Secondary hyperparathyroidism is a nearly constant feature of CKD. Other than its well known effects on the bone, namely osteitis fibrosa and mixed bone disease, it has been incriminated in many other complications of patients with CKD: vascular and other soft tissue calcification, cardiovascular morbidity and mortality, hematologic disorders, neurologic disturbances, and endocrine abnormalities. If insufficiently treated or left untreated, severe parathyroid hyperplasia will ensue in many patients with ESRD, ultimately leading to clonal, tumoral growth.1 The treatment of severe hyperparathyroidism in patients with ESRD by either parathyroidectomy or cinacalcet generally leads to a marked decrease in serum calcium, phosphate, parathyroid hormone (PTH), and as shown more recently, serum fibroblast growth factor-23.2,3

When such patients receive a kidney graft, generally polyclonal parathyroid hyperplasia will slowly regress because of the recovery of renal function and correction of metabolic and endocrine disturbances. This is not so with tumoral growth, where the response of parathyroid secretion and proliferation to physiologic regulatory mechanisms is reduced or lost.4,5 The result can be persistent, so-called tertiary hyperparathyroidism with hypercalcemia, hypophosphatemia, high bone turnover with excessive bone resorption, and rapidly progressive soft tissue calcifications, including nephrocalcinosis. Hypercalcemia develops more easily post-transplant, probably because the skeletal resistance to the action of PTH decreases or even disappears with the correction of the uremic syndrome.

The management of persistent hyperparathyroidism after renal transplantation is not always easy.6 This is the reason why, in several nephrology centers, severe parathyroid overfunction is systematically corrected by surgery before performing a kidney graft. In patients with persistent hyperparathyroidism post-transplant, there are several options. In the first 12 months after transplantation, close biochemical follow-up and adequate therapy can allow one to observe a progressive decrease in serum calcium.7 In patients who were already receiving cinacalcet when undergoing dialysis therapy before, the same treatment is often continued after kidney transplantation, although it has not been approved for this indication. In a minority of patients, however, medical control proves difficult, probably most so in those with autonomous parathyroid growth and a higher degree of treatment resistance. Hypercalcemic hyperparathyroidism can become a threat to the patient’s kidney function, lead to extrarenal complications, and worsen patient outcomes.8 In this condition, many nephrologists decide to start a treatment with cinacalcet in those who are not yet so treated, although the use of this drug has not been officially approved for this indication. The most frequently used alternative option is surgical parathyroidectomy.

It could seem surprising that there has never been a formal comparison in a randomized, controlled trial between the medical and surgical treatment approaches to severe secondary hyperparathyroidism in patients with CKD or kidney graft recipients with persisting tertiary hyperparathyroidism. However, the explanation is simple. First, patients generally prefer medical to surgical treatments when treatment efficacy is considered to be comparable. Second, surgical parathyroidectomy is not free of complications, especially when done by surgeons with limited experience. Transient and sometimes permanent laryngeal nerve palsy is one of them. Third, in contrast to the condition of primary parathyroid adenoma in patients with normal renal function, the secondary hyperparathyroidism of CKD leads to hyperplasia of four (or more) parathyroid glands. Unless total parathyroidectomy is performed, the remaining parathyroid tissue left in place will start growing again. At present, in the majority of centers, the preferred surgical procedure is subtotal and not total parathyroidectomy. In Japan, the more commonly used approach is total parathyroidectomy with autotransplantation, which may also relapse. One of the arguments against total parathyroidectomy is that permanently hypoparathyroid kidney transplant recipients need lifelong substitutive therapy to avoid hypocalemia in the presence of a new functioning kidney.

**Parathyroidectomy or Calcimimetic to Treat Hypercalcemia after Kidney Transplantation?**

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Cruzado et al.\textsuperscript{8} have to be congratulated for having undertaken a randomized, controlled trial to examine the question of whether medical treatment of hypercalcemic hyperparathyroidism is superior or inferior to surgical treatment. Cruzado et al.\textsuperscript{8} conducted the study not on patients with CKD and their native kidneys in place but rather, on kidney graft recipients at different stages of CKD. Cruzado et al.\textsuperscript{8} randomly allocated 30 stable patients with transplants on various immunosuppressive drugs with persistent, hypercalcemic hyperparathyroidism to either cinacalcet treatment or subtotal parathyroidectomy. A previous randomized, placebo-controlled study has shown that cinacalcet is superior to placebo at correcting hypercalcemia and hypophosphatemia\textsuperscript{9}; however, a formal comparison with parathyroidectomy has never been done. The primary endpoint was the proportion of patients with normocalcemia at 12 months. At baseline, patients were well matched for clinical and biochemical parameters, eGFR, and severity of vascular calcification. All patients in the parathyroidectomy arm but only two thirds of those in the cinacalcet arm achieved normal serum calcium concentrations at study termination. Serum phosphate concentration was normalized in nearly all patients. Serum PTH decreased to a greater extent in the patients who were parathyroidectomized, and this was associated with a significant increase in bone mineral density at femoral neck but not at lumbar spine or ultradistal radius. Interestingly, the serum level of the bone resorption biomarker C–terminal telopeptide increased in the cinacalcet group but decreased in the parathyroidectomy group, whereas that of the bone formation biomarker alkaline phosphatase decreased in both groups. Vascular calcification did not change in either group. As to adverse effects, nausea and/or vomiting occurred in two patients treated with cinacalcet but none of the patients who were parathyroidectomized. In contrast, hypocalcemia was observed in four of the latter group but zero of the former group of patients.

