

Review Article

Clinical Impact of Hypercalcemia in Kidney Transplant

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Hypercalcemia (HC) has been variably reported in kidney transplanted (KTx) recipients (5–15%). Calcium levels peak around the 3rd month after KTx and thereafter slightly reduce and stabilize. Though many factors have been claimed to induce HC after KTx, the persistence of posttransplant hyperparathyroidism (PT-HPT) of moderate-severe degree is universally considered the first causal factor. Though not proven, there are experimental and clinical suggestions that HC can adversely affect either the graft (nephrocalcinosis) and other organs or systems (vascular calcifications, erythrocytosis, pancreatitis, etc.). However, there is no conclusive evidence that correction of serum calcium levels might avoid the occurrence of these claimed clinical effects of HC. The best way to reduce the occurrence of HC after KTx is to treat as best we can the secondary hyperparathyroidism (SHP) during the uraemic stages. The indication to Parathyroidectomy (PTX), either before or after KTx, in order to prevent or to treat, respectively, HC after KTx, is still a matter of debate which has been revived by the availability of the calcimimetic cinacalcet for the treatment of PT-HPT. However, we still need to better clarify many points as regards the potential adverse effects related to either PTX or cinacalcet use in this clinical set, and we are waiting for the results of future randomized controlled trials to achieve some more definite conclusions on this topic.

1. Introduction

Though kidney transplant (KTx) might induce a regression of most metabolic derangements characterizing end-stage renal disease (ESRD), electrolyte disturbances are not uncommonly encountered in patients with an even well-functioning renal graft.

Limiting ourselves to mentioning only the most frequent electrolyte disturbances, we would like to list: metabolic acidosis, hypo- and hyperkalemia, hypomagnesiemia, hypophosphatemia, and hypercalcemia [1–6].

Over the last decade, hypercalcemia (HC) has received much attention from the renal transplant community since it has been claimed to have a negative impact on both the graft and patient outcomes.

In the following paragraphs, we will deal with the main pathogenic aspects, the most relevant clinical consequences, and the possible therapeutic approach of the HC in KTx patients.

2. Prevalence of HC after KTx

HC has been reported to occur with an extremely variable incidence after KTx (from <5% up to >50%) [3, 6–12].

Table 1 shows the main characteristics of some of the most relevant studies, reporting on HC prevalence after KTx. The high variability of prevalence of HC might be explained at least in part by a number of factors.

First, it is worth noting that the older the study was the higher the prevalence of HC was evident, probably due to a less efficient control of SHP in earlier studies.

Second, it is also worth stressing that most studies had a cross-sectional and retrospective design and included a relatively low number of patients or only part of the global cohort of transplanted patients. This might have introduced a selection bias, where only patients with previously recognized severe hyperparathyroidism were included.

Third, the time elapsed from the time of transplantation to the time when serum calcium levels were evaluated was

TABLE 1: Prevalence of Hypercalcemia (HC) after Kidney Transplantation (KTx) in different studies.

Reference	Study protocol	N. of pts	Definition of HC	Time of observation (months from KTx)	% of HC	Vit D suppl
David et al. [6]	RS	64	tot-sCa >2.75 mmol/L	nd	34%	nr
Cundy et al. [7]	POS	100	tot-sCa > 2.65 mmol/L	Multiple assessments from the 2nd to the 24th month	12th → 20% 24th → 12%	nr
Reinhardt et al. [3]	POS	129	corr. tot-sCa > 2.95 mmol/L	Multiple assessments from the 2nd to the 24th month	3rd → 52% 12th → 23% 24th → 10%	No
Leca et al. [8]	nr-PIS	213	tot-sCa > 2.625 mmol/L	6th month	9.9%	No
Egbuna et al. [9]	RS	303	corr. tot-sCa > 2.55 mmol/L	Multiple assessments from the 2nd to the 12th month	3rd → 8% 12th → 9%	nr
Ramezani et al. [10]	RS	398	tot-sCa > 2.625 mmol/L	Assessment over the first 12 months	4.5%	nr
Evenepoel et al. [11]	POS	201	corr. tot-sCa or tot-sCa > 2.575 mmol/L	Multiple assessments over the first 3 months	corr. tot-sCa → up to 14% tot-sCa → up to 27%	No
Evenepoel et al. [12]	POS	268	i-sCa > 1.29 mol/L or corr. tot-sCa > 2.575 mmol/L	Multiple assessments over the first 12 months	i-sCa → up to 58.6% corr. tot-sCa → up to 13.1%	nr

