Mineral and bone disorder after kidney transplantation (KTx)

Distúrbio mineral e ósseo após transplante renal (TxR)

Authors
Carolina Lara Neves[1,2]
Igor Dernizate B. Marques[3]
Melani Ribeiro Custódio[4]

[1]Universidade Federal da Bahia, Hospital das Clínicas, Salvador, BA, Brazil.
[2]Hospital Ana Nery, Salvador, BA, Brazil.
[3]Universidade Federal do Piauí, University Hospital, Teresina, PI, Brazil.
[4]Universidade de São Paulo, SP, Brazil

Submitted on: 05/24/2021.
Approved on: 06/03/2021.

Correspondence to:
Melani R. Custódio.
Email: melrcustodio@yahoo.com.br

DOI: https://doi.org/10.1590/2175-8239-JBN-2021-S113

1. Assessment frequency of biochemical and hormonal abnormalities

1.1 In the pre-KTx assessment, it is recommended to evaluate the mineral and bone profile [calcium (Ca), phosphorus (P), alkaline phosphatase (AP), parathormone (PTH) and 25-hydroxyvitamin (VitD)], and in the first 3 months post-KTx, serum calcium and phosphorus levels should be monitored weekly, or less frequently, according to clinical evolution (Opinion).

1.2 Within 3-12 months after KTx, the assessment frequency of laboratory tests will depend on the magnitude of biochemical changes and the established therapies (Opinion).

1.3 In the period over 12 months after KTx, the assessment frequency will depend on the function of renal graft (follow recommendations for CKD stages) and on the stabilization of biochemical changes, previously detected (Opinion).

2. Treatment of biochemical and hormonal abnormalities

2.1 Treatment of hyperparathyroidism after kidney transplantation or persistent HPT (pHPT) should take serum Ca levels into consideration (Evidence).

2.1.1 In the presence of mild or moderate hypercalcemia (tCa < 14 mg/dL or iCa < 1.80 mmol/L), treatment should be with cinacalcet or parathyroidectomy (PTX) if clinical treatment fails (Evidence).

2.1.2 In the presence of severe hypercalcemia (tCa > 14 mg/dL or iCa > 1.80 mmol/L), treatment should be by PTX and, until its completion, with cinacalcet and/or antiresorptive agents (Evidence).

2.1.3 In the presence of normocalcemia, treatment of pHPT should follow the same recommendations for patients with CKD G3a-5D (Opinion).

2.1.4 The type of PTX in the treatment of pHPT should preferably be subtotal PTX (Opinion).

2.2 P supplementation is indicated for patients with severe, symptomatic hypophosphatemia (P < 1.5 mg/dL) (Evidence).

2.3 Vitamin D supplementation should follow the same recommendations for CKD patients (Opinion).

3. Diagnosis and treatment of post-KTx osteopenia/osteoporosis

3.1 Bone densitometry (DXA), associated or not with FRAX, is the method of choice for assessing bone mass and risk of fracture after KTx (Opinion).

3.2 Bone biopsy should be considered before starting treatment with antiresorptive agents, for patients with eGFR < 30 mL/min/1.73m^2 (Opinion).

3.3 The choice of treatment should consider the presence of biochemical and hormonal abnormalities of CKD-MBD (Evidence).

3.4 For patients in the 1st year after KTx, with low bone mass and eGFR > 30 mL/min/1.73m^2, treatment with vitamin D,

calcitriol and/or antiresorptive agents should be considered (Evidence).

3.5 For patients with CKD G4T-G5T with low bone mass, the same treatment is suggested as for non-dialytic patients with CKD G4-G5.

3.6 For all post-KTx patients with low bone mass, physical activity and cessation of smoking and alcohol abuse should be recommended.

