CKD Patients: The Dilemma of Serum PTH Levels

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\textbf{Introduction}

Over the last 10 years, many studies have demonstrated that abnormalities in mineral and bone metabolism are associated with increased cardiovascular morbidity and mortality in hemodialysis patients [1–3]. More recently, this has also been investigated in non-dialyzed chronic kidney disease (CKD) patients, but the most appropriate serum parathyroid hormone (PTH) level is still a subject of debate.

In a cross-sectional study recently published in the \textit{Journal of American Society of Nephrology}, Bhuriya et al. [4] analyzed a large cohort of 4,472 patients with stage 3–4 CKD selected from the larger patient cohort of the Kidney Early Evaluation Program (KEEP) study [5]. These patients were mainly elderly white women (68%) with multiple cardiovascular risk factors [83% hypertensive, 46% diabetic, 45% obese, 44% with a history of cardiovascular disease (CVD) and 6% smokers], and a median serum intact PTH (iPTH) level of 71 pg/ml (interquartile range: 47–104 pg/ml). Multivariate logistic analysis showed that iPTH and glomerular filtration rate (GFR) were independent predictors of CVD, like conventional risk factors such as age, gender, smoking, diabetes and hypertension. The patients whose iPTH levels were $>70$ pg/ml had a more than 50% higher cardiovascular risk than those whose levels were $<35$ pg/ml. Moreover, there was a significant increase in the prevalence of CVD with increasing PTH levels. Surprisingly, no significant
association was found between the prevalence of CVD and the plasma levels of phosphorus and calcium [4].

As recognized by its authors, this study had a number of limitations. The patients’ CVD diagnosis was self-reported and not confirmed by even simple diagnostic tests, and the analysis could not take into account potential confounding factors such as treatments for secondary hyperparathyroidism (phosphate binders and vitamin D) or relevant cardiovascular risk factors (vitamin D levels and lipid abnormalities). Moreover, the results need to be cautiously generalized to the entire population of patients with stage 3–4 CKD because the selection criteria were clinically well characterized (subjects with diabetes, hypertension or a family history of kidney disease, diabetes or hypertension) and recruitment was voluntary.

The findings of this study do not establish a cause-effect relationship between PTH levels and CVD, but confirm the need to monitor PTH levels from the early stages of CKD and raise the very important question of whether serum iPTH levels should be considered appropriate in stage 3–4 CKD? However, before looking at this in more detail, it is worth seeing whether the findings of Bhuriya et al. [4] are supported by those of other clinical studies and whether they are biologically plausible.

Clinical Studies and Biological Plausibility

Various epidemiological studies have examined the association between secondary hyperparathyroidism and cardiovascular risk in dialyzed patients, but few have considered non-dialyzed patients and, in particular, the relationship between PTH levels, morbidity and mortality. After adjusting for case mix and laboratory tests, a prospective study of 551 male non-dialyzed CKD patients (average GFR: 31 ml/min) found that iPTH levels (median: 103 pg/ml, interquartile range: 65–179 pg/ml) were associated with increased mortality. In comparison with the patients whose PTH levels were <65 pg/ml, those whose levels were >65 pg/ml had an adjusted hazard ratio of mortality of 1.59 (95% CI: 1.02–2.49) [6, 7]. A similar association was found when the composite outcome of pre-dialysis all-cause mortality and end-stage renal disease was taken into account. Interestingly, there was a linear association between PTH levels and mortality, and the increased risk was apparent even when iPTH levels were just above the normal limit of 65 pg/ml. Furthermore, the association between PTH levels and mortality persisted after adjusting for confounding factors (the plasma levels of calcium and phosphorus, and vitamin D therapy), thus suggesting that PTH levels are associated with a high risk of mortality regardless of hyperphosphatemia and vitamin D therapy.

A large cohort study of more than 4,000 non-dialyzed patients with stage 4–5 CKD (mean GFR 33 ml/min) found that the levels of iPTH (median: 105 pg/ml, inter-quartile range: 57–188 pg/ml) and phosphorus were associated with an increased risk of death and the progression of renal failure, whereas vitamin D therapy was associated with better survival [8]. Similar results indicating that secondary hyperparathyroidism is a risk factor associated with progression to dialysis or death have been obtained in cohort studies of the health costs of CKD in pre-dialysis patients [9, 10].

