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REVIEW

Bone Mineral Disease After Kidney Transplantation

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Abstract

Chronic kidney disease-mineral bone disorder (CKD-MBD) after kidney transplantation is a mix of pre-existing disorders and new alterations. The final consequences are reflected fundamentally as abnormal mineral metabolism (hypercalcemia, hypophosphatemia) and bone alterations [high or low bone turnover disease (as fibrous osteitis or adynamic bone disease), an eventual compromise of bone mineralization, decrease bone mineral density and bone fractures]. The major cause of post-transplantation hypercalcemia is the persistence of severe secondary hyperparathyroidism, and treatment options include calcimimetics or parathyroidectomy. On turn, hypophosphatemia is caused by both the persistence of high blood levels of PTH and/or high blood levels of FGF23, with its correction being very difficult to achieve. The most frequent bone morphology alteration is low bone turnover disease, while high-turnover osteopathy decreases in frequency after transplantation. Although the pathogenic mechanisms of these abnormalities have not been fully clarified, the available evidence suggests that there are a number of factors that play a very important role, such as immunosuppressive treatment, persistently high levels of PTH, vitamin D deficiency and hypophosphatemia. Fracture risk is four-fold higher in transplanted patients compared to general population. The most relevant risk factors for fracture in the kidney transplant population are diabetes mellitus, female sex, advanced age (especially > 65 years), dialysis vintage, high PTH levels and low phosphate levels, osteoporosis, pre-transplant stress fracture and high doses or prolonged steroids therapy. Treatment alternatives for CKD-MBD after transplantation include minimization of corticosteroids, use of calcium and vitamin D supplements, antiresorptives (bisphosphonates or Denosumab) and osteoformers (synthetic parathyroid hormone). As both mineral metabolism and bone disorders lead to increased morbidity and mortality, the presence of these changes after transplantation has to be prevented (if possible), minimized, diagnosed, and treated as soon as possible.

Keywords Renal transplantation · Bone disease · Mineral metabolism · Fractures

Introduction

Kidney transplantation (KT) represents the best treatment for patients with chronic kidney disease, by improving both their quality of life and overall survival [1].

Chronic kidney disease-mineral bone disorder (CKD-MBD) after kidney transplantation is a mix of pre-existing alterations and new forms of CKD-MBD post transplant, because of immunosuppression and/or graft dysfunction [2].

Several studies show that alterations in bone mineral metabolism present in CKD, or in the early post-transplant period, influence the evolution of the graft or recipients survival, and that they may contribute to the development of bone alterations after transplant, underlying the importance of preventive measures from the moment of transplantation [3, 4]. After transplantation, it is common to observe the persistence of secondary or tertiary hyperparathyroidism (HPT), renal osteodystrophy (either high or low remodelling), relative vitamin D deficiency, high levels of fibroblast growth factor 23 (FGF23) and a dysfunctional graft.

When studying the changes in mineral metabolism after kidney transplantation, it is necessary to differentiate between the early period, in which the most severe biochemical derangements and a decrease in bone mineral density are

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observed, and the late period after transplantation, in which changes in the mineral metabolism are influenced more by graft dysfunction, in a way similar to advanced chronic kidney disease stages [5].

The final consequences of these adjustments are reflected fundamentally on mineral abnormalities and bone alterations.

Mineral Abnormalities

Calcemia: Hypercalcemia

Regarding calcium, most patients show low calcemia values in the early post-transplantation period that usually normalize after a few days. Nevertheless, in some of them, the pattern is biphasic and the hypocalcemia is substituted by hypercalcemia as soon as one week after transplantation [6]. According to the different series, hypercalcemia may be present, in the first month, in 5 to 60% of patients. This variability in prevalence is due, among others, to different cut-off values chosen for the diagnosis of hypercalcemia; to the definition of hypercalcemia based on either ionized calcium or total calcium; and to the fact that some series correct the value according to albumin levels, while others do not.

It worth to note that the prevalence of hypercalcemia in kidney transplant recipients (KTRs) decreases over time, although it can still be as high as 30% at the end of the first year. Subsequently, it continues to decrease, but in approximately 5–10% of patients still persists in the long term [5, 6]. A very recent study identified hypercalcemia as a risk factor for premature death in these patients [7]. It has to be highlighted that the majority of the studies that assessed the evolution of calcium after kidney transplantation have been performed before the introduction of calcimimetics. The positive impact of calcimimetics on the control of secondary hyperparathyroidism in dialysis explains the increase in the percentage of patients who undergo transplantation with controlled parathyroid hormone (PTH). In these patients, calcimimetic suspension at the time of transplantation can unmask the secondary hyperparathyroidism, thereby increasing the risk of post-transplant hypercalcemia [8, 9].

