Current treatment options in secondary hyperparathyroidism

Sir,

We read with interest the article by Reichel [1] in the January issue of NDT entitled ‘Current treatment options in secondary hyperparathyroidism’ and the algorithm suggesting that calcimimetics be used as first-line therapy while minimizing the use of vitamin D analogues. Since secondary hyperparathyroidism (25 HPT) remains a problem in patients treated with maintenance dialysis, we share the author’s enthusiasm for the newly developed calcimimetic agents as a promising therapeutic option. However, we would urge caution in dispensing with the use of active vitamin D sterols as first line therapy, since in addition to being a safe and effective means of controlling 25 HPT, these sterols have an important role in maintaining bone health and cardiovascular function in the general population as well as in patients treated with dialysis.

Vitamin D sterols have both genomic and non-genomic actions in many tissues, including parathyroid gland, intestine, heart and bone. In patients treated with dialysis, absence of renal 1 alpha-hydroxylase results in low-systemic calcitriol levels. In such individuals, therapy with vitamin D sterols restores intestinal calcium absorption, suppresses parathyroid hormone levels, improves cardiac function [2], and suppresses osteoblastic activity [3]. The induction of hypercalcaemia, hyperphosphataemia and adynamic bone during the treatment of 25 HPT has raised concerns about the safety of high doses of vitamin D sterols; however, these adverse effects have been described primarily in patients treated with calcium-based phosphate binders in conjunction with vitamin D analogues. Recent data from large cohorts of patients treated with non-calcium containing phosphate binders have consistently demonstrated that higher doses of vitamin D can be used without increasing serum calcium levels [3,4]. Furthermore, sevelamer and vitamin D are as effective as vitamin D plus calcium carbonate in suppressing parathyroid hormone (PTH) and controlling of the skeletal lesions of 25 HPT, without inducing adynamic bone or altering serum calcium and phosphorus levels [3]. Treatment with active vitamin D sterols has been used for 30 years to control 25 HPT in both adults and children as well as to improve growth in uraemic children [6]. Indeed, Panda et al. [7] have recently demonstrated that active vitamin D sterol is essential for proper growth plate morphology. While mice lacking the vitamin D receptor (VDR) (although with high levels of endogenous calcitriol) had an altered growth plate morphology that could be rescued with a high calcium and lactate diet, mice lacking 1 alpha-hydroxylase, (and, hence, calcitriol) had skeletal abnormalities that could not be corrected with a high calcium and lactate intake [7]. These findings suggest that active vitamin D sterols are essential for normal bone biology, that these actions are mediated by a receptor other than the VDR, and that correction of calcium and phosphorus metabolism alone is insufficient to normalize bone in the absence of vitamin D.

Recent evidence indicates that 25(OH) vitamin D stores are low in a large portion of the general population, and that chronic kidney disease is a risk factor for this deficiency [8]. However, while in the general population low levels of 25(OH)D have been associated with increased PTH levels and supplementation with control of 25 HPT [9], the impact, in patients treated with dialysis, of restoring 25(OH) vitamin D stores remains to be determined.

In patients undergoing dialysis, promising benefits from the use of calcimimetics have been demonstrated, including a lowering of serum calcium, phosphorus, the calcium x phosphorus product, and PTH levels. Moreover, a retrospective analysis of these data has shown a decrease in fracture rate, decrease in the rate of hospitalization for cardiovascular events, decrease in the rate of parathyroidectomy and improvement in quality of life in patients treated with calcimimetics [10]. However, these data were obtained from patients with persistent 25 HPT—two-thirds of whom received vitamin D analogues and over half of whom received calcium-based phosphate binders during therapy. Current data indicate that calcium-sensing receptor expression is up-regulated by vitamin D sterols [11], suggesting that treatment with vitamin D may be necessary for optimal effect of calcimimetic agents.