PTH levels are also predictors of cardiovascular risk in the general population. A cross-sectional study of a large community-based cohort of 3,570 subjects with normal renal function and serum calcium levels found that those whose PTH levels were higher than the normal range of normal (i.e. iPTH >62 pg/ml) were significantly more likely to have coronary heart disease than those whose levels were within normal limits (relative risk in men: 1.67, 95% CI: 1.26–2.23; relative risk in women: 1.78, 95% CI: 1.22–2.57). Furthermore, the subjects whose PTH levels were in the highest quartile (>32 pg/ml in men and 30 pg/ml in women) were at higher risk of coronary heart disease than those in the lowest quartile (<17 pg/ml in men and 16 pg/ml in women) [11].

These findings have been confirmed in a recently published prospective study of a community-based cohort of 598 elderly men (mean age: 71 years), which found that higher iPTH levels were associated with an increased risk of cardiovascular mortality, and the association remained essentially unchanged even in subjects with normal renal function and no bone mineral disorders (normal plasma levels of Ca, P, PTH and 25-hydroxycholecalciferol [25(OH)D]) [12].

PTH can act directly on the cardiovascular system as specific PTH receptors have been identified on myocytes, and it has been shown that their activation increases intracellular calcium levels as well as the strength and frequency of cardiac contractions [13]. In addition to their known effects on bone and kidney, high PTH levels have also been implicated in a plethora of untoward effects on cardiovascular function and structure, including metabolic lipid abnormalities, impaired insulin sensitivity, hypertension, cardiac hypertrophy and fibrosis, myocardial calcium deposition, valvular calcification, and vascular stiffness and calcification [14]. Moreover, high levels of PTH contribute to the pathogenesis of other typ-
ical complications of CKD, such as anemia [15] and immunodeficiency [16]. This wide range of possible cell and tissue dysfunctions associated with increased serum PTH levels has led to PTH being considered a uremic toxin.

Mineral and bone metabolism can be seen as a complex system in which three hormones [PTH, calcitriol and fibroblast growth factor 23 (FGF-23)] act on three key organs (kidney, intestine and bone) to adjust plasma calcium and phosphorus concentrations. Whenever any event alters the function of any one of the components of this highly integrated system, the others adjust their function in order to ensure the constant balance of calcium/phosphorus homeostasis. More specifically, any increase in serum PTH levels often reflects other disorders such as reduced 1-α-hydroxylase activity, or altered plasma levels of calcium, phosphorus and FGF-23.

It is not easy to disentangle the complex skein of the multiple interactions of secondary hyperparathyroidism, or to differentiate the net effect of each of the possible disorders in mineral metabolism on outcomes such as morbidity and mortality. The only means of establishing cause-effect relationships is to use controlled experimental studies, but no studies of this kind have investigated the pharmacological control of PTH and secondary hyperparathyroidism in non-dialyzed CKD patients. Nevertheless, the findings of the studies discussed above suggest that PTH is a strong predictor of cardiovascular mortality in non-dialyzed CKD patients regardless of the other biomarkers of mineral metabolism usually tested in clinical practice, and that this association exists even in patients without any evident mineral metabolism disorders.

**What PTH Levels Are Appropriate?**

Returning to the question as to what levels of PTH can be considered adequate in non-dialyzed CKD patients, the K/DOQI guidelines on bone and mineral metabolism [17] that have been used as an international reference over the last 6 years recommend serum iPTH levels of 35–70 pg/ml for stage 3 CKD, 70–110 pg/ml for stage 4 and 150–300 pg/ml for stage 5 and dialysis. It is important to note that the recommendations concerning stage 3–4 CKD are based on expert advice.

The more recent KDIGO guidelines on Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) [18] more prudently state that ‘in patients with CKD stages 3–5 not on dialysis, the optimal PTH level is not known’, and suggest finding and treating hyperphosphatemia, hypocalcemia and vitamin D deficiency in patients with above-normal iPTH levels. Treatment with calcitriol or vitamin D analogues is recommended if serum PTH levels are progressively increasing and remain above the upper normal limit despite the correction of any other metabolic disorders. The grade given to this recommendation is 2C, i.e. a suggestion based on low-quality evidence.

