Bone and Vascular Health and the Kidney

Jorge B. Cannata-Andía MD PhD, Pablo Román García BsC,
Ivan Cabezas-Rodriguez MD, M Rodríguez-García MD PhD.

Bone and Mineral Research Unit. Hospital Universitario Central de Asturias. Instituto Reina Sofía de Investigación. REDinREN del ISCIII. Universidad de Oviedo. Oviedo, Asturias, Spain.

Corresponding author:

Professor Jorge B. Cannata-Andía, Bone and Mineral Research Unit

Instituto Reina Sofía de Investigación, Hospital Universitario Central de Asturias

C/ Julián Clavería s/n, 33006 Oviedo, Asturias, Spain

Phone: +34 985106137, Fax: +34 985106142

E-mail: metoseo@hca.es

Key Words

Bone, Vascular calcification, Osteoporosis, Bone density, Bone Fractures, Low Bone Mass, Bone Disease, CKD-MBD

Ruuning title

Bone-Vascular axis

Con formato: Derecha: 0,63 cm

Abstract

In patients with progressive chronic kidney disease (CKD), the homeostatic mechanisms regulating calcium and phosphate metabolism suffer important changes resulting in low serum levels of calcitriol and calcium and phosphorous retention. The regulatory mechanisms fail and several chronic kidney disease mineral bone disorders (CKD-MBD) occur, including bone disease, vascular calcifications, cardiovascular disorders, bone fragility fractures and reduced survival.

Vascular calcification, bone loss and increased fracture risk are severe disorders associated with ageing in chronic CKD, but also generally speaking. Several epidemiological studies have shown the relationship between impaired bone metabolism, vascular calcification and increased mortality. Recent data suggest this association may be not just a consequence of ageing; the common occurrence of severe cases of vascular calcifications together with low bone activity and osteoporosis suggests there might be some direct biological links between the bone and the vascular systems. New challenging experimental data suggest that once the severe vascular calcification appears, vessels may develop a mechanism to diminish the vascular mineralization in the artery wall, this defensive mechanism may have a negative impact favouring the reduction of bone mass.

Con formato: Derecha: 0,63 cm

Introduction

In healthy individuals, the kidneys regulate calcium and phosphorus homeostasis through active tubular mechanisms. Hormones and factors that contribute to kidney regulation of calcium and phosphorus include 1,25-dihydroxyvitamin D (1,25$[OH]_2$D or calcitriol), parathyroid hormone (PTH) and fibroblast growth factor-23 (FGF-23). In patients with progressive chronic kidney disease (CKD), the normal homeostatic mechanisms are challenged, leading to important compensatory changes in serum levels of calcium, phosphorus, calcitriol, FGF-23 and PTH. All these changes lead in part to several manifestations that for almost 60 years have been known as "renal osteodystrophy" (1). In addition, clinical, epidemiological and experimental data have identified a clear association between the above mentioned changes in biochemical markers and some relevant outcomes such as vascular calcification, myocardial dysfunction and mortality. As a result, a new term, -CKD–mineral bone disorder (CKD-MBD)-, has been recently coined to encompass all these disorders (2).

Clinical Impact and Pathogenesis of Mineral and Bone Disorders

The calcium, phosphorus, Vitamin D, PTH and FGF23 axis is closely regulated and interrelated. Several of the compensatory variations in the above mentioned factors take place at the same time under the control of complex feedback mechanisms (3-5). The progression of CKD leads to a decrease of active renal mass and then to a reduction of 1-alpha hydroxylase in the kidney, which in turn results in low levels of calcitriol, the physiological active form of vitamin D, impairing calcium absorption in the intestine and favouring the reduction in serum calcium. As a result, the decreases in serum calcium stimulate parathyroid hormone (PTH) synthesis and release, increasing bone turnover, bone resorption and the stimulation of 1-alpha hydroxylase. All these mechanisms lead to compensatory increases in serum calcium.

