REVIEW ARTICLE

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Is there a link between bone and vessel in dialysis patients?

Teresa Adragão

Department of Nephrology, Hospital de Santa Cruz. Carnaxide, Portugal.

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INTRODUCTION

Haemodialysis patients are at a very high cardiovascular risk not explained by traditional risk factors[1,2]. Conventional treatment which reduces cardiovascular risk in the general population may not be effective in dialysis patients, as shown in the 4D trial which compared atorvastatin with placebo in a group of diabetic patients on haemodialysis[3]. Atorvastatin as compared with placebo did not reduce the primary composite endpoint which included cardiovascular death or non fatal acute myocardial infarction or stroke.

These results may be partially explained by the characteristics of cardiovascular death observed in dialysis patients. Cardiovascular death is the main cause of death in dialysis patients and accounts for 48% of all deaths in dialysis patients in the USA, as shown by USRDS annual report[4]. This report states that sudden death is the main cause of cardiovascular death, responsible for 27% of all deaths, while atherosclerosis and acute myocardial infarction, situations in which statin administration is recommended, accounts for only 11% of all deaths[4].

Another possible explanation for the ineffectiveness of statins observed in the 4D trial is the type of vascular calcification that haemodialysis patients develop. Vascular calcification is another factor associated with cardiovascular mortality in dialysis patients and can onset in two different clinical situations with different treatment options[5]. There are two types of vascular calcifications: intimal and medial calcification. Intimal calcification is associated with atherosclerosis and is related to altered lipid metabolism. Medial calcification is associated with arteriolosclerosis and in chronic kidney disease (CKD) patients is associated with altered mineral metabolism[6], in a clinical setting where statins are probably not operative.

The main manifestations of intimal calcification are the result of the formation of atherosclerotic plaques with stenotic lesions and ischaemia. Medial calcification does not cause obstructive lesions but modifies the properties of the arterial wall and increases arterial stiffness. Arterial stiffness causes an increase in pulse pressure and pulse wave velocity, alterations associated with the development of left ventricular hypertrophy and decrease in coronary perfusion during diastole and which may cause myocardial ischaemia, even in the absence of stenotic lesions.

It has been demonstrated that vascular calcification in dialysis and non-dialysis patients is an active cellular process, similar to bone formation[7-9]. Vascular smooth muscle cells can differentiate into osteoblasts with different stimuli, which, in dialysis patients, may be hyperphosphataemia and hypercalcaemia[8]. Reduction of calcification inhibitors, such as fetuin-A or matrix-Gla protein, may be another factor associated with the development of calcification[10]. CKD patients experience two distinct situations associated with an increase in Ca and P levels: hyperparathyroidism, with high bone turnover where the bone itself is the source of the high levels of Ca and P and adynamic bone disease with low bone turnover. Here the bone behaves as a "frozen bone" and it is not able to capture the Ca and P that the patient receives in food or with treatment.

EVALUATION OF VASCULAR CALCIFICATIONS

KDIGO has recommended a new classification for chronic kidney disease mineral and bone disorder (CKD MBD) which for the first time includes evaluation of vascular calcifications[11]. In haemodialysis patients vascular calcifications can be evaluated by different techniques: electron beam computed tomography (EBCT)[12], multislice computed tomography (MSCT)[13], ultrasonography[5] and plain X-ray[6,14,15]. EBCT and MSCT allow a quantitative measurement and are considered the gold standard for evaluating vascular calcification but are very expensive. The use of plain X-ray for screening vascular calcifications has been suggested by KDOQI[16] and KDIGO[11]. We have developed a vascular calcification score evaluated by plain X-ray of hands and pelvis which is a predictor of cardiovascular death and cardiovascular morbidity in dialysis patients[14] (Fig. 1). This simple vascular calcification score has also been correlated with valvular calcifications[17] and arterial stiffness[18].

