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NEPHROGENIC CALCIFIC ARTERIOPATHY

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Introduction

Vascular calcification in chronic kidney disease (CKD) is extremely common and contributes to significant morbidity and mortality among these patients. The pathogenesis is complex and involves multiple factors, including elevated calcium x phosphorus product as well as deficiencies in circulating or locally produced inhibitors of calcification, parathyroid hormone, hyperlipidemia and inflammation. Similarly, valvular heart calcifications as well as myocardial and pulmonary calcifications of fatal consequences can also occur, presumably related to the same pathogenetic factors (Figures 1, 2). Other forms of extraskeletal tissue calcification of nonfatal consequences but leading to incapacity can also develop in CKD patients (Figure 3). These complications may be prevented by awareness and early intervention directed towards correcting some of the aforementioned participating mechanisms.

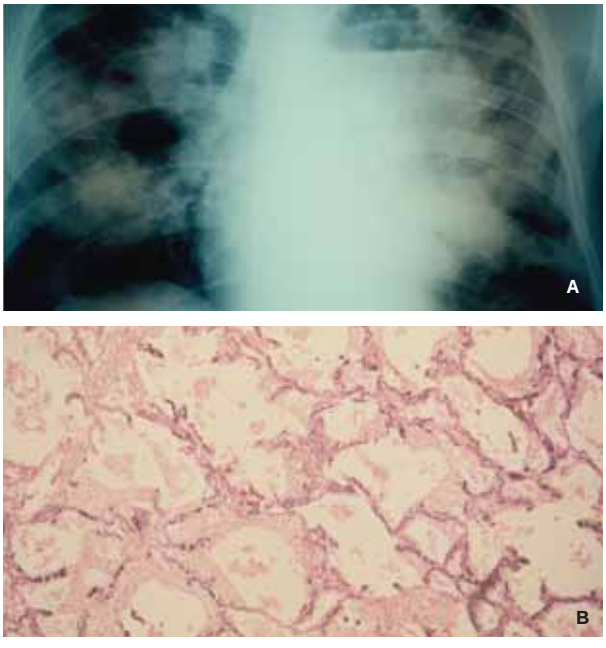

Figure 1. (A) Chest X-ray showing extensive bilateral pulmonary parenchymal calcifications resulting in fatal respiratory failure. (B) Calcium deposits in the alveolar septae and wall of small arteries appears to be the predilect location interfering with gas exchange.[1]

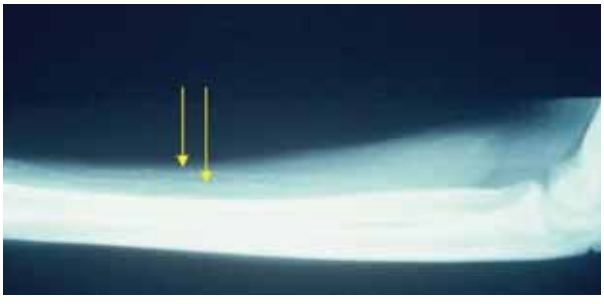

Figure 2. X-ray of the forearm in a 16-year-old patient (note epiphysis not fused) showing extensive medial calcification due to elevated calcium x phosphorus product.

