Kidney Transplantation

Chapter 3

Mineral and Bone Disorders After Kidney Transplantation

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1. Pathophysiology of Post–Transplant Bone Disease

Post transplantation bone disease is a complex disorder markedly different from the mineral and bone disorders often seen in patients with Chronic kidney Disease (CKD). After kidney transplantation, patients exhibit various histologic abnormalities of bone despite restoration of kidney function [1]. Bone disease after kidney transplant is a multifactorial process that includes continuing bone loss superimposed on pre-existing renal osteodystrophy [2]. The severity of bone disease complications, the increase in the number of transplanted patients and the prolonged survival rate has generated interest in prevention and treatment of post-transplant bone disease. It is very important to understand the underlying histologic bone abnormality and their evolution with time in order to develop a preventive therapeutic strategy [3,4]. Kidney transplant recipient could be affected by bone disease as osteoporosis, avascular osteonecrosis, bone fracture with a significant long-term morbidity [5]. Bone loss occurs mostly during the first year after transplantation with a very high rate and then this process continues slower than before or stabilize [6,7]. The high prevalence of low bone turnover 6 months after transplantation is explained with the high doses of glucocorticoids required soon after transplant together with only moderately increased bone turnover at baseline. In addition, it is observed that bone volume decreases in parallel with time after transplantation [8]. Several studies have brought out a reduction in trabecular bone mass, but cortical bone could be affected too [9-12]. Osteoporosis increases the risk of fractures which occur in either peripheral or central location. Several studies have suggested that the most common site of fractions

is those peripheral, involving hands, ankles and feet [13,14]. The risk factors of bone loss after transplantation are immunosuppressive medications especially glucocorticoids, persistent hyperparathyroidism, post-transplant metabolic acidosis and diabetes mellitus (pretransplant diabetes or end-stage renal disease caused by diabetic nephropathy) [15 -17, 9,7,12].

Additional risk factors are low testosterone levels in male, age of > 50 years old, low body weight (weight of <127 pounds or body mass index [BMI] of <20 kg/m2), pretransplant dialysis, pre-existing uremic osteodystrophy, deceased donor transplantation, female gender, genetic predisposition and family history of osteoporosis, lifestyle factors, impaired nutrition and the race. In a study with 68,814 patients was observed that black renal transplant recipients had a 19% lower risk of fracture compared with white patients [1]. The use of proton pump inhibitors has also been associated, as in nontransplant patients, with an increased risk of hip fracture [18]. The presence of any HLA mismatches increased the risk of fracture by 9% because these patients compared with although additional mismatches did not increase the risk of a fracture. This might be reflective of the fact that compared with those with 0-HLA-mismatch patients are more likely to receive more intense initial immunosuppression to prevent any rejection.

1.1. Post-transplant bone loss factors:

Immunosuppressive medications:

1. Glucocorticoids are generally accused in bone loss among transplant kidney recipients. The predominant effect of glucocorticoids on the skeleton is that of reduced bone formation due to direct toxicity on osteoblasts (inhibiting osteoblastogenesis and inducing apoptosis of osteoblasts and osteocytes), and also due to increase of osteoclast activity [9,12] Glucocorticoids also decrease calcium absorption in the gut, enhance renal calcium excretion, diminish insulin-like growth factor 1 production, decrease sensitivity of parathyroid hormone (PTH), increase the activity of nuclear factor kappa-beta ligand (RANKL), and increase the osteoclastogenesis [7,12]. In addition, glucocorticoids decrease secretion of androgens and estrogens, primarily mediated by inhibition of gonadotropin secretion, and increase secretion of PTH [19]. Meanwhile, no evidence indicates that glucocorticoids impair the mineralization process [1]. Additionally, the large doses of glucocorticoids often given immediately after transplantation lead to a large decrease in femoral neck and lumbar spine bone mineral density (BMD, which helps to explain the increased risk of femoral fractures [7].

2. Cyclosporine may contribute to bone loss among patients treated with glucocorticoids [15,20-22]. However there are no evidence recently that cyclosporine alone could cause bone loss [19].

3. The effect of tacrolimus, on (BMD) in transplant patients, is still contradictory. One

study has suggested that tacrolimus had similar effects as cyclosporine on BMD [6] 5 but other studies have not shown this, possibly because the use of tacrolimus permitted lower doses of glucocorticoids [23,24]. It could be possible that the effect of tacrolimus on bone loss be related with the dose of tacrolimus. So, one small study found that kidney transplant recipients with higher blood concentrations of tacrolimus (≥6 mg/mL) had lower BMD compared with those who had lower blood concentrations (<6 ng/mL) [25].

4. Azathioprine has a protective effect on the skeleton but not at the spine, hip or trunk. So, the whole body and limb BMDs did not change over time in patients receiving azathioprine whereas they decreased significantly in patients not receiving that drug [9].

5. Sirolimus may interfere with the proliferation and differentiation of osteoblasts, but more important, it inhibits osteoclast formation. Everolimus may also inhibit bone resorption and prevent bone loss based on experimental studies [26,27].

1.2. Pre transplant CKD-MBD

At the time of transplantation, patients already suffer from renal osteodystrophy and they exhibit various levels of bone volume and bone turnover [1–3]. Traditionally, the renal osteodystrophy has been presented as hyper parathyroid bone disease, a dynamic bone disease, mixed renal osteodystrophy and osteomalacia. Since 2000, the classification system of renal osteodystrophy has been done based on the underlying histological abnormalities in bone, which result in changes in bone volume. Changes in bone volume depend on bone turnover, mineralization and bone balance, and it occurs mostly in hyper parathyroid and a dynamic bone disease. Bone balance describes the equilibrium between bone formation and bone resorption. Meanwhile mineralization abnormalities are present in patients with osteomalacia and mixed renal osteodystrophy [28,29]. Changes in bone volume could happened on cortical part or on cancellous part of bone. Loss of cortical bone occurs in patients with high turnover bone disease, while loss of cancellous bone occurs in patients with low bone turnover. Cortical bone is responsible for the mechanical function of bone and the clinical outcome of decreased cortical bone is fracture. While metabolic activity of bone is served by cancellous bone and its abnormality results in the inability to maintain mineral homeostasis causing vascular and soft tissue calcifications [5, 30,31].

Persistent hyperparathyroidism is associated with cortical bone loss and fractures [14,22]. In one retrospective study, PTH of >130 ng/L three months post transplant was an independent risk factor for fractures [32]. Another retrospective study found that more intensive treatment of the mineral and bone disorders of chronic kidney disease (CKD-MBD) prior to transplantation was associated with lower rates of persistent hyperparathyroidism and fewer fractures in the first year after transplantation [33]. It is observed that PTH level decreases by 50% 6 months after transplantation but in nearly 45% of kidney transplant recipients, PTH lev-

el remains in high level even 2 years after transplantation. The decrease of PTH level could be explained by the improvements in calcium, phosphorus and 1.25-dihydroxy vitamin D levels associated with improving kidney function [34,35]. Meanwhile the persistent hyperparathyroidism occurs due to persistence of structural changes in the parathyroid, such as hyperplasia and adenoma formation, despite removal of the initial stimuli for hyperparathyroidism. Several studies have showed that persistent hyperparathyroidism was independently associated with bone fracture and with worse graft survival but the optimal post transplantation PTH levels remains still unknown [34,36]. The clinical manifestations of persistent hyperparathyroidism in the transplant recipient are characterized by hypercalcemia and hypophosphatemia [37] which differ from those associated with hyperparathyroidism in nontransplant CKD patients.