Plain X-ray and ultrasonography are semi-quantitative, less expensive and useful for screening for vascular calcifications. They can be used to identify patients at higher risk of a cardiovascular event. EBCT and MSCT are useful for evaluating the progression of vascular calcification and the effect of different treatments on vascular calcification progression. These two techniques do not differentiate intimal from medial calcification and the explanation for the very high scores evaluated in dialysis patients is the presence of both intimal and medial calcification.

VASCULAR CALCIFICATIONS AND HISTOMORPHOMETRIC ANALYSIS OF BONE BIOPSIES

London *et al.*[19] demonstrated an association between vascular calcifications and low bone turnover in a study evaluating 58 haemodialysis patients. 23 of these had undergone parathyroidectomy and 33 had aluminium deposits in bone. Vascular calcifications were evaluated by ultrasonography. More calcifications were associated with lower osteoblasts surface and with other

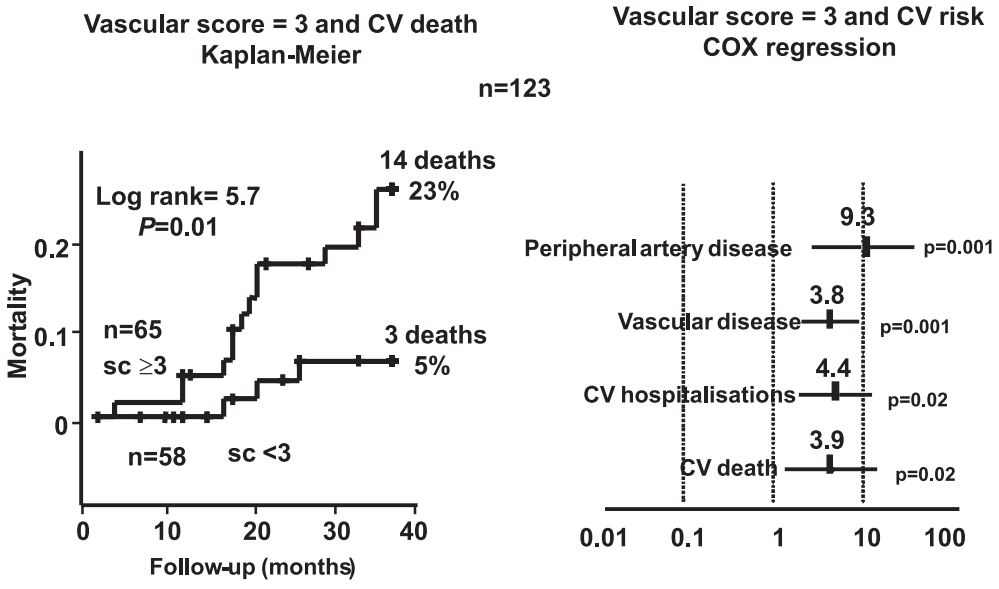


Figure 1

Results after 3 years' follow-up*

*Adragao T, Pires A, Lucas C. et al. Nephrol Dial Transplant 2004;19:1480–8

markers of low bone turnover, with lower PTH levels and with higher calcium dose. In a group of 42 Portuguese haemodialysis patients who underwent bone biopsy[20] we verified that low bone volume was associated with vascular calcifications evaluated by MSCT (Fig. 2) or by plain X-ray and with higher pulse wave velocity. Adynamic bone disease was present in 50% of patients. There were no cases of osteomalacia and no aluminium deposits in bone.

Gulay *et al*. demonstrated in a group of 224 patients that vascular calcifications evaluated by MSCT were associated with lower activation frequency evaluated in bone biopsies[21]. These studies show an association between vascular calcifications with low bone volume and with low bone turnover in dialysis patients, suggesting that patients whose bone is not able to retain calcium or phosphorus have higher vascular calcification scores. One added risk factor for the development of vascular calcifications in the setting of low bone turnover could be the administration of higher calcium doses, as verified in the London study.