POR = prospective observational study, RS: retrospective study, nr-PIS: not randomized prospective intervention study, tot-sCa: total serum Calcium, corr-tot-sCa: total serum calcium corrected for albumin, i-sCa: ionized serum calcium; nd: not defined, nr: not reported.

consistently variable in the different studies. In fact, an increase in HC prevalence would be expected during the first year after KTx, with a reduction thereafter. However, the changes in the prevalence of HC over time was also consistently different among the various studies. In fact, some AA reported that calcium levels had a trend toward an early reduction (first 3 months) and then increased up to the sixth month, stabilizing thereafter over all the first year [11, 13], while others [9] found an almost constant prevalence of HC over all the first year after KTx.

A fourth possible confounding factor might be a possible different use of vitamin D and/or calcium supplements in the KTx patients. In fact, most of the quoted studies do not report on this aspect.

Another possible confounder in the evaluation of the real prevalence of HC in transplanted patients is the different methodology used for calcium assessment. In fact, it has been reported that elevated Ca levels might be often overlooked if evaluated as total serum Ca rather than ionized serum Ca, since the former underestimates HC in KTx patients [12]. This effect can be only in part explained by the reduction of serum albumin levels, which often characterize the early period after KTx, since the total serum calcium corrected by albumin does not predict ionized calcium levels substantially better than the uncorrected ones [12].

Finally, these different results might also be explained by differences among the various transplant centres in the wait-listing policy for the patients with severe SHP.

Summarizing, though HC after KTx has been reported to occur with an extremely high variability, when calcium

levels are evaluated by the appropriate methodology (ionized calcium), its prevalence is relatively high, particularly during the first year.

3. Pathogenic Mechanisms of HC in KTx Patients

The first-well recognized factor in causing the occurrence of HC after KTx is the persistence of SHP after transplantation [11, 13].

PT-HPT after KTx is much more likely to occur when a severe form of SHP was present during the uraemic state preceding KTx.

It is also well acknowledged that the most severe degree of SHP is almost invariably associated with the nodular form of parathyroid gland hyperplasia which is much less prone to undergo spontaneous regression even after the uraemic state has been corrected [11, 14]. This also explains why, when the uraemic milieu has been corrected, the phosphate levels have been reduced, and the bone cell sensitivity to both PTH and vitamin D has been recovered by a functioning renal graft, the exceedingly high PTH levels are more effective in inducing HC due to enhanced bone response to its calcemic action [15].

However, the increased PTH-mediated bone resorption does not seem to be the only mechanism responsible for the HC in renal transplanted patients. One of the few studies which explored the skeletal status in KTx by bone biopsy found that HC was indifferently associated to either the