Con formato: Derecha: 0,63 cm

In addition, the progressive reduction of the renal function impairs phosphorous excretion, leading to increases in serum phosphorous which stimulates the synthesis of both FGF23 and PTH. Thee two factors work in the same direction increasing urinary phosphorous excretion. However, it is important to stress that, regarding vitamin D metabolism, the response is more complex and FGF23 and PTH work in opposite directions, regarding calcitriol synthesis FGF23 inhibits 1-alpha hydroxylase reducing calcitriol synthesis, whereas PTH stimulates it (6-8). As the renal function decreases, all these complex and tightly interrelated mechanisms of parathyroid gland regulation result insufficient and fail to adequately control the parathyroid gland function and the calcium and phosphorous homeostasis.

As a result, low serum levels of calcitriol and calcium coupled with a trend towards phosphorous retention become the current picture in the more advanced stages of CKD (3-5). Furthermore, in CKD stage 5D, severe forms of secondary hyperparathyroidism are frequently found with diffuse and nodular parathyroid hyperplasia, as well as clinically relevant monoclonal growth with reduction in the expression of the vitamin D and Calcium-sensing receptors (VDR and CaSR) (9-11). These changes are the main culprits for the poor response of the parathyroid glands to the increments of serum calcium and the active vitamin D therapy. Finally, due to the lack of adequate parathyroid gland control, there is a clear trend towards autonomous parathyroid gland behaviour (tertiary hyperparathyroidism) which frequently requires surgical intervention.

Many of the above mentioned abnormalities and others beyond the scope of this review end up not only inducing several forms of bone disease, but also vascular calcifications, cardiovascular disorders, bone fragility fractures and a greater risk of mortality. The recently coined term CKD-MBD, encompasses all these mineral and bone metabolism disorders (2, 12). As CKD is subdivided according to the degree of renal function into five stages, it is important to stress that marked differences exist between the initial and final periods of CKD.

Con formato: Derecha: 0,63 cm

Clinical Impact and Pathogenesis of Vascular Calcification

The predisposition of CKD patients towards the development of vascular calcifications was mentioned for the first time in the 19th century; since then, many studies have analysed this subject. Vascular calcification can be classified in three types according to the size and structure of the arteries: elastic or large-calibre arteries, muscular or medium-calibre arteries, and small calibre arteries (13).

Elastic or large-calibre arteries show a relatively thin wall in proportion to their diameter and the tunica media contains more elastic fibres than smooth muscle fibres. Muscular or medium calibre arteries contain a greater proportion of smooth muscle fibres than elastic fibres in the tunica media; finally, the small calibre arteries contain only smooth muscle fibres in the tunica media. The classical description of arterial calcification specifies it may occur in two locations: the intimae and the media layers (14). Nevertheless, this classical concept is not fully accepted by all authors (15-16) .

Intimae calcification begins and progresses under the influence of both genetic and lifestyle-related circumstances. It is associated with a sequence of atherosclerotic events such as endothelial dysfunction, intimae oedema, lipid cell formation, plaque rupture, and formation of the thrombus (17). They show a patchy distribution along the length of the artery and they are the cause of local stenos and occlusions. They are associated to several risk factors such as inflammation, alterations in lipid metabolism, obesity, hypertension, diabetes, smoking and a family history of heart disease.

Media calcification occurs in the elastic lamina of large-calibre and medium-small size arteries; it can be independent of atherosclerosis, but it can be associated with it. Using X rays they are seen as railroads; they are commonly found in the aorta but they also appear in arteries that are less likely to develop atherosclerosis, such as the visceral, abdominal, limb and femoral arteries (18). Calcification of the media increases linearly with age and it

Código de campo cambiado

Con formato: Derecha: 0,63 cm

is frequently found in CKD, vitamin D metabolism disturbances, and diabetes, among other scenarios (19-22).

Table 1 summarizes the most prevalent traditional, uraemia-related and non-traditional risk factors for vascular calcification in CKD patients. Like in the general population, the traditional cardiovascular risk factors, present in a large proportion of patients with CKD, are responsible to a great extent for the progression of vascular calcifications. Among them non-traditional cardiovascular risk factors, including uraemia-related risk factors, time on dialysis and hyperphosphatemia, are the risk factors more strongly associated with increased vascular calcifications and mortality. Elevated CRP and IL-6, as expressions of chronic inflammations, have been also frequently associated with vascular calcifications (17).