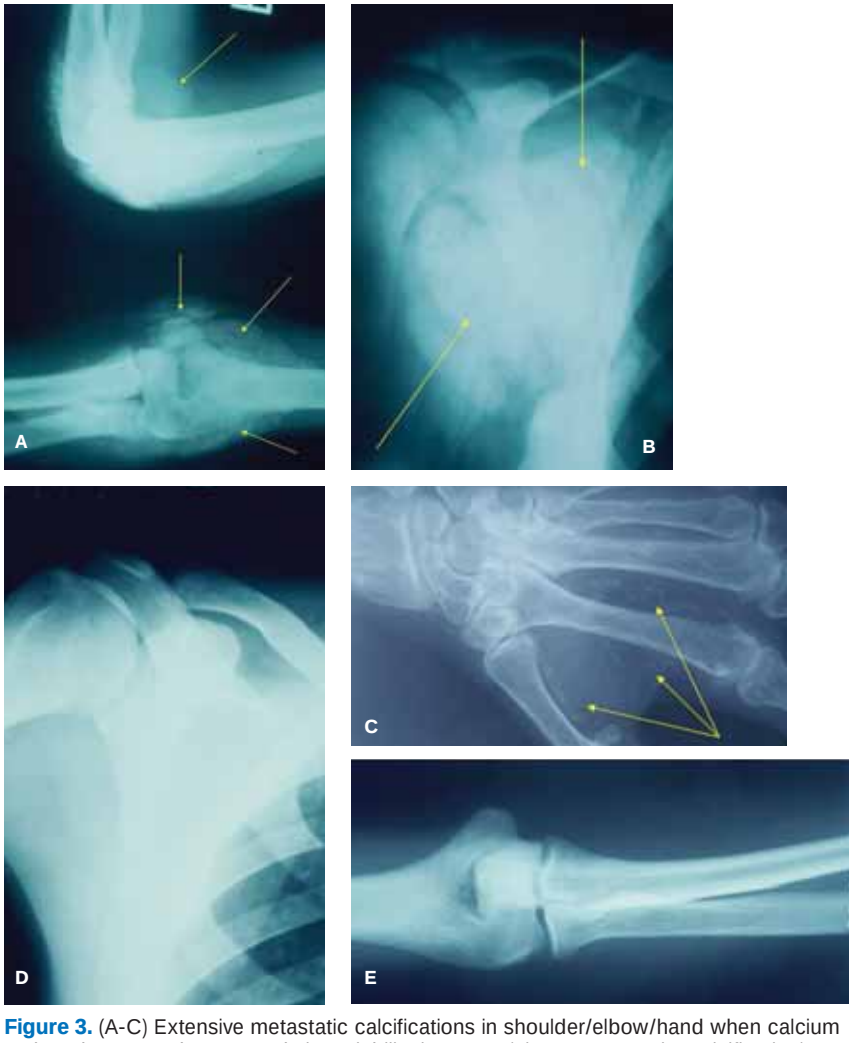

Figure 3. (A-C) Extensive metastatic calcifications in shoulder/elbow/hand when calcium x phosphorus product exceeds its solubility in serum (also note vascular calcification). This form of metastatic calcification is composed mostly of hydroxyapatite. (D-E) Following treatment and normalization of serum phosphorus, aggressive dialysis and parathyroidectomy resulted in dramatic resolution of these deposits.[2]

Abnormal Mineral Metabolism in CKD and Cardiovascular Injury

The regulation of calcium and phosphorus in individuals with normal kidney function is mediated by the interactions of parathyroid hormone (PTH) and calcitriol–hormone D– [1,25 $(OH)_2$ D_3], the active metabolite of vitamin D. The main function of PTH is to maintain calcium homeostasis acting directly on bone and kidney and indirectly in the intestine, enhancing bowel calcium absorption mediated by calcitriol. Elevation of PTH triggered by hypocalcemia increases mobilization of calcium and phosphorus from bone and enhances renal tubular calcium reabsorption with decreasing renal tubular phosphorus reabsorption.

Values of serum phosphorus between 2.5 and 4.5 mg/dL remain stable despite different oral phosphorus dietary intake ranging from 900 to 1800 mg/day. Seventy percent of the phosphorus ingested is eliminated by the kidneys and 30% through the gastrointestinal tract. As CKD progresses and the glomerular filtration rate drops to usually less than 30 mL/min, the compensatory increment in PTH (secondary hyperparathyroidism), observed earlier as a result of evolving hypocalcemia, can no longer induce further excretion of phosphorus, and frank hyperphosphatemia develops (Table 1).[3] Elevated phosphorus levels inhibit 1-alpha-hydroxylase thus decreasing calcitriol synthesis. This in turn leads to decreasing calcium absorption in the gut with the ensuing hypocalcemia, further aggravating the excess of PTH release.[4, 5] Moreover, there are studies suggesting a direct effect of hyperphosphatemia in stimulating PTH release leading to osteodystrophy.[6]

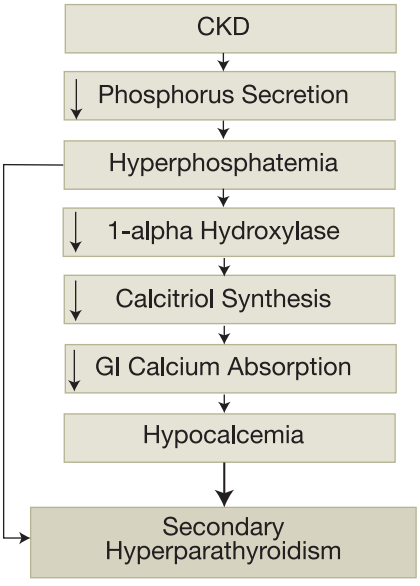

Table 1. Hyperphosphatemia in CKD.

