CKD-MBD diagnosis: biochemical abnormalities

Diagnóstico do DMO-DRC: anormalidades bioquímicas

Authors

Leandro Junior Lucca[1]
Rosa Maria Affonso Moysés[2]
Fabiana Rodrigues Hernandes[3]
José Edvanilson Barros Gueiros[4]

[1]Universidade de São Paulo, Faculdade de Medicina, Hospital de Clínicas, Ribeirão Preto, SP, Brasil.
[2]Universidade de São Paulo, Laboratório de Fisiopatologia, Hospital das Clínicas da Faculdade de Medicina, São Paulo, SP, Brasil.
[3]Faculdade Santa Marcelina, Hospital Santa Marcelina, Unidade de Nefrologia, São Paulo, SP, Brasil.
[4]Universidade Federal de Pernambuco, Hospital de Clínicas, Recife, PE, Brasil.

Submitted on: 06/03/2021.
Approved on: 06/10/2021.

Correspondence to:
Leandro Junior Lucca.
Email: leandro.ibene@gmail.com

DOI: https://doi.org/10.1590/2175-8239-JBN-2021-S102

1. General Recommendations

1.1 The dosing methods, type of analyzed sample (blood or plasma), and sample collection and handling protocols should be considered when interpreting laboratory test results (Evidence).

1.2 Monitoring of calcium, phosphorus, alkaline phosphatase, parathyroid hormone and 25OH vitamin D [25(OH)D] in chronic kidney disease (CKD) should be started from stage 3a (Evidence).

1.3 The dosing frequency should be established according to the CKD stage and the trend of the result, or for treatment control (Opinion).

1.4 To consider the trend, rather than an isolated value, of calcium, phosphorus, alkaline phosphatase, parathormone, and 25OH vitamin D results to guide therapeutic decisions (Opinion).

1.5 The decision for starting, adjusting or switching treatment should consider the set of biochemical parameters of mineral metabolism.

1.6 Do not consider the Ca x P product but the individual value of Ca and P to guide therapeutic decision (Evidence).

2. Measurement of serum calcium and phosphorus

2.1 In CKD G3a-G5D, serum calcium and phosphorus should be maintained within the normal range for the chosen method (Evidence).

2.2 Calcemia should preferably be assessed by dosing the ionized Ca (Evidence).

2.2.1 When ionized calcium measurement is not available, calcemia could be assessed using serum albumin-adjusted total Ca (Opinion).

2.3 Serum phosphorus values up to 5.5 mg/dL are accepted for the use of active vitamin D derivatives in the treatment of hyperparathyroidism secondary to CKD.

3. Measurement of total alkaline phosphatase (TAP)

3.1 In CKD G3a-5, total AP measurement should be performed at least every 12 months or, more frequently, if PTH is high (Opinion).

3.2 In CKD G5D, total AP measurement should be performed every 3 months (Opinion).

3.3 In the presence of liver diseases, bone AP (BAP) measurement, instead of TAP, should be considered (Opinion).

4. Measurement of parathormone (PTH)

4.1 In CKD G3a-5, optimal intact PTH levels are not yet established (Evidence).

4.2 In CKD G5D, intact PTH levels should be maintained between 2 to 9 times the upper value of the method (Evidence).

4.3 Depending on the method of intact PTH dosing, consider the different proportions of amino-terminal (biologically

active) and carboxyl-terminal (biologically inactive) fractions (Opinion).

4.4 The blood sample for intact PTH measurement should be immediately stored on ice, while serum may be stored in a freezer at -80 °C for further analysis (Opinion).

5. Measurement of calcidiol – 25(OH)D

5.1 In CKD G3a-G5D, the serum 25(OH)D level should be in the range of 30 to 100 ng/dL (Opinion).

5.2 The blood sample for 25(OH)D measurement should be preserved under protection from light (Evidence).

Rational

It is necessary to know the methodology used by the clinical analysis laboratory, since there are different processes, materials and analysis trials, normality reference values, material transportation and packaging processes, among other factors that could interfere in the decision making regarding treatment and control of the disease[1].