CKD is associated with a high prevalence of vascular calcifications (18, 22-25), which lead to a high prevalence of cardiovascular disease, and reduced life expectancy (26). The high prevalence of vascular calcifications has been also reported in early stages of CKD where it has been shown that 40% of patients (CKD stages 2-4, mean GFR of 33 ml/min) showed calcification of the coronary arteries compared with a 13% of control subjects (similar age with normal renal function (24)]). However, vascular calcification is not only seen in CKD patients; A subgroup of randomly selected European population older than 50 years (Vertebral Osteoporosis Study [EVOS]) showed aortic calcification in 54.2% of men and 43.1% of women (20).

In a recent study, the prevalence of aortic calcification was higher in HD patients (79%) than in a random-based and age-matched general population (37.5%) (22). Time on renal replacement therapy has been also positively associated with vascular calcification, mainly in medium calibre arteries; in fact, each year on renal replacement therapy increased the risk of vascular calcifications by 15% (27). In addition, the number and severity of vascular calcifications have been positively associated with mortality, both in general

Con formato: Derecha: 0,63 cm

population and in CKD patients (20, 22, 26). In CKD, it has been reported up to between 10 to 30 times higher mortality than in the general population (28) . Women on HD showed an increased risk of severe aortic calcifications compared with women from the general population, probably due to a combination of atherosclerosis and arteriosclerosis (22).

Until recently, vascular calcification was considered the result of a simple precipitation of the circulating calcium and phosphate. However, the mechanism by which the process of vascular calcification is produced is complex; it does not consist in a simple precipitation of calcium and phosphate; on the contrary, it is an active and regulated process in which, step by step, vascular smooth cells undergo apoptosis and vesicle formation changing the phenotype of smooth vascular cells into osteoblast like-cells. Vascular calcification can be considered as the result of the lack of the current equilibrium between the promoters and inhibitors of the calcification process, in which several uraemic factors - phosphorus on the top of the list-, play a key role.

In humans and mammals, serum concentrations of calcium and phosphate exceed the calcium-phosphate solubility product; however, intra-vessel precipitation does not take place. This fact has stressed the important role played by physiological inhibitors of the calcification, which counterbalance the well-known effect of calcification promoters. The list of promoters and inhibitors of the calcification process has increased in recent years (29-32). The main interest has been put on the “modifiable promoters of calcification” with the aim to develop strategies to minimize them. Some have been associated to the risk of mortality, such as phosphorus, calcium, vitamin D, PTH, dyslipidaemia, inflammation, nutrition, CRP, homocystein, fibrinogen and albumin. Among them, serum phosphorus needs to be highlighted as one of the more important risk factors which has been strongly associated with increased vascular calcifications and mortality (29-34).

Today, the fact that high phosphorus is a key factor in the differentiation of smooth vascular cells into osteoblasts-like cells triggering signals which will end promoting

Con formato: Derecha: 0,63 cm

mineralization is well accepted (30, 32, 35) *In vitro* experiments have demonstrated that high phosphorus levels act directly on the transcription of bone-related genes, such as Cbfa-1 and osteocalcin, resulting in the activation of several osteogenic pathways (35-36). In addition, phosphorus is capable of acting as a secondary intracellular messenger activating several molecular pathways involved in bone formation. Other important factors from this list of promoters such as the BMPs (bone morphogenic proteins), an important family of proteins involved in bone formation and vascular calcifications; Cbfa-1, BMP-Msx-Wnt axis, vitamin D, calcium, phosphorus, TNF alpha, oxidative stress, matrix GLA protein (MGP), osteoprotegerin (OPG), fetuin A, pyrophosphates and bisphosphonates are among the more studied mineralization promoters and inhibitors (13, 29-31, 36-37).

Links between Bone Metabolism and Vascular Calcification

Bone loss, increased fracture risk and vascular calcification are severe disorders associated with ageing in chronic kidney disease (CKD) patients and the general population (19-20, 22, 38). Furthermore, several epidemiological studies suggest a relationship between impaired bone metabolism, vascular calcification and increased mortality.