Observational studies have shown an increased incidence of cardiovascular disease due to elevated serum phosphorus levels even in individuals without CKD. It appears that in susceptible patients, perhaps a depletion in fibroblast growth factor-23 gene (which regulates intestinal and renal phosphorus transport) or the Klotho gene[7] (which encodes a transmembrane protein in the distal tubule) is associated with a phenotype resulting in hyperphosphatemia, premature aging, and atherosclerosis that leads to cardiovascular disease (Table 2).

Mineral Bone Disorder of CKD Associated with Vascular Calcification
• Active vitamin D (calcitriol) deficiency
• 25 (OH) vitamin D deficiency
• Hyperparathyroidism (PTH >600 units) — increased bone turnover disease
• Relative hypoparathyroidism (PTH <150 units) — adynamic bone disease
• Hyperphosphatemia (phosphorus >4.5 mg/dL)
• Hypercalcemia (calcium >10.5 mg/dL)
• Hypocalcemia (calcium <8 mg/dL)

Table 2. "Kidney bone disease" vascular calcifications.[8]

Hyperphosphatemia, usually in combination with other factors including hyperparathyroidism with evidence of bone disease (elevated bone alkaline phosphatase), can transform vascular smooth muscle cells to chondrocytes or osteoblast-like cells, resulting in intimal and medial arterial calcification.[9]

Phosphorus as a Cardiovascular Risk Factor in CKD

Individuals with hyperphosphatemia (phosphorus >4.5 mg/dL) have a 52% higher risk of death from coronary artery disease, 26% higher risk for sudden death, 34% higher risk of death from other cardiovascular causes, and 35% higher risk of death from cerebrovascular accidents.[10]

In a study of 3,490 individuals with CKD from the Veteran's Affairs medical centers in the Pacific Northwest, after statistical adjustments, serum phosphorus levels greater than 3.5 mg/dL were associated with a significant increased risk for death. Mortality increased linearly with each subsequent 0.5 mg/dL elevation of serum phosphorus.[11] Similarly, a different series reported an association between hyperphosphatemia and mortality among 385 dialysis patients.[12]

Since the kidneys are highly vascular organs, evolving hyperphosphatemia even in the early stages of CKD has been associated with the progression of CKD.[13] The mechanism of phosphorus-excess-induced vascular injury is multifactorial and includes stimulation of the osteoblastic transcriptional program in the vasculature that is mediated by osterix activation in cells of the vascular tunica media and intima.[14] Block et al.[15] clearly demonstrated increased mortality with calcium x phosphorus >72 mg/dL, and since more than 45% of deaths among dialysis patients arise from cardiovascular disease, the conclusion is that the increased mortality is related to vascular calcification resulting from high calcium x phosphorus product.

Calcification Inhibitors in CKD

Vascular calcifications can occur in the absence of hyperphosphatemia, indicating that additional factors are involved in this complication. Several proteins have been implicated in this process.[16] Decreased levels of pyrophosphate, Matrix Gla protein, and/or fetuin-A are associated with reduced survival rates and have been found to be either deficient or nonfunctional in CKD. Moreover, bone proteins including osteopontin, osteocalcin, and bone morphogenic protein 2 have been found in vascular smooth muscle cells. These can differentiate into osteoblast-like cells in the presence of elevated calcium/phosphorus product.[17] In experimental animals, pyrophosphate inhibited vascular

calcifications even in the presence of elevated calcium and phosphorus. On the other hand, alkaline phosphatase can promote calcification by hydrolyzing pyrophosphate.[18] Fetuin-A also appears to function as a circulating inhibitor and is decreased in CKD, thus contributing to increased vascular calcifications (Table 3).[19]

Calcification Inhibitor in CKD	Clinical Relevance in CKD
Fetuin-A	Low Fetuin-A level is an inflammatory marker of all-cause mortality among CKD patients.
Matrix Gla Protein	Low levels due to undercarboxylation can decrease its potential beneficial effect. Warfarin can contribute by interfering with its ability to prevent calcification.
Osteoprotegerin (OPG)	Increased OPG levels correlate with aortic calcifications and severity of cardiovascular disease.