The major cause of post-transplantation hypercalcemia is the persistence of secondary or tertiary hyperparathyroidism, and patients presenting higher serum PTH and calcium levels at the time of transplantation have a greater long-term risk of persistent hyperparathyroidism [4, 6, 10]. The consequences of persistent hyperparathyroidism are:

Greater tubular calcium reabsorption, due to the action of PTH. The results of different studies are conflicting; while some show a decrease in the fraction of calcium excretion; others report greater urinary calcium excretion. It seems that the effect of PTH in increasing tubular calcium reabsorption would be more evident in the long term and less evident immediately after transplant, probably because of tubular dysfunction [6].

Greater intestinal absorption of calcium, due to an increase in serum levels of calcitriol caused by the increase in its synthesis due to the kidney graft function and to the stimulation of PTH. Serum calcitriol levels recover gradually afterwards in most patients after kidney transplantation [11, 12]. We have observed that this is due to the rapid and progressive decrease in serum FGF23 levels. However, there have been no studies that have observed differences in calcitriol values between patients with hypercalcemia and normocalcemia.

Increased bone resorption of calcium mediated by PTH. This seems to be the mechanism involved mostly in recent KTRs. Significantly higher serum alkaline phosphatase values are observed in patients with hypercalcemia than in patients with normocalcemia, suggesting increased bone turnover. These findings suggest that the release of calcium from the skeleton mediated by excess PTH, is the most plausible mechanism of hypercalcemia, in the first 6 months after kidney transplantation [6, 11, 12].

Post-transplant hypercalcemia has been considered as a factor associated with long-term graft dysfunction, as well as for acute tubulointerstitial micro calcifications of the kidney graft, besides its deleterious effect on the cardiovascular system [13–15]. Nevertheless, one prospective study showed that renal function after a mean follow-up of 33 months was similar in patients with and without tubular calcium phosphate deposition, at month 3 [16].

Treatment Alternatives

In the management of post-transplant hypercalcemia, due to the persistence of secondary hyperparathyroidism, three strategies can be employed:

Expectant Behaviour

In the presence of moderate hypercalcemia (serum Ca^{2+} < 10.5 mg / dL), it is reasonable to choose for a close monitoring of serum calcium value, while waiting for its normalization.

However, when faced with persistent hypercalcemia greater than 10.5 mg / dL, more severe hypercalcemia (> 11 mg / dL), or symptomatic hypercalcemia, a more proactive attitude has to be employed [6, 17].

If the patient was receiving high doses of cinacalcet pre-transplantation (> 60 mg / day), there is a high probability that the patient will develop hypercalcemia after its

suspension. In this case, it is suggested to restart cinacalcet early after transplantation or not to suspend it at all (8).

Calcimimetics

Since 2006, calcimimetics have been used as an alternative treatment for hypercalcemia due to the persistence of secondary severe HPT (also called tertiary HPT) in patients with a functioning kidney graft [18, 19]. The use of calcimimetics is highly effective in restoring normal calcium levels along with a substantial improvement in serum PTH and phosphatemia, without deterioration of renal function in most patients.

However, in some exceptional cases, a mild deterioration of renal function has been described during the first three months or one year after treatment start, especially in patients with already impaired renal function. In any case this worsening was reversible in all cases after cessation of the medication [20]. Even though it is not clear why this deterioration occurs, it has been suggested that it could be related to the decrease in PTH values, as occurs after parathyroidectomy [21]. This had already been described in experimental studies that demonstrated that PTH plays a role in the regulation of renal perfusion and in the function of mesangial cells. Another possible mechanism related is the hypercalciuria that follows the decrease in PTH; however, in most studies of patients receiving cinacalcet no relevant hypercalciuria has been observed.

On turn, a retrospective study that compared the use of calcimimetics versus parathyroidectomy versus medical observation in kidney transplant recipients with stable renal function and tertiary hyperparathyroidism has detected a higher rate of acute renal failure in the group of patients who did not receive treatment for their tertiary hyperparathyroidism [22]

Currently we do not know how long calcimimetics have to be maintained after transplantation and there are no known biomarkers that can guide treatment decisions. Considering that this is a group of patients who is usually polymedicated and considering the economic cost derived using cinacalcet, there is a need to explore if any biomarker could predict the absence of HPT recurrence after treatment withdrawal. In any case, in our opinion, treatment with calcimimetics should be tried for the management of hypercalcemia after renal transplantation before deciding to propose a parathyroidectomy.