According to the trade-off hypothesis, the increase in PTH levels with the progression of renal failure is a compensatory mechanism necessary to maintain the homeostasis of calcium/phosphorus metabolism. However, excessive PTH production may have deleterious effects on the cardiovascular system and bone, and is also associated with nodular parathyroid gland hyperplasia resistant to medical therapy. It is clearly difficult to say when an appropriate compensatory response changes to a maladaptive phase in which the price to pay for balanced (or at least acceptable) plasma calcium and phosphorus levels is the ‘toxic’ systemic effect of PTH.

In clinical practice, serum PTH is often used together with bone alkaline phosphatase (ALP) levels to assess bone turnover as a non-invasive alternative to bone biopsy. However, using PTH as a surrogate of bone biopsy has a number of limitations: first of all, bone remodeling is a slow process, and a single determination of the serum levels of PTH may not accurately reflect the effect of months of PTH activity on bone; secondly, the drugs used to control parathyroid activity may have a direct effect on bone regardless of PTH levels; and thirdly, PTH levels do not always predict bone turnover [19, 20]. In a clinical setting, it is therefore difficult to decide the level of PTH that offers the best compromise between ensuring the adequate control of secondary hyperparathyroidism and limiting the risk of fractures and vascular calcifications due to an adynamic bone disease caused by the oversuppression of PTH.

It has very recently been shown that high serum ALP levels – which reflect increased bone turnover – are associated with increased mortality in non-dialyzed CKD patients: a 50 U/l higher time-averaged serum ALP level was associated with a multivariable adjusted hazard ratio of all-cause mortality of 1.17 (95% CI: 1.08–1.28, p < 0.001) [Kovesdy et al.: Association of Serum Alkaline Phosphatase Levels with Mortality in Non-Dialysis Dependent Chronic Kidney Disease. Poster Number: F-PO1896. American Society of Nephrology 2009, unpbl. data]. Interventional trials are needed to determine whether lowering serum ALP levels improves outcomes.
Of course, the relationship between increased PTH levels and the progression of renal failure may vary from one person to another, depending on the overall balance of mineral homeostasis. Cross-sectional studies have shown that the progression of renal failure not only leads to an increase in median PTH levels, but also broadens their range [8], and this clearly makes it difficult to establish clear-cut targets for the five stages of CKD (particularly the more advanced stages). Things are made even more complicated by the limitations of the PTH assay kits that are currently available in the clinical setting, which differ in their measurement of accumulating PTH fragments and are affected by considerable interassay variability [21]. To overcome these methodological limitations, PTH should be assayed with standardized methods of sample collection, preparation and analysis, and PTH targets should be set according to the normal limit for the assay, as suggested by the KDIGO guidelines [18].

In this still uncertain scenario, the recent KEEP data confirm previous findings of the increased cardiovascular risk associated with even small increases in PTH levels, and strengthen recommendations for the early and effective control of secondary hyperparathyroidism. On the basis of these data, it seems clear that we should pursue lower PTH levels than the targets recommended for stage 3–4 CKD by the K/DOQI guidelines. But what should be our clinical approach?

First of all, in addition to serum calcium and phosphorus levels, serum PTH and 25(OH)D should be monitored from the earliest stages of CKD. Treating any vitamin D deficiency is particularly important because recent studies have shown a 25(OH)D substrate-dependent increase in PTH levels that can be at least partially corrected by means of vitamin D3 supplementation [22], and the oral intake of ordinary doses of vitamin D supplements seems to be associated with a decrease in total mortality in the general population [23].