Metabolic changes in CKD-MBD become more evident from CKD G3a onward. Thus, the measurement of calcium, phosphorus, alkaline phosphatase, PTH and 25 vitamin D is recommended to be initiated at this stage and based on the frequency shown in the tables 1, 2, 3, and 4[1]. When evaluating the laboratory parameters involved in CKD-MBD, it is salutary to consider them over time, instead of the current isolated result, since the current values often represent recent attitudes. This could result in important serum changes, leading to a metabolic diagnosis disconnected from the histological pattern of the bone. The biochemical background of at least 1-2 years leads us to a trend of these variables and it is necessary for the correct diagnosis and treatment decision.

Serum calcium, phosphorus and PTH levels are influenced by several factors, including diet and dietary changes, adherence and time of drug intake, type of assay and their intra-assay coefficient of variation, circadian rhythm and the interval between the last hemodialysis session and the analysis[2-4], in addition to collection, transport, packaging and centrifugation procedures.

Block et al[5], in a *post hoc* analysis assessing a large cohort of patients undergoing dialysis, suggested that biochemical markers involved in CKD-MBD have limited prognostic implication, since several CKD-MBD phenotypic behaviors are observed, according to KDIGO[1]/KDOQI[6] targets, when based on calcium, phosphorus and PTH. This highlights potential interactions among them for predicting risk of death and cardiovascular events, which reinforces the need to rely on the set of results to the detriment of the unit. Finally, it should be considered that any therapeutic attitude based on a parameter has effects, even if unintentional, on the others, as observed in the EVOLVE trial[7]. We suggest that, although there is no evidence, but based on current literature, not only calcium, phosphorus and PTH together should be considered for therapeutic decision-making, but also alkaline phosphatase.

The soluble fraction of calcium in the human body is mainly present in the extracellular fluid and distributed in the interstitial fluid and serum. The soluble fraction is found in 3 forms: a) free calcium (ionized - CaI), which is the physiologically active form and responsible for several physiological and metabolic actions; b) calcium ions bound to albumin; c) calcium bound to organic ions, such as phosphate, sulfate, and bicarbonate. Small changes in soluble calcium could result in alterations in neurological, renal, gastrointestinal, and cardiac functions[8]. Moore, however, highlights CaI as the metabolically active form responsible for biological actions in pathological and physiological conditions[3]. Thus, since the serum calcium level depends on its binding to organic anions and albumin, it is questionable whether it is preferable to consider TCa, aTCa (adjusted total calcium), or CaI as the best method to be used in clinical conditions. Formulas for calculating CaI should not be used, since they do not correlate with calcium measured directly in critically ill patients, with chronic kidney disease, hyperparathyroidism, acidemia, those receiving transfusion, and those on hemodialysis[9-13]. The formula [adjusted total calcium (aTCa) = total calcium + (4 - serum albumin) x 0.8] is suggested for correction of total calcium based on serum albumin[12]. The 2009 KDIGO[14] suggested that serum calcium in renal function stages 3a-5D should be maintained within the normal range for the analytical method used. KDIGO 2017[1], meanwhile, observing the evidence profile of studies that assessed serum calcium level in renal function stages 3a-5D, all observational, classified them as moderate risk of bias and low quality of evidence for clinical outcomes. Most of these studies observed elevated risk of death and cardiovascular events for increasing calcium levels, but showed no evidence for maintaining calcium

levels within the normal range. Thus, the guideline only suggests avoiding hypercalcemia. Mild, asymptomatic hypocalcemia, on the other hand, could be tolerated, as it shows low risk tendency for clinical outcomes[7]. With the advent of calcimimetics, vigorous correction of hypocalcemia was initially postulated, justified by the risk of side effects secondary to it. However, KDIGO 2017[1] highlights that the risk of replacement outweighs the risk of hypocalcemia, suggesting that it should be tolerated, provided that it is asymptomatic and without influence on the other biochemical elements involved in CKD-MBD.