While we are encouraged by the studies demonstrating the usefulness of calcimimetic agents in the management of 25 HPT, we would urge caution in eliminating the use of active vitamin D sterols as first-line therapy, since they are a safe and effective means of suppressing PTH and are associated with cardiac and skeletal benefits in dialyzed patients. The role of 25(OH) vitamin D in the treatment of renal osteodystrophy (ROD) is as yet unclear, but may also play an important role. Since the current data on calcimimetics are limited to trials in which the majority of patients also received vitamin D sterols, long-term prospective trials are warranted prior to routine use of calcimimetics is adopted as first-line therapy for dialysed patients.

Conflict of interest statement. K.W. has no conflicts of interest; however, I.B.S. has the following: (1) Grants/Research Support: NIH, NIDDK, NCRR; (2) Consultant: Bone Care International, Genzyme, Abbott, Amgen; (3) Scientific Advisor: Genzyme, Abbott, Bone Care International; (4) Honoraria: Genzyme, Abbott, Bone Care International.
The first comment concerns the current justification of the so called ‘active’ vitamin D metabolites. This adjective is actually a misnomer, since it is used for designating 1α,25-dihydroxyvitamin D derivatives, which are the most potent vitamin D derivatives to increase intestinal absorption of calcium and phosphate and the serum concentrations of these divalent ions, but not necessarily the most ‘efficace’ at suppressing parathyroid hormone (PTH) when used at physiological dose. Recently, the Ritter and group [1] showed, on bovine parathyroid cell culture that calcidiol at the physiological concentration of 40 ng/ml was as effective as maximal PTH-suppressing calcitriol dose.

Two reasons may explain this observation:

(i) physiological systemic concentrations of calcidiol are 10^3 times greater than those of calcitriol;

(ii) parathyroid cells have a megalin receptor which allows the introduction of calcidiol and its in situ transformation into calcitriol, thanks to a local mitochondrial 25 OH vitamin D-1α hydroxylase [2].

Furthermore, the in situ synthesis of calcitriol has also been evidenced in the monocytes, macrophages [3] and in the vascular smooth muscle cells [4]. Even though ureaemia induces a decrease of 25 OH vitamin D uptake by these cells, the production of calcitriol can be normalized by just increasing 25 OH vitamin D levels below the hypercalcaemic threshold [3].

This local production of calcitriol in various cells explains the possibility of these cells to exert physiologically beneficial effects on PTH, immunomodulation and vascular remodelling even in uraemic patients in order to compensate for the non-optimal calcitriol systemic levels in these patients. Thus, the most physiological and safest vitamin D compound to give to these patients may actually be native vitamin D or 25 OH vitamin D, rather than 1α OH vitamin D derivatives, specially when given intermittently by intravenous route, which induces unphysiological systemic peaks responsible within a year for a significant increase of SCa (12 and 14%) with intravenous paricalcitol, compared to 15 ng/ml in 87% and 5 ng/ml in 5% of these patients [6], i.e. far from the physiological repletion range level (≥30 mg/ml) recommended by the K/DOQI.

The fact that in American dialysis cohorts systematic injection of paricalcitol or calcitriol gave some survival benefit compared with no treatment, may be explained by the fact that, according to Kidney Disease outcome Quality Initiative (K/DOQI), American dialysis patients—in contrast to chronic kidney disease (CKD) stage 3–4 patients—should not be repleted in native vitamin D, so that their serum calcidiol is actually <15 ng/ml in 87% and <5 ng/ml in 5% of these patients [6], i.e. far from the physiological repletion range level (≥30 mg/ml) recommended by the K/DOQI.

Since epidemiological studies have shown that vitamin D repletion is associated with lower cardiovascular mortality and lower prevalence of diabetes, immunological, cancerous and infectious diseases [7], whereas its depletion in uraemic patients is associated with heart failure and inflammatory state [8], the partial correction of this vitamin D depletry by intravenous paricalcitol or calcitriol, may explain the better clinical outcome of the patients who received these drugs. The fact that mortality was, however, 4% lower in the patients treated with paricalcitol, compared with those treated with calcitriol, merely suggests that the beneficial effect of this partial vitamin D repletion has been lower with calcitriol, because of its greater hypercalcaemic and hyperphosphataemic effects. We, therefore, suggest that the benefit would have still been greater, if just native or 25 OH vitamin D had been given to restore