Calcium. In the first few weeks after transplantation, it occurs a fall in calcium level, explained secondary by a significant fall in PTH. This initial fall of calcium level is followed then by a rise in serum calcium, reflecting a combination of increased 1.25 dihydroxy vitamin D production and persistent SHPT. The increase of 1.25 dihydroxy vitamin D is a result of allograft function improvement. Some patients have an increase in total plasma calcium because of an increase in the plasma albumin concentration (which is often due to better nutrition after transplantation). However, the increase in total calcium due to an increase in albumin is generally mild and of no clinical significance [38]. Hypercalcemia is most prevalent 3-6 months after transplantation and both with high level of PTH contributes in interstitial micro-calcification and poorer long-term graft outcomes [35,39].

Phosphorous. Hypophosphatemia occurs in less than 50% of incident kidney transplant recipients [35] and it is associated with a decrease in osteoblast activity and defective mineralization. Hypophosphatemia has been attributed to proximal tubule dysfunction, persistence of secondary hyperparathyroidism, use of calcineurin inhibitors or glucocorticoids, and elevated Fibroblast Growth factor-23 (FGF-23) [40,41]. The relative contribution of excess PTH and FGF-23 to phosphate wasting after transplantation depends on the timing of onset after transplantation [41-44]. However, it is usually self-limiting, reflecting an improvement in kidney function, elevated PTH levels and an increase in renal tubular sensitivity to PTH and FGF23 production. In addition, FGF-23 is secreted by bone osteocytes and osteoblasts in response to calcitriol, increased dietary phosphate load, parathyroid hormone (PTH), and calcium. Also, tacrolimus has been accused for low phosphorus serum levels compared with cyclosporine, related to its mitochondrial alterations in proximal tubule cells [45].

Low plasma calcidiol 25(OH) vitamin D level may also contribute to bone disease in kidney transplant recipients, with a reported prevalence of calcidiol deficiency of 30% and insufficiency of 81%. Several causative factors are been suggested like nutritional deficiency, malabsorption, decreased sun exposure, and increased metabolism of calcidiol to calcitriol after a successful kidney transplant [46]. In contrast with this, another study found a high num-

ber of patients with generalized or focal osteomalacia in the presence of normal circulating levels of calcitriol. Even the level of vitamin D metabolites were normal, after transplantation, bone cells showed to be resistant against them. This resistance was due to abnormal response of its receptor (VDR) or post receptor defect. The direct or indirect mechanisms responsible for such VDR resistance is unknown [1].

Hypogonadism. As we know, most of ERSD patients suffer from hypogonadism and gonadal hormones remain in low level even post-transplant, in both male and female. So, it is observed that about 50 % of male patients have low testosterone levels after kidney transplant. Aging and postmenopausal status at women are risk factor for bone loss and bone fracture after kidney transplant [13,19,47].

1.3. Osteonecrosis:

Osteonecrosis or avascular necrosis commonly affects the femoral head, knee, shoulder or elbow and it is characterized by the ischemic death of bone marrow cells and osteocytes, and loss of trabeculae. It presents with joint pain that worsens with weight bearing. The cumulative incidence of hospitalization for osteonecrosis is described to be 7.1 episodes per 1,000 patient-years [48]. The main etiology of avascular necrosis is steroid usage, especially the high cumulative dose of steroid or pulse steroid therapy used as induction or anti-transplant rejection. Other risk factors are preexisting bone disease, diabetes and lupus nephritis [49,50].

1.4. Post-transplant bone pain syndrome:

About 10 to 20% of transplant recipients experience bone pain, usually diffuse, particularly in the lower extremities. Several medications have been described as the possible cause as are calcineurin inhibitors (cyclosporine and tacrolimus) [51]. In contrast, calcium channel blockers have been demonstrated to reduce bone pain [52]. The pathophysiology of this syndrome is the intraosseous vasoconstriction and ischemia caused by calcineurin inhibitors but opposed by calcium channel blockers.

1.5. Post-transplant bone fracture and osteoporosis:

Fractures occurred in 8% kidney transplant patients in the first year and in 15%-22% in 5 years, mostly on vertebral bones, hips and foot [32,14]. Patients with persistent HPT (pHPT) at 3 months have a greater risk of fracture in the 5 years posttransplant. The impact of pHPT on bone may be mediated by the stimulation of bone turnover by PTH. Bone abnormalities induced by pHPT may be explained by the removal of skeletal resistance to PTH after kidney transplantation. In CKD patients, bone becomes hyporesponsive to PTH because of the down-regulation of PTH receptors and decreased pulsativity of PTH. This resistance to PTH is due to phosphate loading and calcitriol decreasing. After transplantation, these factors decrease,

most likely inducing an important bone response to PTH. Studies have demonstrated that the bone response to PTH is enhanced by glucocorticoid treatment but pHPT is observed to be an independent risk factor for fractures after kidney transplantation. An elevated risk of fracture was also observed for patients with pretransplant osteopenia. Another risk factor for fractures, in renal graft recipients, is hypoalbuminemia [54-58]. So, it is suggested that malnutrition and sarcopenia play a significant role in the pathogenesis of fracture. Additional risk factors for fracture in kidney transplant recipients include female gender, combined kidney–pancreas transplantation, advanced age, history of diabetic nephropathy and pretransplant dialysis. Kidney recipients, who have received dialysis before transplantation, are more in risk for fracture compare with the recipients, who have not.

2. Evaluation of Kidney Transplant Bone Disease

Evaluation of kidney transplant bone disease involves biochemical parameters, imaging and bone biopsy.

2.1. Biochemical parameters

Serum calcium, phosphate, PTH, and 25(OH)D (calcidiol) are considered valid biochemical markers for evaluation of kidney transplant bone disease. It is important to emphasize that frequency of monitoring of these parameters is guided by the rate of CKD progression, abnormality degree and therapeutic intervention.

Some authors recommend also measuring fasting morning serum bone turnover markers, including bone-specific alkaline phosphatase and C-telopeptide crosslink (CTX) [59].

2.2. Serum calcium and Phosphate

As already mentioned, in the first few weeks following kidney transplantation there is a fall in serum calcium levels and phosphate levels reported low in around 50% of cases [17]. Initial hypocalcemia could be followed by hypercalcemia, which can persist beyond 1-year post-transplantation in some patients [58]. Hypophosphatemia occurs early after kidney transplantation. That flactuation seems to be the rationale behind the KDIGO recommendation of measuring serum calcium and phosphate at least weekly (until stable) in the immediate post-kidney transplant period [59] **Tabel 1**. Although not graded, the recommendation of KDIGO is that after the immediate post-kidney transplant period, the frequency of monitoring serum calcium and phosphorus levels can be based on the rate of progression of CKD, the presence and magnitude of abnormalities, and whether the patient is receiving treatments for CKD-MBD.

2.3 Parathyroid hormone (PTH)

Despite the fact that in real practice there is not a good correlation between PTH levels

and bone turnover, as long as no more specific, non- kidney function dependent markers of bone turnover are introduced into rutine practice, PTH is still in use [58]. According to a non graded recommendation of KDIGO, in the immediate post- transplant period it is recommended measuring a baseline PTH level. Afterwards, the frequency of monitoring is dependent on this baseline level, rate of CKD progression, and CKD-MBD treatment use.