Calcium concentration in the dialysate should always be individualized, considering not only serum calcium level and its need for adjustment, but also the possible histological profile of the patient. Karohl C et al.[15] have shown that during hemodialysis, calcium balance could affect or be affected by mineral metabolism. Only two randomized controlled studies have attempted to elucidate the importance of calcium concentration in the dialysate in clinical and histological outcomes. Ok et al.[16] submitted hemodialysis patients to a calcium concentration of 2.5 and 3.5 mEq/L for 24 months and subsequent bone biopsy. They have demonstrated a greater trend to hypercalcemia with 3.5 mEq/L calcium, a trend to reduce the coronary artery calcification score with 2.5 mEq/L calcium, and improvement in histomorphometric parameters with the use of 2.5 mEq/L calcium. Spasovsky et al.[17] on the other hand, submitted patients with non-histologic diagnosis of adynamic disease (PTH <100 pg/mL) to calcium of 2.5 and 3.5 mEq/L in the hemodialysis bath, for 6 months, observing that those submitted to 2.5 mEq/L calcium showed better biochemical parameters, suggesting an improvement in bone mineral metabolism. However, neither has demonstrated whether an intermediate calcium concentration (3.0 mEq/L) could be beneficial in the same way. Furthermore, it is important to consider the high risk of bias in the overall, cardiovascular and cerebrovascular mortality outcomes, in addition to the low quality for evidence of results and, consequently, not demonstrating improvement in the cited outcomes.

The onset of serum phosphorus measurement during the course of CKD has been the focus of debate in literature. Although hyperphosphatemia is a late event in the CKD progression, the effect of phosphorus on PTH, calcitriol and FGF-23 is recognized. Based on observational data, phosphorus dosing during the progression of CKD and in the dialysis period is suggested, according to Table 1.

Table 1 Recommendation of values and serum dosing of calcium and phosphorus in CKD stages

CKD Stage	GFR (mL/min)	Serum Ca and P (mg/dL)	Dosing frequency
3a - 3b	30-59	Within reference ranges	6-12 m
4	15-29	Within reference ranges	3-6 m
5	< 15	Within reference ranges	1-3 m
5D	dialysis	Within reference ranges	1-3 m

In patients with biochemical abnormalities, the frequency of serum dosing could be increased to monitor treatment results, efficacy and side effects.

CKD: Chronic kidney disease; GFR: Glomerular filtration rate; Ca: Calcium; P: Phosphorus

Table 2 Recommendation of values and serum dosing of alkaline phosphatase in CKD stages

CKD Stage	GFR (mL/min)	Serum AP (UI/L)	Dosing frequency
3a - 3b	30-59	Within reference ranges	12 m or more if PTH is high
4	15-29	Within reference ranges	
5	< 15	Within reference ranges	
5D	dialysis	1.5x upper limit of normal	3 m

In patients with biochemical abnormalities, the frequency of serum dosing could be increased to monitor treatment results, efficacy and side effects.

CKD: Chronic kidney disease; GFR: Glomerular filtration rate, AP: alkaline phosphatase

Table 3 Recommendation of values and serum dosing of PTH in CKD stages

CKD Stage	GFR (mL/min)	Serum PTH (pg/mL)	Dosing frequency
3a-3b	30-59	Within reference ranges	6-12 m
4	15-29	Within reference ranges	3-6 m
5	< 15	Within reference ranges	3 m
5D	dialysis	Within reference ranges	3 m

In patients with biochemical abnormalities, the frequency of serum dosing could be increased to monitor treatment results, efficacy and side effects.

CKD: Chronic kidney disease; GFR: Glomerular filtration rate

Table 4 Recommendation of values and serum dosing of vitamin D in CKD stages

CKD Stage	GFR (mL/min)	Serum 25(OH)D (ng/dL)	Dosing frequency
3a - 3b	30-59	30-100 ng/dL	variable, according to baseline value and to monitor treatment
4	15-29		
5	< 15		
5D	dialysis		

In patients with biochemical abnormalities, the frequency of serum dosing could be increased to monitor treatment results, efficacy and side effects.