The pathogenetic factors linking bone fragility with vascular calcification are not fully understood, but this relationship has been known for almost 20 years, since for the first time a significant inverse correlation between osteoporosis and aortic calcification was reported (39). However, during the following years, this association was probably underestimated because osteoporosis and vascular calcification were considered non-modifiable age-dependent disorders. Nevertheless, recent data suggest this association may not be just a consequence of ageing (20, 22). The role of ageing cannot be completely dismissed, but the clinical coincidence of vascular calcifications with low bone activity and osteoporosis suggests there might be direct biological links between arteriosclerosis and osteoporosis. In fact, osteoporosis and vascular calcifications are influenced by several

Con formato: Derecha: 0,63 cm

common risk factors such as inflammation, dyslipidemia, oxidative stress, and oestrogen, vitamin D and K deficiencies.

Some population-based longitudinal studies have demonstrated an association between osteoporosis and vascular calcification or arterial stiffness (25). A study with a large cohort published in 2004 showed that the degree of vascular calcification inversely correlated with bone mineral density. Furthermore, in part of the same cohort followed up for 2 years, the progression of vascular calcification inversely correlated with the rate of bone loss (40).

In agreement with previous results, a recent study showed that after 4 years of follow-up, individuals who showed the most severe vascular calcification or the greatest progression of vascular calcification were those who showed not only the lowest bone mass, but also the highest incidence of new osteoporotic fractures (20). In addition, as expected,, bone mass decreased and non-traumatic vertebral fractures increased in both sexes as age increased. Also, serum levels of 25(OH)D_3 inversely correlated with vascular calcification and bone mass, and positively correlated with the prevalence of secondary hyperparathyroidism and non-traumatic vertebral fractures.

The progression of aortic vascular calcifications (new calcifications or increase in the size of pre-existing calcifications) were significantly higher in patients who had a previous aortic calcification regardless of severity (mild, moderate, severe; $p< 0.001$, age-adjusted). Interestingly, after 4 years of follow-up, mortality was also significantly and positively associated with the rate of severe vascular calcifications in men and with the rate of non-traumatic bone fractures in women (20).

Similar results have been also published about patients on haemodialysis, which showed that vascular calcification in some areas (e.g., the large and medium calibre arteries [utero-sperm], femoral, iliac; hands [digital, palm arch, radial]), was associated with an increased risk of vertebral fractures (22). In addition, comparing the data from haemodialysis patients with the EVOS study (age- and sex-matched population), the risk of

Con formato: Derecha: 0,63 cm

aortic calcifications was significantly higher in haemodialysis patients (men: OR:7.7: women: OR:9.0). In addition, women on haemodialysis with severe vascular calcifications (any localisation), and also women with vertebral fractures showed a high mortality risk after all adjustments including age (Figure 1). Similarly, women who died during the 2-year follow-up period had a prevalence of vertebral fractures 3 times higher (58.8 vs. 19.3%) than those women who were alive at the end of the observation period (adjusted for the same variables) (Figure 2).

Age and diabetes were strongly associated with vascular calcifications but other well-know modifiable risk factors such as serum PTH, Ca and P levels, vitamin D, calcium-based phosphate binders intake, dyslipidaemia, hypertension, and smoking were not associated with the prevalence, severity or progression of the vascular calcifications.

If we combine the clinic and epidemiologic data, the association between serum 25(OH)D3 levels, vascular calcifications, bone mass and non-traumatic bone fractures, we may speculate that all of them might be linked by reasons which are beyond ageing (20, 25-26, 41).

The relationship between vascular calcification and low bone turnover has been also assessed by histomorphometry in haemodialysis patients (25). A negative relationship between low bone turnover and the degree of vascular calcification has been found (41-43). An inverse relationship between coronary calcification and vascular stiffness with mineralized bone volume has been recently published (42). Nevertheless, despite all these evidences, the relationship between low bone turnover and vascular calcification is still a matter of debate. A recent publication found that vascular calcification was not influenced by bone turnover when a multivariate analysis was performed (43), even though a great percentage of patients with high bone turnover were included in this study. It is known that high PTH concentration, is another important pathogenetic factor positively associated with vascular calcification. In fact, it has been reported that the correction of the balance in bone turnover, either high or low bone turnover, protects against the progression of vascular

Con formato: Derecha: 0,63 cm

calcification (44). In any case, overall, the sum of the epidemiological and clinical studies strongly suggests that the prevalence and progression of vascular calcification are related to bone mass, bone turnover and mineralization, bone loss and osteoporotic fragility fractures.