Table 1. Monitoring recommendations

CKD stage	1-3T	4T	5T
PTH	Variable**	every 6–12 months	every 3– 6 months
Serum Calcim & phosphate	every 6–12 months	every 3–6 months	every 1–3 months
Serum 25(OH)D	Frequency dependent on Baseline values and interventions		
DXA	Every 12 months in high risk and every 24 months in subjects not at high risk of fracture		

*Not valid for immediate post-transplant period ** depending on CKD progression & baseline level in CKD stage 5T

2.4 Serum 25(OH)D

The KDIGO 2017 guideline update suggests that a baseline 25(OH)D level might be measured in the immediate post- transplant period, and repeated testing should be determined by baseline values and interventions [59].

2.5. Dual Energy X-ray Absorptiometry Bone Mineral Density – assessment of osteoporosis and fracture risk

Although inability of DXA to distinguish between differentially affected trabecular and cortical bone in secondary hyperparathyroidism, or confounding signals of vascular calcification in patients with CKD G1T-G5T with risk factors for osteoporosis (age, steroid use, diabetes, etc.) based on data from one meta-analysis [60], prospective studies in adults with CKD G3a to G5D stages [60-63], and a recent study in kidney transplant recipients [64] BMD testing is recommended by KDIGO guidelines 2017 update to assess fracture risk in transplant recipients, if results will alter therapy (grade 2C). Observations that glucocorticoid-induced fractures occur at higher BMD compared with non-glucocorticoid- induced osteoporosis might add a limitation to DXA use for fracture prediction in transplant patients [65]. Aiming to assess the stability of BMD and the response to treatment, some authors monitor DXA annually in patients at high risk of incident fracture, and every two years In patients not at high risk of incident fracture [66].

2.6 Bone Biopsy

Double-tetracycline labeling bone biopsy is the gold standard for the diagnosis of posttransplant bone disease in kidney transplant recipients, providing the most direct information to evaluate abnormalities of the bone [58]. Because of patient intolerance and the

lack of adequate expertise in performance and interpretation, it is not frequently used, except in a few centers. To describe bone histology the TMV classification is used consisting on bone turnover (T) -classified as low, normal or high, mineralization (M)- classified as normal or abnormal and volume (V)- classified as low, normal or high [59].

In kidney transplant recipients, the indications for bone biopsy are not well established. To rule out adynamic bone disease prior to initiating treatment with bisphosphonates, a bone biopsy should, if possible, be performed, in patients with persistent bone pain, frequent fractures or severe osteoporosis [66].

3. Management of Post transplant bone Disease

Treatment of MBD post-transplant often requires a full approach with focus on bone health, it is Metabolic and bone changes after transplantation tend to be dynamic and a strict approach may not be appropriate for all patients.

3.1. General Measures

Preventive measures for osteoporosis in the general population also would be in consideration to transplant recipients. All patients should be encouraged to change their life style, to do early mobilization after transplantation, should receive counseling regarding smoking cessation, decreased alcohol consumption, fall risk reduction, and to perform weight-bearing exercise [66].

3.2. Glucocorticoid dose minimization

Glucocorticoid have marked inhibitory effects on osteoblast function, and have moderate stimulatory effects on osteoclast function, thus it is expected that management of post-transplantation immunosuppression without corticosteroids would significantly reduce rates of bone loss and fractures. There is a tendency to use the lowest glucocorticoid dose compatible with graft based this on well-established described risk of osteoporosis, avascular necrosis and other side effects [67] a large observational study of 77 430 RTRs who were followed for a median of 3.9 years, glucocorticoid withdrawal was associated with a 31 % reduction in fracture risk [14]. It was reported to increase BMD with improvement at the lumbar spine and the total hip 1 year after TR. Moreover even late GC withdrawal has been shown to improve BMD [68,69]. On the other hand significant osteoporosis and bone loss has been observed with low doses of prednisone even in patients on early corticosteroid withdrawal protocols. A retrospective study by Edwards et al. found that corticosteroid withdrawal did not result in a fracture reduction a benefit [70].

In addition, Sapna et al, tried to explain that ECSW was associated with preservation of bone mineral density at the central skeleton but it was also associated with progressive declines

in cortical and trabecular bone density at the peripheral skeleton. While cortical decreases related directly to PTH levels, the relationship between PTH and trabecular bone decreases was bimodal so pharmacologic agents that suppress PTH would prevent cortical and trabecular losses and post-transplant fractures.

`Steroid-sparing or withdrawal has the potential to improve bone loss post-transplantation; however, this needs to be balanced against the potential risk of higher rates of rejection but this needs further investigation. Taking in consideration the increased risk of acute rejection, and all the evidence on the topic KDIGO guidelines [71] do not currently recommend steroid withdrawal and avoidance [72,73].

3.3. Phosphate, Calcium and Vitamin D Supplementation

Hyperphosphatemia is usually only seen in patients with delayed graft function whereas Hypophosphatemia is common in KTRs and occurs in ~50% of patients. It most commonly occurs 3–4 weeks after transplantation, especially in patients with immediate graft function and high pre-transplant PTH levels and FGF-23. These two phosphaturic hormones increase urinary fractional excretion of phosphate with a result in significant urinary loss of phosphorus. Steroid therapy is another possible reason, which reduced intestinal phosphorus absorption, reduced proximal tubular Na/Pi cotransporter expression or increased tubular sensitivity to PTH [40,41]. Phosphate supplement are usually given when phosphate level is less that 2 mg/dl, but sometimes it is often difficult to achieve and maintain normal serum phosphate levels with oral replacements. In addition is recommended high phosphate diet. Hypophosphatemia is usually self-limited persist few months and serum phosphate level start to normalize correlating with decline in FGF-23 levels [74]. However, when it persist it may be related to persistent hyperparathyroidism. In these cases administration of calcimimetic was reported to significantly decrease renal phosphate wasting [58,75].

Hypercalcemia is not uncommon among kidney transplant recipients, because of persistent hyperparathyroidism. In this group of patients is not recommended to give calcium and vitamin D. Patients with normal serum calcium would receive should receive calcium and vitamin D3 (cholecalciferol). The optimal dose of Calcium is not known but mostly is preferred to be taken by food. In addition Vit D should be measured and a target of serum 25-hydroxyvitamin D level of >30 ng/mL should be considered as a first-line therapy against HPTH. The KDIGO 2009 guidelines suggest Vitamin D deficiency should be corrected as recommended for the general population (graded 2C) Especially when steroids are given, administration of vitamin D improves GI calcium absorption [37,59].