Parathyroidectomy

Until very recently, it was the only possible alternative for patients with sustained hypercalcemia after KT that was secondary to HPT, and still is the option that best corrects hypercalcemia [23]. Although few studies have assessed the effects of parathyroidectomy after kidney transplantation, it has been shown that it controls calcium and improves BMD [21, 24]. In some studies, short-term deterioration of renal function has been observed after parathyroidectomy [21], Renal function deterioration is independent of the type of parathyroidectomy and it seems that mostly occurs in patients whose renal function was already deteriorated before parathyroidectomy.

Parathyroidectomy is also associated with risks that must not be undervalued, as hungry bone syndrome or local surgical complications. As we all know, hungry bone syndrome leads to severe hypocalcemia after the surgical intervention, with symptoms ranging from paresthesias to frank tetany. This clinical picture can be challenging, requiring acute high doses of calcium and vitamin D supplements to restore normal total calcium values. Parathyroidectomy can induce an iatrogenic adynamic bone disease, at long term, particularly in those transplanted patients exposed to high and prolonged corticoid therapy.

The two most frequently associated local surgical complications are the surgical wound infection, and the recurrent nerve palsy, described in 1% of the surgeries and with progressive recovery in the majority of them.

The surgical options are [16]:

1. Total parathyroidectomy with forearm auto-transplantation which leads to a faster correction of the calcemia; however, it results in an increased risk of hypocalcemia. Anther limitation is that in patients with functioning KT, the recurrence rate seems similar between this technique and subtotal parathyroidectomy. In case of recurrence / persistence, it is sometimes difficult to discern whether this is due to hyperplasia of the auto-transplant or possible residual tissue in the cervical area. In this case, the MIBI scintigraphy can be helpful [25]. The auto-transplanted gland in the forearm, in case of recurrence, seems to be more accessible, although in case of significant hyperplasia (also called parathyromatosis), it tends to spread over the implant area and is very difficult to resect.
2. Subtotal parathyroidectomy. consists in the exeresis of all parathyroids, except for a portion of a well-vascularized gland that should have a normal gross appearance or that of a simple diffuse hyperplasia. Many authors advocate it as the least aggressive technique [26]
3. Total parathyroidectomy without auto-transplantation. It is the most effective alternative in terms of improvement of bone pain and, probably, in the number of recurrence / relapses of HPT. In contrast, most of these patients usually require long-term calcium and vitamin D supplementation in order to avoid the development of hypocalcemia and osteomalacia, respectively [27].

4. Selective parathyroidectomy: consists in performing a parathyroidectomy of only one or two parathyroid glands. If the cervical ultrasound examination and / or MIBI scintigraphy shows that there are one or two adenomatous glands, some authors advocate removing only those pathological ones (enlarged and / or hyper-fixing on Sesta-MIBI). With this technique, the percentage of acute hypocalcemia is lower than with the previous techniques and the percentage of persistent hypocalcemia is anecdotal [28]. On the contrary, it seems that the risk of persistence / recurrence of HPT is higher, even though in most series there is a low incidence of HPT recurrence.

In our opinion, parathyroidectomy should be reserved for patients who do not respond to medical treatment.

Phosphatemia: Hypophosphatemia

Post-transplant hypophosphatemia is a well-known entity that can occur in up to 90% of cases in the early post-transplant period [29]. However, this event is usually self-limited, and only 6–27% of patients will maintain low phosphorus, at long-term follow-up [30]. This complication, which rarely becomes serious reaching phosphatemia < 1.5 mg / dL, has traditionally been attributed to the persistence of secondary or tertiary hyperparathyroidism after transplantation. Recently, it has been demonstrated that the most important factor is not PTH, rather the persistence of high serum levels of FGF23 [31, 32].

A further point in favour of the dominant role of FGF23 is the inadequate high phosphaturia that sometimes is observed, even if PTH is normalized after transplant. Moreover, in many cases, post-transplant hypophosphatemia is not associated with hypercalcemia, which reinforces the idea that secondary hyperparathyroidism is not the main responsible. We cannot forget that renal denervation is another factor for the hyperphosphaturia observed in these patients [33].