Table 3. Calcification inhibitors and their clinical relevance in chronic kidney disease.

Uremia, Parathyroid Hormone and Cardiovascular Injury

Several factors may affect myocardial performance in uremia including hypertension, anemia, hyperlipidemia, malnutrition, metabolic acidosis, glucose intolerance, electrolyte imbalance — notably abnormalities in calcium and phosphorus, all leading to accelerated atherosclerosis.

In the 1960s in experimental animal models, acute uremia resulting from bilateral nephrectomies or bilateral ureteral ligations lead to myocardial calcification and coronary artery calcifications that were further aggravated by the addition of exogenous PTH. Parathyroidectomy either inhibited or altogether prevented calcium deposition. In humans, PTH excess exerts deleterious effects on myocardial metabolism and function. PTH augments the entry of calcium into myocardial cells, and chronic excess of this hormone leads to elevated basal levels of cytosolic calcium in many mammal cells including cardiac myocytes.[20] As such, a PTH-induced increase in calcium burden appears to play a role in myocardial calcification. Conversely, studies have shown high arterial calcification scores in patients with suppressed parathyroid hormone activity, which results in adynamic bone turnover that in turn leads to more free calcium available to deposit in the arteries.[21] However, the exact role of PTH excess in myocardial injury remains a matter of discussion.

Dyslipidemia and Vascular Injury in CKD

Abnormalities in calcium/phosphorus and parathyroid hormone appear to be independently associated with the activities of lipoprotein-regulating enzymes. Hypercalcemia, hyperphosphatemia, hyperparathyroidism, and hypovitaminosis D adversely affect the lipoprotein profile by inhibiting hepatic triglyceride lipase, which plays an important role in the metabolism of intermediate-density lipoprotein (IDL) and high-density lipoprotein (HDL). HDL is reduced in CKD patients, whereas IDL is elevated and is considered an independent risk factor for aortic sclerosis among these individuals. Replacing vitamin D3 when indicated may help suppress the uptake of modified lipoproteins by macrophages.[22]

Inflammatory Response and Vascular Injury in CKD Patients

Inflammation and oxidative stress are risk factors for atherosclerosis and are responsible for accelerated vascular injury among patients with CKD stage 3–5 compared to healthy subjects. Elevated C-reactive protein, fibrinogen levels, and advanced oxidation protein products predict cardiovascular complications in these individuals.[23, 24] These problems tend to worsen after patients begin dialysis as evidenced by increased fibrinogen levels during and after dialysis.[25] Also, an increment in interleukin-6 after dialysis has been directly associated with carotid atherosclerosis in these patients.[26] An association between coronary calcification score with lipid abnormalities and markers of chronic inflammation in dialysis-dependent CKD stage 5 patients has also been established.[27]

Another interesting association is that of malnutrition, inflammation, cachexia, and low lipid levels with cardiovascular mortality in CKD patients.[28] An example of this is periodontitis, a frequently overlooked source of chronic inflammation leading to hypoalbuminemia among CKD patients.[29] Aggressive treatment of this condition results in improved endothelial function.[30] Omega-3 fatty acids and statins have been shown to be safe and effective agents as antioxidants and cardioprotective.[31, 32] Removing sources of chronic inflammation such as periodontitis, clotted arteriovenous grafts, and at times a nonfunctioning transplanted kidney may need to be done to minimize endothelial dysfunction.

Conclusion

Hyperphosphatemia appears to be one of the most important metabolic abnormalities among CKD patients, resulting in a sequence of events leading to major cardiovascular morbidity and mortality. As such, early recognition and correction of this complication is imperative in preventing and slowing the progression of vascular injury, as is treatment of hypertension, hyperlipidemia, and hyperglycemia and cessation of smoking. For this reason, serum phosphorus levels should be measured as part of the routine blood work in patients with CKD. Avoidance of phosphorus-rich foods such as dairy products, dark carbonated colas, nuts, and processed meats is also important in preventing and treating hyperphosphatemia, although strict dietary restriction could result in protein malnutrition. The use of phosphate binders definitely plays a significant role in controlling hyperphosphatemia by preventing absorption of dietary phosphorus. At present there are several products available to achieve this goal, including calcium-based compounds, nonabsorbable polymers, magnesium-based compounds, and nicotinic acid (prodrug) and its active metabolite, niacin, which has lipid-lowering benefits as well. The latter exerts its beneficial effect by inhibiting sodium-phosphorus cotransport at the level of the brush border membrane vesicles of the duodenal and jejunal epithelial cells, whereas the other compounds trap phosphorus provided by food intake, resulting in stool phosphate excretion.