CKD: Chronic kidney disease; GFR: Glomerular filtration rate

KDIGO 2017[1], after reviewing the evidence from the available studies regarding the serum phosphorus level that should be adopted as a target, cites the main conclusions: (i) the association between serum phosphate and clinical result is not monotonic; (ii) there is a lack of demonstrated efficacy of phosphate binders in reducing serum phosphate in patients with CKD 3a-4; (iii) safety of phosphate binders in this population is not proven; and (iv) there is a lack of data showing that dietary phosphate restriction improves clinical results. Consequently, the work group abandoned the previous suggestion (KDIGO 2009)[14] of maintaining phosphate in the normal range, suggesting the treatment to be focused on patients with hyperphosphatemia. The work group recognized that preventing hyperphosphatemia rather than treating it, may be useful in patients with stage 3a-5D CKD, but it acknowledges that current data are insufficient to support the safety or efficacy of such an approach and encourages research in this area.

There is still no consensus on what the "best" serum phosphorus level would be for stage 5D patients. Considering the prospective observational study COSMOS[18], which evaluated a cohort of hemodialysis patients, the best survival was observed with serum phosphate close to 4.4 mg/dL, i.e., the upper limit considered normal in most laboratory tests. In addition, high quality of evidence has been reported linking high serum phosphorus concentrations to mortality in patients with CKD functional stage 3A-5D and after kidney transplantation[19-27]. Despite these considerations, it is accepted, for the purposes of treatment with active vitamin D derivatives, the limit of serum phosphorus up to 5.5 mg/dL. The association between high serum levels of TAP and relative risk of fractures has been reported in hemodialysis patients[28], which justifies its monitoring, preferably in consonance with PTH. BAP correlates better with the bone formation rate, besides having a better predictive value for high and low bone turnover than PTH[29-32].

KDIGO 2017 recommends keeping serum PTH within normal ranges in the non-dialytic stages of CKD[1]. However, to date, there are no publications defining the best value, as well as mortality, hospitalization, and fracture outcomes. In this context, it is suggested to consider the PTH evolution over time [persistently above the upper limit of normal, or progressively increasing] in conjunction with modifiable factors (serum phosphorus, calcium and vitamin D). There is a tendency to recognize that high phosphorus intake does not always result in hyperphosphatemia, especially in the non-dialytic stages of CKD, but it may worsen SHPT.

The control of PTH elevation is necessary due to its association with morbidity and mortality and it should first go through the control of phosphorus intake (observing the phosphorus/protein intake ratio), correction of hypocalcemia, correction of hyperphosphatemia with binders and vitamin D replacement[1,33]. If PTH is not controlled with the above measures, the use of calcitriol or vitamin D analogues (paricalcitol or alfacalcidol) may be considered, especially in CKD stages 4-5. The risk of hypercalcemia[1,34,35] and possible CKD progression[1] are limiting factors for routine use, since the available publications show no benefits in mortality and hospitalization hard outcomes, but only in biochemical and histological control[11,35,36].

There is no consensus on the appropriate or toxic serum level of 25(OH)D. However, the Brazilian Society of Clinical Pathology and the American Society of Endocrinology are unanimous in stating that in CKD, regardless of stage, it should be above 30 ng/mL and lower than 100 ng/mL.

The decision whether to measure, when and how often to measure, and the serum level required should be individualized according to the other CKD-MBD biomarkers condition. There is a demonstrated association between 25(OH)D deficiency (< 10 or 15 ng/mL) with several diseases[37,38] and, in CKD, with mortality[39]. However, there is no publication showing that calcidiol repletion at a certain level reduces it. Since KDIGO 2009[14], only one randomized controlled study has been reported, by Oksa et al.[40], assessing cholecalciferol supplementation at high (80,000 IU/month) and low (20,000 IU/month) doses in adult patients with CKD stage 2-4, showing increased serum levels in both groups, greater in the high dose group. However, PTH did not significantly differ between them.

Routine serum calcitriol dosing is not recommended, since the analysis trials are not completely standardized, half-life is short, measurements could be artificially altered by the provision of exogenous calcitriol and vitamin D analogues, and there are no data indicating that its measurement is helpful in therapeutic definition or predicts clinical outcomes[14].