Kidney transplant recipients usually have low vitamin D levels, especially in the early post transplantation period, but the association between vitamin D status with renal outcomes is not well described in this population. This persistent 25-OHD deficiency leads to hypocalcemia

and abnormal bone mineralization [76] also associated with poor graft outcomes, including an increased risk of acute cellular rejection. Treatment of calcidiol deficiency with either cholecalciferol or ergocalciferol appears reasonable given to improve in calcium balance, decreasing PTH levels, potential beneficial effects on the renin angiotensin-aldosterone system, proteinuria [37,76] and immune-modulatory effects on T cells and dendritic cells, which may affect graft function [77]. Although the effects of correcting calcidiol deficiency on BMD in transplant recipients remain controversial. No specific guidelines currently address nutritional vitamin D replenishment in KTRs, leading to heterogeneous interventions to correct vitamin D deficiency in clinical studies Some reports suggest that treatment with active vitamin D analogs may help to prevent bone loss after kidney transplantation but on the other hand these agents may also increase the risk of hypercalcemia and hypercalciuria. Josephason et al [78], showed that kidney transplant recipients who were given calcium and calcitriol had significantly less bone loss in the lumbar spine and increased BMD in the distal radius and femoral neck compared with transplant patients given calcium alone or placebo in well control blind study. The treated patients did not develop significant hypercalcemia or deterioration of kidney function during the two years of the study. Therapy with low-dose calcium supplements during the first year, plus intermittent calcitriol was reported to decrease PTH levels more rapidly, prevent bone loss at the proximal femur and was safe post transplantation whereas Wissing et al, showed that although cholecalciferol supplementation (25,000 IU/mo) contributed to normalization of PTH levels, it did not prevent posttransplantation bone loss [79,80].

Paricalcitol, a synthetic metabolically active vitamin D analog of calcitriol, has been shown to be an effective therapy for secondary hyperparathyroidismin in kidney transplant recipients to suppress PTH post-transplantation although sometimes reported to be associated with a higher risk of hypercalcemia [81]. When used in patients receiving cinacalcet, paricalcitol results in a significant PTH fall, with paricalcitol doses being similar to those used in patients not receiving cinacalcet [82]. Trillini et al. showed that patients randomized to paricalcitol improved L3 and L4 vertebral BMD as well as reduced serum levels of bone formation biomarkers like osteocalcin and bone alkaline phosphatase, and reduced urinary levels of deoxypyridinoline, a biomarker of osteoclastic-mediated bone resorption. In addition, it was not observed a higher risk of hypercalcemia, the few hypercalcemic episodes being easily reversed by a down-titration of dosage [83]. In fact, paricalcitol, whether given intravenously or orally, has even been shown to be more effective than cinacalcet in reaching goal PTH and reducing markers of bone turnover [84]. Active vitamin D reduced PTH levels and improved BMD after transplantation thereby becoming a well-accepted preventive therapy against bone loss in KTRs with osteopenia or osteoporosis [80,85]. Despite all positive effects, active vitamin D supplementation results in relative increases in FGF-23, the downstream effects of which are still not completely understood.

3.4. PTH, Hyperparathyroidism and Calcimimetic

After a successful transplantation with a good graft function, usually a decline of all stimuli of parathyroid hyperplasia happens. This often leads to a gradual decline in PTH concentrations which are slower in comparison with FGF-23 levels. It has been reported than more than half of the patients still have inappropriately high PTH beyond 1-year post transplant [86]. Pre-transplant cinacalcet use, development of nodular hyperplasia, and dialysis vintage are associated with high PTH levels after transplant (87), while use of vitamin D pre-transplant appears to be protective [86]. About 5% of kidney transplant recipients, with a reported range of 1 to 20%, undergo a surgical parathyroidectomy. The indications for surgery vary among the transplant centers, but the two major indications are severe symptomatic hypercalcemia (> 11.5 mg/dl), usually occurring in the early post transplant period, and persistent hypercalcemia more than 1 year after transplant. Cinacalcet was reported to reduces PTH levels and to improve serum calcium and phosphate levels [75] Cohen et al, in his systematic review showed that cinacalcet appears to be safe and effective for the treatment of posttransplant hyperparathyroidism but this topic need further larger observational studies and randomized controlled trials, performed over longer follow-up times and looking at clinical outcomes [87]. However, these potential benefits of calcimimetics must be balanced by the commonly encountered gastrointestinal intolerance and higher urinary fractional excretion of calcium, hypercalciuria [75,88] reports of nephrolithiasis and associated allograft nephrocalcinosis [89]. Despite this risk, long-term treatment with cinacalcet in kidney transplant recipients with secondary hyperparathyroidism is effective in controlling hypercalcemia and correcting hypophosphatemia, without affecting graft function while being well-tolerated [90]. However, it is needed to be underlined that there are no randomized controlled trials that have shown improvement in patient survival, and much less fractures in patients getting cinacalcet.Cinacalcet has postpone the time of parathyroidectomy after transplantation in patient which persist to have secondary or perparathyroidism or is an alternative for patient which refuse to do it [87].

In the management of severe post transplant hypercalcemic hyperparathyroidism, parathyroidectomy is regarded as the gold-standard [71]. With the availability of therapeutic use of cinacalcet in KTRs, the role of parathyroidectomy (PTX) in tertiary hyperparathyroidism has evolved, being limited to KTRs with profoundly elevated parathyroid hormone and calcium levels, symptomatic disease (fractures, EKG changes, neurologic sequalae, etc.) or failure of long-term medical management. Recently in clinical practice, the choice of intervention is mainly influenced by several factors, including patient suitably, patient preference, access to therapy (Cinacalcet), and potential financial costs. Cinacalcet appears to be an effective treatment of persistent hyperparathyroidism and may serve as a bridge to parathyroidectomy or as an alternative of it [91].

Patients with in adequate parathyroid hormone control on cinacalcet at 1-year

posttransplant should be considered for parathyroidectomy to prevent potential allograft failure. In the condition where higher-quality data on important clinical endpoints such as cardiovascular morbidity and renal bone disease are lacking, the decision has to be individual taking in consideration the clinical and biochemical parameters of the patients. Parathyroidectomy for tertiary hyperparathyroidism is associated with lesser rates of renal allograft failure compared with cinacalcet management. Dr Dulfer and colleagues had underlined the importance of future research based in randomized trials with focus on clinical endpoints such as quality of life, cardiovascular morbidity and renal bone disease so that the optimal treatment for an individual patient can be chosen [92].

3.5. Teripatide

Teripatide is a recombinant human PTH (comparising amino acids 1-34) that has anabolic bone effects and is shown to reduce fracture risk in postmenopausal women receiving glucocorticoids. There is a limited evidence for teripatide therapy post renal transplantation. A large sample study has shown that patients who receive long-term GC treatment use teriparatide (20 μg, once daily) to increase more bone mineral density than in those receiving alendronate [93]. There were reported also good results without side effects in patients with severe hypocalcemia and low PTH [94]. Teripatide would be an alternative of treatment for severe hypoparathyroidism after kidney transplantation in pre-transplant parathyroidectomized patients requiring intravenous infusions of calcium in patients [95].

3.6. Denosumab and Bisphosphonates

Bisphosphonates and denosumab are the two most commonly used therapy for osteoporosis.

They are used to prevent bone mass loss and to treat osteoporosis and other osteopenic conditions. They tend to accumulate at sites of active bone resorption, enter in osteoclasts, inhibit farnesyl pyrophosphate synthase, which results in osteoclast apoptosis, and inhibition of bone resorption [15].

Low turnover bone diseases are common in dialysis patients and may persist after transplantation so additional suppression of bone remodeling without stimulation of new bone formation may not improve the mechanical strength and quality of bone so it is important to think for a bone biopsy before initiating therapy especially in the patients which are considered high risk and had done previous parathyroidectomy.

Denosumab, a humanized monoclonal antibody against the receptor activator of NF-κB ligand, a potent antiresorptive agent, decreases bone resorption, significantly increases BMD, tends to decrease the risk of vertebral, nonvertebral, and hip fractures in women with

osteoporosis [96].