Likely Negative Effect of Vascular Calcification on Bone Health: A Challenging Hypothesis for Further Research

An intriguing question is whether the presence of vascular calcification can have a further negative impact on bone metabolism. In a recent study, rats that developed severe vascular calcification after a phosphorus load showed no increase of bone mass at any of the sites studied after 20 weeks (34) . In contrast, rats with no phosphorus load did not develop vascular calcification. In addition, bone mass increased during the study period as expected. The microarray analysis of the aortas with severe vascular calcification showed over-expression of the secreted frizzled-related protein (SFRPs) family. It is well-known that SFRPs are inhibitors of the canonical Wnt signalling pathway, which is actively involved in bone formation and vascular calcification (34, 45-46).

The increase of SFRPs proteins in areas of severe vascular calcification may be indicative of a wall artery defensive mechanism triggered in order to block the activation of the Wnt pathway with the aim to attenuate mineralization in the calcified aortic wall. Since SFRPs are secreted proteins, they can act not only locally on the artery wall trying to reduce the mineralization; oSFRPs might be able to reach the bone, where they could act as in the vessels, trying to decrease mineralization resulting in reduction of bone mass. This is a challenging feedback hypothesis that might help to explain the results observed in the clinical and epidemiological studies discussed above, in which the most severe cases of progressive vascular calcification were associated to low bone mass and a greater percentage of bone fractures.

Con formato: Derecha: 0,63 cm

In summary, in both the general and CKD populations, vascular calcification and its severity seems to be inversely related to bone mass, increasing bone fractures. In addition, the increase of vascular calcification and bone fractures are associated to a reduced survival. Interestingly, once vascular calcification appears and progresses, arteries may develop a defensive mechanism with the aim to attenuate or regress the vascular mineralization at the artery wall, which in turn can exert a negative impact on bone health.

Con formato: Derecha: 0,63 cm

Acknowledgements.

Part of the works presented in this review were supported by Fondo de Investigaciones Sanitarias (FIS 04/1567, 07/0893 and 08/90136), Fundación para el Fomento en Asturias de la Investigación Científica aplicada Y Técnica (FICYT I30P06P and IB 05-060), Instituto de Salud Carlos III (Retic-RD06), Red Investigación Renal (16/06), Fondo de Desarrollo Regional (FEDER), Instituto Reina Sofía de Investigación and Fundación Renal Íñigo Álvarez de Toledo.

We also thank Marino Santirso for the lenguaje review.

Pablo Román-García is supported by Fundación para el Fomento en Asturias de la Investigación Científica aplicada Y Técnica (FICYT), Spain. Iván Cabezas-Rodriguez is supported by the Rio Hortega programme, Instituto de Salud Carlos III, Spain.