VASCULAR CALCIFICATIONS AND BONE MINERAL DENSITY

An association between low bone mineral density and vascular calcifications has already been described in the general population. In post-menopausal women it was demonstrated that low bone mineral density is associated with increase in aortic calcifications[22].

Few studies correlating bone mineral density with vascular calcifications have been performed in dialysis patients. Taal *et al.*[23] verified that osteopenia and osteoporosis evaluated by DEXA were associated with decreased survival in dialysis patients. Raggi *et al.*[24] showed that lower bone mineral density evaluated in lumbar spine by quantitative computed tomography was associated with higher pulse wave velocity. In a group of 70 Portuguese peritoneal dialysis patients we verified that low bone mineral density evaluated by DEXA at the femoral neck, but not at the lumbar spine, was associated with more vascular calcifications evaluated by plain X-ray, with higher pulse wave velocity and with peripheral artery disease[25] (Fig. 3).

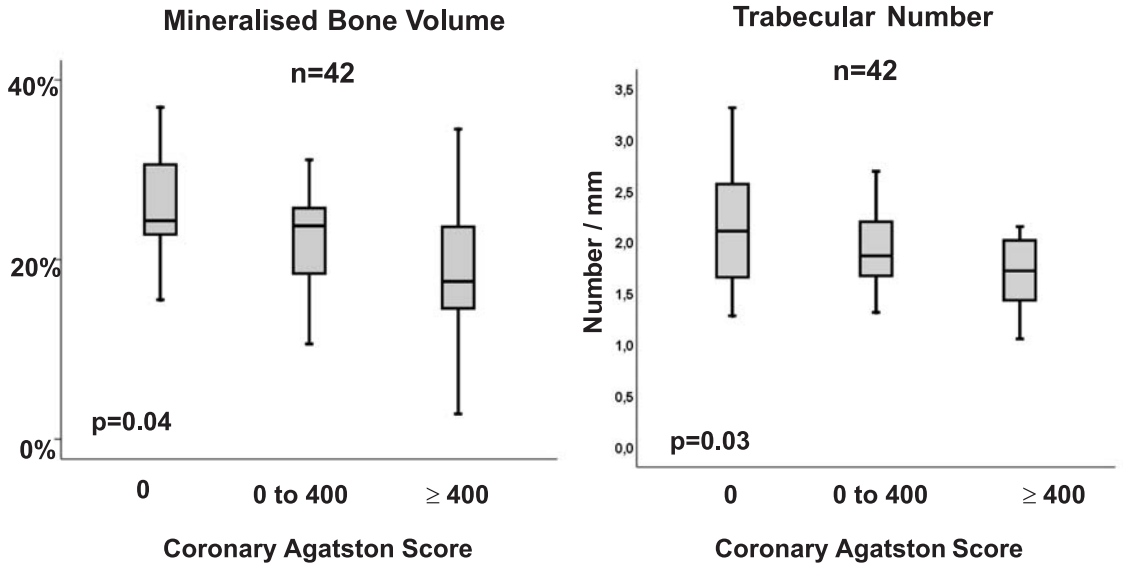


Figure 2

Vascular Calcifications and Bone Biopsies*

*Adragao T, Ferreira A, Frazao J, et al. Nephrol Dial Transplant 2006; 21(4), iv 292 (abstract)

Patients with osteopenia or osteoporosis had higher prevalence of peripheral artery disease (37%) than patients with normal bone mineral density (7%). These associations were adjusted for age, gender, diabetes, haemodialysis duration, systolic pressure and CaxP product. The absence of correlation of bone mineral density evaluated at the lumbar spine with vascular calcifications and arterial stiffness is probably explained by the presence of vascular calcifications in the aorta which may affect the correct measurement of bone mineral density.