Thongprayoon et al, recently in their systematic review and meta-analysis included 162 patients reported that denosumab effectively increases BMD and T scores in the lumbar spine and femur neck. From baseline to post-treatment, there was not observed differences in serum Ca and PTH. However, may occur mild hypocalcemia during treatment with denosumab which needs close monitoring and titration of dose of Ca and Vit D supplements [97].

Wang J et al. in his systematic review reported that in eight trials (406 patients) were shown changes in BMD at the femoral neck also showed improved outcomes after treatment with bisphosphonates (WMD, 0.06; 95 % CI, 0.03-0.09). Bisphosphonates also improve BMD at the lumbar spine and femoral neck after 12 months in renal-transplant recipients [98].

Toth-Manikowski SM et al. in his metanalysis evaluated all studies which compare bisphosphonate therapy to standard of care with a follow-up duration with more than 6 months. Bisphosphonates improved femoral neck and lumbar spine BMD compared with controls (0.055 g/cm(2), 95% CI 0.012-0.099 and 0.053 g/cm(2), 95% CI 0.032-0.074, respectively) without adversely affecting allograft dysfunction or calcium but without difference in fracture incidence .

Edwards et al. reported in a small study [70] showed that bisphosphonate use was associated with lower risk of self-reported fractures.

Stein et al. in his metaanalysis of 11 trials with 780 patients showed that use of bisphosphonates or VDRAs within the first 12 months postransplantation was associated with reduced fractures [100] showing that the preventive therapy with either bisphosphonates or VDRAs likely is better than no therapy in terms of preventing posttransplantation bone loss and possibly fractures

Recently Yang et al. showed that combination of bisphosphonate with calcium and vitamin D analogs showed greater beneficial effects than calcium alone or with either vitamin D analogs or calcitonin (MD, 10.51; 95% CrI, 5.92 to 15.34; MD, 5.48; 95% CrI, 2.57 to 8.42; MD, 6.39; 95% CrI, 0.55 to 12.89). Both bisphosphonate and vitamin D analogs combined with calcium displayed a notable improvement compared to calcium alone (MD, 7.24; 95% CrI, 3.73 to 10.69; MD, 5.02; 95% CrI, 1.20 to 8.84). Their conclusion was that bisphosphonate was well-tolerated and more favorable in KTRs to improve BMD [101].

In conclusion it would be said that bisphosphonate is well -tolerated therapy in Transplant patients which improved BMD mainly in lumbar spine and femoral neck but it is not clear due the lack of evidence whether antiresorptive therapy has an effect on the overall number of fractures [102]. It should be underlined that studies of bisphosphonate use in the post transplantation

period have not been designed to detect fracture risk reduction. Also there is consensus for the increase incidence of a adynamic bone disease during the therapy with bisphosphonate, but is important to be underlined that the risk of ABD as a result of bisphosphonate therapy has not been a consistently observed phenomenon in observational trial but it is important to keep thinking for it [103].

The differences between studies may be connected to differences in bisphosphonate compounds, or the timing of the bone biopsies relative to treatment. Always should be monitor the renal function and bisphosphonates should be avoided in patients with GFR<30 mL/min/1.73 m2 secondary to the prolonged half-life, acute worsening of kidney function, an increase risk of of adynamic bone disease and fracture risk. There is also no consensus about the duration of therapy, but taking in consideration that the bone loss happens typically during the first year after transplantation and tend to improve after the first year, the duration of 12 up to 18 months is usually prescribed for most of the patients.

The heterogeneity of KTRs and the impact of several factors make difficult to study the therapeutic alternatives directed at MBD. Having more specific surrogate markers, would be more able to design feasible studies with increased clinical relevance.

4. References

1. Monier-Faugere MC, Mawad H, Qi Q, Friedler RM, Malluche HH. High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. J Am Soc Nephrol. 2000 Jun;11(6):1093-9.

2. Brandenburg VM, Westenfeld R, Ketteler M. The fate of bone after renal transplantation. Journal of Nephrology 2004;17:190-204.

3. Malluche HH, Faugere MC: Renal bone disease 1990: An unmet challenge for the nephrologist. Kidney Int 1990; 38: 193–211.

4. Hruska KA, Teitelbaum SL: Renal osteodystrophy. N Engl J Med 1995; 333: 166–174.

5. Malluche HM, Faugere MC, Herberth J. Bone disease after renal transplantation.Nat Rev Nephrol. 2010 J ; 6(1): 32–40. doi:10.1038/nrneph.2009.192.

6. Marcén R, Caballero C, Pascual J, Teruel JL, Tenorio M, Ocaña J, Villafruela JJ, Burgos FJ, Fernández AM, Muriel A, Ortuño. Lumbar bone mineral density in renal transplant patients on neoral and tacrolimus: a four-year prospective study. J Transplantation. 2006;81(6):826.

7. Evenepoel P, Behets GJ, Viaene L, D'Haese PC. Bone histomorphometry in de novo renal transplant recipients indicates a further decline in bone resorption 1 year posttransplantation Kidney Int. 2017;91(2):469.

8. Mikuls TR, Julian BA, Bartolucci A, Saag. Bone mineral density changes within six months of renal transplantation. KG Transplantation. 2003;75(1):49.

9. Casez JP, Lippuner K, Horber FF, Montandon A, Jaeger P. Changes in bone mineral density over 18 months following kidney transplantation: the respective roles of prednisone and parathyroid hormone. Nephrol Dial Transplant. 2002;17(7):1318.

10. Julian BA, Laskow DA, Dubovsky J, Dubovsky EV, Curtis JJ, Quarles LD. Rapid loss of vertebral mineral density

after renal transplantation. N Engl J Med. 1991;325(8):544.

11. Almond MK, Kwan JT, Evans K, Cunningham Loss of regional bone mineral density in the first 12 months following renal transplantation. J Nephron. 1994;66(1):52.

12. Iyer SP, Nikkel LE, Nishiyama KK, Dworakowski E, Cremers S, Zhang C, McMahon DJ, Boutroy S, Liu XS, Ratner LE, Cohen DJ, Guo XE, Shane E, Nickolas TL. Kidney transplantation with early corticosteroid withdrawal: paradoxical effects at the central and peripheral skeleton. J Am Soc Nephrol. 2014 Jun;25(6):1331-41.

13. Zisman AL, Sprague . Bone disease after kidney transplantation. SM Adv Chronic Kidney Dis. 2006;13(1):35.

14. Nikkel LE, Hollenbeak CS, Fox EJ, Uemura T, Ghahramani N. Risk of fractures after renal transplantation in the United States. Transplantation. 2009 ;87(12):1846-51.

15. Bouquegneau A, Salam S, Delanaye P, Eastell R, KhwajaA. Bone Disease after Kidney Transplantation..Clin J Am SocNephrol. 2016 ;11(7):1282-96.

16. Yakupoglu HY, Corsenca A, Wahl P, Wüthrich RP, Ambühl PM Transplantation. 2007;84(9):115.

17. Ulivieri FM, Piodi LP, Aroldi A, Cesana. Effect of kidney transplantation on bone mass and body composition in males. Effect of kidney transplantation on bone mass and body composition in males.Ulivieri FM, Piodi LP, Aroldi A, Cesana BM Transplantation. 2002;73(4):612.