Con formato: Derecha: 0,63 cm

References

1. Cannata-Andia JB. Changing the current terminology in medicine--always a challenge. Nephrol Dial Transplant. 2007 Jul;22(7):1811-2.
2. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). Kidney Int. 2006 Jun;69(11):1945-53.
3. Slatopolsky E. The role of calcium, phosphorus and vitamin D metabolism in the development of secondary hyperparathyroidism. Nephrol Dial Transplant. 1998;13 Suppl 3:3-8.
4. Silver J, Levi R. Regulation of PTH synthesis and secretion relevant to the management of secondary hyperparathyroidism in chronic kidney disease. Kidney Int Suppl. 2005 Jun(95):S8-12.
5. Carrillo-Lopez N, Roman-Garcia P, Fernandez-Martin JL, Cannata-Andía JB. Parathyroid gland regulation: contribution of the in vivo and in vitro models. Expert Opinion on Drug Discovery. 2010;(in press).
6. Shimada T, Kakitani M, Yamazaki Y, Hasegawa H, Takeuchi Y, Fujita T, et al. Targeted ablation of Fgf23 demonstrates an essential physiological role of FGF23 in phosphate and vitamin D metabolism. J Clin Invest. 2004 Feb;113(4):561-8.
7. Quarles LD. Endocrine functions of bone in mineral metabolism regulation. J Clin Invest. 2008 Dec;118(12):3820-8.
8. Carrillo-Lopez N, Roman-Garcia P, Rodriguez-Rebollar A, Fernandez-Martin JL, Naves-Diaz M, Cannata-Andia JB. Indirect regulation of PTH by estrogens may require FGF23. J Am Soc Nephrol. 2009 Sep;20(9):2009-17.
9. Imanishi Y, Tahara H, Palanisamy N, Spitalny S, Salusky IB, Goodman W, et al. Clonal chromosomal defects in the molecular pathogenesis of refractory hyperparathyroidism of uremia. J Am Soc Nephrol. 2002 Jun;13(6):1490-8.
10. Afonso S, Santamaria I, Guinsburg ME, Gomez AO, Miranda JL, Jofre R, et al. Chromosomal aberrations, the consequence of refractory hyperparathyroidism: its relationship with biochemical parameters. Kidney Int Suppl. 2003 Jun(85):S32-8.
11. Santamaria I, Alvarez-Hernandez D, Jofre R, Polo JR, Menarguez J, Cannata-Andia JB. Progression of secondary hyperparathyroidism involves deregulation of genes related to DNA and RNA stability. Kidney Int. 2005 Jun;67(6):2267-79.
12. Introduction and definition of CKD-MBD and the development of the guideline statements. Kidney Int Suppl. 2009;76(113):S3-S8.
13. Román-García P, Rodríguez García M, Cabezas-Rodríguez I, López-Ongil S, Díaz-López JB, Cannata-Andía JB. Vascular calcification: Pathogenesis, Epidemiology and clinical impact. Med Prin Pract 2010 (in press).
14. Amann K. Media calcification and intima calcification are distinct entities in chronic kidney disease. Clin J Am Soc Nephrol. 2008 Nov;3(6):1599-605.
15. Micheletti RG, Fishbein GA, Currier JS, Singer EJ, Fishbein MC. Calcification of the internal elastic lamina of coronary arteries. Mod Pathol. 2008 Aug;21(8):1019-28.
16. McCullough PA, Agrawal V, Danielewicz E, Abela GS. Accelerated atherosclerotic calcification and Monckeberg's sclerosis: a continuum of advanced vascular pathology in chronic kidney disease. Clin J Am Soc Nephrol. 2008 Nov;3(6):1585-98.
17. Ross R. Atherosclerosis is an inflammatory disease. American heart journal. 1999 Nov;138(5 Pt 2):S419-20.
18. Blacher J, Guerin AP, Pannier B, Marchais SJ, London GM. Arterial calcifications, arterial stiffness, and cardiovascular risk in end-stage renal disease. Hypertension. 2001 Oct;38(4):938-42.

