Parathyroidectomy vs calcimimetics for treatment of persistent hyperparathyroidism after kidney transplantation

Ewa Lewin\textsuperscript{1} and Klaus Olgaard\textsuperscript{2}

\textsuperscript{1}Nephrological Department B, Herlev Hospital and \textsuperscript{2}Nephrological Department P, Rigshospitalet, University of Copenhagen, Denmark

**Keywords:** calcimimetics; kidney transplantation; parathyroidectomy; persistent hyperparathyroidism

**Persistent hyperparathyroidism after kidney transplantation**

Ideally, a successful kidney transplantation corrects the abnormalities in mineral metabolism that, during uraemia, lead to secondary hyperparathyroidism (HPT) and renal osteodystrophy. This includes reversal of uraemia, abolition of hypocalcaemia, hyperphosphataemia and acidosis, and restoration of calcitriol production and reversal of skeletal resistance to parathyroid hormone (PTH) and vitamin D [1].

Elevated PTH levels persist in a significant number of renal transplant patients. In addition to its potential negative consequences on bone mineralization, persistent HPT might worsen hypercalcaemia, induce hypophosphataemia, and may be a risk factor for acute tubular necrosis in the renal allograft [2].

The incidence of hypercalcaemia after kidney transplantation is significant and varies between 8.5 and 65%. The natural evolution of hypercalcaemia after successful kidney transplantation is, however, in most cases a spontaneous resolution [3,4] and the pathogenesis of post-transplant hypercalcaemia is not necessarily due to persistent HPT. Several factors, such as resolution of soft tissue calcifications, immobilization, high doses of corticosteroids and hypophosphataemia, may all contribute to hypercalcaemia [4].

In the clinical situation, the majority of the patients with secondary HPT will, despite previous long-term uraemia, present a significant and gradual fall in plasma PTH after kidney transplantation. Some part of this fall might be due to clearance of C-terminal PTH fragments as a result of the improvement in the glomerular filtration rate (GFR), as the intact PTH assays, which have been used until recently, co-measure some long C-terminal PTH fragments [5]. In most cases, plasma PTH returns to near normal with time, although not all studies are confirmative [6]. The normalization of GFR seems, however, to be decisive for the normalization of the PTH levels [7]. In transplanted patients with reduced GFR, elevated PTH levels are to be expected, due to the degree of uraemia and, independently of whether the patients are transplanted or not. The risk for developing post-transplant HPT increases with the duration of dialysis [3,8] and with the severity of the pre-transplant HPT [8,9].

Among kidney-transplanted patients, between 1.3 and 20% (on average 5%) will later require parathyroidectomy (PTX) [3,4,7,10]. The general criteria for PTX after kidney transplantation are in most centres symptomatic or asymptomatic hypercalcaemia with inappropriately elevated levels of PTH, one or more years after a successful kidney transplantation resulting in normal kidney function [3,4]. The degree of parathyroid hyperplasia is believed to determine the ability of the parathyroid glandular function to involute after transplantation [11]. One would expect patients requiring PTX to have the most severe changes of the parathyroid glands, such as monoclonal nodular hyperplasia.

**Parathyroidectomy after kidney transplantation**

Two important aspects must be considered in the therapeutic decision of persistent HPT. A possible negative effect on kidney graft function and a negative effect on the skeleton. Five studies, each containing relatively small numbers of parathyroidectomized kidney-transplanted patients, all demonstrate a fall in GFR after PTX. In long-term transplanted patients, Schmid \textit{et al.} [10] found in a retrospective study that 35% of the 37 patients experienced a rejection episode between 1 and 76 months after PTX, performed on average 36 months after transplantation. In another retrospective study, Rostaing \textit{et al.} [12] reported that serum creatinine increased significantly within 6 months after PTX, while no increase in serum
creatinine was seen in control group. In this study, a more than 30% increase in serum creatinine was observed in 23% of the 34 investigated patients. Garcia et al. [13] observed in another, more recent, retrospective study that seven out of 22 patients had an acute and significant impairment of renal function after PTX, which persisted in five of the seven patients. Evenepoel et al. [14] recently described in NDT, a similar detrimental effect of PTX on serum creatinine in 32 stable kidney-transplanted patients, among whom 65% experienced a significant increase in serum creatinine and a decline in creatinine clearance. Finally, in a retrospective analysis, Lee et al. [15] looked at the effect of PTX on allograft function in a group of 22 long-term kidney-transplanted patients. Compared with a control group without PTX, graft survival in the PTX group was significantly reduced by 60% at 6 years. At present, the pathophysiological mechanism behind this decline in kidney function remains obscure. Most of the patients had a subtotal PTX performed, which in nearly all the patients was considered successful with a significant decrease in plasma calcium, and in some instances with an improvement in blood pressure regulation effects that, if any, should improve kidney function. The increased rejection rate observed in the study of Schmid et al. [10] might suggest an immunological involvement. As such, PTX, whenever it is performed after transplantation, appears to be related to deterioration of graft function. On the other hand, it should also be stressed that no study has shown that patients with high PTH levels maintain a better graft function or better graft survival. On the contrary, severe HPT is considered to be a risk factor for deterioration of GFR. Gwinner et al. [16] examined the occurrence of early calcifications in protocol renal allograft biopsies, obtained within the first year after transplantation, from 213 transplanted patients. Calcifications, mainly located in the tubular lumina, were found in 17.8% of the patients at 6 months. Patients with allograft calcifications had significantly higher plasma PTH and calcium levels, and the high PTH levels correlated with an inferior outcome of graft function at 1 year after transplantation. This means that PTX or, better, subtotal PTX should optimally be performed before transplantation in order to minimize the risk for deterioration of GFR after transplantation.

