Serum intact parathyroid hormone in diabetic patients on haemodialysis: what is the treatment goal?

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Keywords: bone osteodystrophy; diabetes; iPTH; vascular disease

In this issue, Murakami et al. describe an interesting association between intact parathyroid hormone (iPTH) circulating levels and glycaemic control in diabetic patients on haemodialysis [1]. The findings describe an inverse correlation between iPTH serum levels and glycaemic control. Specifically, diabetic patients with poor glycaemic control (HbA1c; 7–8%) are characterized by low circulating iPTH, which is conversely found at higher levels in diabetic patients with good glycaemic control (HbA1c; 5–6%).

Both elevated and low circulating iPTH levels have been linked respectively to high and low bone turnover osteodystrophy (or ‘adynamic bone disease’) in patients on haemodialysis [2–6]; despite the fact that iPTH serum levels are considered important for the understanding of the mechanisms leading to renal-related bone disease, changes in iPTH biological action play a significant role in the pathogenesis of renal osteodystrophy [2]. To further complicate the understanding of the exact pathogenesis of renal osteodystrophy, studies have shown that high bone turnover osteodystrophy may present with low PTH levels, and low bone turnover may occur with a high PTH level.

Hence the rationale for some authors to suggest that bone biopsy, which is considered by many the ‘gold standard’ diagnostic tool for renal osteodystrophy [2], is required for the understanding of this complex medical condition.

In haemodialysis patients, diabetes per se has been associated with lower iPTH levels when compared to non-diabetic patients [3, 7]. In diabetic haemodialyzed patients, impaired iPTH secretion appears to be the main determinant responsible for decreased bone turnover and ‘adynamic bone disease’, as reports have proposed similar degree of iPTH biological action on bone in the diabetic and non-diabetic population [3].
If low iPTH circulating levels represent the main determinant of aplastic and low turnover osteodystrophy in diabetic patients on haemodialysis, the relationship existing between better glycaemic control and higher iPTH serum levels represents an important and novel finding, as improvement in metabolic control may become an important tool to prevent/ameliorate low bone turnover renal osteodystrophy.

It has also been suggested that raised iPTH levels in diabetic patients with better glycaemic control could be paralleled by a lower mortality risk, as low iPTH levels have been prospectively related to increased mortality in uraemic patients, independent of the diabetic status or duration of diabetes [8].

It is therefore intuitive that the higher iPTH levels that characterize diabetic patients with better glycaemic control would protect from both mortality and ameliorate renal bone disease.

The inability of the bone to buffer excess PO4 and Ca × PO4 ion products in patients on haemodialysis with low iPTH and low bone turnover ostearthropathy has been shown to lead to excessive calcification of soft tissues and secondary increase vessels calcification [9]. The mechanism that regulates the shift of Ca × PO4 ion products from bone to soft tissues is still incompletely understood, but studies have observed that a significant increase in vascular calcifications is often paralleled by low serum iPTH [10,11]. As low iPTH levels have been associated with vascular calcification and increased cardiovascular mortality [8,12], it could be speculated that low bone turnover ostearthropathy (where low iPTH secretion is a major mechanism [3]) represents a risk factor for accelerated peripheral vascular disease in patients on haemodialysis. Furthermore, it has been noted that in dialysis patients, the presence of low iPTH paralleled by elevated Ca × PO4 is associated with a higher risk of cardiovascular mortality [13].

Nevertheless controversy still exists as to the relationship between iPTH and cardiovascular morbidity and mortality: other studies have observed a positive correlation between iPTH (especially at very elevated iPTH serum levels: >480 pg/dl) and the cardiovascular risk [14] and vascular calcifications [15] in haemodialyzed patients. Many studies have described as negative the iPTH-mediated effects on the cardiovascular system: elevated iPTH levels have been implicated in the pathogenesis of myocardial hypertrophy and fibrosis, vascular calcifications, and impaired endothelial vasodilation in both humans and animal models of uraemia [16–18].

To date, despite the limitation of the few studies looking at associations between iPTH and cardiovascular disease, it seems that both low and very high iPTH serum levels correlate with increased cardiovascular morbidity and mortality.

The role of iPTH as a potential predictor in cardiovascular morbidity and mortality in haemodialysis patients certainly deserves more attention, and prospective studies are urgently needed.

In line with the current knowledge of low iPTH levels and the increased cardiovascular risk [8] is the work of Kalantar-Zadeh et al. [19], where a clear association was found between poor glycaemic control (HbA1c ≥ 6%) and the increased cardiovascular death risk in diabetic patient on haemodialysis. Unfortunately no iPTH was measured in this study, but haemodialysis patients with poor glycaemic control HbA1c levels (≥6%) are expected to have low circulating levels of iPTH; these results were importantly controlled for different variables including markers of malnutrition and inflammation, as these could interfere both with increased mortality and with low HbA1c levels. Other studies have described similar findings where poor glycaemic control (HbA1c > 8%) was again found as a predictor of poor survival [20]; in contrast, others were unable to relate HbA1c to survival rate, warranting more controlled prospective studies to definitively establish the role of HbA1c and glycaemic control on survival in diabetes patient on haemodialysis [21].

As pointed out by Murakami in this issue, the use of HbA1c as an index of glycaemic control in haemodialysis diabetic patients does not totally reflect the metabolic milieu, because of the issues related to erythropoiesis and its treatment; nevertheless, improvement in glycaemic control (assessed with HbA1c) was paralleled by changes in iPTH in this study and better HbA1c levels, as mentioned above, have been associated with increased survival in the diabetic population on haemodialysis [19].

Studies have demonstrated a negative role for iPTH on both insulin action and secretion in both primary and secondary hyperparathyroidism [22,23]. iPTH could represent a ‘toxic’ agent on metabolic control; however, the picture is yet not as clear as studies suggest that poor metabolic control per se, via increase in advanced glycation end product, could inhibit low calcium-mediated iPTH secretion [24].

Interestingly, leptin, a marker of adipose mass found to be raised in diabetic obese patients [25], has been linked to bone mass and iPTH in dialysis patients, and has been proposed to reduce bone turnover [26]. Indeed leptin induces vascular calcifications in vitro, and has been associated with cardiovascular events in overweight and obese dialysis patients [27]. Importantly it must be remembered that pro-inflammatory cytokines, increased under insulin resistant conditions, have also been involved in the pathogenesis of both vascular [28] and bone disease [29], and cytokines and/or toxic metabolites, which accumulate under uraemic conditions, may contribute towards vascular and bone disease in patients with renal disease [30].

Prevention of bone and cardiovascular disease is clearly linked and should not be forgotten in the renal patient approaching, or on, haemodialysis. Vascular calcification is a common clinical presentation in patients on haemodialysis and predicts both cardiovascular morbidity and mortality.

Future studies are needed to investigate whether targeting iPTH and other determinants involved in renal bone disease in dialysis patients may prevent or delay the development of vessel calcifications and frail bones.

Conflict of interest statement. None declared.

(See related article by Reiichi Murakami et al. Glycaemic control and serum intact parathyroid hormone levels in diabetic patients on haemodialysis therapy. Nephrol Dial Transplant 2008; 23: 315–320.)