Con formato: Derecha: 0,63 cm

19. Cannata-Andia JB, Rodriguez-Garcia M, Carrillo-Lopez N, Naves-Diaz M, Diaz-Lopez B. Vascular calcifications: pathogenesis, management, and impact on clinical outcomes. J Am Soc Nephrol. 2006 Dec;17(12 Suppl 3):S267-73.
20. Naves M, Rodriguez-Garcia M, Diaz-Lopez JB, Gomez-Alonso C, Cannata-Andia JB. Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. Osteoporos Int. 2008 Aug;19(8):1161-6.
21. Rodriguez Garcia M, Naves Diaz M, Cannata Andia JB. Bone metabolism, vascular calcifications and mortality: associations beyond mere coincidence. J Nephrol. 2005 Jul-Aug;18(4):458-63.
22. Rodriguez-Garcia M, Gomez-Alonso C, Naves-Diaz M, Diaz-Lopez JB, Diaz-Corte C, Cannata-Andia JB. Vascular calcifications, vertebral fractures and mortality in haemodialysis patients. Nephrol Dial Transplant. 2008 Aug 25.
23. Goodman WG, Goldin J, Kuizon BD, Yoon C, Gales B, Sider D, et al. Coronary-artery calcification in young adults with end-stage renal disease who are undergoing dialysis. N Engl J Med. 2000 May 18;342(20):1478-83.
24. Russo D, Palmiero G, De Blasio AP, Balletta MM, Andreucci VE. Coronary artery calcification in patients with CRF not undergoing dialysis. Am J Kidney Dis. 2004 Dec;44(6):1024-30.
25. 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.
26. Matias PJ, Ferreira C, Jorge C, Borges M, Aires I, Amaral T, et al. 25-Hydroxyvitamin D3, arterial calcifications and cardiovascular risk markers in haemodialysis patients. Nephrol Dial Transplant. 2009 Feb;24(2):611-8.
27. Yuen D, Pierratos A, Richardson RM, Chan CT. The natural history of coronary calcification progression in a cohort of nocturnal haemodialysis patients. Nephrol Dial Transplant. 2006 May;21(5):1407-12.
28. Foley RN, Parfrey PS, Harnett JD, Kent GM, Martin CJ, Murray DC, et al. Clinical and echocardiographic disease in patients starting end-stage renal disease therapy. Kidney Int. 1995 Jan;47(1):186-92.
29. Schoppet M, Shroff RC, Hofbauer LC, Shanahan CM. Exploring the biology of vascular calcification in chronic kidney disease: what's circulating? Kidney Int. 2008 Feb;73(4):384-90.
30. 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.
31. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol. 2008 Feb;19(2):213-6.
32. Giachelli CM. Vascular calcification mechanisms. J Am Soc Nephrol. 2004 Dec;15(12):2959-64.
33. Block GA, Klassen PS, Lazarus JM, Ofsthun N, Lowrie EG, Chertow GM. Mineral metabolism, mortality, and morbidity in maintenance hemodialysis. J Am Soc Nephrol. 2004 Aug;15(8):2208-18.
34. Roman-Garcia P, Carrillo-Lopez N, Fernandez-Martin JL, Naves-Diaz M, Ruiz-Torres MP, Cannata-Andia JB. High phosphorus diet induces vascular calcification, a related decrease in bone mass and changes in the aortic gene expression. Bone. 2009 Sep 17.
35. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. Circ Res. 2004 Sep 17;95(6):560-7.
36. Jono S, McKee MD, Murry CE, Shioi A, Nishizawa Y, Mori K, et al. Phosphate regulation of vascular smooth muscle cell calcification. Circ Res. 2000 Sep 29;87(7):E10-7.

Con formato: Derecha: 0,63 cm

37. Hruska KA, Mathew S, Saab G. Bone morphogenetic proteins in vascular calcification. Circ Res. 2005 Jul 22;97(2):105-14.
38. Goldsmith D, Ritz E, Covic A. Vascular calcification: a stiff challenge for the nephrologist: does preventing bone disease cause arterial disease? Kidney Int. 2004 Oct;66(4):1315-33.
39. Frye MA, Melton LJ, 3rd, Bryant SC, Fitzpatrick LA, Wahner HW, Schwartz RS, et al. Osteoporosis and calcification of the aorta. Bone Miner. 1992 Nov;19(2):185-94.
40. Schulz E, Arfai K, Liu X, Sayre J, Gilsanz V. Aortic calcification and the risk of osteoporosis and fractures. J Clin Endocrinol Metab. 2004 Sep;89(9):4246-53.
41. London GM, Marchais SJ, Guerin AP, Boutouyrie P, Metivier F, de Vernejoul MC. Association of bone activity, calcium load, aortic stiffness, and calcifications in ESRD. J Am Soc Nephrol. 2008 Sep;19(9):1827-35.
42. Adragao T, Herberth J, Monier-Faugere MC, Branscum AJ, Ferreira A, Frazao JM, et al. Low bone volume--a risk factor for coronary calcifications in hemodialysis patients. Clin J Am Soc Nephrol. 2009 Feb;4(2):450-5.
43. Coen G, Ballanti P, Mantella D, Manni M, Lippi B, Pierantozzi A, et al. Bone turnover, osteopenia and vascular calcifications in hemodialysis patients. A histomorphometric and multislice CT study. Am J Nephrol. 2009;29(3):145-52.
44. Barreto DV, Barreto Fde C, Carvalho AB, Cuppari L, Draibe SA, Dalboni MA, et al. Association of changes in bone remodeling and coronary calcification in hemodialysis patients: a prospective study. Am J Kidney Dis. 2008 Dec;52(6):1139-50.
45. Al-Aly Z, Shao JS, Lai CF, Huang E, Cai J, Behrmann A, et al. Aortic Msx2-Wnt calcification cascade is regulated by TNF-alpha-dependent signals in diabetic Ldlr-/- mice. Arterioscler Thromb Vasc Biol. 2007 Dec;27(12):2589-96.
46. Towler DA, Shao JS, Cheng SL, Pingsterhaus JM, Loewy AP. Osteogenic regulation of vascular calcification. Ann N Y Acad Sci. 2006 Apr;1068:327-33.