Rational

Mineral metabolism disorders (MBD) are prevalent in the first 3 months post-KTx, and some metabolic changes persist, such as elevated PTH levels and/or hypercalcemia, characterizing pHPT[1-4]. Hypophosphatemia is observed immediately after KTx in 50% of patients, caused by the reestablishment of the glomerular filtration function and by the elevated serum levels of PTH and FGF23, which lead to increased phosphaturia. Prolonged hypophosphatemia, serum P < 2.4 mg/dL, can lead to disturbances in bone mineralization. However, phosphorus replacement should be avoided, since it contributes to increase serum PTH levels, being recommended only in cases of severe and symptomatic hypophosphatemia (serum P < 1.5 mg/dL)[1,5,6].

The presence of hypercalcemia ranges from 11% to 31%, with some studies showing an incidence of up to 50%, depending on the severity of SHPT at the time of KTx and dialysis vintage[1,2,3]. The main etiology of hypercalcemia is pHPT, since, with the return of renal function, there is an improvement in bone resistance to PTH action, increased calcitriol synthesis, increased intestinal Ca absorption and distal tubular Ca reabsorption[4,7]. In addition, other factors contribute to the presence of hypercalcemia, such as resorption of vascular and ectopic calcifications, prolonged postoperative immobility, and abrupt discontinuation of post-KTx cinacalcet, which, associated with high PTH levels, can lead to severe hypercalcemia. In the late period of KTx, episodes of hypercalcemia should be investigated to exclude neoplasms or serious systemic infections. Hypercalcemia-associated complications are the presence of tubulointerstitial calcifications (nephrocalcinosis), association with chronic graft nephropathy, and exacerbation of aortic calcification[7,8,9].

Treatment of mild to moderate hypercalcemia (iCa 1.40 to 1.80 mmol/L) includes suspension of Ca supplements, use of thiazides and, frequently, use of cinacalcet, provided there is a satisfactory response to low doses of the medication (30-60 mg); otherwise, subtotal PTX is recommended. The treatment of severe hypercalcemia (iCa > 1.80 mmol/L), in addition to the aforementioned measures, recommends intravenous hydration with crystalloid solutions, use of loop diuretics, short-acting bisphosphonates such as pamidronate 60-90 mg/dose every 1-3 months and/or cinacalcet while awaiting PTX.

Serum PTH levels fall rapidly between 3-6 months and stabilize at 6-12 months after KTx and, to establish whether they are normal or not, it is always necessary to draw a parallel with the current glomerular filtration rate. The prevalence of pHPT ranges from 25-80% among studies, depending on the serum PTH level considered in the normal range/renal function, since there is no agreement in literature on the optimal post-KTx PTH. Most authors consider a range of serum PTH levels between 100-150 pg/mL acceptable for patients with glomerular filtration ≥ 30 mL/min[1,10,11,12].

The pHPT may be associated or not with hypercalcemia, as in cases of significant loss of graft function, equivalent to CKD in stages 3-5. Treatment should be started with cinacalcet and, in cases of failure or severe pHPT, subtotal PTX is indicated.

There is a gap regarding randomized studies in post-transplant that show, in addition to calcemia and PTH control, improvement in bone mass, graft function, fracture reduction, as well as the use of cinacalcet *versus* PTX.

A systematic review/meta-analysis published in 2012 reports that most studies, using cinacalcet for the treatment of pHPT and hypercalcemia, were not randomized, but showed good control of Ca and PTH[13]. Two clinical studies presenting small case series showed benefit from the use of cinacalcet in the control of hypercalcemia and improved bone mineral density of the radius and hip[14,15]. On the other hand, four studies comparing the use of cinacalcet versus PTX in patients with pHPT showed that patients undergoing PTX had better control of calcemia and PTH levels[16,17,18,19].

Subtotal PTX seems to be the most effective and efficient treatment for hypercalcemia associated with pHPT. Although slight worsening of kidney function may occur after the procedure, it is usually transient and does not decrease graft survival[20,21]. Some authors suggest that, when possible, surgery should be indicated after the first year of KTx, since the risk of worsening kidney function is lower, although there is disagreement with respect to this schedule[22,23]. The pHPT is associated

with worsening of graft function[11,24], increased risk of fracture[25,26] and mortality [27]. Considering the complications caused by pHPT and hypercalcemia, it is recommended, when possible, to perform PTX before KTx[13,28].

