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Editorial Review

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Bone disease after renal transplantation

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Introduction

Because of increasing life expectancy after renal transplantation, the prevention of long-term complications, such as bone disease, has become an essential part of post-renal-transplant care. Bone disease is one of the possible long-term complications that can significantly influence quality of life. Compared to members of the normal population of the same age, the fracture rate in renal transplant patients is four times higher. In addition, there is a risk for avascular bone necrosis after transplantation, which mainly affects weight-bearing bone structures, such as femoral heads, and as a rule, can only be treated by hip replacement with endoprosthesis. Histological evidence of abnormal bone structure, osteodystrophy and osteopaenia is already present shortly after transplantation in almost all transplant recipients [1].

Bone disease after renal transplantation differs from bone disease after transplantation of non-renal solid organs. Bone disease after non-renal solid organs is often similar to steroid-induced osteoporosis. In addition, accessory factors such as low 25-hydrolylase activity in liver graft recipients may lead to osteomalacia. However, after renal transplantation, bone disease is in large part due to pre-existing bone damage acquired during dialysis therapy and renal insufficiency and because of factors that affect the bone to varying degrees after successful renal transplantation. Apart from immunosuppressive agents, metabolic factors such as hyperphosphaturia, persistent hyperparathyroidism with hypercalcaemia, disturbances to the acid–base balance and hypomagnesaemia also play an important role.

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Renal bone disease before transplantation has once again become the object of attention because of our better understanding of important pathogenic mechanisms underlying hyperparathyroidism and its regulation, bone metabolism and the impact of hyperphosphataemia and hypercalcaemia on cardiovascular mortality. In addition, new drugs have been developed, such as the calcium-free phosphate binders sevelamer and lanthanum carbonate, or the calcimimetic drug cinacalcet, which have broadened the range of available therapeutic options. Moreover, these pharmacological approaches provide new understanding of and therapy for bone disease after successful renal transplantation. These aspects will be described below.

Clinical importance of bone disease after renal transplantation

A retrospective analysis of 1572 kidney graft recipients showed a fracture incidence of 19.1% within an average observation period of 6.5 years, with 6.4% of all patients suffering multiple fractures [2]. After the exclusion of malleolar fractures (8.3%) and avascular bone necroses (5.0%), the cumulative fracture incidence was 12.0% after 5 years, 18.5% after 10 years and 23.0% after 15 years. Over 16% of the patients had deformations of the spine and vertebral fractures inappropriate for the force causing the injury [3]. Consequently, the long-term risk of fracture far exceeds that of the normal population, which is ∼1% in women 65 years of age and below and ∼6–10% in 75-year-old women [4]. What is the risk of fracture for patients on the waiting list for transplantation compared to renal transplant recipients? Retrospectively, 101 039 patients on the waiting list for renal transplantation were evaluated [5]. Of those, 41 095 (40.7%) had never received a transplant and could thus be compared with 59 944 (59.3%) transplant recipients. The mean follow-up duration was 2.98 years. In total, 971 patients had a hip fracture. In dialysis patients, the fracture rate was 2.9 fractures per 1000 patient-years versus 3.3

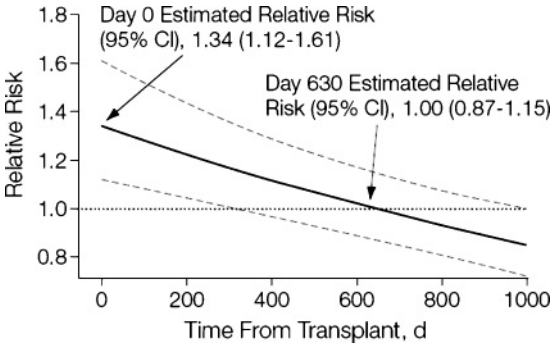

Fig. 1. Calculated relative risk of fractures after renal transplantation in comparison with patients on the waiting list for renal transplantation (the interrupted line marks the 95% confidence interval) (Reprint with permission from American Medical Association [5]).