18. Lenihan CR, Sukumaran Nair S, Vangala C, Ramanathan V, Montez-Rath ME, Winkelmayer WC. Proton Pump Inhibitor Use and Risk of Hip Fracture in Kidney Transplant Recipients. Am J Kidney Dis. 2017 May;69(5):595-601. doi: 10.1053/j.ajkd.2016.09.019.

19. Cunningham J. Posttransplant bone disease. Transplantation 2005;79:629-32.

20. Movsowitz C, Epstein S, Fallon M, Ismail F, Thomas S. Cyclosporin-A in vivo produces severe osteopenia in the rat: effect of dose and duration of administration. Endocrinology. 1988;123(5):2571.

21. Cayco AV, Wysolmerski J, Simpson C, Mitnick MA, Gundberg C, Kliger A, Lorber M, Silver D, Basadonna G, Friedman A, Insogna K, Cruz D, Bia M. Posttransplant bone disease: evidence for a high bone resorption state. Transplantation. 2000;70(12):1722.

22. Cueto-Manzano AM, Konel S, Crowley V, France MW, Freemont AJ, Adams JE, Mawer B, Gokal R, Hutchison AJ. Bone histopathology and densitometry comparison between cyclosporine a monotherapy and prednisolone plus azathioprine dual immunosuppression in renal transplant patients. Transplantation. 2003;75(12):2053.

23. Goffin E, Devogelaer JP, Lalaoui A, Depresseux G, De Naeyer P, Squifflet JP, Pirson Y, van Ypersele de Strihou C . Tacrolimus and low-dose steroid immunosuppression preserves bone mass after renal transplantation. Transpl Int. 2002;15(2-3):73. Epub 2002 Feb 28.

24. Monegal A, Navasa M, Guañabens N, Peris P, Pons F, Martínez de Osaba MJ, Rimola A, Rodés J, Muñoz-Gómez. Bone mass and mineral metabolism in liver transplant patients treated with FK506 or cyclosporine A. J . Calcif Tissue Int. 2001;68(2):83.

25. Luo L, Shi Y, Bai Y, Zou Y, Cai B, Tao Y, Lin T, Wang L. Impact of tacrolimus on bone metabolism after kidney transplantation. Int Immunopharmacol. 2012;13(1):69. Epub 2012 Mar 31.

26. Westenfeld R, Schlieper G, Wöltje M, et al. Impact of sirolimus, tacrolimus and mycophenolate mofetil on osteoclastogenesis—implications for posttransplantation bone disease. Nephrol Dial Transplant. 2011;26:4115-4123.

27. Kneissel M, Luong-Nguyen NH, Baptist M, et al. Everolimus suppresses cancellous bone loss, bone resorption, and cathepsin K expression by osteoclasts. Bone. 2004;35:1144-1156.

28. Malluche HH, Monier-Faugere MC. Renal osteodystrophy: what's in a name? Presentation of a clinically useful new

model to interpret bone histologic findings. Clin Nephrol. 2006; 65:235–42. [PubMed: 16629221]

29. Malluche H, Lee J, Wang G, Herberth J, Faugere MC. Usefulness of the new TMV classification of renal osteodystrophy. J Am Soc Nephrol. 2008; 19:38A.

30. London GM, et al. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol. 2004; 15:1943–51. [PubMed: 15213285]

31. Bell KL, et al. A novel mechanism for induction of increased cortical porosity in cases of intracapsular hip fracture. Bone. 2000; 27:297–304. [PubMed: 10913926]

32. Perrin P, Caillard S, Javier RM, Braun L, Heibel F, Borni-Duval C, Muller C, Olagne J, Moulin B. Persistent hyperparathyroidism is a major risk factor for fractures in the five years after kidney transplantation. Am J Transplant. 2013 Oct;13(10):2653-63. Epub 2013 Aug 26.

33. Perrin P, Kiener C, Javier RM, Braun L, Cognard N, Gautier-Vargas G, Heibel F, Muller C, Olagne J, Moulin B, Caillard S. Recent changes in chronic kidney disease-mineral and bone disorders (CKD-MBD) and associated fractures after kidney transplantation. Transplantation. 2017;101(8):1897-1905.

34. Briner VA, et al. Prevention of cancellous bone loss but persistence of renal bone disease despite normal 1,25 vitamin D levels two years after kidney transplantation. Transplantation. 1995; 59:1393–400. [PubMed: 7770924]

35. Grotz WH, et al. Bone loss after kidney transplantation: a longitudinal study in 115 graft recipients. Nephrol Dial Transplant. 1995; 10:2096–100. [PubMed: 8643174]

36. Monier-Faugere MC, Mawad H, Qi Q, Friedler RM, Malluche HH. High prevalence of low bone turnover and occurrence of osteomalacia after kidney transplantation. J Am Soc Nephrol. 2000; 11:1093–9. [PubMed: 10820173]

37. Evenepoel P, Claes K, Kuypers D, Maes B, Bammens B, Vanrenterghem Y. Natural history of parathyroid function and calcium metabolism after kidney transplantation: a single-centre study. Nephrol Dial Transplant. 2004 May;19(5):1281-7. Epub 2004 Feb 19.

38. Cundy T, Kanis JA, Heynen G, Morris PJ, Oliver DO. Calcium metabolism and hyperparathyroidism after renal transplantation. Q J Med. 1983;52(205):67.

39. Marcen R, Teruel JL. Patient outcomes after kidney allograft loss. Transplant Rev (Orlando). 2008; 22:62–72. [PubMed: 18631859]

40. Evenepoel P, Meijers BK, de Jonge H, et al. Recovery of hyperphosphatoninism and renal phosphorus wasting one year after successful renal transplantation. Clin J Am Soc Nephrol 2008; 3: 1829.

41. Bhan I, Shah A, Holmes J, et al. Post-transplant hypophosphatemia: tertiary ‘‘hyper-phosphatoninism’’? Kidney Int 2006; 70: 1486.

42. Pande S, Ritter CS, Rothstein M, Wiesen K, Vassiliadis J, Kumar R, Schiavi SC, Slatapolsky E, Brown AJ.FGF-23 and sFRP-4 in chronic kidney disease and post-renal transplantation. Nephron Physiol. 2006;104(1):p23. Epub 2006 May 10.

43. Ghanekar H, Welch BJ, Moe OW, Sakhaee K.Post-renal transplantation hypophosphatemia: a review and novel insights. Curr Opin Nephrol Hypertens. 2006;15(2):97.

44. Evenepoel P, Naesens M, Claes K, Kuypers D, Vanrenterghem Y.Tertiary ‘hyperphosphatoninism’ accentuates hypophosphatemia and suppresses calcitriol levels in renal transplant recipients. Am J Transplant. 2007;7(5):1193. Epub 2007 Mar 12.

45. Bayrakci US, Baskin E, Ozcay F, et al. Renal Fanconi syndrome and myopathy after liver transplantation: drug-related mitochondrial cytopathy? Pediatr Transplant 2008; 12: 109-12.

46. Alshayeb HM, Josephson MA, Sprague SM. CKD–mineral and bone disorder management in kidney transplant recipients. Am J Kidney Dis. 2013;61:310- 325.

47. Cohen A, Sambrook P, Shane E. Management of bone loss after organ transplantation. Journal of Bone and Mineral Research 2004; 19:1919-1932.

48. Abbott KC, Oglesby RJ, Agodoa LY. Hospitalized avascular necrosis after renal transplant in the United States. Kidney International 2002; 62:2250-53.