**Treatment with calcimimetics after kidney transplantation**

The introduction of calcimimetics was a major breakthrough in the treatment of secondary HPT. These compounds increase the sensitivity of the calcium sensing receptor (CaR) to extracellular calcium. It has been shown in clinical trials that cinacalcet was effective in suppressing PTH secretion in uraemic patients with severe HPT where PTX might be considered and as such, treatment with calcimimetics is a clear alternative to PTX. Experience with calcimimetics in kidney-transplanted patients is sparse and limited to three small prospective studies. In two of these studies, a slight impairment of kidney function was observed. Serra et al. [17] reported, in 11 allograft recipients with normal kidney function who were transplanted 28 months previously on average, and still had hypercalcaemia and persistent HPT, that treatment with cinacalcet 30 mg/day for 10 weeks was effective in correcting hypercalcaemia, and was associated with significantly decreased PTH levels by 18%. No rejection episodes were observed and ciclosporin dosages and concentrations were unaltered. Serum creatinine levels did not significantly increase, although a slight increase from 118 ± 10 to 125 ± 12 μmol/l was observed. No follow-up data were registered in this rapid communication. Similar results were reported by Kruse et al. [18], again showing a clear reduction in plasma calcium levels. In this study, a significant increase in serum creatinine was observed at 2 and 3 months after initiation of a similar dose of cinacalcet in 14 kidney-transplanted patients with persistent HPT. No control group and no follow-up data were included in this study. Srinivas et al. [19] treated with cinacalcet 30 mg/d, 10 kidney transplant recipients and 1 kidney-pancreas recipient, who all had persistent post-transplant hypercalcaemia, stable graft function and intact PTH greater than twice the upper normal limit. As in previous communications, cinacalcet significantly reduced calcium levels however no changes in renal function were observed.

**Effects on the skeleton**

Besides being negatively affected by persisting HPT, the skeleton is severely influenced by the immunosuppressive treatment, especially by corticosteroids and calcineurin inhibitors. Glucocorticoids affect bone directly by an inhibition of bone formation due to a decrease of osteoblast recruitment and differentiation, induction of apoptosis of the mature osteoblasts and osteocytes and inhibition of the synthesis of type I collagen. Bone resorption is increased due to a direct enhancing effect on the osteoclast activity [20]. Osteoblasts are target cells for circulating PTH, and locally produced parathyroid hormone related peptide (PTHrP) [21,22]. Osteoblast-produced PTHrP functions as a powerful endogenous bone anabolic agent, promoting recruitment of osteogenic cells and preventing the apoptotic death of osteoblasts and osteocytes. Exogenous PTH 1–34 has, via activation of the common PTH/PTHrP receptor, a similar effect, stimulating bone formation, and is at present the only anabolic agent available for treatment of osteoporosis. Its efficacy depends on intermittent injections, each resulting in a sharp peak of circulating PTH levels. However, more sustained elevation of PTH levels favours osteoclast formation through the generation of receptor activator of nuclear factor-kappaB ligand (RANKL) system in target cells which promotes
osteoclast production from haematopoietic precursors. As such, sustained long-term increased PTH levels in kidney-transplanted patients have been shown to contribute to bone loss.

The fluctuations in PTH levels, induced by treatment with calcimimetics, might theoretically promote a potential anabolic effect of PTH, although such an effect remains to be shown in transplanted patients. As mentioned above, immunosuppressive therapy with glucocorticoids has detrimental skeletal effects. The most dramatic bone loss after transplantation takes place within the first few months when in general, large doses of steroids are used. Rojas et al. [23] studied the very early changes in bone histology on average 35 days after transplantation and revealed an impaired osteoblastogenesis and early osteoblast apoptosis, possibly induced by the high doses of glucocorticoids at this early stage. Interestingly, however, high PTH levels seemed to have a protective effect by preserving osteoblast survival.

PTX might, in the long run, decrease bone loss in kidney-transplanted patients, but should probably not be performed in the very early phase after transplantation, at a time when large doses of glucocorticoids are given and when PTH theoretically might be a ‘survival factor’ for the osteoblasts.

**Conclusions**

A clinically important question is, when to perform the PTX. Due to the risk of deterioration of graft function and graft survival, the optimal choice must be to perform a subtotal PTX before kidney transplantation. This will eliminate the need for PTX post-transplant, and at the same time preserve sufficient parathyroid function to avoid development of adynamic bone after transplantation. In patients with persistent secondary HPT after transplantation, it seems rational to wait with PTX, in order to observe an eventual spontaneous resolution and to profit from the possible protective effect of PTH on the skeleton, at a time when high doses of corticosteroids are often administered. In patients with severe secondary HPT, who are treated with calcimimetics before transplantation, the question is whether this treatment should be continued after transplantation. No clinical studies exist to provide guidance on this issue. At present, we would recommend waiting, for the same reasons that PTX is not recommended immediately after transplantation. However, the fluctuating PTH levels which are induced by calcimimetic treatment might theoretically provide some protection against the early bone loss after transplantation. Prospective studies including bone biopsies are urgently needed in order to elucidate this potential beneficial effect of calcimimetics.

What to choose for the treatment of severe post-transplant HPT; PTX or calcimimetics? Without including considerations on the economical aspects of life-long treatment with calcimimetics, a permanent solution must be preferred. A subtotal PTX will cure the patient with an otherwise successful kidney allograft and must as such still be considered the treatment of choice. The deterioration of graft function after PTX is, however, an unsolved problem as the mechanism is not known. Whether calcimimetics will provide better graft survival, as compared with PTX, remains to be shown.

**Conflict of interest statement.** None declared.

**References**


Received for publication: 13.4.06
Accepted in revised form: 26.4.06