In RTRs hypophosphatemia, if persistent, has a negative effect on osteoblasts and may contribute to complications such as osteomalacia and progressive bone demineralization, which, in combination with low bone mass, could predispose patients to a high risk of fracture.

Hypophosphatemia in the first weeks after transplantation has also been associated with muscle weakness and the deposition of calcium phosphate complexes in the kidney graft, independently of PTH levels, possibly leading to kidney graft dysfunction [34]. As a matter of fact, elevated fractional excretion of phosphate, hypercalcemia, and uncontrolled HPT have been evoked as contributing factors for the development of microscopic nephrocalcinosis after transplantation [16].

Treatment Alternatives

Phosphate Supplementation

Although most of the time the only treatment alternative is oral administration of phosphorus salts, one should assume that inadequate hyperphosphaturia will persist. The administration of oral phosphorus can cause an increase in serum values of PTH and FGF23, which will further decrease the tubular reabsorption of phosphorus, in a vicious circle as described in a prospective study in 32 patients with hypophosphatemia (< 3.5 mg / dL), in late post-transplantation [35]. Furthermore, phosphate preparations also reduce active vitamin D level, with a consequent increase in PTH. For these reasons, the administration of phosphate preparations is not actively recommended, except in patients with symptomatic and severe hypophosphatemia.

Nevertheless, oral phosphate supplementation soon after KT is effective in normalizing serum phosphate levels and metabolic acidosis and in improving muscle phosphate content [36], however, with the previous referred complications, as exacerbation of persistent HPT or hyperphosphaturia which can, in extreme, lead to acute renal failure [37]. Furthermore, there are no data on the long-term consequences of phosphate salts in post-transplant hypophosphatemic recipients.

Vitamin D and Others

A treatment alternative is the administration of active vitamin D, but only when hypercalcemia is not present. Other possible medications for hypophosphatemia include dipyridamole and anti-FGF23 antibodies [38]. Dipyridamole administration to hypophosphatemic post-transplant patients resulted in a decrease in urinary phosphate excretion and an increase in serum phosphate levels.

When treating post-transplant hypophosphatemia, treatment should be addressed according to whether patients are in the early or in the late period after transplantation. This distinction is important because the underlying causes of hypophosphatemia are different. Tubular damage, FGF23 levels, and persistent tertiary hyperparathyroidism are responsible for early hypophosphatemia soon after transplantation. In contrast, late hypophosphatemia is mainly due to persistent HPT, and in this case either vitamin D analogues or calcimimetics, could be able to slow the elimination of phosphorus at the renal level, even though there is little clinical experience.

Bone Disease

Bone Turnover and Mineralization

Alterations in bone turnover and mineralization before the transplant likely dictate the evolution in the post-transplant period. However, there are few bone biopsies studies that allow us to take conclusions about the evolution of bone turnover and mineralization, after transplantation.

The first double bone biopsy study dates back to 1991 [39]. It included 20 patients who underwent bone biopsy at baseline and after a 6-month period. The results showed normalization from high turnover, with a reduction in the bone formation rate and without morphological evidences of reduced bone volume. More recently, 3 double bone biopsies studies were published. In 2016, Evenepoel and co-workers performed a double bone biopsy in 36 renal transplanted patients [40]. Half of patients presented with normal turnover, almost 45% showed low bone turnover disease and near 3% high-turnover disease; 8% had low volume; and more than 16% presented abnormal mineralization. Twelve months after, no significant differences in volume or mineralization were found overall; patients with hypercalcemia secondary to tertiary HPT showed normal or low turnover disease; and the loss of trabecular bone was related to steroids cumulative dosage. More recently, a study from Brazil with 31 double bone biopsies at baseline and after 12 months showed an improvement in cortical porosity and thickness, but no improvement in trabecular bone, without significant alterations in mineralization [41]. A third prospective study from Finland [42] enrolled 27 renal transplant recipients submitted to a first bone biopsy 15 months before the transplant, while they were on dialysis, and a second bone biopsy 2 years after transplantation. This study showed that low turnover disease replaced high-turnover disease after transplantation (63 to 19% for the first and 26% to 52% for the second), with no major changes in bone volume and no demineralization. Curiously, bone densitometry and bone turnover markers didn't correlate with the histomorphometric findings.