49. Abbott KC, Koff J, Bohen EM, et al. Maintenance immunosuppresion use and the associated risk of avascular necrosis after kidney transplantation in the United States. Transplantation 2005;79:330-34.

50. Felten R, Perrin P, Caillard S, Moulin B, Javier R-M (2019) Avascular osteonecrosis in kidney transplant recipients: Risk factors in a recent cohort study and evaluation of the role of secondary hyperparathyroidism. PLoSONE 14(2): e0212931.https://doi.org/10.1371/journal. pone.0212931

51. Grotz WH, Breitenfeldt MK, Braune SW, et al. Calcineurin inhibitor induced pain syndrome: a severe disabling complication after organ transplantation. Transplant International 2001; 14:16-23.

52. Goffin E, Vande Berg B, Devogelaer JP, et al. Post-renal transplant syndrome of transient lower limb joint pain : description under a tracolimus-based immunosuppression. Clinical Nephrology 2003; 59 :98-02.

53. Barbosa LM, Gauthier VJ, Davis CL. Bone pain that responds to calcium channel blockers. Transplantation 1995; 59:541-544.

54. Molnar M, Naser MS, Rhee CM, Kamyar Kalantar-Zadeh,et al. Management of mineral and bone disorders in renal transplant recipients. Nephrology (Carlton). 2017;22 Suppl 2:65-69. doi: 10.1111/nep.13028.

55. Damasiewicz MJ Ebeling PR. Management of mineral and bone disorders in renal transplant recipients. Nephrology (Carlton). 2017 Mar;22 Suppl 2:65-69. doi: 10.1111/nep.13028.

56. Peter R. Ebeling. Approach to the Patient with Transplantation-Related Bone Loss. J Clin Endocrinol Metab, May 2009, 94(5):1483–1490.

57. Kalantar-Zadeh K1, Molnar MZ, Kovesdy CP, Mucsi I, Bunnapradist S. Management of mineral and bone disorder after kidney transplantation. Curr Opin Nephrol Hypertens. 2012 Jul;21(4):389-403. doi: 10.1097/MNH.0b013e3283546ee0.

58. Vangala C, Pan J, Cotton RT, Ramanathan V. Mineral and Bone Disorders After Kidney Transplantation. Front Med (Lausanne). 2018 Jul 31;5:211. doi: 10.3389/fmed.2018.00211. eCollection 2018.

59. Kidney Disease: Improving Global Outcomes CKDMBDWG. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD- MBD). Kidney Int Suppl. (2009) 113:S1–130. doi: 10.1038/ki.2009.188.

60. Bucur RC, Panjwani DD, Turner L, Rader T, West SL, Jamal SA. Low bone mineral density and fractures in stages 3-5 CKD: an updated systematic review and meta-analysis. Osteoporos Int. (2015) 26:449–58. doi: 10.1007/s00198-014-2813-3

61. West SL, Lok CE, Langsetmo L, Cheung AM, Szabo E, Pearce D, et al. Bone mineral density predicts fractures in chronic kidney disease. J Bone Min Res. 2015; 30:913–9. doi: 10.1002/jbmr.2406.

62. Yenchek RH, Ix JH, Shlipak MG, Bauer DC, Rianon NJ, Kritchevsky SB, et al. Bone mineral density and fracture risk in older individuals with CKD. Clin J Am Soc Nephrol. 2012; 7:1130–6. doi: 10.2215/CJN.12871211.

63. Iimori S, Mori Y, Akita W, Kuyama T, Takada S, Asai T, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients–a single-center cohort study.

Nephrol Dialysis Transplant. 2012; 27:345–51. doi: 10.1093/ndt/ gfr3.

64. Akaberi S, Simonsen O, Lindergard B, Nyberg G. Can DXA predict fractures in renal transplant patients? Am J Transplant. (2008) 8:2647–51.

65. Van Staa TP, Laan RF, Barton IP, Cohen S, Reid DM, Cooper C. Bone density threshold and other predictors of vertebral fracture in patients receiving oral glucocorticoid therapy. Arthritis Rheum. 2003; 48:3224–9. doi: 10.1002/ art.11283

66. Thomas Nickolas, MD, MSSri G Yarlagadda, MDL Darryl Quarles, MDKathryn Diemer, MDElizabeth Shane, MD. Bone disease after kidney transplantation – UpToDate August 2018.

67. Sapna P. Iyer, Lucas E. Nikkel, Kyle K. Nishiyama, Elzbieta Dworakowski, Serge Cremers, Chiyuan Zhang, Donald J. McMahon, Stephanie Boutroy, X. Sherry Liu, Lloyd E. Ratner, David J. Cohen, X. Edward Guo, Elizabeth Shane, Thomas L. Nickolas.Kidney Transplantation with Early Corticosteroid Withdrawal: Paradoxical Effects at the Central and Peripheral Skeleton. J Am Soc Nephrol. 2014; 25(6): 1331–1341.

68. Ing SW, Sinnott LT, Donepudi S, Davies EA, Pelletier RP, Lane NE.: Change in bone mineral density at one year following glucocorticoid withdrawal in kidney transplant recipients. Clin Transplant 2011;25: E113–E123.

69. Farmer CKT, Hampson G, Abbs IC, Hilton RM, Koffman CG, Fogelman I, Sacks SH.: Late low-dose steroid withdrawal in renal transplant recipients increases bone formation and bone mineral density. Am J Transplant 2006: 6: 2929–2936.

70. Edwards BJ, Desai A, Tsai J, Du H, Edwards GR, Bunta AD, Hahr A, Abecassis M, Sprague S: Elevated incidence of fractures in solid-organ transplant recipients on glucocorticoid-sparing immunosuppressive regimens. J Osteoporos 2011: 591793.

71. KDIGO clinical practice guideline for the care of kidney transplant recipients. American journal of transplantation : official journal of the American Society of Transplantation and the American Society of Transplant Surgeons. Nov; 2009 9(Suppl 3):S1–155.

72. Kasiske BL, Chakkera HA, Louis TA, Ma JZ. A meta-analysis of immunosuppression withdrawal trials in renal transplantation. Journal of the American Society of Nephrology : JASN 2000;11(10):1910–1917.

73. Pascual J, Quereda C, Zamora J, Hernandez D. Steroid withdrawal in renal transplant patients on triple therapy with a calcineurin inhibitor and mycophenolatemofetil: a meta-analysis of randomized, controlled trials. Transplantation. 2004;78(10):1548–1556.

74. Wolf M, Weir MR, Kopyt N, Mannon RB, Von Visger J, Deng H, et al. A prospective cohort study of mineral metabolism after kidney transplantation. Transplantation 2016; 100:184–93. doi: 10.1097/TP.0000000000000823.

75. Serra AL, Wuhrmann C and Wuthrich RP. Phosphatemic effect of cinacalcet in kidney transplant recipients with persistent hyperparathyroidism. American Journal of Kidney Disease 2008; 52:1151-7.

76. McGregor R, Li G, Penny H, Lombardi G, Afzali B, Goldsmith DJ.: Vitamin D in renal transplantation - from biological mechanisms to clinical benefits. Am J Transplant2014; 14: 1259–1270.

77. Lee JR, Dadhania D, August P, Lee JB, Suthanthiran M, Muthukumar T.: Circulating levels of 25-hydroxyvitamin D and acute cellular rejection in kidney allograft recipients. Transplantation 2014;98: 292–299.