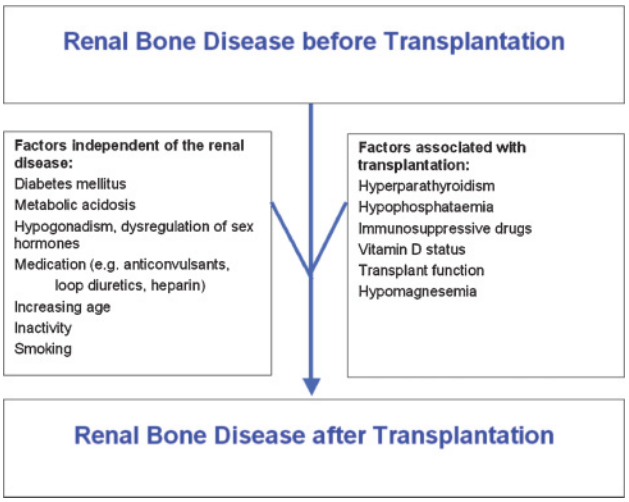

Fig. 2. Factors causing bone disease after transplantation [5,68].

fractures in transplant recipients. Consequently, their risk was 34% higher. However, the risk of fracture in transplant recipients compared to patients on the waiting list decreases continuously over time. In the first 6 months after transplantation, the relative risk among transplant recipients is 1.34 times higher, but it decreases by 1% per month, so after ~630 days, a similar risk is found in both groups. After this point, the risk of fracture for transplant recipients falls below that of patients from the waiting list (Figure 1).

To answer the question of how to avoid fractures and which type of prophylaxis is the most adequate, the pathogenesis of bone disease after renal transplantation will be reviewed. Special attention will be paid to the fact that the individual components of bone disease change over time. From these considerations, the appropriateness and timing of the respective therapies can be derived.

Because the aim of an optimal prophylaxis is to reduce the fracture rate after transplantation, therapeutic interventions have to be proven in prospective, randomized, blinded studies. Most published studies cannot answer this question, either because of insufficient duration or number of patients. Studies based on the examination of histological changes in bone are also rare. Therefore, change in bone density is almost always chosen as a surrogate parameter, even though change in bone density does not provide any information on the architecture or histology of bone. Although stability of bone density or even an increase in bone density represents a good surrogate parameter for an effective prophylaxis of osteoporotic fractures [6], this does not fully apply to situations present after transplantation. Renal transplant recipients with abnormally low bone density may have a low fracture rate; more than one-third of the patients with fractures showed no signs of osteoporosis in bone density measurements [7,8]. Nonetheless, changes in bone density remain the standard parameter for most studies in regard to the efficacy of various prophylactic measures.

Pathogenesis of bone disease after transplantation

Bone disease in transplant recipients is based on pre-existing damage to the bone acquired during the period of renal insufficiency, damage to the bone starting in the period of transplantation and modulating influences independent of renal disease or renal transplantation (Figure 2).

Important factors comparatively independent of renal disease will not be discussed here in detail, even though they are significant. Some of these factors, such as smoking or physical inactivity, should be actively considered as a part of the preventive actions.

The starting point for bone disease after transplantation is the period during pre-terminal renal insufficiency and renal replacement therapy. The different factors contributing to bone disease, including secondary hyperparathyroidism accompanied by hyperphosphataemia, decreased calcitriol concentrations and variable calcium concentrations can be identified to various degrees in biopsies of patients immediately after renal transplantation, thus reflecting the 'baseline' before other factors that affect the bone after transplantation have time to produce detectable changes. In a study on the effectiveness of bisphosphonates, 50% of the biopsies taken from patients immediately after transplantation showed bone with high turnover, with the dominant picture being osteitis fibrosa, while ~30% had adynamic bone and ~20% showed a mixed picture [9]. This distribution of bone disease shows geographic variation and is primarily subject to the therapeutic regimen that was in place prior to transplantation.

Development of bone disease after renal transplantation

Immediately after transplantation and along with the start of transplant function, many factors, which are responsible for the development of renal osteodystrophy, undergo some fundamental changes. Often as early as during the first post-transplant week, hyperphosphataemia-–one of the earliest factors to develop-–turns into hypophosphataemia because of marked hyperphosphaturia. The increase in parathyroid hormone excretion, which becomes autonomous over time,

continues and calcitriol concentration, which varies widely in renal transplant recipients immediately after the procedure, is often accompanied by episodes of hypercalcaemia. To detect the developing changes at an early stage, monitoring according to the K/DOQI guidelines is recommended [10].

