

Risk factors associated with subendocardial ischemia in hemodialysis patients

Fatores de Risco associados com Isquemia Subendocárdica nos Pacientes em hemodiálise

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Cardiovascular events are the major cause of morbidity and mortality among chronic kidney disease (CKD) patients. A burden of cardiovascular risk factors play a role to adverse outcome in this population, including traditional cardiovascular risk factors as well as several CKD-related factors. It is known that CKD-related mineral bone disorder (BMD) such as hyperphosphatemia, calcium overload, vitamin D deficiency, excess of vitamin D analogues, secondary hyperparathyroidism (SHPT), and low PTH levels might contribute for cardiovascular disease (CVD).

In the article published in this issue of the *Brazilian Journal of Nephrology*, title “*Factors associated with subendocardial ischemia risk in patients on hemodialysis*”, Silva *et al.* evaluated the association between subendocardial viability ratio (SEVR) and BMD markers in a cohort of patients on hemodialysis. The authors reported that a more prolonged time spent under severe SHPT is related to higher risk of subendocardial ischemia, which might not be reversed by parathyroidectomy (PTX). In addition, they observed that lower SERV was associated with female sex and patients with lower levels of 25 Vitamin-D.

Although this study has limitation by cross-sectional observational design and small sample size, it adds relevant information regarding non-invasive vascular functional assessment for vascular dysfunction and long-term impact of SHPT on cardiovascular system.

Cardiovascular assessment using non-invasive structural and functional imaging techniques has increased our understanding of the cardiovascular complications

associated with CKD, including vascular and cardiac valvular calcification, cardiomyopathy, and arterial stiffness. A number of techniques are currently available such as cardiac computer tomography, single-plane radiography, Doppler ultrasound, echocardiography, myocardial perfusion scintigraphy, applanation tonometry, and magnetic resonance imaging.¹ Pulse wave analysis (PWA) using applanation tonometry has emerged as a technique for assessing vascular function and has been applied as an important research tool in CKD. PWA provides several vascular indices such as pulse wave velocity (PWV), augmentation index, ejection duration index, and SERV. PWV has been largely used in patients with CKD and mostly reflects arterial stiffness. Arterial stiffness causes an increase in afterload on the left ventricle resulting in left ventricular hypertrophy and reduced coronary perfusion. Several studies have demonstrated an association between vascular calcification and increased arterial stiffness in patients with CKD.² Furthermore, PWV enables risk stratification for all-cause and cardiovascular mortality on CKD. However, PWA measurement has limitation mainly because is operator dependent.

In the study from Silva *et al.*, SERV, also known as Buckberg index, was determined to assess the impact of BMD markers on hemodialysis patients. SERV is an index of myocardial oxygen supply and demand calculated through PWA. Contrary to PWV, SERV has been barely used in CKD, however this index appears to be an interesting surrogate marker for CVD and deserve further investigation. Recently Ekart *et al.*³ evaluated a cohort

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of 90 non-dialysis CKD patients and 39 healthy controls and demonstrated that patients with stage 4-5 CKD and albuminuria more than 1000mg/g showed significantly lower SEVR. Furthermore, in a post hoc analysis, 212 asymptomatic outpatients with stage 3-4 CKD followed by 6 months. SEVR correlated inversely with vascular calcifications and myocardial mass. In addition, reduction of SEVR values during follow-up was associated with cardiovascular mortality.⁴ In the study by Silva *et al.*, new advances were added since lower SERV was associated with suboptimal vitamin D levels and severe SHPT. Al Mheid *et al.*⁵ reported an association of vitamin D insufficiency and lower SERV in 554 healthy adults. Normalization of vitamin D status at 6 months was associated with increases in SERV. However, impact of PTH on vascular dysfunction assessed by SERV in CKD patients had not yet been demonstrated.

Secondary hyperparathyroidism is associated with an increased risk of cardiovascular morbidity and mortality. Cardiovascular effect of PTH is recognized but complex due to coexistence of many confounding factors able to impair vascular function in CKD patients. Although the mechanisms underlying leading to CVD are not clearly understood, there are evidence that the cardiovascular system can be target for PTH. Actually, mRNA expression of PTH receptors have been demonstrated on vascular endothelial and smooth muscle cells. In addition, PTH is thought to have direct and indirect effects on cardiomyocytes, vascular smooth muscle cells of myocardial arterioles, and even fibroblasts that might contribute for cardiac hypertrophy, and fibrosis.⁶

Furthermore, Neves *et al.*⁷ demonstrated that administration of PTH induced aortic calcification in the presence of normal calcium and phosphorus serum levels in a model of parathyroidectomized chronic kidney disease rat, suggesting that PTH may also have a contributory role in vascular calcification. Therefore, it is plausible that high PTH levels for long-term might contribute in the pathophysiology of CVD such as atherosclerosis, arterial stiffness, vascular calcification, and cardiomyopathy in CKD patients. However, the reverse of vascular dysfunction with SHPT treatment by reducing PTH levels is a matter of discussion. In a clinical study from Osto *et al.*,⁸ coronary microvascular dysfunction was completely restored in patients with primary HPT who underwent to PTX.

Unlike, Silva *et al.* observed that the time spent on SHPT was independent associated with lower SERV and

it was no reverted after PTX. Permanent cardiovascular damage might be a plausible reason due to long-time of severe SHPT. Additionally, patients of the study had a long-time on dialysis treatment and under several cardiovascular risk factors other than those related to BMD. Despite of fact that microvascular dysfunction was no reverted after PTX, recent systematic review and meta-analysis demonstrated that PTX was associated with decreased risks of all-cause and cardiovascular mortalities compared to medical treatments in CKD patients with SHPT.⁹

In conclusion, paper from Silva *et al.* is really welcome. It is important to highlight that our understanding of the cardiovascular manifestations of SHPT remains still incomplete. Can cardiovascular damage and subendocardial ischemia be prevented or treated in patients with CKD and SHPT? This and many other questions need to be addressed in further studies. Furthermore, we need to keep in mind that effort should be done to find better control of BMD early on CKD avoiding future adverse consequences including severe SHPT. In this same way, PTX should not be delayed to avoid permanent damage on cardiovascular system due to long-time under severe SHPT.

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