Although eGFR decreased in both groups, with no between-group difference, it was surprising to see that the decrease from baseline was significant in the cinacalcet arm but not the parathyroidectomy arm. Rejection episodes in the two groups were comparable. The only randomized, controlled trial that compared cinacalcet with placebo in kidney transplant recipients did not find a difference in eGFR decline,\textsuperscript{9} which is in line with a meta-analysis of 21 observational studies in a total of 411 such patients.\textsuperscript{10} To our knowledge, there is no randomized, controlled study comparing parathyroidectomy with placebo after renal transplantation. In at least two observational studies, parathyroidectomy was followed by a more rapid decline in kidney graft function in the months after parathyroidectomy compared with the decline before surgery.\textsuperscript{11,12} However, long–term graft survival apparently was not altered.\textsuperscript{11}

Several limitations of the study by Cruzado et al.\textsuperscript{8} need to be emphasized. Cruzado et al.\textsuperscript{8} pointed out themselves that the follow-up was probably too short to assess long–term effects of the two respective treatment modalities, such as fracture risk, changes in vascular calcification, and recurrence of hyperparathyroidism after subtotal parathyroidectomy. Moreover, cinacalcet dosage was adjusted on the basis of achieved serum levels of calcium and not PTH. Another important limitation is the small sample size of the study population; therefore, some of the observed differences may not be real but by chance.

In addition to the differing effects of cinacalcet and parathyroidectomy on various parameters observed by Cruzado et al.\textsuperscript{8} long–term patient outcomes may not be the same. The long–term effects of cinacalcet therapy on hard outcomes in kidney transplant recipients are unknown at present. As to parathyroidectomy, a recent observational study reported that it was associated with improved survival in patients on maintenance dialysis, which was also shown by one of us before\textsuperscript{13} but not in patients with a renal allograft.\textsuperscript{14} Another issue lacking consensus is the relative merit of subtotal compared with total parathyroidectomy.

At present, what are the respective indications of cinacalcet administration and parathyroidectomy after renal transplantation? The answer to this question is not easy. The study by Cruzado et al.\textsuperscript{8} showed that parathyroidectomy was superior to cinacalcet in controlling hypercalcemia. However, serum calcium is not a hard endpoint. Moreover, in a certain number of renal graft recipients, hypercalcemic hyperparathyroidism resolves spontaneously after various periods of time. Therefore, the performance of a parathyroidectomy may be premature before a prolonged period of time\textsuperscript{6} (e.g., 12 months post–transplant\textsuperscript{7}), and medical treatment may suffice. Another aspect that deserves attention is that hyperparathyroidism may recur from remaining gland tissue, even after so–called total parathyroidectomy. In other patients, the surgery may be incomplete, and a second intervention may be necessary. Last but not least, parathyroid surgery is not free of complications, although admittedly, they are very rare with experienced surgeons. However, the sometimes limited tolerance and the still uncertain safety of chronic cinacalcet treatment also need to be considered. It could have a negative effect on immunosuppressive therapy and induce worsening of kidney graft function.\textsuperscript{6} Finally, the cost of long–term cinacalcet treatment needs to be weighed against the benefits and risks of parathyroidectomy, an issue of particular importance given the budgetary constraints in the provision of healthcare. Cruzado et al.\textsuperscript{8} have estimated that surgery would be more cost–effective than cinacalcet if cinacalcet duration reached 14 months.

This work by Cruzado et al.\textsuperscript{8} indicates that most patients with hyperparathyroidism after kidney transplantation will respond to either cinacalcet or parathyroidectomy, although the surgical correction of parathyroid overfunction was slightly superior to medical correction in terms of serum calcium and PTH control. Clearly, a more prolonged observation period examining hard patient outcomes is needed to adequately weigh the pros and cons of each treatment modality in the long run.
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