In addition to these factors, immunosuppressive regimens, especially the use of steroids, play a decisive role. Because all the above-mentioned factors act simultaneously on the bone-–which is already affected by a wide variety of pre-existing pathological changes-–while simultaneously interacting with each other, bone disease after transplantation manifests as a complex condition. For the prophylactic or therapeutic treatment of bone disease after transplantation in an individualized, targeted and rational manner, it is helpful to look at the individual factors acting on the bone after transplantation in greater detail.

Importance of hyperparathyroidism for the development of bone disease

The lack of guidelines to define what is considered a 'normal' PTH concentration in kidney graft recipients is due to the lack of well-controlled studies that correlate PTH concentrations with alterations of the bone after transplantation. Most often, a target PTH concentration adjusted to the kidney function as in other patients with kidney diseases has been used. One must be aware of the possibility that this may not adequately reflect the complex situation in the transplant setting.

Parathyroid function after renal transplantation has been evaluated in a number of studies. In about two-thirds of renal transplant recipients, increased parathyroid hormone levels are found immediately after transplantation [11]. The parathyroid hormone concentration falls by ∼50% within the first 2 weeks, followed by a more gradual decrease; as a result, approximately half of the renal transplant recipients with good transplant function have normal parathyroid hormone levels after about 3 months, and after 1 year, only between 10 and 50% of patients suffer from hyperparathyroidism [12]. In the further course, there is only a slight additional decrease in the hyperparathyroidism rate; 21% of the transplant recipients still show abnormally high levels of parathyroid hormone up to 15 years after transplantation [13]. Hyperparathyroidism is associated with a high percentage of hypercalcaemic episodes. During a post-renal-transplant follow-up period of up to 5 years, hypercalcaemic episodes were found in 46% of cases after 1 year, 40% after 3 years and 24% after 5 years [11]. The progression from secondary to tertiary hyperparathyroidism, i.e. the form that no longer responds to the normalization of calcium, phosphate and calcitriol, is promoted by both prolonged periods of hyperphosphataemia and delayed calcitriol therapy prior to transplantation, and is very difficult to reverse after transplantation. Tertiary hyperparathyroidism is based on somatic mutations in individual parathyroid gland cells finally resulting in clonal expansion and adenoma formation, which are associated with a depressed expression of calcium-sensing and vitamin D receptors [14]. Finally, impaired renal transplant function with far below normal performance in many patients is another factor that prevents normalization of hyperparathyroidism.

The primary target of parathyroid hormone is osteoblasts. Osteoblasts, but not osteoclasts, express PTH receptors. PTH increases the number, activity and lifespan of osteoblasts and also protects osteoblasts against steroid-induced apoptosis [15]. The activation of osteoclasts by parathyroid hormone is an indirect effect based on cell–cell contacts with osteoblast-like cells. In addition, increasing evidence suggests a binding of intact PTH, but not PTH 1–34 to osteoclasts, possibly through the novel PTH receptors (CPTHRs) resulting in an increased osteoclast activity and number [16–18]. In physiological concentrations, PTH leads to increased bone remodelling and an increase in trabecular bone volume compared to cortical bone.

In summary, bone damage caused by chronic hyperparathyroidism most closely resembles osteitis fibrosa.

However, hyperparathyroidism and hypercalcaemia also correlate with interstitial microcalcifications in the transplant. Interstitial microcalcifications are, in turn, an indicator of poor prognosis regarding long-term function [19]. Thus, apart from bone disease, pathological changes in extraosseous organs also have to be taken into consideration.

Importance of hypophosphataemia for the development of bone disease

The development of hypophosphataemia as a result of hyperphosphaturia soon after renal transplantation is a common complication, observed in more than 90% of transplant patients [20]. Although the serum phosphate concentration normalizes in most patients after 1 year, this does not apply to hyperphosphaturia; increased fractional phosphate excretion can still be detected after 1 year [21]. Even hypophosphataemia can be detected up to 10 years after transplantation in some patients [22]. This hypophosphataemia is the result of impaired reabsorption of phosphate in the proximal tubule, where up to 80% of the filtered phosphate is reabsorbed. Tubular reabsorption can be decreased by various factors, including: hyperparathyroidism, calcitriol deficiency, corticosteroid therapy, phosphatonins (e.g. FGF23), hormones (e.g. insulin, thyroid hormones, glucagons), cytokines (e.g. insulin-like growth factor I, EGF), phosphate-rich diet, and metabolic acidosis.