78. Josephson MA, Schumm LP, Chiu MY, Marshall C, Thistlethwaite JR, Sprague SM. Calcium and calcitriol prophylaxis attenuates posttransplant bone loss. Transplantation. Oct 27; 2004 78(8):1233–1236.

79. Sahin G, Yasar NS, Sirmagul B, Bal C, Yalcin AU. The effect of low-dose cholecalciferol and calcium treatment on posttransplant bone loss in renal transplant patients: a prospective study. Ren Fail. 2008;30(10):992-999.

80. Torres A, Garcia S, Gomez A, et al. Treatment with intermittent calcitriol and calcium reduces bone loss after renal transplantation. Kidney international 2004; 65(2):705-12.

81. Amer H, Griffin MD, Stegall MD, Cosio FG, Park WD, Kremers WK, Heilman RL, Mazur MJ, Hamawi K, Larson TS, Kumar R.: Oral paricalcitol reduces the prevalence of posttransplant hyperparathyroidism: Results of an open label randomized trial. Am J Transplant 2013;13: 1576–1585.

82. Utiel BJF, Soto BAJ, Perez MJM et al. Effect Of paricalcitol on mineral bone metabolismIn kidney transplant recipients with Secondary hyperparathyroidism. nefrologia.2015;35(4):363–373.

83. Trillini M, Cortinovis M, Ruggenenti P, et al: Paricalcitol for secondary hyperparathyroidism in renal transplantation. J Am Soc Nephrol 2015;26:1205-1214.

84. Cozzolino M, Ketteler M, Martin KJ, Sharma A, Goldsmith D, Khan S. Paricalcitol- or cinacalcet-centred therapy affects markers of bone mineral disease in patients with secondary hyperparathyroidism receiving haemodialysis: results of the IMPACT-SHPT study. Nephrol Dialysis Transplant. (2014) 29:899–905. doi: 10.1093/ndt/gfu011.

85. Cueto-Manzano AM, Konel S, Freemont AJ, et al: Effect of 1,25-dihydroxyvitamin D3 and calcium carbonate on bone loss associated with long-term renal transplantation. Am J Kidney Dis 2000;35:227-236.

86. Koch Nogueira PC, David L, Cochat P. Evolution of secondary hyperparathyroidism after renal transplantation. Pediatr Nephrol 2000;14:342–6. doi: 10.1007/s004670050772

87. Cohen JB, Gordon CE, Balk EM, Francis JM. Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients: a systematic review and meta-analysis. Transplantation (2012) 94:1041–8. doi: 10.1097/TP.0b013e31826c3968

88. Borchhardt KA, Heinzl H, Mayerwoger E, Horl WH, Haas M, SunderPlassmann G. Cinacalcet increases calcium excretion in hypercalcemic hyperparathyroidism after kidney transplantation. Transplantation (2008) 86:919–24. doi: 10.1097/TP.0b013e318186b7fb

89. Seager CM, Srinivas TR, Flechner SM. Development of nephrolithiasis in a renal transplant patient during treatment with Cinacalcet. Ann Transplant 2013;18:31–5. doi: 10.12659/AOT.883809.

90. Zavvos V, Fyssa L, Papasotiriou M, Goumenos D et al. Long-Term Use of Cinacalcet in Kidney Transplant Recipients. With Hypercalcemic Secondary Hyperparathyroidism: A Single-Center Prospective Study. Experimental and Clinical Transplantation 2017, DOI: 10.6002/ect.2016.0342.

91. Mawad H, bouchard H, Tran D, et al. Retrospective study looking at cinacalcet in the management of hyperparathyroidism after kidney transplantation. J Transplant 2017:8720283. doi: 10.1155/2017/8720283

92. Dulfer R, Franssen G, Hesselink D, et al. Systematic review of surgical and medical treatment for tertiary hyperparathyroidism. Br J Surg. 2017;104:804-813. doi: 10.1002/bjs.10554.

93. B. Hofstetter, S. Gamsjaeger, F. Varga et al., “Bone quality of the newest bone formed after two years of teriparatide therapy in patients who were previously treatment-naïve or on long-term alendronate therapy,” Osteoporosis International,2014; 25(12): 2709–2719.

94. Nogueira E. L., Costa A. C., Santana A., et al. Teriparatide efficacy in the treatment of severe hypocalcemia after kidney transplantation in parathyroidectomized patients: a series of five case reports. Transplantation. 2011;92(3):316–320. doi: 10.1097/tp.0b013e3182247b98.

95. Hod T, Riella LV, Chandraker A. Recombinant PTH therapy for severe hypoparathyroidism after kidney transplantation in pre-transplant parathyroidectomized patients: review of the literature and a case report. Clin Transplant. 2015;29(11):951-7. doi: 10.1111/ctr.12622

96. Jamal SA, Ljunggren O, Stehman-Breen C, Cummings SR, McClung MR, Goemaere S, Ebeling PR, Franek E, Yang

YC, Egbuna OI, Boonen S, Miller PD.: Effects of denosumab on fracture and bone mineral density by level of kidney function. J Bone Miner Res 2011; 26:1829–1835.

97. Thongprayoon C, Acharya P, Aeddula NR, Torres-Ortiz A, Bathini T, Sharma K, Ungprasert P, Watthanasuntorn K, Suarez MLG, Salim SA, Kaewput W, Chenbhanich J8, Mao MA, Cheungpasitporn W.Effects of denosumab on bone metabolism and bone mineral density in kidney transplant patients: a systematic review and meta-analysis. Arch Osteoporos. 2019 Mar 9;14(1):35. Osteoporos Int. 2016 May;27(5):1683-90. doi: 10.1007/s00198-015-3465-7. Epub 2016 Jan 5.

98. Wang J, Yao M, Xu JH, Shu B, Wang YJ, Cui XJ. Bisphosphonates for prevention of osteopenia in kidney-transplant recipients: a systematic review of randomized controlled trials. Osteoporos Int. 2016 May;27(5):1683-90. doi: 10.1007/s00198-015-3465-7.

99. Toth-Manikowski SM, Francis JM, Gautam A, Gordon CE. Outcomes of bisphosphonate therapy in kidney transplant recipients: a systematic review and meta-analysis. Clin Transplant. 2016 ;30(9):1090-6.

100. Stein EM, Ortiz D, Jin Z, McMahon DJ, Shane E. Prevention of fractures after solid organ transplantation: a meta-analysis. J Clin Endocrinol Metab. 2011;96(11):3457-3465. BMC Nephrol. 2018 Oct 19;19(1):269. doi: 10.1186/s12882-018-1076-1.

101. Yang Y, Qiu S, Deng L, Tang X, Li X, Wei Q, Fu P.Outcomes of bisphosphonate and its supplements for bone loss in kidney transplant recipients: a systematic review and network meta-analysis. BMC Nephrol. 2018 Oct 19;19(1):269. doi: 10.1186/s12882-018-1076-1.

102. Palmer SC, McGregor DO, Strippoli GF. Interventions for preventing bone disease in kidney transplant recipients. Cochrane Database Syst Rev. 2007;3:CD005015.

103. Coco M, Glicklich D, Faugere MC, et al. Prevention of bone loss in renal transplant recipients: a prospective, randomized trial of intravenous pamidronate, Journal of American Society of Nephrology 2003; 14:2669-2676