Reply

Sir,

I would like to thank Bonne et al. [1] and Wesseling and Salusky [2] for their interest in the review on secondary hyperparathyroidism [3] and their comments.

Bonne et al. [1] suggest that vitamin D repletion (i.e. supplementation of vitamin D to raise serum 25(OH)D above 30 ng/ml) may be the safest and most physiological way to suppress parathyroid hormone (PTH) in dialysis patients. The rationale for this proposal is based on the presence of several extrarenal 1α-hydroxylase enzyme systems (among others in parathyroid glands), which can convert 25(OH)D locally to calcitriol. Moreover, anephric dialysis patients when given large pharmacological amounts (but not physiological amounts) of vitamin D or 25(OH)D experience a measurable rise in their serum calcitriol concentration [4]. However, this practice has not found entrance into clinical routine because of to the very long (several weeks) biological half-life of 25(OH)D (in contrast to calcitriol) and the risk of prolonged hypercalcemia.

The association between 25(OH)D and iPTH in dialysis patients is inconsistent. While there was a significant association between iPTH and 25(OH)D in a group of North African dialysis patients [5], Coen et al. [6] found no difference of plasma iPTH in patients groups with varying 25(OH)D serum concentrations. In another study, Krause et al. [7] performed controlled UV irradiation of the skin in a group of dialysis patients, raising their median serum 25(OH)D from 97.8 to 233.6 nmol/l and their median serum 1,25(OH)2D from 21.3 to 37.5 pg/ml. However, plasma iPTH did not decrease significantly in those patients. Firm clinical evidence for a role of 25(OH)D in renal bone disease is scarce. Associations between low serum 25(OH)D and radiological bone lesions or impaired bone mineralization, respectively, were reported [5,6]. However, the negative results of a recently published trial [8] investigating calcium and vitamin D supplementation in the prevention of colorectal cancer (albeit an association between vitamin D deficiency and incidence of colorectal cancer has been repeatedly reported in the literature) warn us not to over-interpret the presence of associations.

Taken together, there are several intriguing and attractive hypotheses why serum 25(OH)D may play a role in disturbed mineral metabolism and bone disease in dialysis patients and may even be associated with non-calcitropic vitamin D effects. However, if an increase of serum 25(OH)D above 30 ng/ml will result in clinical benefits for dialysis patients is currently not known. As Wesseling and Salusky [2] comment in their letter, the role of 25(OH)D in the treatment of renal bone disease remains to be established.

Both letters comment on the emerging literature showing an association of therapy with active vitamin D metabolites and decreased mortality in dialysis patients [9,10]. We know since the 1980s that calcitriol has a variety of non-calcitropic effects [11], and it was speculated [9] that those effects may be responsible for a possible survival advantage with active vitamin D metabolites. This attractive possibility clearly deserves further investigation.

Bonne et al. [1] suggest that a difference in mortality between paricalcitol- and calcitriol-treated dialysis patients found in a retrospective analysis [12] may have been due to more pronounced caecal and phaethoaeic effects of calcitriol as compared with vitamin D3. However, the observed effect of paricalcitol in this retrospective study was independent of prevailing serum concentrations of calcium, phosphorus and iPTH [12]. Moreover, it remains to be established if paricalcitol has consistent and clear clinical advantages over calcitriol with respect to induction of hypercalcemia and phosphatemia [13].

The cinacalcet phase III studies [14] demonstrate that cinacalcet, in addition to therapy with active vitamin D metabolites and phosphate binders, largely improves iPTH, calcium and phosphorus and confers, at least in a post hoc analysis [15], a number of clinical benefits. Newer data show that calcimimetics, besides their acute suppressive effect on PTH release from parathyroid glands, reduce PTH mRNA by decreasing mRNA stability [16] and inhibit parathyroid proliferation [17]. Moreover, calcimimetics induce up-regulation of the calcium-sensing receptor in parathyroid glands [18], and Wesseling and Salusky pointed out [2] that active vitamin D metabolites also up-regulate parathyroid calcium-sensing receptor expression. However, the suggestion of Wesseling and Salusky that vitamin D treatment may be necessary for an optimal effect of cinacalcet in secondary hyperparathyroidism (SHPT) is not supported by available data. The results of cinacalcet phase III studies demonstrate that the effects of cinacalcet are independent of concomitant vitamin D therapy [19].

As outlined in my review [3] the exact role of calcimimetics in relation to standard SHPT therapies remains to be established. With respect to the comments of Wesseling and Salusky [2], it is obvious that our SHPT therapy should be a combination therapy of available drugs given that contraindications (i.e. elevated Ca×P) are absent. As suggested by preliminary results from the OPTIMA study [20], the availability of calcimimetics may even increase the proportion of patients receiving active vitamin D (in combination with cinacalcet), albeit possibly in lower doses.

The proposed algorithm in the review [3] is based on patients not receiving vitamin D [21]. Another proposed algorithm on the use of cinacalcet in patients receiving active vitamin D metabolites has been published in an attempt to combine available SHPT therapies [22]. Clearly, it is necessary to individually consider in each patient the available treatment options with regard to prevailing PTH, Ca and P.

Bonne et al. [1] further mention a brief report showing that a high calcium dialysate (1.75 mmol/l) in conjunction with cinacalcet effectively suppressed iPTH [22]. A possible concern is that, in the presence of a lower serum calcium, a 1.75 mmol/l dialysate calcium induces a large positive calcium balance during dialysis. This could theoretically be disadvantageous since, in the presence of calcimimetics, the sensitivity of the parathyroid cell to calcium alters, PTH is lowered and the capacity to incorporate calcium into bone may be lower. Nevertheless, such a procedure may eventually emerge as one of several potential possibilities to regulate serum calcium during cinacalcet therapy when more experience with cinacalcet has been gained.
Bonne et al. [1] also comment on a variation in the reduction of serum phosphorus by cinacalcet doses of 50 and 100 mg/day, respectively, in phase II cinacalcet studies [23,24]. They suggest that the smaller reduction of serum phosphorus with the higher cinacalcet dose [24] was due to an increased use of active vitamin D metabolites. In both studies [23,24], the study algorithm was designed to keep vitamin D usage as constant as possible in order to distinguish effects of cinacalcet from those of active vitamin D. In both studies, both the proportion of patients receiving vitamin D at study begin and the dose of active vitamin D metabolites during the study were very similar in rendering a major effect of different utilization of active vitamin D unlikely.

It is clear from several studies that less elemental calcium is required with calcium acetate than with calcium carbonate for comparable binding of phosphate. Some studies reported a higher serum calcium concentration and/or a higher frequency of hypercalcaemia with calcium carbonate than with calcium acetate [25,26], while two other studies, as Bonne et al. [1] pointed out, found no difference. In that respect, it remains to be shown if the average serum calcium concentration and the incidence of hypercalcaemia fully reflect calcium balance in dialysis patients [27].

Conflict of interest statement. None declared.

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Crippling of inflammatory markers as predictors of death by dichotomization and multicollinearity

Sir,

Caravaca et al. [1] recently addressed the important issue of whether the determination of inflammatory markers, in