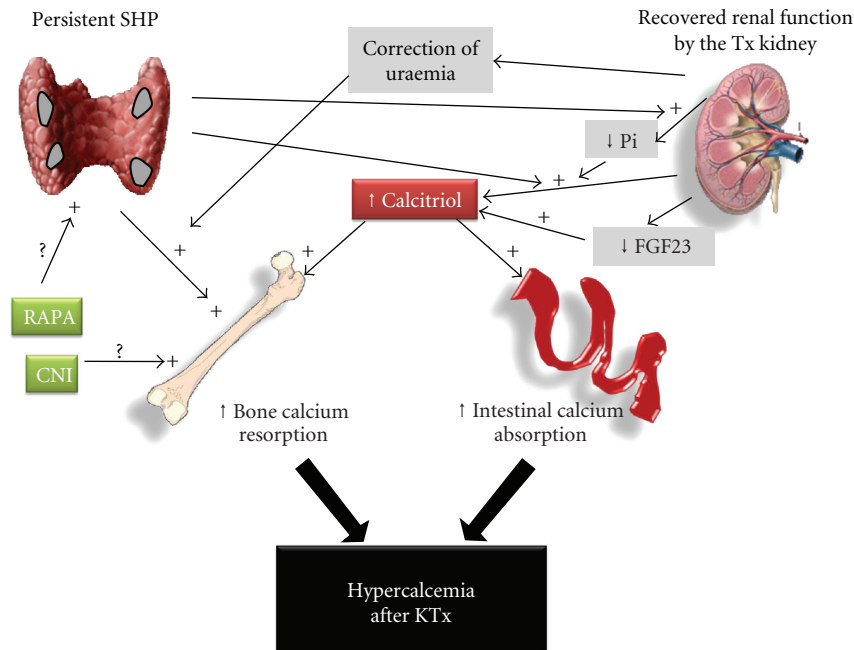


FIGURE 1: The main supposed mechanisms responsible for the occurrence of hypercalcemia after kidney transplant. (Pi: inorganic phosphorus; CNI: calcineurin inhibitors; RAPA: rapamycin; FGF23: fibroblast growth factor 23).

increased bone turnover disease or to the adynamic bone disease [16].

Another potential factor causing HC after KT_x is the recovered circulating levels of calcitriol, secondary to its increased renal tubular synthesis, further stimulated by the inappropriately high PTH and low phosphorus levels. The recovered calcitriol levels might concur in inducing HC by both its intestinal and bone effects [17].

This potential hypercalcemic condition might be in part counteracted by two opposing factors: the persistence of elevated FGF-23 levels, which is a strong inhibitor of 1- α -OHase activity, and the very frequent occurrence of the deficiency/insufficiency of the calcitriol precursor, calcifediol in KT_x patients [18, 19]. This point might have some therapeutic consequences, as will be discussed more in depth later on. In fact, with the progressive reduction of FGF23, which is often observed after a few months from KT_x, and particularly when patients are supplemented with vitamin D, overt HC might develop.

Another factor which has been cited as a potential cause of HC after KT_x is the supposed reabsorption of vascular calcifications (VC) [20]. However, there are no data in the literature supporting the above hypothesis, and on the contrary some AA have reported a trend toward an increase of VC after KT_x [21, 22]. Furthermore, some preliminary data of ours [23] seem to suggest that the higher the serum calcium levels, the higher the progression of VC after KT_x. From all these data, it seems quite unlikely that VC reabsorption might play any major role among the causes of HC of KT_x patients.

Whether different immune-suppressive drugs might be in some way related to HC is not completely clear. Steroids

have been recognized to carry with them a number of effects potentially affecting calcium metabolism (antivitamin D effect, calciuretic activity, induction of osteoblast apoptosis, etc.). However, most of these effects are expected to induce more hypocalcemia rather than hypercalcemia [24].

There is some evidence that calcineurin inhibitors (CNIs), in particular cyclosporine, might increase bone resorption and thus potentially promote the development of HC [25]. However, there is no clear data supporting this putative hypercalcemic effect of CNIs.

A recent paper reported that KT_x patients on rapamycin therapy would be more prone to develop persistent SHP, frequently associated with HC [26].

Finally, the possibility that some polymorphic variations in genes coding for some calcium controlling factors might increase the propensity to develop HC after KT_x cannot be excluded. In fact, some years ago we found that the *BB* polymorphic variant of Vitamin D receptor (VDR) gene was associated with lower prevalence of HC PT-HPT [13]. Our results were substantially confirmed by further data [27]. More recently, a genome-wide association study (GWAS) has clearly demonstrated that a single nucleotide polymorphism in the gene coding for the calcium sensing receptor (CaSR) is strongly associated with the levels of serum calcium in the general population [28]. Whether this genetic background might contribute also to the occurrence of HC after KT_x might be also worth studying.

Taken together all these data strongly suggest that the occurrence of HC after KT_x is mostly sustained by the persistence of a severe form of PT-HPT which is mainly secondary to the previous state of mineral metabolism

derangement developed throughout the often long story of chronic kidney disease.

Figure 1 summarizes the main hypothesized pathogenic mechanisms through which HC might develop after KTx.

4. Clinical Consequences of HC in KTx

There is some evidence that HC may have a negative clinical impact on either the graft and/or the patient outcome. Though it is not always easy to dissect the two clinical fields from each other, we will deal with each one separately so as to treat more clearly the topic.