The pathogenesis of the association between low bone mineral density parameters and vascular calcifications is not yet known and may be explained by a cause-effect relationship or by a common aetiological factor affecting both the bone and the vessel. Increase in calcium and phosphorus are some of the factors that induce vascular calcification[8]. Either hyperparathyroidism or adynamic bone disease may be associated with osteoporosis[26] and may be the cause of hyperphosphataemia and hypercalcaemia. Oestrogen deficiency is associated with osteoporosis[27] and oestrogen receptors have been identified in vascular smooth muscle cells[28] and in osteoblasts[29].

CARDIOVASCULAR RISK FACTORS AND VITAMIN D DEFICIENCY

In several observational studies, treatment with active vitamin D has been associated with reduced mortality[30-32]. This effect was independent of PTH, Ca and P levels[31], suggesting a pleiotropic effect of vitamin D, beyond the control of hyperparathyroidism. London *et al.* demonstrated that vitamin D deficiency in dialysis patients was associated with vascular calcification and arterial stiffness[33]. Vitamin D deficiency may also be associated with development of cardiac ventricular hypertrophy, as demonstrated in Vitamin D receptor knock-out mice[34].

One possible explanation for this hypothetical beneficial effect of vitamin D is given by the discovery that 1,25-vitD suppresses renin gene expression[35] and by the association between vitamin D deficiency and activation of the renin angiotensin system[34]. Activation of vitamin D receptor has also been associated with reduction of vascular calcifications[36]. In a group of 48 Portuguese haemodialysis patients we verified that vitamin D deficiency was independently associated with vascular calcifications evaluated either by plain X-ray or by MSCT. Vitamin D deficiency was also associated with aortic augmentation

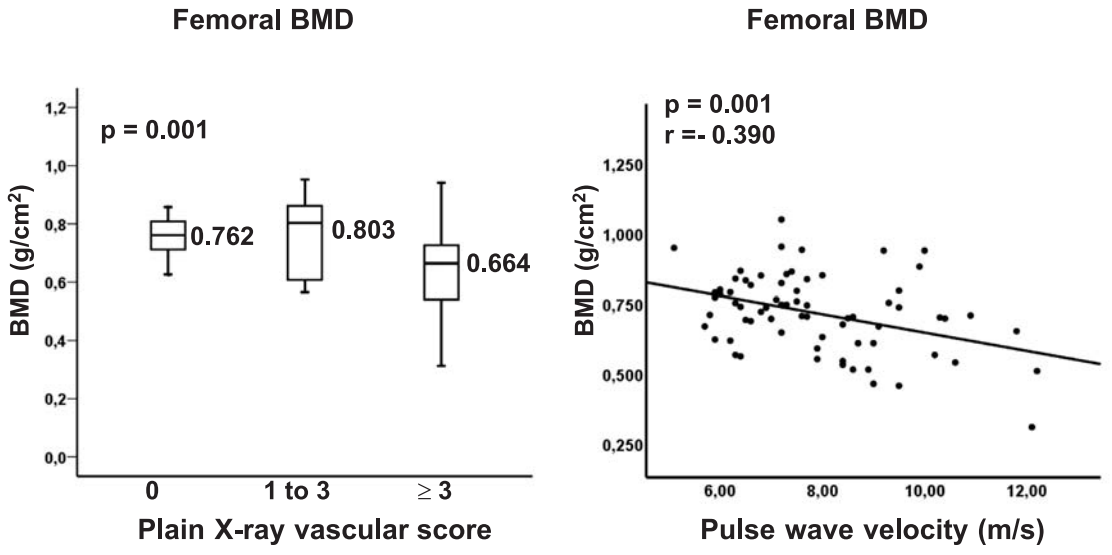


Figure 3

Vascular Calcifications, Arterial Stiffness and Bone Mineral Density*

*Adragao T, Branco P, Birne R. J Am Soc Nephrol 2006;17:272A TH-PO779 (abstract)

index, a marker of arterial stiffness and with left ventricular mass index (LVMI) evaluated by M Mode echocardiography[37] (Fig. 4). This association was adjusted for age, mean arterial pressure, haemoglobin and cholesterol levels.