Currently, the life expectancy of patients and kidney grafts has increased significantly. Thus, the prevention of complications is important, such as bone disease, which leads to diffuse pain, fractures, deformities, and limitations. It is known that, even after successful KTx, in addition to pHPT or other bone disease, the patient may also present with osteopenia/osteoporosis developed before or after transplantation. The association of these metabolic bone changes increases the risk of fractures, favors the early onset of hypercalcemia and hypophosphatemia and, later, acute rejection and mortality[12]. For this reason, as stated earlier, it is recommended that control of the patients' bone disease occurs prior to KTx, either with medication or subtotal PTX.

Bone mass loss prior to KTx (verified by DXA) occurs especially in patients in which the etiology of CKD requires prolonged corticosteroids use. After KTx, bone loss occurs more in the lumbar spine, due to the action of immunosuppressants, but increasingly less significant with the new regimens[29,30]. However, risk factors persist, such as those observed in the general population: age, female gender, sedentary lifestyle, inadequate nutritional status, chronic use of corticosteroids, previous fracture, and diabetes *mellitus*.

FRAX is a tool that is used in association with DXA to assess risks of fracture. Although not specific for CKD patients, FRAX has been recognized and validated for this population as well, providing information on the 10-year risk of hip fracture[31]. Another test that complements the data provided by DXA (quantity of bone mass) is the high-resolution peripheral quantitative computed tomography (HR-pQCT), which assesses the quality of bone tissue[32]. Unfortunately, the performance of HR-pQCT is restricted to a few diagnostic centers and it is not routinely used.

In clinical practice, the suggested practice for treatment of osteoporosis in patients after KTx should be based on the control of existing metabolic changes and on the institution of general measures, such as changing habits and lifestyle, introduction of physical exercise, smoking cessation, moderation in alcohol consumption, among others[33]. These measures aim to stimulate increased bone mass and improve balance, preventing falls and fractures, and thus improving quality of life. Drug treatment for osteoporosis should be individualized. In the general population, this treatment is well established, with several drugs available that could reduce bone mass loss and/or stimulate bone mass formation, reducing the incidence of fractures[33]. However, the use of these drugs in patients after KTx, with glomerular filtration above 30 mL/min, presents some particularities:

Vitamin D

The incidence of hypovitaminosis D in patients after KTx is around 50%. Vitamin D replacement is important for reducing bone mass loss, but it is contraindicated in the presence of hypercalcemia[33].

Bisphosphonates

Bisphosphonates are widely used, due to their effectiveness and low cost, in patients in the general population and in transplant patients. The widespread and preventive use of bisphosphonates, in the loss of bone mass immediately after KTx, has been questioned even with studies showing that this medication preserves bone mass without interfering with PTH levels[34,35]. However, as mentioned above, bone mass loss in the central skeleton no longer occurs as significantly as before[36] due to new immunosuppressive regimens, low rates of acute rejection, decreased use of glucocorticoids, and widespread use of vitamin D. Furthermore, there are studies showing that the use of this medication does not reduce the risk of fracture in this population[36,37].

Bisphosphonates inhibit osteoclast function, and without careful monitoring, may cause a decoupling between bone formation and resorption, inducing the development of low turnover (adynamic) bone disease or mineralization defect. Although serum PTH levels and other bone markers do not reflect bone histology, patients with suspected or diagnosed adynamic bone disease should not receive bisphosphonates. Recently, some studies have shown that bisphosphonates do not induce adynamic bone disease, as demonstrated in previous publications[38,39,40], but their indication remains controversial in KTx patients with glomerular filtration lower than 30 mL/min/1.73m², similar to patients in CKD stages 4, 5 and 5D[1].

A study by Marques et al., using HR-pQCT and bone biopsy, demonstrated that KTx induces a loss of bone tissue connectivity, especially in the peripheral

skeleton, where most fractures occur[41]. This fact justifies the fracture in patients with DXA within the normal range, demonstrating that bone changes occur in its microarchitecture. Therefore, bisphosphonates should be considered for patients at high risk of fracture, evidenced by loss of bone mass, especially at these sites.