Considering these results, we can conclude that high-turnover bone disease decreases in frequency after transplantation and that adynamic bone disease is more frequent. Osteomalacia seemed to be uncommon after renal transplantation. In this setting, early steroids withdrawal and vitamin D supplementation may halt bone loss.

Bone Volume: Decreased Bone Mineral Density (BMD)

Bone loss, with osteopenia or osteoporosis, is associated with an increased risk of fractures and reflects the imbalance between bone formation and bone resorption [43]. KDIGO and the Spanish Society of Nephrology guidelines recommend evaluating bone volume through the measurement of bone mineral density using dual X-ray absorptiometry (DXA) [44, 45].

The loss of bone volume occurs mainly in the first six months after kidney transplantation and appears to slow down thereafter, possibly due to corticosteroids withdrawal or reduction [46, 47]. The decrease is 5.5–19.5% during the first six months, 2–8% between six and twelve months and 1–2% thereafter, with a slight increase in BMD over time. These findings highlight the importance of initiating prophylactic measures from the very beginning of transplantation.

Although the pathogenic mechanisms of these abnormalities have not been fully clarified, the available evidence suggests different factors are implicated (Fig. 1), such as the immunosuppressive treatment, the persistently high levels of PTH after transplantation, and hypophosphatemia.

Immunosuppressive Treatment

Glucocorticoids: Glucocorticoids inhibit osteoblastic differentiation and induce apoptosis of mature osteoblasts and osteocytes [48]. In addition, corticosteroids decrease

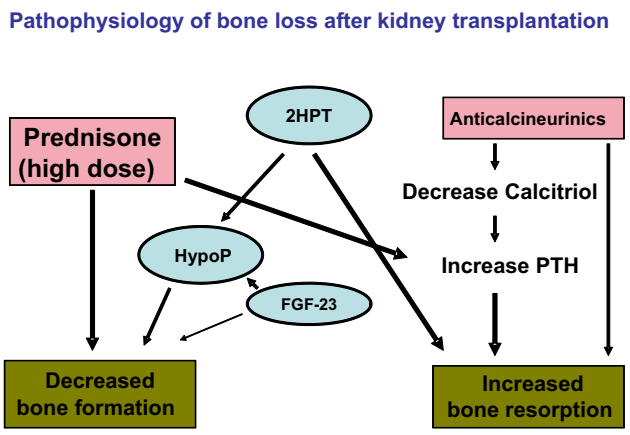

Fig. 1 Pathophysiology of bone loss after kidney transplantation: 2HPT: secondary hyperparathyroidism and HypoP: hypophosphatemia

intestinal calcium absorption, creating negative calcium balance, and induce hypogonadism.

Anticalcineurinics: Although some in vivo studies in rats have shown that both cyclosporine and tacrolimus induce high-turnover osteoporosis, epidemiological studies have not been able to demonstrate an association between the use of calcineurin inhibitors and the risk of fracture [49].

Other immunosuppressants; Studies in experimental animals have shown that neither azathioprine nor mycophenolate mofetil nor sirolimus have negative effect on bone volume. More recently it has been observed that sirolimus could interfere with the proliferation and differentiation of osteoblasts in an in vitro model [50]. On the other hand, everolimus may reduce the loss of cancellous bone in ovarectomized rats through a decrease in bone resorption mediated by osteoclasts [51].

Persistently High Levels of Parathyroid Hormone After Transplantation

Refractory or tertiary hyperparathyroidism is preceded by severe pre-transplantation secondary hyperparathyroidism and causes hypercalcemia and hypophosphatemia in the presence of a functioning graft. In contrast, secondary hyperparathyroidism develops in transplant recipients with an impaired glomerular filtration and is usually associated with hypocalcemia, hyperphosphatemia, and vitamin D deficiency.

Tertiary hyperparathyroidism ensues as the hyperplastic parathyroid glands continue to produce PTH autonomously, even if renal function is restored. During the first 3–6 months post-transplantation, PTH values usually decrease quickly (> 50%) due to a reduction in the glandular hyperplasia, while the following decrease is more gradual, likely attributed to a slower glandular involution [52]. In any case, persistence of hyperparathyroidism has been described in 30% of transplant recipients with a GFR > 30 ml / min one year after surgery [53, 54].