High parathyroid hormone levels can reduce phosphate reabsorption in the proximal tubule from 80 to 20%. Certainly, persistent hyperparathyroidism is not the only factor. In patients with normal kidneys, a primary hyperparathyroidism with very high parathyroid hormone levels is often only associated with mild hypophosphataemia or none at all. The underlying mechanism may also be the increased production of calcitriol as a result of the parathyroid hormone-induced stimulation of renal 1α-hydroxylase because calcitriol can increase the activity of the Na/Pi cotransporter, both in the intestines and in the proximal tubule [23]. In

renal transplant recipients, however, low calcitriol levels are often found despite normal 25-OH-D_3-concentrations and persistent hyperparathyroidism [24], which increases the hypophosphataemia. That parathyroid hormone cannot be the only factor responsible for the development of hypophosphataemia is further demonstrated by renal transplant recipients who develop severe hypophosphataemia in the presence of normal parathyroid hormone concentrations or after parathyroidectomy and normal calcitriol concentrations [21]. Apart from steroids, which inhibit the Na/Pi cotransporter independently of parathyroid hormone and vitamin D_{23}, phosphatonins, such as FGF23, seem to play a significant role in the development of hypophosphataemia. The serum concentrations of FGF23 immediately after renal transplantation are markedly increased and drop off gradually over a period of days and weeks to a level that is still above the reference range for healthy controls [25]. While FGF23 concentration among controls is directly correlated with serum phosphate concentration-–a finding also confirmed in animal experiments using phosphate infusions–an inverse correlation is found among hypophosphataemic transplant recipients. Pre-transplant FGF23 concentrations are the strongest predictor of the post-transplant FGF23 concentration independently of the post-transplant serum phosphate. Recently, it has been suggested to call these findings 'tertiary hyperphosphatoninism' [25,26]. In addition to direct effects of FGF23 on phosphate regulation, FGF23 also inhibits the 1α-hydroxylase activity resulting in an impaired production of calcitriol that may accentuate hypophospatemia [27]. That phosphatonins play a significant role in phosphate regulation is demonstrated by various genetic models and disorders [28,29]. Hypophosphataemia is associated with increased osteoblast apoptosis, diminished osteoblast activity and decreased osteoblastogenesis—factors also promoting the development of osteomalacia after transplantation.

In summary, hypophosphataemia causes changes that most closely resemble osteomalacia.

Importance of immunosuppressive agents on the development of bone disease

The standard immunosuppressive regimen after renal transplantation consists of a calcineurin inhibitor (cyclosporine or tacrolimus), mycophenolate or an mTOR inhibitor, such as rapamycin or everolimus, and steroids. An antibody for induction or rejection therapy may be added to this immunosuppressive regimen. No study data on the effects of antibodies on bone is available. Likewise, the effect of mycophenolic acid and mTOR inhibitors is poorly investigated. Rapamycin may contribute to the development of hypophosphataemic osteomalacia by increasing hyperphosphaturia. For calcineurin inhibitors, especially cyclosporine, data from various *in vitro* and *in vivo* studies have been published. In rat models, the administration of cyclosporine resulted in bone loss, especially of the trabecular bone, with increased bone remodelling and high osteocalcin levels [30,31]. Studies in transplant recipients are hampered by the fact that it is virtually impossible to exclude the influences of other factors on the bone that act in addition to cyclosporine. Consequently, the significance of bone injury caused by cyclosporine remains uncertain in patients. However, bone loss is not observed in steroid-free patients treated with cyclosporine; thus, cyclosporine's contribution to bone disease appears to be of lesser significance [32,33]. Tacrolimus also causes bone loss in rats and again, the trabecular bone is most affected [31]. In a direct comparison between cyclosporine and tacrolimus in liver transplant recipients, patients treated with tacrolimus showed a higher degree of bone loss [34].