The regular monitoring of urinary calcium, phosphorus and urea excretion may help to identify any dietary excesses or deficiencies, and prevent an inadequate balance of calcium (negative) and phosphorus (positive) that could be the primum movens triggering an excessive synthesis and secretion of PTH. Hypocalcemia should be prevented, and any persistent increase in serum phosphorus levels to above normal limits should be treated with phosphate binders. In a study of 3,490 patients with stage 3–4 CKD, serum phosphorus levels of more than 3.5 mg/dl were associated with a significantly increased risk of death (each additional 1 mg/dl was associated with an estimated 23% greater risk of all-cause mortality) [24], and it has recently been proposed to perform randomized placebo-controlled trials of phosphate binders in pre-dialysis CKD patients with normal serum phosphate levels in order to test the hypothesis that lowering serum phosphorus levels may decrease mortality. It is interesting to note that the promoters believe the benefit expected from the binders may be mediated by attenuating the potential ‘toxicity’ of markedly increased FGF-23 levels in patients with early subclinical disorders of phosphorus metabolism [25, 26].

If PTH levels continue to rise, the activity of the parathyroid glands should be suppressed using an active metabolite of vitamin D, but great care must be taken to avoid an excessive reduction in PTH levels as this is associated with adynamic bone disease and increased risk of cardiovascular calcification. The selective vitamin D receptor activator paricalcitol should be preferred over calcitriol because of its milder hypercalcemic and hyperphosphatemic effect, and especially in the light of growing evidence that it has been associated with positive effects on survival, vascular calcification and heart function [27], as well as reduces proteinuria [de Zeeuw et al.: Selective Vitamin D Receptor Activator (VDRA) for Albuminuria Lowering (VITAL) Study in Type 2 Diabetic Nephropathy, [LB-002] Late-Breaking Clinical Trial Session, October 30, 2009, American Society of Nephrology 2009, unpubl. data].

A recent controlled trial has shown that calcimimetics also effectively decrease PTH levels in patients with stage 3–4 CKD, but their use is limited by hypocalcemia and increased plasma phosphorus levels [28]. However, only a small proportion of the patients in this trial were also treated with active vitamin D metabolites (21%) or phosphate binders (19%); therefore it is worth testing whether adding a calcimimetic to an active vitamin D metabolite improves PTH control in the more severe forms of secondary hyperparathyroidism in non-dialyzed patients with stage 4–5 CKD.

Conclusions

The new KDIGO guidelines on CKD-MBD do not define an optimal range for PTH in patients with stage 3–4 CKD, but the KEEP results show a significantly increased cardiovascular risk even in the case of slight increases in PTH levels. They also indicate the need for controlled studies to test whether new therapeutic strategies aimed at improving the control of secondary hyperparathyroidism from its early stages improve outcomes in patients with mild-to-moderate CKD.
The widespread nature of CKD, together with its costs and associated mortality, has led to it having a major impact on society as a whole. Any new therapeutic agent capable of controlling calcium, phosphate and PTH imbalances and the progression of renal disease could therefore become critical in controlling renal and cardiovascular morbidity and mortality in CKD patients.

References


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Conflicts of Interest

G.P. received honoraria from Abbott, Amgen Dompé and Shire; M.C. received honoraria from Abbott, Amgen, Genzyme, Roche, Shire; F.L. is on an advisory board of Abbott, Amgen Dompé, Mitsubishi, Novartis and Shire; and D.B. received honoraria for lectures from Abbott, Amgen, GSK Shire.
Editorial Comment
M. El Nahas, Sheffield

This review by Pontoriero and colleagues from Lecco and Milan in Italy addresses the very important issue of PTH optimal levels at different stages of CKD, including those on renal replacement therapy. Raised PTH, along with changes in calcium and phosphorus balance are not only implicated in mineral and bone disorders, but are also key players in the pathogenesis of the associated cardiovascular disease morbidity and mortality in CKD patients. The latest KDIGO CKD-MBD guidelines clearly state that the optimal PTH level in stages 3–5 is unknown. Perhaps, of equal importance is not to focus exclusively on one hormone such as PTH, but to take into consideration changes in the whole range of known modulators of MBD, including circulating levels of vitamin D and FGF23. These hormones/growth factors are gaining attention as predictors of cardiovascular disease and all-cause mortality in CKD patients. It is also essential to bear in mind other confounders such as age and gender. Guidelines are most useful when tailored to individual patients and most counterproductive when they take away the initiative from clinicians. After all, there may be an optimal level of PTH for each patient – the astute nephrologist may be able to find it!