The latest recommendations by KDIGO (Kidney Disease International Global Outcomes) include maintaining levels of calcium between 8.6–10 mg/dL, phosphorus up to 4.5 mg/dL, and PTH between 120–600 pg/mL by utilizing vitamin D analogues (hormone D), calcimimetics agents, or at times parathyroid surgery. In patients with CKD stages 3–5 who are not on dialysis, the optimal PTH level is not known. However, continued increment of PTH levels above normal over time, most likely representing a maladaptive response, requires suppressive therapy rather than absolute values. Identifying and treating patients at risk for vascular injury is important in preventing morbidity and mortality in CKD patients.

References

1. Conger JD, Hammond WS, Alfrey AC, Contiguglia SR, Stanford RE, Huffer WE. Pulmonary calcification in chronic dialysis patients. Clinical and pathologic studies. Ann Intern Med. 1975 Sep;83(3):330-6.
2. Kim SJ, Goldstein M, Szabo T, Pierratos A. Resolution of massive uremic tumoral calcinosis with daily nocturnal home hemodialysis. Am J Kidney Dis. 2003 Mar;41(3):E12.
3. Hollick MF, Krane SM, Potts JT. Calcium, phosphorus and bone metabolism: calcium regulating hormones. In: Fauci AS, Braunwald E, Isselbacher KJ, Wilson JD, Martin JB, Kasper DL, et al., editors. Harrison's principles of internal medicine. 14th ed. New York: McGraw-Hill Companies, Inc.; 1998. p. 2214-27.
4. Slatopolsky E, Bricker NS. The role of phosphorus restriction in the prevention of secondary hyperparathyroidism in chronic renal disease. Kidney Int. 1973 Aug;4(2):141-5.
5. Portale AA, Halloran BP, Morris RC Jr. Physiologic regulation of the serum concentration of 1,25-dihydroxyvitamin D by phosphorus in normal men. J Clin Invest. 1989 May;83(5): 1494-9.
6. Lopez-Hilker S, Dusso AS, Rapp NS, Martin KJ, Slatopolsky E. Phosphorus restriction reverses hyperparathyroidism in uremia independent of calcium and calcitriol. Am J Physiol. 1990 Sep;259(3 Pt 2):F432-7.
7. Dhingra R, Sullivan LM, Fox CS, Wang TJ, D'Agostino RB Sr, Gaziano JM, et al. Relations of serum phosphorus and calcium levels to the incidence of cardiovascular disease in the community. Arch Intern Med. 2007 May 14;167(9):879-85.
8. Kalantar-Zadeh K, Shah A, Duong U, Hechter RC, Dukkipati R, Kovesdy CP. Kidney bone disease and mortality in CKD: revisiting the role of vitamin D, calcimimetics, alkaline phosphatase, and minerals. Kidney Int Suppl. 2010 Aug;(117):S10-21.
9. Reynolds JL, Joannides AJ, Skepper JN, McNair R, Schurgers LJ, Proudfoot D, et al. Human vascular smooth muscle cells undergo vesicle-mediated calcification in response to changes in extracellular calcium and phosphate concentrations: a potential mechanism for accelerated vascular calcification in ESRD. J Am Soc Nephrol. 2004 Nov;15(11):2857-67.
10. Amann K, Gross ML, London GM, Ritz E. Hyperphosphatemia — a silent killer of patients with renal failure? Nephrol Dial Transplant.1999;14:2085-7.
11. Kestenbaum B, Sampson JN, Rudser KD, Patterson DJ, Seliger SL, Young B, et al. Serum phosphate levels and mortality risk among people with chronic kidney disease. J Am Soc Nephrol. 2005 Feb;16(2):520-8.
12. Rodriguez-Benot A, Martin-Malo A, Alvarez-Lara MA, Rodriguez M, Aljama P. Mild hyperphosphatemia and mortality in hemodialysis patients. Am J Kidney Dis. 2005 Jul;46(1): 68-77.
13. Schwarz S, Trivedi BK, Kalantar-Zadeh K, Kovesdy CP. Association of disorders in mineral metabolism with progression of chronic kidney disease. Clin J Am Soc Nephrol. 2006 July;1(4):825-31.