4.1. Clinical Impact of HC on the Graft Outcome. A number of experimental studies have clearly demonstrated that HC can induce renal damage by different mechanisms. In animal models, three different types of Calcium-mediated kidney damage have been described. The first type is represented by macroscopic nephrocalcinosis, which is characterized by coarse deposits of calcium salts both in renal papillae and the urinary tract which can be detected also by ultra-sound and/or radiological examination. The second one is defined microscopic nephrocalcinosis, characterized by smaller calcium salt depositions at the tubular cell and/or the interstitial space level and can be detected only by microscopic examination. The last type of Calcium-mediated kidney damage is recognized as chemical nephrocalcinosis. This type of kidney damage can be defined as unspecific morphologic and/or functional cell changes which occur in the presence of HC and can regress or reduce after calcium level correction. The pathogenesis of this last type of kidney damage is mostly speculative and has been ascribed to some hemodynamic and biochemical effects of HC (vasoconstriction; increased natriuresis and diuresis; activation of a huge number of enzymes, cytokines, growth factors; etc.), even in the absence of any observable calcium salt deposition [29, 30].

The data present in the literature establishing a clear relationship between the presence of high calcium levels and kidney damage in humans and particularly in KTx patients are scanty and not fully conclusive.

Some years ago, Nankivell et al. [31] pointed out that microcalcifications were a common finding in protocol biopsies performed in transplanted kidneys, since they were observed in 43% and 79% of biopsies at 1 year and 10 years after KTx, respectively. Later studies demonstrated that the presence of HC is associated with a higher prevalence of calcium salt deposits within the transplanted kidney and that this nephrocalcinosis can adversely affect the graft survival [9, 32–35]. At variance with these results, other AA [36], though confirming that calcium deposits are frequently found (44%) in transplanted kidney biopsies, were not able to find any relationship between nephrocalcinosis and serum calcium levels. On the other hand, in the experience of the above AA it was the presence of low citrate and high oxalate urinary excretion which were more associated with calcium deposition within renal graft.

Independently of the presence or not of clear calcium deposits, it is worth remembering that HC can induce an indirect kidney damage, secondary to its well-recognized

sodiuretic and aquaretic effects which, in addition to its vasoconstrictor action, can consistently reduce renal perfusion, inducing a fall in glomerular filtration rate, which can progress in the long term from an initial functional form to a stabilized organic kidney injury condition.

Summarizing, though we have no conclusive evidence that HC can be responsible for the nephrocalcinosis, which is frequently observed in kidney graft biopsies, there are plausible reasons for thinking that persistently high serum calcium levels might adversely affect kidney graft outcome.

4.2. Clinical Impact of HC on the Patient Outcome. A number of potential negative effects of HC on different tissues, organs, and systems have been extensively reported in the literature. In the following paragraphs, we will just limit ourselves to briefly mention the most relevant ones which can more frequently occur in KTx patients.

4.2.1. Cardiovascular Effects of HC. It has been well acknowledged for some time that acute changes in extracellular calcium concentration might induce consensual changes of intracellular calcium levels which are the ultimate controller of cardiomyocyte and vascular smooth muscle cell contraction and relaxation [37–39]. On the other hand, there is not much evidence that chronic changes of serum calcium levels, in particular chronic HC, might cause any sustained cardiovascular effect, either in healthy people or in pathological conditions, such as in KTx patients.

However, there are some plausible reasons for believing that sustained high calcium levels might have some potential negative effect at least on the vascular calcification (VC) process. As previously mentioned, VCs not infrequently tend to progress after KTx, even though at a lower rate as compared with dialysis patients [21, 22, 40, 41]. Some of our preliminary results, produced as yet only in abstract form [23], suggested that aortic calcifications, evaluated according to Kauppila et al. [42], increased in 30% of patients over the first year after KTx. Furthermore, patients heading for a progression of their VC process had consistently higher serum Calcium levels as compared with patients who did not have any VC worsening.

However, these data alone cannot be considered to be definite proof of a casual role of HC in inducing negative cardiovascular effects. Randomized controlled studies are needed for reaching a conclusive answer to this important question.