Denosumab

Denosumab increases bone mass mainly in the lumbar spine, but it also has a positive impact on the femoral neck. This difference observed between the two sites is justified by the greater action of denosumab on trabecular bone, which is more prevalent in the lumbar spine. A study comparing the efficacy of denosumab and bisphosphonates showed that bone mass increased in the lumbar spine and femoral neck in both arms of the study, with this increase being more important in the denosumab group[42].

Mechanisms that justify these differences:

1. Inhibitory effect: bisphosphonates are absorbed by the mature osteoclast, and thus inhibit the resorptive action of this cell. On the other hand, the action of denosumab is more effective in reducing bone resorption, by preventing osteoclasts maturation, activation and survival.

2. Antifracture efficacy: denosumab has a greater impact on cortical bone, since, in addition to acting on bone mass, it improves microarchitecture parameters, as evidenced by a study using HR-pQCT[43]. By its action, altering bone microarchitecture, denosumab promotes a more complete inhibition of bone resorption and reduces the risk of fracture when compared to bisphosphonates.

The side effect of denosumab is hypocalcemia, which may occur even with stable PTH levels and may be prevented and/or corrected with concomitant use of calcitriol[44,45]. Despite this, it is a safe and effective drug in the treatment of osteoporosis in kidney transplant patients, and could be used at any stage of graft dysfunction.

Other drug therapies

The use of recombinant human parathyroid hormone, teriparatide, has no consistent data for the treatment of post-KTx osteoporosis. Cejka et al. showed that after 6 months of teriparatide use there was no improvement in bone mass, histology or bone turnover markers compared to control group [46]. It is probably indicated in some cases of persistent hypoparathyroidism that may occur in transplant patients undergoing PTX.

Regarding hormone replacement in transplant patients, there are no consistent studies that indicate the best therapy in terms of efficacy, safety and doses of the drugs already available. Early menopause occurs in women at all CKD stages, and clinical trials are needed to define the best therapy and the impact of CKD on menopause[47].

References

1. Alagoz S, Trabulus S. Long-term evaluation of mineral metabolism after kidney transplantation. Transplant Proc. 2019 Sep;51(7):2330-3. https://doi.org/10.1016/j.transproceed.2019.01.181
2. 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 Jan;100(1):184-93. https://doi.org/10.1097/TP.0000000000000823
3. Torres A, Lorenzo V, Salido E. Calcium metabolism and skeletal problems after transplantation. J Am Soc Nephrol. 2002 Feb;13(2):551-8. https://doi.org/10.1681/ASN.V132551
4. 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. https://doi.org/10.1093/ndt/gfh128
5. Bouquegneau A, Salam S, Delanaye P, Eastell R, Khwaja A. Bone disease after kidney transplantation. Clin J Am Soc Nephrol. 2016 Jul 7;11(7):1282–96. https://doi.org/10.2215/CJN.11371015
6. Seeherunvong W, Wolf M. Tertiary excess of fibroblast growth factor 23 and hypophosphatemia following kidney transplantation. Pediatr Transplant. 2011 Feb;15(1):37-46. https://doi.org/10.1111/j.1399-3046.2010.01405.x
7. Evenepoel P. Recovery versus persistence of disordered mineral metabolism in kidney transplantation recipients. Semin Nephrol. 2013 Mar 1;33(2):P191-203. https://doi.org/10.1016/j.semnephrol.2012.12.019
8. Çeltik A, Şen S, Yılmaz M, Demirci MS, Aşçı G, Tamer AF, et al. The effect of hypercalcemia on allograft calcification after kidney transplantation. Int Urol Nephrol. 2016 Nov;48(11):1919-25. https://doi.org/10.1007/s11255-016-1391-z
9. Ozdemir FN, Afsar B, Akgul A, Usluoğullari C, Akçay A, Haberal M. Persistent hypercalcemia is a significant risk factor for graft dysfunction in renal transplantation recipients. Transplant Proc. 2006 Mar;38(2):480-2. https://doi.org/10.1016/j.transproceed.2005.12.065
10. Santos RD, Rossi A, Coyne D, Maw TT. Management of post-transplant hyperparathyroidism and bone disease. Drugs. 2019 Apr 1;79(5):501–13. https://doi.org/10.1007/s40265-019-01074-4
11. Araujo MJCLN, Ramalho JAM, Elias RM, Jorgetti V, Nahas W, Custodio M, et al. Persistent hyperparathyroidism as a risk factor for long-term graft failure: the need to discuss indication for parathyroidectomy. Surgery. 2018 May 1;163(5):P1144-50. https://doi.org/10.1016/j.surg.2017.12.010
12. Bouquegneau A, Salam S, Delanaye P, Eastell R, Khwaja A. Bone disease after kidney transplantation. Clin J Am Soc Nephrol. 2016 Jul 7;11(7):1282-96. https://doi.org/10.2215/CJN.11371015
13. Cohen JB, Gordon CE, Balk EM, Francis JM. Cinacalcet for the treatment of hyperparathyroidism in kidney transplant recipients:

a systematic review and meta-analysids. Transplantation. 2012 Nov 27;9(10):1041-8. https://doi.org/10.1097/TP.0b013e31826c3968
14. Bergua C, Torregrosa J-V, Fuster D, Gutierrez-Dalmau A, Oppenheimer F, Campistol JM. Effect of cinacalcet on hypercalcemia and bone mineral density in renal transplanted patients with secondary hyperparathyroidism. Transplantation. 2008 Aug 15;86(3):413-7. https://doi.org/10.1097/TP.0b013e31817c13e1
15. Cho ME, Duan Z, Chamberlain CE, Reynolds JC, Ring MS, Mannon RB. Cinacalcet improves bone density in post-kidney transplant hyperparathyroidism. Transplant Proc. 2010 Nov;42(9):3554-8. https://doi.org/10.1016/j.transproceed.2010.06.027
16. Dulfer RR, Koh EY, van der Plas WY, Engelsman AF, van Dijkum EJMN, Pol RA, et al. Parathyroidectomy versus cinacalcet for tertiary hyperparathyroidism; a retrospective analysis. Langenbecks Arch Surg. 2019 Feb 15;404(1):71-9. https://doi.org/10.1007/s00423-019-01755-4
17. Lou I, Schneider DF, Leverson G, Foley D, Sippel R, Chen H. Parathyroidectomy is underused in patients with tertiary hyperparathyroidism after renal transplantation. Surgery. 2016 Jan 1;15(1):P172-9. https://doi.org/10.1016/j.surg.2015.08.039
18. Soliman AR, Maamoun HA, Soliman MA, Darwish H, Elbanna E. Cinacalcet versus parathyroidectomy in the treatment of secondary hyperparathyroidism post renal transplantation. Rom J Intern Med. 2016 Sep 1;54(3):184-9. https://doi.org/10.1515/rjim-2016-0027
19. Cruzado JM, Moreno P, Torregrosa JV, Taco O, Mast R, Gómez-Vaquero C, et al. A randomized study comparing parathyroidectomy with Cinacalcet for treating hypercalcemia in kidney allograft recipients with hyperparathyroidism. J Am Soc Nephrol. 2016 Aug;27(8):2487-94. https://doi.org/10.1681/ASN.2015060622
20. Evenepoel P, Claes K, Kuypers DR, Debruyne F, Vanrenterghem Y. Parathyroidectomy after successful kidney transplant: a single centre study. Nephrol Dial Transplant. 2007 Jun;22(6):1730-7. https://doi.org/10.1093/ndt/gfm044
21. Triponez F, Clark OH, Vanrenthergem Y, Evenepoel P. Surgical treatment of persistent hyperparathyroidism after renal transplantation. Ann Surgery. 2008 Jul;248(1):18-30. https://doi.org/10.1097/SLA.0b013e3181728a2d
22. Littbarski SA, Kaltenborn A, Gwiasda J, Beneke J, Arelin V, Schwager Y, et al. Timing of parathyroidectomy in kidney transplant candidates with secondary hyperparathryroidism: effect of pretransplant versus early or late post-transplant parathyroidectomy. Surgery. 2018 Feb 1;163(2):P373-80. https://doi.org/10.1016/j.surg.2017.10.016
23. van der Plas WY, Moumni ME, von Forstner PJ, Koh EY, Dulfer RR, van Ginhoven TM, et al. Timing of parathyroidectomy does not influence renal function after kidney transplantation. World J Surg. 2019 Aug 15;43(8):1972-80. https://doi.org/10.1007/s00268-019-04952-w
24. Prakobsuk S, Sirilak S, Vipattawat K, Taweesedt PT, Sumethkul V, Kantachuvesiri S, et al. Hyperparathyroidism and increased fractional excretion of phosphate predict allograft loss in long-term kidney transplant recipients. Clin Exp Nephrol. 2017 Oct;21(5):926–31. https://doi.org/10.1007/s10157-016-1370-9
25. Perrin P, Kiener C, Javier R-M, Braun L, Cognard N, Gautier-Vargas G, et al. Recent changes in chronic kidney disease–mineral and bone disorders and associated fractures after kidney transplantation. Transplantation. 2017 Aug;101(8):1897–1905. https://doi.org/10.1097/TP.0000000000001449
26. Perrin P, Caillard S, Javier RM, Braun L, Heibel F, Borni-Duval C, et al. 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. https://doi.org/10.1111/ajt.12425
27. Pihlstrøm H, Dahle DO, Mjøen G, Pilz S, März W, Abedini S, et al. Increased risk of all-cause mortality and renal graft loss in stable renal transplant recipients with hyperparathyroidism. Transplantation. 2015 Feb;99(2):351–9. https://doi.org/10.1097/TP.0000000000000583