The association of 25-vitD deficiency with LVMI increase that we verified in our patients is an important finding that goes towards explaining the reduction of mortality associated with treatment with active vitamin D. Left ventricular hypertrophy is associated with arrhythmic risk and with sudden death[38,39] and sudden death is the main cause of cardiovascular death in the dialysis population[4].

WILL TREATMENT OF BONE DISEASE REDUCE CARDIOVASCULAR RISK IN DIALYSIS PATIENTS?

If it is true that there is a link between bone disease and cardiovascular disease, it is necessary to demonstrate that the management of mineral and bone disorder is associated with a reduction in cardiovascular risk. There is already some evidence demonstrating this effect. The TTG[40] and RIND[41] trials have evaluated the progression of coronary calcifications in patients with hyperphosphataemia treated with sevelamer or calcium salts. The TTG evaluated prevalent patients and the RIND evaluated incident patients. The TTG showed that patients treated with calcium showed a 25% increase in the coronary Agatston score while coronary calcification did not increase in patients treated with sevelamer. In the RIND trial patients treated with calcium had an 11-fold increase in median coronary calcification score as compared with patients treated with sevelamer.

Both studies also demonstrated that calcium and sevelamer had a similar effect on the reduction of phosphorus levels, showing that it is not enough to reduce phosphorus levels to avoid progression of vascular calcifications. In terms of biochemical parameters, the main difference was that in patients treated with calcium there was also an increase in Ca levels and a decrease in PTH levels.

Raggi *et al.*[42] evaluated the effect of phosphate binders on bone mineral density in a group of 200 haemodialysis patients. Vascular calcifications and bone mineral density were assessed at baseline and at the end of treatment by either sevelamer or

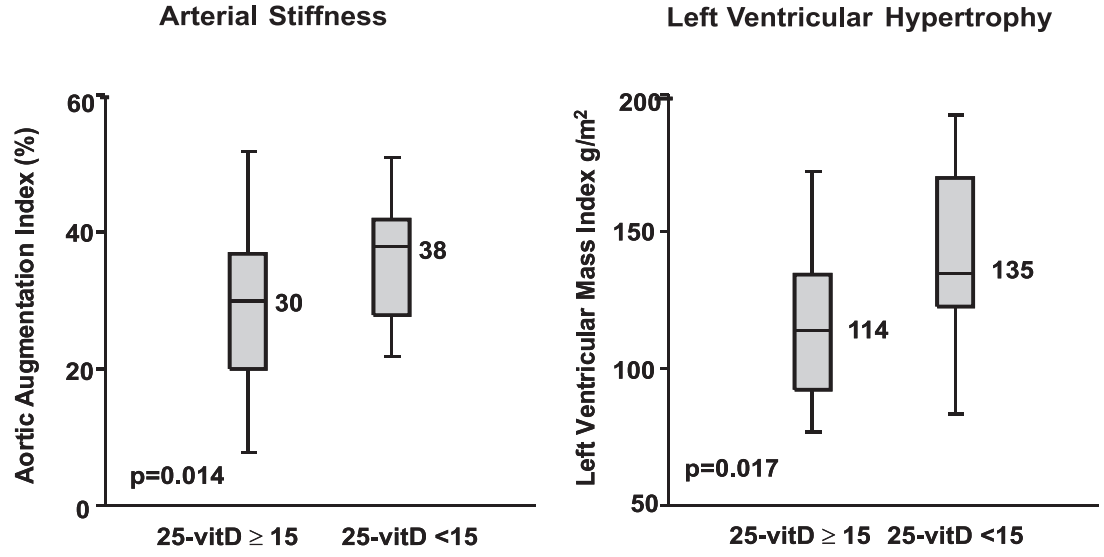


Figure 4

Vitamin D deficiency and cardiovascular risk factors*

*AdragaoT, Ferreira A, Frazão J. Port J Nephrol Hypert 2008;22:66 (abstract)