4.2.2. Hematological Effects. After KTx; increases in red blood cell number and in hemoglobin levels are not infrequently observed [43]. Though the prominent causal factor of the erythrocytosis in KTx patients can be recognized in the recovered synthesis of erythropoietin (EPO) by the functioning kidney graft, in the presence of a well-responding bone marrow, after the correction of the uraemic state, other potential players might be also involved in this process.

Among them, an increased local and/or systemic activity of renin-angiotensin-system (RAS) has been advocated as a potential pathogenic factor, since RAS has been shown to

increase EPO synthesis, and furthermore the use of either ACE-inhibitors or angiotensin-receptor blockers has been demonstrated to be effective in controlling posttransplant erythrocytosis [44, 45].

Recently, it has been suggested that calcium may contribute to the RAS-mediated EPO stimulation [46]. Furthermore, recently some AA reported that posttransplant erythrocytosis is 2-3 times more frequent in KTx patients who have higher serum calcium levels as compared with normocalcemic patients [47, 48]. However, there are as yet no data demonstrating that the correction of HC might translate into a correction of posttransplant erythrocytosis.

4.2.3. Gastrointestinal Effects. Severe HC, particularly encountered in the most advanced stages of neoplasias, can be complicated by a relevant pancreatic damage [49]. If this is also true for the degree of HC usually observed in KTx patients is not clear.

Two decades ago, Frick et al. [50], studying 224 consecutive KTx patients, reported 8 patients who experienced an acute pancreatitis episode and 20 patients who had an asymptomatic increase of serum pancreatic enzymes. The AA did not observe any association between the pancreatitis episodes and the well-known specific risk factors, such as immune suppressive therapy doses, viral infections, alcohol consumption, or biliary tract lithiasis. The only factor which was significantly associated with the pancreatitis episodes was the presence of HC. However, no further paper, as far as we know, has been published in the following decades proving or disproving these findings.

In conclusion, it has been suggested that HC occurring after a KTx can negatively impact both graft and patient clinical outcomes. However, there is no evidence which clearly demonstrates the mechanisms by which these negative effects might act, nor can we exclude that the high PTH levels, which are almost invariably associated with HC, more than the elevated calcium level per se, might be the possible primary adverse factor.

Furthermore, it is still to be demonstrated which is the threshold calcium concentration, if any, over which these negative effects can happen.

5. Therapeutic Intervention

The presence of persistently elevated serum calcium concentrations, associated with elevated PTH levels, has for some time been considered a possible indication to parathyroidectomy (PTX) in KTx patients.

However, it is worth underlining that there is no guideline for establishing which are the PTH and the serum calcium levels over which the indication to PTX should be given in the KTx clinical set. Therefore, the indication for the PTX intervention is quite variable from one transplant centre to another. Furthermore, there is no general agreement on which type of PTX should be preferred: total, subtotal with or without the auto-transplantation of a parathyroid gland.

It has long been considered that PTX might negatively affect the graft outcome, possibly due to either the haemodynamic and/or immune-mediated changes triggered by the

acute changes in PTH and/or electrolyte concentrations after the parathyroid gland removal [51, 52]. On the other hand, recent data lessened this conviction, showing that no difference in the long-term graft outcome was evident between KTx patients who were submitted to PTX as compared with a comparable group of patients who were not [53].

However, the need to face a PTX intervention is still a matter of concern for many nephrologists in the early phase after a KTx, given the burden of clinical problems which can be present during this period. Furthermore, some of these patients have already undergone such an intervention and for this or any other reason they may not be prepared to undergo a new intervention.

For this reason, many Transplant Centers warmly recommend PTX in waiting-listed patients, before KTx when even a moderate form of SHP is present.