Unlike the immunosuppressive agents mentioned so far, a large number of studies have established that steroids cause bone density loss and induce both osteoporosis and bone necroses, which correspond to an increased fracture rate. The bone mass-decreasing effect of steroids is the result of reduced bone formation along with concomitantly increased bone resorption. (1) *Reduced bone formation*: as in a number of other cell types, steroids induce apoptosis in osteoblasts and osteocytes and inhibit osteoblastogenesis by blocking the division and differentiation of osteoblasts [35]. In addition, they inhibit the generation of several proteins essential for bone formation, such as collagen type I, insulin-like growth factor, TGF-β and bone matrix proteins, and interfere with central elements of cell activation, e.g. by inhibiting the activation of NFκ-B. Indirect steroid effects that impair bone formation are mediated by a number of hormones; steroids, for example inhibit testosterone synthesis [36]. Finally, steroid therapy leads to serum calcium depletion directly and independently of vitamin D by reducing intestinal calcium reabsorption through the mobilization of calcium from bone and the inhibition of tubular calcium reabsorption by the kidneys [37,38]. (2) *Increased bone resorption*: in comparison to decreased bone formation, increased bone resorption is of less significance. The increase in bone resorption is directly caused by the stimulation of osteoclast-like cells [39] and indirectly by the steroid-induced inhibition of androgen, oestrogen and gonadotropin synthesis. Steroids can increase parathyroid hormone synthesis, which again results in increased bone remodelling and resorption, either directly or indirectly through steroid-induced calcium depletion.

In summary, steroid-based immunosuppression triggers complex bone changes that most closely resemble osteoporosis.

Prevention of and therapy for bone disease after transplantation

On a background of pre-existing bone damage, immunosuppressive agents, especially high steroid doses during the first 3–6 months and, in a large proportion of the patient population, both newly developing hypophosphataemia and the persisting hyperparathyroidism all affect the bone. Guidelines for the prevention of post-transplant bone disease have been published by various transplantation societies.

Table 1. Treatment and prevention of bone disease after renal transplantation according to the European Best Practice Guidelines [69]

Vitamin D[a]	Calcitriol 0.25–0.5 μg/day or cholecalciferol 600 units/day
Calcium[b]	1000 mg/day, or 1500 mg/day in post-menopausal women
Bisphosphonates	In patients with an increased fracture risk[b] and good transplant function GFR > 60 ml/min

- Avoidance of loop diuretics
- Sex hormone replacement therapy
- Treatment of
  - Thyroid dysfunction
  - Hyperparathyroidism
  - Hypophosphataemia
  - Hypomagnesaemia
- Physical activity
- Not smoking
- Use of calcitonin

[a]Hypercalciaemia is a contraindication. Consider, calcitriol may further impair a deteriorated kidney function [70].
[b]Factors associated with increased fracture risk include: severe osteoporosis, previous fractures, diabetes mellitus, combined kidney–pancreas transplantation and post-menopausal women.

Guidelines for the prevention of bone disease after kidney transplantation

For the prevention of bone injury in the early phase after transplantation and during steroid therapy, guidelines have been issued, which will be described in the following section (Table 1). The use of vitamin D and calcium is generally recommended in the absence of contraindications. Corresponding recommendations are made in the K/DOQI guidelines. Because hypercalcaemia is a contraindication, this type of prophylaxis is not suitable for all patients. While the use of calcitriol consistently prevented bone density loss compared to placebo, this is not the case for cholecalciferol [40,41].

The use of bisphosphonates is limited to the high-risk group (Table 1). Likewise, the K/DOQI guidelines restrict therapies using bisphosphonates with recommended use starting at a *T*-score of >-2 SD [10]. Various bisphosphonates have proven their efficacy in studies, and some examples are provided in Table 2.

A meta-analysis showed that a therapy consisting of calcium, vitamin D or bisphosphonates alone significantly reduced bone density loss. A combination of vitamin D and calcium was superior to calcium alone [40].

Bisphosphonates directly inhibit osteoclast activity [42]. However, this approach is associated with the risk that although bone density loss is prevented, the bone remodelling process almost comes to a standstill such that bisphosphonate treatment of bone disease results in adynamic bone [9,43]. For this reason, their use is limited to risk groups. In addition, there are several reports regarding bisphosphonate-associated osteonecrosis after long-term treatment [44].

