (used as phosphate binder in association with physiological repletion in native vitamin D) and associated to a statin to obtain a comparable control of dyslipidaemia. The present monthly cost estimation for a combination of sevelamer (Renagel®) + alfalcacidol is 150 Euros whereas that for calcium + statin it is only 52 Euros. Therefore, 100 Euros is the price to pay for a still unknown reduction of cardiovascular morbidity and mortality with sevelamer ± alfalcacidol in uraemic patients.

As blood pressure [11] and oestrogen status are of particular importance in the incidence of vascular calcifications, the design of such a study should also include a comparable control of blood pressure and oestrogen status with comparable medications in each study group.

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