Some studies have shown a direct correlation between the magnitude of bone loss in the lumbar spine, femoral neck and hip soon after or in the first months after transplantation seems to be related to pre-transplant PTH levels [56]. Patients with greater bone remodelling at the time of transplantation are likely to experience greater negative bone balance after corticosteroid have been started. On the contrary, most of the cross-sectional studies in long-term stable kidney transplant recipients have not demonstrated a correlation of prevalent PTH levels with BMD or with different histomorphometric parameters [57]. In other studies, however, PTH levels were related to BMD in different locations, especially in the femoral neck and distal radius, although only in men [58].

In any case, one argument in favour of the deleterious effects of uncontrolled hyperparathyroidism after KT is that, after parathyroidectomy or treatment with vitamin D analogues or calcimimetics, there is a recovery of bone mass that ranges between 1 and 8% in different locations [59, 60].

It has to be highlighted that the persistence of hyperparathyroidism is a risk factor for loss of bone mass and increased risk of fractures [55]. Hyperparathyroidism has been associated with a risk of fracture, progression of vascular calcification and chronic graft nephropathy. For this reason, it must be searched for and treated after KT.

Hypophosphatemia

Hypophosphatemia in the first weeks after transplantation has been associated with a decrease in bone formation and a delay in mineralization, these being independent of PTH levels [61]. It is likely that many patients with suspected steroid-induced osteoporosis actually have a bone mineralization defect and osteomalacia secondary to hypophosphatemia.

Bone Fractures

The rapid bone loss that occurs after transplantation is associated with a high prevalence (7–20%) and incidence (3–4% per year) of fractures [4]. It has been estimated that fracture risk is four-fold higher in transplanted patients comparing to general population, and a third higher than dialysis patients [62]. A recent meta-analysis failed to reach the same conclusions, based on the fact that the selected studies were heterogeneous [63].

Some authors suggests that the highest incidence of fractures occurs during the first 3 to 6 months after transplantation, and slowly decreases thereafter, while other authors claim that they are more frequent later. A recent study showed a fracture incidence of 14.2 fractures per 1000 person-years, with a median time to first fracture of 17 months [64] Although bone loss occurs preferentially at the level of the trabecular bone, in most cases affects the appendicular skeleton, particularly the feet and ankles. However, the prevalence of vertebral fracture is minimized, as asymptomatic deformities are not systematically investigated [65].

A vertebral fracture prevalence of 32% has been observed when deformities were investigated with conventional radiological or by DXA [66]. As the vertebral fracture is a powerful risk factor for the development of future fractures, its detection provides the opportunity to intervene as a secondary prevention measure. Hence, an imaging technique must be incorporated routinely for the detection of asymptomatic vertebral fractures in high-risk kidney transplant recipients.

The known risk factors for fracture in kidney transplant recipients include diabetes mellitus, female sex, advanced age (especially > 65 years), dialysis vintage, osteoporosis

or pre-transplant stress fracture and high doses of steroids, abnormal PTH and hypophosphatemia [4, 43, 49, 67].

A current matter of debate is whether or not BMD measured by DXA has the same predictive value for fracture in kidney transplantation as in the general population. Several cross-sectional studies have compared BMD in kidney transplant patients with and without fractures. Although the values are lower in those with fractures, there is a huge overlap of values between both groups, both at the spine and at the hip level. However, in a recent prospective study, low BMD predicts incident fractures in de novo kidney transplant recipients [64].

Treatment Alternatives

Prevention of bone loss and fractures begins at the time of transplantation.

Immunosuppression

The first measure is to minimize the doses of corticosteroids and suspend them as soon as it is considered safe. Therefore, the minimization of corticosteroids with withdrawal at 3–6 months, or their total suppression one week after transplantation will effectively prevent bone mass decrease.

Vitamin D and Calcium Supplements

Use of calcium and vitamin D supplements seem to be basic preventive measures, especially in patients who receive a high dose of corticosteroids. Oral calcium supplements (0.5 g / day) and vitamin D, either calcitriol or alpha-calcidol, may prevent the loss of bone mass in the first months after transplantation. However, calcium levels should be determined regularly to avoid the risk of hypercalcemia. Still, it has to be noted that no study has shown a decrease in the risk of new fracture with calcium and vitamin D supplements [68, 69].

On the other hand, the deficit of nutritional vitamin D, detected by low levels of 25OHD3, is frequent after kidney transplantation. 25OHD3 has pleiotropic and immunomodulatory properties. Therefore, it is recommended to periodically measure 25OHD3 levels after transplantation and normalize its values [70, 71].