Conflicting with this trend, other nephrologists advocate some grounds for limiting the indication to PTX before KTx to only the most severe forms of SHP. The main reason is that there is some evidence which suggests that a regression of parathyroid gland hyperplasia could be expected after a well-functioning KTx. Some years ago, it was first reported that the maximal PTH response to a hypocalcemic challenge, which is considered a good marker of the functional parathyroid gland mass, substantially reduced from the 1st to the 6th month after renal transplantation [54]. More recently it has been also reported that in the parathyroid glands removed from KTx recipients, the cellular proliferative events are reduced and apoptotic figures increased as compared to the glands removed from uraemic patients on dialysis, even though in both groups the parathyroid hyperplasia was in the most advanced form characterized by nodular hyperplasia [55]. These observed histological changes might suggest that in the long run even the most severe form of SHP might be expected to regress after KTx.

Reinforcing this view, recent papers observed a regression of parathyroid gland volume, as assessed by US methodology, in KTx patients treated with a calcimimetic drug [56, 57].

These observations introduce the second potential therapeutic approach to HC of KTx patients.

It is widely recognized that the introduction of cinacalcet, as yet the only calcimimetic drug in clinical use, has consistently increased the possibility for controlling, in particular, the most severe forms of SHP in dialysis patients, reducing the indications for PTX in this clinical set. This fact enhances the complexity of the indication for PTX for the patients on a transplant waiting-list who suffer from a severe form of SHP which is well controlled by cinacalcet.

To further complicate this issue, it is worth remembering that, at the present time, this drug has not been registered for use also in transplanted patients.

On the other hand, a number of small studies have been published in recent years on the use of cinacalcet in KTx recipients which can give some indicative instruction on this topic [8, 58–68].

The main results of these studies have been extensively discussed in a recent review [69]. All these studies homogeneously demonstrated that cinacalcet is effective in reducing serum calcium concentration. Another constant finding of

these studies was a consistent increase in serum phosphorus levels. This last result can be considered a positive result, since it is well known that KTx recipients are prone to develop hypophosphatemia, which might contribute to the skeletal problem frequently observed in transplanted patients.

On the other hand, the behavior of PTH levels was less homogeneous. In fact, though PTH levels significantly reduced in most studies, the extent of these changes was quite variable, since some authors described no significant change at all [65] while others found up to a 40–50% reduction in PTH levels [8, 60, 61].

It is also worth underlining that only a part of these studies reported on the effect of cinacalcet on urinary calcium excretion. Furthermore, the results were very contradictory, with unchanged, increased, or reduced calcium excretion having been reported.

This variability might be at least in part dependent on the time when the assessment was performed. In fact, in the early treatment phase, when serum calcium levels (and consequently the glomerular filtered load of calcium) are still high, the reduction in renal tubular calcium absorption induced by cinacalcet, due to both the reduced PTH levels and to the cinacalcet direct calciuretic effects, is expected to induce high urinary calcium output. With ongoing treatment, these effects can be counteracted by the reduced glomerular filtered calcium load, secondary to the reduction of serum calcium levels which eventually bring its urinary excretion back to the pretreatment levels.

On the other hand, we cannot rule out that some genetic variability in the CaSR gene might play some role in the possible variable calciuretic effect of CaSR activation by cinacalcet. In fact a recent paper demonstrated that some polymorphic variants of the CaSR gene might play some role in the different urinary calcium excretion found in primary hyperparathyroid patients with or without nephrolithiasis [70].

Whatever the extent of the potential calciuretic effect of cinacalcet, this is a potentially negative effect of the drug, since, as previously mentioned, KTx patients are already prone to develop nephrocalcinosis. So, any metabolic change which might potentially increase this risk should be considered with great caution. To reinforce this concern, a case of nephrocalcinosis which occurred in a KTx patient treated with cinacalcet has been recently reported [62].

The problem of nephrocalcinosis in KTx patients indirectly introduces another linked therapeutic issue in this clinical set. In fact, though KTx patients often present a more or less severe vitamin D deficiency, there is much controversy on whether this deficit should be replaced even in the presence of elevated serum calcium levels. As previously mentioned, it is also to be expected that also in nonhypercalcemic KTx patients overt HC might ensue after starting the replacement therapy with vitamin D metabolites. However, some recent studies seem to minimize this concern, since no relevant adverse event related to HC episodes have been reported in KTx patients treated with cholecalciferol [71, 72]. In any case, it seems to be advisable to carefully check serum calcium levels when vitamin D therapy is

started. Whether the new less calcemic vitamin D analogues would represent a clinical advantage also in this field deserves specific prospective studies.