Finally, there is not sufficient evidence to date to justify the routine serum dosing of other biomarkers, such as sclerostin, FGF-23, klotho, CTX, P1NP, in the management of CKD-MBD.

References

1. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Update Work Group. KDIGO 2017 Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). Kidney Int Suppl (2011). 2017 Jul;7(1):1-59. https://doi.org/10.1016/j.kisu.2017.04.001
2. Moe SM, Zidehsarai MP, Chambers MA, Jackman LA, Radcliffe JS, Trevino LL, et al. Vegetarian compared with meat dietary protein source and phosphorus homeostasis in chronic kidney disease. Clin J Am Soc Nephrol. 2011 Feb;6(2):257–64. https://doi.org/10.2215/CJN.05040610
3. Viaene L, Meijers B, Vanrenterghem Y, Evenepoel P. Daytime rhythm and treatment-related fluctuations of serum phosphorus concentration in dialysis patients. Am J Nephrol. 2012;35(3):242-8. https://doi.org/10.1159/000336308
4. Dario KA, Dalboni MA, da Silva BC, Martins CSW, de Araujo LKRP, Elias RM, et al. Predialysis serum phosphate levels according to hemodialysis shift: circadian rhythm matters. Hemodial Int. 2021 Jan;25(1):134-6. https://doi.org/10.1111/hdi.12882
5. Block GA, Kilpatrick RD, Lowe KA, Wang W, Danese MD. CKD-mineral and bone disorder and risk of death and cardiovascular hospitalization in patients on hemodialysis. Clin J Am Soc Nephrol. 2013 Dec;8(12):2132-40. https://doi.org/10.2215/CJN.04260413
6. National Kidney Foundation. K/DOQI clinical practice guidelines for bone metabolism and disease in chronic kidney disease. Am J Kidney Dis. 2003 Oct;42(4 Suppl 3):S1-201.
7. EVOLVE Trial Investigators, Chertow GM, Block GA, Correa-Rotter R, Drueke TB, Floege J, et al. Effect of cinacalcet on cardiovascular disease in patients undergoing dialysis. N Engl J Med. 2012 Dec 27;367(26):2482-94. https://doi.org/10.1056/NEJMoa1205624
8. Baird GS. Ionized calcium. Clin Chim Acta. 2011 Apr 11;412(9-10):696-701. https://doi.org/10.1016/j.cca.2011.01.004
9. Szyfelbein SK, Drop LJ, Martyn JA. Persistent ionized hypocalcemia in patients during resuscitation and recovery phases of body burns. Crit Care Med. 1981 Jun;9(6):454-8. https://doi.org/10.1097/00003246-198106000-00004
10. Drop LJ, Laver MB. Low plasma ionized calcium and response to calcium therapy in critically ill man. Anesthesiology. 1975 Sep;43(3):300-6. https://doi.org/10.1097/00000542-197509000-00005
11. Zaloga GP, Chernow B, Cook D, Snyder R, Clapper M, O'Brian JT. Assessment of calcium homeostasis in the critically ill surgical patient. The diagnostic pitfalls of the McLean-Hastings nomogram. Ann Surg. 1985 Nov;202(5):587-94. https://doi.org/10.1097/00000658-198511000-00009
12. Byrnes MC, Huynh K, Helmer SD, Stevens C, Dort JM, Smith RS. A comparison of corrected serum calcium levels to ionized calcium levels among critically ill surgical patients. Am J Surg. 2005 Mar;189(3):310-4. https://doi.org/10.1016/j.amjsurg.2004.11.017
13. Mir AA, Goyal B, Datta SK, Ikkurthi S, Pal A. Comparison between measured and calculated free calcium values at different serum albumin concentrations. J Lab Physicians. 2016 Jul-Dec;8(2):71-6. https://doi.org/10.4103/0974-2727.180785
14. Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD Work Group. 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 Aug;(113):S1-130. https://doi.org/10.1038/ki.2009.188