28. Taweesedt PT, Disthabanchong S. Mineral and bone disorder after kidney transplantation. World J Transplant. 2015 Dec 24;5(4):231–42. https://doi.org/10.5500/wjt.v5.i4.231
29. Malluche HH, Monier-Faugere M-C, Herberth J. Bone disease after renal transplantation Nat Rev Nephrol. 2010 Jan;6(1):32-40. https://doi.org/10.1038/nrneph.2009.192
30. Molnar MZ, Naser MS, Rhee CM, Kalantar-Zadeh K, Bunnapradist S. Bone and mineral disorders after kidney transplantation: therapeutic strategies. Transplant Rev (Orlando). 2014 Apr;28(2):56–62. https://doi.org/10.1016/j.tre.2013.12.003
31. Przedlacki J, Buczyńska-Chyl J, Koźmiński P, Niemczyk E, Wojtaszek E, Gieglis E, et al. The utility of FRAX ® in predicting bone fractures in patients with chronic kidney disease on hemodialysis: a two-year prospective multicenter cohort study. Osteoporos Int. 2018 May;29(5):1105-15. https://doi.org/10.1007/s00198-018-4406-z
32. Nishiyama KK, Pauchard Y, Nikkel LE, Iyer S, Zhang C, McMahon DJ, et al. Longitudinal HR-pQCT and image registration detects endocortical bone loss in kidney transplantation patients. J Bone Miner Res. 2015 Mar;30(3):554-61. https://doi.org/10.1002/jbmr.2358
33. Radominski SC, Bernardo W, Paula AP, Albergaria B-H, Moreira C, Fernandes CE, et al. Brazilian guidelines for the diagnosis and treatment of postmenopausal osteoporosis. Rev Bras Reumatol Engl Ed. 2017;57 Suppl 2:452-66. https://doi.org/10.1016/j.rbre.2017.07.001
34. Coco M, Pullman J, Cohen HW, Lee S, Shapiro C, Solorzano C, et al. Effect of risedronate on bone in renal transplant recipients. J Am Soc Nephrol. 2012 Aug;23(8):1426-37. https://doi.org/10.1681/ASN.2011060623
35. Wang Z, Han Z, Tao J, Lu P, Liu X, Wang J, et al. Clinical efficacy and safety of pamidronate therapy on bone mass density in early post-renal transplant period: a meta-analysis of randomized controlled trials. PLoS One. 2014 Sep 29;9(9):e108106. https://doi.org/10.1371/journal.pone.0108106
36. Lan G-B, Xie X-B, Peng L-K, Liu L, Song L, Dai H-L. Current status of research on osteoporosis after solid organ transplantation: pathogenesis and management. Biomed Res Int. 2015;2015:413169. https://doi.org/10.1155/2015/413169
37. Conley E, Muth B, Samaniego M, Lotfi M, Voss B, Armbrust M, et al. Bisphosphonates and bone fractures in long-term kidney transplant recipients. Transplantation. 2008 Jul 27;86(2):231–7. https://doi.org/10.1097/TP.0b013e318176b40f
38. Bover J, Bailone L, López-Báez V, Benito S, Ciceri P, Galassi A, et al. Osteoporosis, bone mineral density and CKD-MBD: treatment considerations. J Nephrol. 2017 Oct;30(5):677-87. https://doi.org/10.1007/s40620-017-0404-z
39. Smerud KT, Dolgos S, Olsen IC, Åsberg A, Sagedal S, Reisæter AV, et al. A 1-year randomized, double-blind, placebo-controlled study of intravenous ibandronate on bone loss following renal transplantation. Am J Transplant. 2012 Dec;12(12):3316-25. https://doi.org/10.1111/j.1600-6143.2012.04233.x
40. Amerling R, Harbord NB, Pullman J, Feinfeld DA. Bisphosphonate use in chronic kidney disease: association with adynamic bone disease in a bone histology series. Blood Purif. 2010;29(3):293-9. https://doi.org/10.1159/000276666
41. Marques IDB, Araújo MJCLN, Graciolli FG, Dos Reis LM, Pereira RMR, Alvarenga JC, et al. A randomized trial of zoledronic acid to prevent bone loss in the first year after kidney transplantation. J Am Soc Nephrol. 2019 Feb;30(2):355-65. https://doi.org/10.1681/ASN.2018060656
42. McKee H, Ioannidis G, Lau A, Treleaven D, Gangji A, Ribic C, et al. Comparison of the clinical effectiveness and safety between the use of denosumab vs bisphosphonates in renal transplant patients. Osteoporos Int. 2020 May;31(5):973-80. https://doi.org/10.1007/s00198-019-05267-1
43. Seeman E, Delmas PD, Hanley DA, Sellmeyer D, Cheung AM, Shane E, et al. Microarchitectural deterioration of cortical and