A significant number of studies were incorporated in the recommendations of transplantation societies, but these studies were not end-point studies measuring fracture rate. In these studies, the efficacy of a preventative therapy was determined by missing or retarded decrease in bone mineral density.

The European Best Practice Guidelines recommend the initiation of treatment for hypophosphataemia in the presence of 'severe hypophosphataemia'; the K/DOQI guideline recommends treatment initiation below 0.81 mmol/l [10,45]. Because hypophosphataemia therapy is a common condition associated with specific clinical challenges, it will be discussed in detail in the following section. This also applies to the treatment of hyperparathyroidism after transplantation.

Hypophosphataemia treatment

The effects of such guideline-based therapies on the bone and extraosseous organs, such as the transplant and the cardiovascular system, have not yet been studied adequately. In hypophosphataemic transplant recipients, parathyroid hormone production is induced by the administration of phosphate, which results in the worsening of any pre-existing hyperparathyroidism, with associated mild decreases in calcitriol concentrations and serum calcium concentrations [46]. With the aggravation of hyperparathyroidism, the serum calcium–phosphate product increases, and the additional inhibition of phosphate reabsorption in the proximal tubule exacerbates the hyperphosphaturia. The hyperphosphaturia is even further augmented because the administration of phosphate also results in an increase in serum FGF23 levels [47]. The role of the higher calcium/phosphate excretion and increased calcium–phosphate product remains to be investigated in randomized studies in renal transplant recipients. However, this constellation is associated with an increased mortality rate among haemodialysis patients [48]. In protocol biopsies, the detection of interstitial microcalcifications early in the course is associated with a significantly poorer prognosis [19]. These patients also showed increased serum parathyroid hormone concentrations. Consequently, the call for a rigorous therapy for hypophosphataemia, as in the K/DOQI guidelines, should be treated with caution. In symptom-free patients, we are very reluctant to administer phosphate to treat hypophosphataemia. Whether dipyridamol, which increases reabsorption of phosphate in the proximal tubule even in transplanted kidneys, may be considered as an alternative treatment option needs to be evaluated in larger studies [49].

Table 2. Dosage of selected bisphosphonates after renal transplantation

Active ingredient		Dosage	Reference
Pamidronate	Aredia®	60 mg i.v. peri-operatively (p.o.)	[9]
30 mg i.v. after Months 1, 2, 3 and 6			
Ibandronate	Bondronat®	1 mg i.v. preoperatively	[71]
2 mg i.v. after Months 3, 6 and 9			
Alendronate	Fosamax®	5–10 mg/day p.o.	[72]
70 mg/1× weekly p.o.			
Risedronate	Actonel®	5 mg p.o./day from Month 2	[73]

Note: To date, the use of bisphosphonates for the prophylactic treatment of osteoporosis after transplantation has not been approved in Germany and other countries.

Table 3. Success of cinacalcet treatment of persistent hyperparathyroidism after renal transplantation

Number of patients treated	Parathyroid hormone (pg/ml)	Calcium (mmol/l)	Phosphate (mmol/l)	Creatinine (μmol/l)	Reference
($n = 14$) Day 0	300	2.7	1.0	140	[74]
Month 3	150	2.4	1.1[a]	148	
($n = 11$) Day 0	176	2.73	0.8	118	[75]
Week 10	135	2.42	1.0	125	
($n = 9$) Day 0	171	2.75	0.70	49.8	[76]
Month 6	134	2.44	0.77	51.3	
($n = 10$) Day 0	721	2.75	0.87	106	[77]
Month 6	331	2.4	1.03	unavailable	
($n = 18$) Day 0	627	2.55	1.00	159.1	[78]
Month 6	365	2.35	1.13	176.8	

[a]Two additional patients had a mild hyperphosphataemia of 1.65 mol/l and 1.77 mol/l, respectively.