14. Mathew S, Tustison KS, Sugatani T, Chaudhary LR, Rifas L, Hruska KA. The mechanism of phosphorus as a cardiovascular risk factor in CKD. J Am Soc Nephrol. 2008 Jun;19(6): 1092-105.
15. Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. Am J Kidney Dis. 1998 Apr;31(4):607-17.
16. Ketteler M, Gross ML, Ritz E. Calcification and cardiovascular problems in renal failure. Kidney Int Suppl. 2005 Apr;(94):S120-7.
17. Moe SM, Reslerova M, Ketteler M, O'Neill K, Duan D, Koczman J, et al. Role of calcification inhibitors in the pathogenesis of vascular calcification in chronic kidney disease (CKD). Kidney Int. 2005 Jun;67(6):2295-304.
18. Lomashvill KA, Cobbs S, Hennigar RA, Hardcastle KI, O'Neill WC. Phosphate-induced vascular calcification: role of pyrophosphate and osteopontin. J Am Soc Nephrol. 2004 Jun;15(6):1392-401.
19. Pertosa G, Simone S, Ciccone M, Porreca S, Zaza G, Dalfino G, et al. Serum fetuin a in hemodialysis: a link between derangement of calcium-phosphorus homeostasis and progression of atherosclerosis? Am J Kidney Dis. 2009 Mar;53(3):467-74.
20. Smogorzewski M, Massry SG. Uremic cardiomyopathy: role of parathyroid hormone. Kidney Int Suppl. 1997 Nov;62:S12-4.
21. London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. J Am Soc Nephrol. 2004 Jul;15(7):1943-51.
22. Nishizawa Y, Shoji T, Kawagishi T, Morii H. Atherosclerosis in uremia: possible roles of hyperparathyroidism and intermediate density lipoprotein accumulation. Kidney Int Suppl. 1997 Nov;62:S90-2.
23. Descamps-Latscha B, Witko-Sarsat V, Nguyen-Khoa T, Nguyen AT, Gausson V, Mothu N, et al. Advanced oxidation protein products as risk factors for atherosclerotic cardiovascular events in nondiabetic predialysis patients. Am J Kidney Dis. 2005 Jan;45(1):39-47.
24. Oberg BP, McMenamin E, Lucas FL, McMonagie E, Morrow J, Ikizler TA, et al. Increased prevalence of oxidant stress and inflammation in patients with moderate to severe chronic kidney disease. Kidney Int. 2004 Mar;65(3):1009-16.
25. Caglar K, Peng Y, Pupim LB, Flakoll PJ, Levenhagen D, Hakim RM, et al. Inflammatory signals associated with hemodialysis. Kidney Int. 2002 Oct;62(4):1408-16.
26. Kato A, Odamaki M, Takita T, Maruyama Y, Kumagai H, Hishida A. Association between interleukin-6 and carotid atherosclerosis in hemodialysis patients. Kidney Int. 2002 Mar;61(3):1143-52.
27. Goldsmith DJ, Covic A. Coronary artery disease in uremia: Etiology, diagnosis, and therapy. Kidney Int. 2001 Dec;60(6):2059-78.
28. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. Inverse association between lipid levels and mortality in men with chronic kidney disease who are not yet on dialysis: effects of case mix and the malnutrition-inflammation-cachexia syndrome. J Am Soc Nephrol. 2007 Jan;18(1):304-11.
29. Kshirsagar AV, Craig RG, Beck JD, Moss K, Offenbacher S, Kotanko P, et al. Severe periodontitis is associated with low serum albumin among patients on maintenance hemodialysis therapy. Clin J Am Soc Nephrol. 2007 Mar;2(2):239-44.
30. Tonetti MS, D'Aiuto F, Nibali L, Donald A, Storry C, Parkar M, et al. Treatment of periodontitis and endothelial function. N Engl J Med. 2007 Mar 1;356(9):911-20.
31. Svensson M, Schmidt EB, Jorgensen KA, Christensen JH; OPACH Study Group. N-3 fatty acids as secondary prevention against cardiovascular events in patients who undergo chronic hemodialysis: a randomized placebo-controlled intervention trial. Clin J Am Soc Nephrol. 2006 Jul;1(4):780-6.
32. Blanco-Colio LM, Tuñón J, Martin-Ventura JL, Egido J. Anti-inflammatory and immunomodulatory effects of statins. Kidney Int. 2003 Jan;63(1):12-23.