trabecular bone: differing effects of denosumab and alendronate. J Bone Miner Res. 2010 Aug;25(8):1886–94. https://doi.org/10.1002/jbmr.81
44. Brunova J, Kratochvilova S, Stepankova J. Osteoporosis therapy with denosumab in organ transplant recipients. Front Endocrinol (Lausanne). 2018 Apr 17;9:162. https://doi.org/10.3389/fendo.2018.00162
45. Wada Y, Iyoda M, Iseri K, Arai-Nunota N, Saito T, Hamada T, et al. Combination therapy of denosumab and calcitriol for a renal transplant recipient with severe bone loss due to therapy-resistant hyperparathyroidism. Tohoku J Exp Med. 2016 Mar;238(3):205-12. https://doi.org/10.1620/tjem.238.205
46. Cejka D, Benesch T, Krestan C, Roschger P, Klaushofer K, Pietschmann PM, et al. Effect of teriparatide on early bone loss after kidney transplantation. Am J Transplant. 2008 Sep;8(9):1864-70. https://doi.org/10.1111/j.1600-6143.2008.02327.x
47. Vellanki K, Hou S. Menopause in CKD. Am J Kidney Dis. 2018 May 1;71(5):P710-9. https://doi.org/10.1053/j.ajkd.2017.12.019