Hyperparathyroidism therapy after transplantation

Successful renal transplantation eliminates a number of aetiological factors that lead to the development of hyperparathyroidism during renal insufficiency. As already mentioned above, parathyroid function tends to normalize over time in many patients. However, this normalization process may be very slow, especially in cases of suboptimal transplant function. In particular, during the early post-transplant phase, there is a need to take action for several reasons. (1) After renal transplantation, the early phase is characterized by a particularly high rate of hypercalcaemic episodes because the persisting hyperparathyroidism that is frequently accompanied by normalized calcitriol production and the resorption of extraosseous calcium–phosphate deposits after the normalization of serum phosphate levels [50]. These hypercalcaemias have a negative impact on the whole organism as well as on the transplant. (2) The management of bone disease in renal transplant recipients with hyperparathyroidism poses a particular challenge to the clinician because (a) the proven prophylactic therapy of the post-transplant bone disease with vitamin D and calcium supplementation is contraindicated by the hypercalcaemic episodes and (b) bisphosphonates inhibit osteoclastic bone resorption by accumulating in the bone, especially in areas of bone resorption. They reduce the number of osteoclasts by inhibiting the division and differentiation of osteoclastic precursors and by the induction of apoptosis in mature osteoclasts. Although the plasma half-life of bisphosphonates is in the range of 30 min because of rapid renal elimination in the presence of normal renal function, bisphosphonates are deposited in the bone for long periods of time, even for life. If parathyroid hormone levels fail to normalize and a parathyroidectomy becomes necessary at a later stage, this intervention will be associated with the long-term risk of inducing the development of adynamic bone. (3) In up to 70% of the kidneys, the hyperparathyroidism is associated with interstitial calcifications. These microcalcifications predict a poor long-term prognosis for the transplant [19,51]. Therefore, it is already necessary at an early stage after transplantation to treat hyperparathyroidism. Parathyroidectomy and therapy with calcimimetics are available for this purpose.

Parathyroidectomy

Apart from immediate intraoperative and perioperative complications including hypocalcaemia, parathyroidectomy is associated with the risk of aggravating the bone disease and causing partial transplant function loss. As described above, parathyroid hormone plays a central role in bone formation because of its effect on osteoblasts. Parathyroid hormone can partially counteract the pro-apoptotic effect of steroids on osteoblasts. Recombinant parathyroid hormone has become an integral part of the management of osteoporosis with histologically confirmed bone formation and a significantly reduced fracture rate [52,53]. Consequently, in the critical phase of most severe bone damage [1] and with the highest fracture risk [5], subtotal or total parathyroidectomy may result in the loss of the protective effect of the parathyroid hormone by an uncontrolled decrease or complete loss of parathyroid hormone production.

Finally, parathyroidectomy may have a negative effect on transplant function. On average, patients with hyperparathyroidism have significantly better transplant function [54]. As a result, increases in serum creatinine

concentrations by up to 30% are observed after parathyroidectomy [55]. The mechanism underlying this deterioration is not fully understood. While some studies found an increased rate of renal graft rejections after parathyroidectomy, evidence from other studies does not support this finding. The extent of the parathyroid hormone decrease correlates with the extent of the creatinine increase [51]. Consequently, functional changes may underlie this observation. In fact, parathyroid hormone can directly dilate pre-glomerular arterioles in isolated perfused kidneys [56]. In rat models as well as in humans, however, parathyroid hormone infusion increases GFR and diuresis without changing the filtration fraction [57,58]. The importance of parathyroidectomy for long-term renal graft function remains unclear. Studies comparing long-term renal graft survival in patients after parathyroidectomy with those of patients without parathyroidectomy provide conflicting evidence with some research showing significantly poorer long-term survival for renal grafts while in other studies, no significant differences were found [59,51]. To perform a parathyroidectomy in the early post-transplant phase, when the highest steroid doses are administered and the protective effect of parathyroid hormone on osteoclasts is most needed, is problematic. Likewise, since no definite conclusions on the long-term effects of a decrease in renal graft function observed after parathyroidectomy can be drawn, it seems sensible to delay a parathyroidectomy until the spontaneous normalization of persistently high parathyroid hormone levels appears to be rather unlikely.

Use of calcimimetics

The use of cinacalcet has been investigated most extensively in patients on dialysis. The study results consistently showed a decrease in parathyroid hormone levels and, retrospectively, analysed a reduction in fracture risk and the number of hospital stays due to cardiovascular complications [60,61].

The therapeutic use of cinacalcet in renal transplant recipients with persistent hyperparathyroidism has been evaluated in a number of smaller studies (Table 3).