15. Karohl C, Paschoal J de P, de Castro MCM, Elias RM, Abensur H, Romão Jr JE, et al. Effects of bone remodelling on calcium mass transfer during haemodialysis. Nephrol Dial Transplant. 2010 Apr;25(4):1244-51. https://doi.org/10.1093/ndt/gfp597
16. Ok E, Asci G, Bayraktaroglu S, Toz H, Ozkahya M, Yilmaz M, et al. Reduction of dialysate calcium level reduces progression of coronary artery calcification and improves low bone turnover in patients on hemodialysis. J Am Soc Nephrol. 2016 Aug;27(8):2475-86. https://doi.org/10.1681/ASN.2015030268
17. Spasovski G, Gelev S, Masin-Spasovska J, Selim G, Sikole A, Vanholder R. Improvement of bone and mineral parameters related to adynamic bone disease by diminishing dialysate calcium. Bone. 2007 Oct;41(4):698-703. https://doi.org/10.1016/j.bone.2007.06.014
18. Fernandez-Martin JL, Martinez-Camblor P, Dionisi MP, Floege J, Ketteler M, London G, et al. Improvement of mineral and bone metabolism markers is associated with better survival in haemodialysis patients: the COSMOS study. Nephrol Dial Transplant. 2015 Sep;30(9):1542-51. https://doi.org/10.1093/ndt/gfv099
19. Connolly GM, Cunningham R, McNamee PT, Young IS, Maxwell AP. Elevated serum phosphate predicts mortality in renal transplant recipients. Transplantation. 2009 Apr 15;87(7):1040-4. https://doi.org/10.1097/TP.0b013e31819cd122
20. Eddington H, Hoefield R, Sinha S, Chrysochou C, Lane B, Foley RN, et al. Serum phosphate and mortality in patients with chronic kidney disease. Clin J Am Soc Nephrol. 2010 Dec;5(12):2251-7. https://doi.org/10.2215/CJN.00810110
21. Fouque D, Roth H, Pelletier S, London GM, Hannedouche T, Jean G, et al. Control of mineral metabolism and bone disease in haemodialysis patients: which optimal targets? Nephrol Dial Transplant. 2013 Feb;28(2):360-7. https://doi.org/10.1093/ndt/gfs404
22. Fukagawa M, Kido R, Komaba H, Onishi Y, Yamaguchi T, Hasegawa T, et al. Abnormal mineral metabolism and mortality in hemodialysis patients with secondary hyperparathyroidism: evidence from marginal structural models used to adjust for time-dependent confounding. Am J Kidney Dis. 2014 Jun 1;63(6):P979-87. https://doi.org/10.1053/j.ajkd.2013.08.011
23. Lacson Jr E, Wang W, Hakim RM, Teng M, Lazarus JM. Associates of mortality and hospitalization in hemodialysis: potentially actionable laboratory variables and vascular access. Am J Kidney Dis. 2009 Jan 1;53(1):P79-90. https://doi.org/10.1053/j.ajkd.2008.07.031
24. McGovern AP, de Lusignan S, van Vlymen J, Liyanage H, Tomson CR, Gallagher H, et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. PLoS One. 2013 Sep 10;8(9):e74996. https://doi.org/10.1371/journal.pone.0074996
25. Moore J, Tomson CRV, Savage MT, Borrows R, Ferro CJ. Serum phosphate and calcium concentrations are associated with reduced patient survival following kidney transplantation. Clin Transplant. 2011 May-Jun;25(3):406-16. https://doi.org/10.1111/j.1399-0012.2010.01292.x
26. Nakai S, Akiba T, Kazama J, Yokoyama K, Fukagawa M, Tominaga Y, et al. Effects of serum calcium, phosphorous, and intact parathyroid hormone levels on survival in chronic hemodialysis patients in Japan. Ther Apher Dial. 2008 Feb;12(1):49-54. https://doi.org/10.1111/j.1744-9987.2007.00540.x