Antiresoptives

1. Bisphosphonates: Bisphosphonates are pyrophosphate analogues widely used for the treatment of osteoporosis. As they are eliminated by glomerular filtration and tubular secretion, caution must be exercised in patients with impaired renal function in order to avoid renal toxicity and drug accumulation [72]. Oral administration has not been associated with adverse renal events. With intravenous administration, it is important to maintain and even prolong the infusion time in order to avoid side effects. All bisphosphonates, with different dosing schedules and associated with calcium and vitamin D supplements, have been shown to be effective both in the prevention of bone loss and in the treatment of established bone mass deficit after KT [73–75]. Their use may be indicated in RTPs with osteoporosis (t-score or z-score < -2.5) and stress fractures. Nevertheless, before starting its administration, PTH should be assessed and a bone biopsy should be considered in order to exclude a low turnover disease. The universal use of bisphosphonates after transplantation should not be recommended, as demonstrated in a recent Brazilian trial, in which no differences was found with a generalizing use of bisphosphonates [41].
2. Denosumab: Denosumab is a fully human monoclonal antibody against RANKL that was developed for treatment of osteoporosis and prevention of fractures. By inhibiting the development and the activity of osteoclasts, denosumab decreases bone resorption and increases bone density. Compared with bisphosphonates, denosumab has superior efficacy in improving BMD and preventing fractures in post-menopausal women with osteoporosis [76]. It has been demonstrated, in a randomized controlled clinical trial, that denosumab effectively increased bone mineral density during the first year after KT, with a stronger therapeutic effect than that of the previously described treatments [77, 78]. Except for a higher number of urinary tract infections and asymptomatic episodes of hypocalcemia, denosumab was safe [79]. When administered, calcium and PTH should be checked within 15 days after the first dose, due to the risk of hypocalcemia and acute PTH increase. To avoid this side effect, the daily administration of vitamin D and oral calcium is recommended. It should be noted that patients with adynamic bone disease probably would not experience any benefit [80].

Osteoformers

1. Parathyroid hormone: Teriparatide is a fragment of natural human parathyroid hormone that replicates the first 34 amino acids of the N-terminal end of natural PTH. It is obtained by bioengineering in Escherichia coli. The peptide interacts with the type 1 PTH receptor that is expressed by osteoblasts and in renal tubular cells. Intermittent teriparatide therapy increases the number of osteoblasts with consequent bone formation; this is due to a decrease in osteoblastic apoptosis and an increase in the maturation and activation of osteoblasts and preosteoblasts [78]. Thus, it could be reasonably used in

kidney transplant patients with hypoparathyroidism and hypocalcemia, with the latter that can be further aggravated by the use of steroids. In these patients, the use of synthetic PTH represents a valid therapeutic option, since it improves bone mineralization by decreasing its resorption and also reducing the fractional excretion of urinary calcium and increasing its intestinal absorption. However, it has shown no effects in preventing rapid bone loss that occurs in the first months after transplantation [81, 82]. Its use should be reserved for transplant patients with fractures and adynamic bone disease, such as those who are older (> 60 years) or diabetics, with low serum PTH values [4].

In patients with stress fractures, the performance of a bone biopsy after tetracycline marking can help to choose the best option based on the state of remodelling and bone mineralization.

Conclusions

Although chronic kidney disease patients benefit from having a functioning kidney graft, bone and mineral metabolism disorders are still common after transplantation. Mineral abnormalities are common and probably contribute to bone disease and the very high bone fracture prevalence observed in this population. Nevertheless, osteomalacia and low bone volume are not so frequent as previously suspected in the light of the results of double bone biopsy studies. New therapeutic options are available for reducing the possibility of bone fractures in these patients but, as they induce opposite results, the treatment decisions should be supported, if possible, by the results of a previous bone biopsy. In fact, presently, the evaluation of CKD-MBD after transplantation is the most frequent motive to perform a bone biopsy in the nephrology field.

Compliance with Ethical standards

Disclosure Josep-Vicent Torregrosa has no conflict of interest, and Ana Carina Ferreira reports personal fees from Amgen and Vifor Pharma, outside the submitted work. David Cucchiari has no conflict of interest. Aníbal Ferreira reports personal fees, grants and participation in advisory boards from Abbvie, Astellas, Amgen, Baxter, Merck Sharp and Dhome, Mundipharma, Nephrocare-Fresenius Medical Care, Sanofi and Vifor Pharma, outside the submitted work.

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