calcium salts. Patients treated with calcium salts showed an increase in coronary calcifications and a decrease in trabecular bone density, in association with higher Ca levels, lower PTH levels and lower total and bone-specific alkaline-phosphatase levels. This effect of calcium treatment on bone density was confirmed in the Asmus *et al.*[43] study, showing that treatment of 72 haemodialysis patients with calcium carbonate was associated with a decrease in bone density as compared with sevelamer.

The follow-up study of the RIND trial[44] showed that in incident patients treatment with calcium was associated with lower survival than sevelamer. The DCOR trial[45], a multicentre, open-label study, compared the effect on mortality of sevelamer *versus* calcium salts in 2100 prevalent haemodialysis patients. All-cause and cardiovascular mortality were not statistically different between the two treatment groups. This study could only demonstrate that treatment with sevelamer reduced mortality in patients over 65 years of age, and in patients treated for more than 2 years.

There are many reasons which could explain the different outcomes of the DCOR and RIND trials. The former evaluated prevalent patients while the latter was performed in patients new to dialysis. The mean follow-up was shorter in the DCOR trial: 20 months in DCOR *versus* 44 months in RIND. In the DCOR trial, the number of previewed cardiovascular events necessary to demonstrate a difference between the two treatment groups was not reached. Annual mortality rate in the DCOR trial was lower than the annual mortality rate reported in USRDS[4]: 15.02% in the sevelamer group and 16.15% in the calcium binders group. Vascular calcification was not evaluated in DCOR but prevalent patients may have a higher vascular calcification score than incident patients. For instance, baseline coronary calcification score was higher in prevalent patients in the TTG trial, where median score was 641 Hounsfield units, than in incident patients in the RIND trial with a median score of 473 Hounsfield units. These results underline the need to begin treatment at an earlier phase in haemodialysis patients.

In non-randomised studies, treatment with active vitamin D has been associated with a reduction of mortality in dialysis patients. In a small cohort of haemodialysis patients with secondary hyperparathyroidism, treatment with calcitriol was associated with regression of left ventricular hypertrophy[46]. This result may be the consequence of a cardioprotective effect of vitamin D or could be associated with control of hyperparathyroidism. It is necessary to demonstrate if correction of 25-vitD deficiency with or without treatment with active vitamin D contributes to a reduced cardiovascular risk in dialysis patients.

CONCLUSIONS

Vascular calcifications are the result of a complex balance between calcification inducers and inhibitors and are associated with cardiovascular risk in dialysis patients.

Vascular calcifications are associated with low bone turnover, low bone volume and low bone density. Management of bone and mineral disorders in chronic kidney disease may be associated with cardiovascular risk reduction. Plain X-ray can be used for screening vascular calcifications in dialysis patients and the evaluation of the simple vascular calcification score identifies patients at higher cardiovascular risk. This information is an important aid in choosing the most suitable treatment for these patients.

Presence of vascular calcifications, old age, diabetes mellitus, haemodialysis vintage, previous parathyroidectomy and adynamic bone disease are the most frequent factors associated with development or progression of vascular calcifications. In these patients it is important to avoid positive calcium balance, hyperphosphataemia and oversuppression of PTH. Vitamin D deficiency has also been associated with vascular calcifications, arterial stiffness and left ventricular hypertrophy and it is necessary to demonstrate if treatment with vitamin D is associated with a reduced cardiovascular risk.

Understanding the mechanisms linking bone disease to cardiovascular disease is opening up a new treatment field that might reduce the high cardiovascular risk of dialysis patients.

Conflict of interest statement. Dr Adragão has received research grants from Amgen and Genzyme and has received lecture fees from Amgen, Genzyme and Abbott.

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