27. Tentori F, Blayney MJ, Albert JM, Gillespie BW, Kerr PG, Bommer J, et al. Mortality risk for dialysis patients with different levels of serum calcium, phosphorus, and PTH: the Dialysis Outcomes and Practice Patterns Study (DOPPS). Am J Kidney Dis. 2008 Sep 1;52(3):P519-30. https://doi.org/10.1053/j.ajkd.2008.03.020
28. Blayney MJ, Pisoni RL, Bragg-Gresham JL, Bommer J, Piera L, Saito A, et al. High alkaline phosphatase levels in hemodialysis patients are associated with higher risk of hospitalization and death. Kidney Int. 2008 Sep 1;74(5):P655-63. https://doi.org/10.1038/ki.2008.248
29. Fletcher S, Jones RG, Rayner HC, Harnden P, Hordon LD, Aaron JE, et al. Assessment of renal osteodystrophy in dialysis patients: use of bone alkaline phosphatase, bone mineral density and parathyroid ultrasound in comparison with bone histology. Nephron. 1997;75(4):412-9. https://doi.org/10.1159/000189578
30. Ureña P, Hruby M, Ferreira A, Ang KS, de Vernejoul MC. Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. J Am Soc Nephrol. 1996 Mar;7(3):506-12. https://doi.org/10.1681/ASN.V73506
31. Couttenye MM, D'Haese PC, Van Hoof VO, Lemoniatou E, Goodman W, Verpooten GA, et al. Low serum levels of alkaline phosphatase of bone origin: a good marker of adynamic bone disease in haemodialysis patients. Nephrol Dial Transplant. 1996 Jun;11(6):1065-72.
32. Lehmann G, Ott U, Kaemmerer D, Schuetze J, Wolf G. Bone histomorphometry and biochemical markers of bone turnover in patients with chronic kidney disease stages 3 - 5. Clin Nephrol. 2008 Oct;70(4):296-305. https://doi.org/10.5414/cnp70296
33. Moe SM, Saifullah A, LaClair RE, Usman SA, Yu Z. A randomized trial of cholecalciferol versus doxercalciferol for lowering parathyroid hormone in chronic kidney disease. Clin J Am Soc Nephrol. 2010 Feb;5(2):299-306. https://doi.org/10.2215/CJN.07131009
34. Coburn JW, Maung HM, Elangovan L, Germain MJ, Lindberg JS, Sprague SM, et al. Doxercalciferol safely suppresses PTH levels in patients with secondary hyperparathyroidism associated with chronic kidney disease stages 3 and 4. Am J Kidney Dis. 2004 May 1;43(5):P877-90. https://doi.org/10.1053/j.ajkd.2004.01.012
35. Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttmann JR, Jordans JG, et al. Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. BMJ. 1995 Feb 11;310(6976):358-63. https://doi.org/10.1136/bmj.310.6976.358
36. Wang AY-M, Fang F, Chan J, Wen Y-Y, Qing S, Chan IH-S, et al. Effect of paricalcitol on left ventricular mass and function in CKD--the OPERA trial. J Am Soc Nephrol. 2014 Jan;25(1):175-86. https://doi.org/10.1681/ASN.2013010103
37. Holick MF. Vitamin D for health and in chronic kidney disease. Semin Dial. 2005 Jul-Aug;18(4):266-75. https://doi.org/10.1111/j.1525-139X.2005.18402.x
38. Hollis BW, Wagner CL. Normal serum vitamin D levels. N Engl J Med. 2005 Feb 3;352(5):515-6; https://doi.org/10.1056/NEJM200502033520521
39. Wolf M, Shah A, Gutierrez O, Ankers E, Monroy M, Tamez H, et al. Vitamin D levels and early mortality among incident hemodialysis patients. Kidney Int. 2007 Oct 2;72(8):P1004-13.
40. Oksa A, Spustová V, Krivosíková Z, Gazdíková K, Fedelesová V, Lajdová I, et al. Effects of long-term cholecalciferol supplementation on mineral metabolism and calciotropic hormones in chronic kidney disease. Kidney Blood Press Res. 2008;31(5):322-9. https://doi.org/10.1159/000157177