Although the potential effects of cinacalcet treatment on bone metabolism in KTx patients is an important issue, only two papers have dealt with this problem. The first study reported on a significant increase of bone mineral density at the radial level in 9 patients treated with cinacalcet [64]. To the best of our knowledge, the second study was the only one that prospectively examined bone histomorphometric parameters in 10 transplant recipients before and after 18–24-month treatment with cinacalcet [68]. The main results were a decrease of bone formation rate in 7, an increase in 2, and no change in 1 patient. These conflicting results, far from being conclusive, underline the need for gaining further information on this critical issue.

Another point of potential concern is the possible interference of cinacalcet with the immune-suppressive (IS) drugs and its potential effect on the graft function.

The first reports on the topic exploring the possible interference between cinacalcet and the IS therapy demonstrated no or only marginal effects of cinacalcet on the blood levels of the most frequently used immune-suppressive drugs [73, 74]. However, following studies, though performed in small groups of patients, provided results which suggest that cinacalcet might reduce Tacrolimus AUC_{0–24} by approximately 14% and might also promote the accumulation of a nephrotoxic metabolite of cyclosporine (AM19) [75, 76]. As far as the effects of cinacalcet on renal function are concerned, some of the quoted studies reported on the change in serum creatinine levels and/or on the variably evaluated glomerular filtration rate. The results were quite variable with some studies showing a slight worsening [63, 73, 74], others a slight improvement [60, 64, 67], and the other studies [58, 59, 65] no change of renal function at all.

It is worth stressing that the results of all the quoted studies are flawed in many critical aspects, since most of them were performed in relatively small groups of patients, had a retrospective design, and a lack of a control group. Furthermore, the criteria for choosing the treated patients were not homogeneous, and many treated patients had normal or slightly increased Ca levels before treatment, with PTH levels only moderately increased. In fact, in our opinion it is questionable to treat KTx patients with normocalcemic PT-HPT with cinacalcet.

6. Conclusions and Opinions

HC after KTx is mainly the terminal event of an evolved and uncontrolled SHP which maybe began long before transplantation.

Even though not completely clear, it is plausible that HC might negatively impact both graft and patient outcome.

The best way for avoiding HC after KTx is to optimally treat SHP before KTx. However, two main questions still remain unsolved.

The first question concerns the criteria for choosing the patient on the transplant waiting-list who should be referred to PTX or maintained on medical therapy. Given

the complete lack of evidence on this issue, in our opinion an absolute indication to PTX for a patient on the KTx waiting list can be the presence of a severe SHP, defined by contemporary high PTH levels (intact PTH > 800 pg/mL) and HC (tot s-Ca > 10.4 mg/dl), which cannot be controlled by the available medical therapy. A strong, though not absolute, further indication to the surgical intervention before renal transplantation might be also the presence of a SHP controlled only by maximal doses of medical therapy. In all the other cases, we do not believe that there is any compelling indication to PTX.

A second critical point is the management of PT-HPT associated with HC. PTX has long been considered the only treatment of this clinical condition. However, independently of its possible negative impact on graft function, which moreover still remains unproven, PTX entails a number of problems such as the type and the timing of the intervention to be performed, the need for a continuous treatment for the correction of the residual hypoparathyroidism after a successful intervention, the problems related to some comorbid clinical conditions which make the surgical intervention a risk procedure and more. For all these reasons, the recent availability of a medical approach to hypercalcemic PT-HPT based on the use of cinacalcet challenged the concept of considering PTX the best choice for this clinical condition.

However, it should be also considered that many unsolved issues bring into question the prolonged use of cinacalcet. These areas of uncertainty should be clarified by a randomized controlled trial before a widespread use of the drug can be suggested in KTx patients.

In this critical scenario, it is our opinion that cinacalcet should be reserved to some specific cases such as the KTx patients with PT-HPT associated with overt HC (> 12 mg/dl) and have been already submitted to a previous PTX and/or have clinical conditions which make the intervention a risk procedure and/or refuse the intervention for any reason.

At the present time, the clinical evaluation of each single patient still remains the best guide-line for choosing the best treatment of HC in KTx patients.

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