Con formato: Derecha: 0,63 cm

Table 1.

Risk factors associated to vascular calcification in CKD patients. *Reproduced with permission of the original authors.(reference 13)*

Traditional risk factors

- Hypertension
- Dyslipidemia
- Diabetes mellitus
- Smoking
- Older age
- Family history of premature coronary heart disease

Uraemia-related and non-traditional risk factors

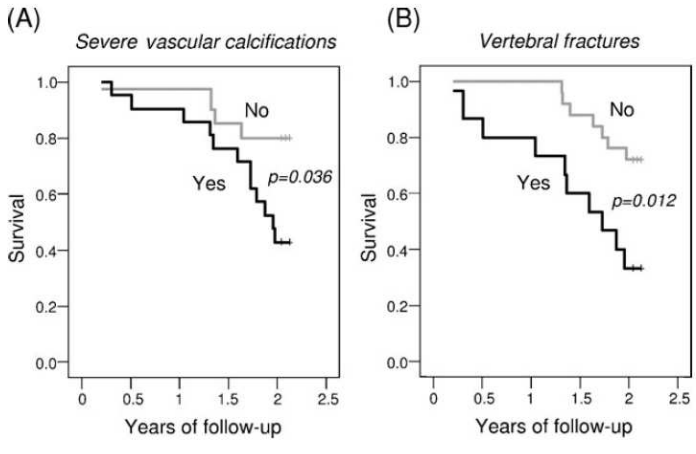
- Time on dialysis
- Hyperphosphatemia
- High Calcium-phosphorus product
- Hyperparathyroidism and hypoparathyroidism
- High dosage of vitamin D metabolites
- Low fetuin-A
- Anaemia
- Poor nutrition (low albumin)
- Chronic Inflammation (CRP, IL-1, IL-6, TNFα)*
- Hyperhomocysteinemia
- Advanced glycated end products

* CRP: C reactive protein; IL-1 : interleukin 1 ; IL-6 : interleukin 6 ; TNFα : tumoral necrosis factor α.

Con formato: Derecha: 0,63 cm

Figure 1

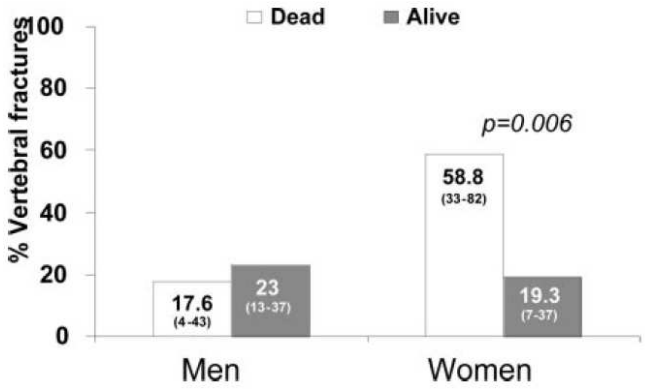
Kaplan meyer analysis in women (A) with prevalent severe vascular calcifications at any vascular site, (B) with prevalent vertebral fractures. *Reproduced with permission of the original authors.(reference 22)*



Con formato: Derecha: 0,63 cm

Figure 2

Effect of vertebral fractures on the risk for mortality in men and women who were on hemodialysis after a two-year follow-up period. *Reproduced with permission of the original authors.(reference 19)*



Con formato: Derecha: 0,63 cm