The studies mentioned above show that in renal transplant recipients, the use of cinacalcet to lower PTH levels also leads to a decrease in calcium concentration and an increase in phosphate concentration. Similar to the situation after parathyroidectomy, four of the five studies described a decrease in transplant function but this reduction is mild. In contrast, a single case study reports that despite high doses of cinacalcet of up to 180 mg/day and a decrease in parathyroid hormone concentration from 607 pg/ml to 314 pg/ml, no change in persistent hypercalcaemia occurred.

Apart from initiating cinacalcet therapy after transplantation, there is the question of whether this therapy should be continued in patients on haemodialysis prior to renal transplantation. What are the consequences of a pre-operative discontinuation of cinacalcet therapy prior to transplantation? Pharmacokinetic data on cinacalcet reveal that the maximum serum concentration is reached ∼3–5 h after oral administration. With a half-life of approximately 24 h, a steady state of cinacalcet serum concentration is achieved after 4 days [62]. According to the pharmacokinetic data, parathyroid hormone serum concentration reaches its lowest level ∼4–6 h after a single dose of cinacalcet, increases in the subsequent 4–6 h and then stabilizes on a plateau below the baseline concentration for the next 24 h [63]. Upon discontinuing cinacalcet therapy, serum parathyroid hormone concentration increases as cinacalcet serum concentration decreases and finally settles, within a few days or weeks, at the original level that was found prior to treatment. In addition, hyperparathyroidism becomes clinically apparent during hypercalcaemic episodes [64,65]. To avoid the recurrence of hyperparathyroidism immediately after transplantation, therapy with cinacalcet should be continued after intervention. A pharmacokinetic interaction between cinacalcet and immunosuppressive agents appears to be unlikely. Although cinacalcet interacts with CYP1A2, 2D6, 3A4 when metabolized and inhibits CYP2D6, clinically relevant interactions with the standard immunosuppressive drugs cyclosporine, tacrolimus, sirolimus and everolimus have not been reported [66]. Consequently, the use of cinacalcet appears to be a very interesting option for the *de novo* treatment of hyperparathyroidism after renal transplantation or for the continuation of treatment started during haemodialysis. How many patients require permanent cinacalcet therapy, and in how many patients the normalization of elevated parathyroid hormone levels occurs at a later stage has yet to be established. At least in some patients, it is possible to gradually reduce cinacalcet and eventually discontinue it altogether at a later time point without the recurrence of hyperparathyroidism [67]. Nevertheless, therapy with cinacalcet should be initiated using low doses because hypocalcaemic episodes may be associated with this therapeutic regimen, especially if a hungry bone syndrome develops.

Summary

Bone disease after renal transplantation requires preventive therapies to reduce high fracture rates as well as to assuage other conditions associated with the disturbance of calcium–phosphate metabolism. The bone disease that develops with renal insufficiency is aggravated after renal transplantation by a number of factors, including immunosuppressive therapy, especially a high-dose steroid regimen, hypophosphataemia and persistent hyperparathyroidism. The administration of vitamin D and calcium is effective in preventing post-transplant bone density loss. This also applies to therapies with bisphosphonates, which are indicated in patients with a high fracture risk. However, the use of vitamin D and calcium is limited by hypercalcaemic episodes and hyperparathyroidism in many cases. The development of adynamic bone is a risk factor associated with bisphosphonate therapy, especially when parathyroidectomy cannot be avoided. Treatment of hypophosphataemia by oral phosphate administration aggravates hyperphosphaturia and may support the development of nephrocalcinosis, with a possible negative effect on transplant function. Hyperparathyroidism after transplantation frequently improves over time, and parathyroid hormone levels return to normal in a number of cases. However, this process may take months or even years. For early,

effective treatment of hyperparathyroidism during the period of the most severe bone damage after transplantation and to take advantage of existing therapeutic options for the preventive treatment of bone disease, cinacalcet is available, apart from parathyroidectomy. Preliminary data from renal transplant recipients show that cinacalcet can lower parathyroid hormone levels, reduce the frequency of hypercalcaemic episodes and improve hyperphosphataemia. The potency of this substance should be evaluated in larger studies to lay the foundation for its widespread use among renal transplant recipients, in *de novo* therapies after transplantation, or for the continuation of treatment initiated during haemodialysis. However, the use of cinacalcet for the treatment of hyperparathyroidism after transplantation has not been approved.

Conflict of interest statement. None declared.

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