



EDITORIAL COMMENT

What is the meaning and importance of cardiovascular risk in peritoneal dialysis? Many issues remain to be clarified[☆]



Qual é o significado e a importância do risco cardiovascular em diálise peritoneal? – Muitas questões ainda por esclarecer

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Cardiovascular risk has been demonstrated to be substantially increased in patients with end-stage renal disease (ESRD) under dialysis. In both the US and Europe, cardiovascular mortality is around 40%, and is particularly high within three months of beginning treatment. This implies that long before beginning dialysis, progressive renal failure and uremia create a pathogenic environment that is especially conducive to atherogenesis, whatever the etiology of the disease.¹ This in turn means that when considering the problem of cardiovascular disease in patients undergoing dialysis, it is necessary to distinguish between the contributions of traditional cardiovascular risk factors, those

related to the causes of renal disease, and risk factors related to renal replacement therapy, whether peritoneal dialysis (PD), hemodialysis (HD), or kidney transplantation. Which of these dialysis techniques is used can influence the atherogenic process, depending on characteristics of the procedure such as the dialyzer or the peritoneal membrane, but the most important parameters are the clearance rate and correction of the hydroelectrolyte, acid/base, endocrine and metabolic and inflammatory imbalances that characterize renal failure.

Studies comparing cardiovascular risk in patients undergoing HD or PD are generally inconclusive; study populations frequently vary enormously in age, treatment duration and comorbidities, besides the variety of factors affecting the pathophysiology of atherosclerotic disease. However, objective and replicable data indicate the importance of extracellular water accumulation and hypervolemia, malnutrition and hypoalbuminemia associated with protein-energy

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wasting (PEW), and vascular calcification as factors in cardiovascular morbidity and mortality in ESRD patients. All these may be present to varying degrees in both PD and HD and it is difficult to ascertain which of the techniques carries less risk. Although there are specific characteristics that can increase the pathogenicity of these factors, the crucial parameter is residual renal function.

The article by Querido et al.² in this issue of the *Journal* does not set out to compare the two techniques in terms of cardiovascular risk, but rather to identify cardiovascular risk markers in patients beginning PD. The authors studied a large number of incident PD patients for a significant period of time, which is notable given the scarcity of such studies.

The discussion and conclusions of this article prompt the following considerations.

Regarding hypervolemia, extracellular volume in PD tends to increase, due to its limited ability to remove sodium and the variable degree of ultrafiltration across the peritoneum, which contributes to hypertension and left ventricular hypertrophy. At the same time, the presence of solute in the peritoneal cavity increases intra-abdominal pressure and also systemic blood pressure, due to raised peripheral resistance. These alterations act to increase myocardial production of natriuretic peptides, which are indicators of overall mortality in patients undergoing dialysis and particularly PD.³ PD may thus be less effective than HD in reducing volume and controlling hypertension.

To correct hypervolemia and water retention, the solute must contain an osmotic agent, usually glucose, which exposes the peritoneum to high concentrations of advanced glycation end-products (AGEs). These compounds are implicated in inflammation, oxidative stress and structural changes in collagen. However, according to some authors the elevation of AGE levels in PD is also seen in HD, and it is unlikely that AGE production in PD has systemic vascular effects.⁴ When it is deemed necessary to increase peritoneal ultrafiltration rate without using hypertonic glucose, one option is icodextrin solution, which was used by Querido et al. to identify patients with volume overload. The use of more biocompatible alternatives to glucose such as bicarbonate is controversial, although some studies concluded that it improved survival and preserved residual renal function. These solutes do appear to reduce peritoneal neoangiogenesis and thus loss of ultrafiltration.

Concerning hypoalbuminemia, as pointed out by Querido et al., a strong association has been demonstrated between malnutrition, inflammation (reflected in elevated C-reactive protein), and atherosclerosis (MIA syndrome), and this is linked to increased cardiovascular mortality. Although low serum albumin levels in dialysis patients show a strong inverse relationship with mortality, this is generally taken to reflect disease severity rather than nutritional status. Some authors therefore argue that a more accurate term would be PEW, since the precise role of malnutrition and inflammation in the mortality risk of these patients remains to be clarified.⁵ In the case of PD, protein losses through the peritoneum and in urine, as well as variations in protein intake, make it particularly difficult to use albumin levels as indicators of inflammation and/or malnutrition.

With regard to mitral calcification, in dialysis patients, as in the general population, arterial calcification is an important risk factor for cardiovascular mortality. Such calcification occurs in both vessel intima and media, as well as in cardiac valves, and causes hardening of the arterial wall that leads to hypertension and left ventricular hypertrophy. The main pathophysiological factors involved are hyperphosphatemia and, probably, the FGF23/Klotho axis.⁶

Studies on the prevalence of calcification in ESRD have focused mainly on HD patients, but those on PD patients also reveal a significantly increased prevalence. This suggests that PD is no worse than HD in terms of the main pathophysiological mechanisms leading to tissue calcification.

Observational studies have shown a positive correlation between calcification and inflammatory markers, particularly C-reactive protein, interleukin-6 and adhesion molecules. On the other hand, considering the factors that affect the calcification process, higher levels of fetuin-A, an inhibitor of calcium deposition, appear to be inversely related to cardiovascular mortality, and since they are elevated in PD patients, may confer a protective effect.⁷

In the absence of observational or randomized studies comparing PD with HD (which would be impractical to perform), the study by Querido et al. contributes the experience of a single center in identifying markers of cardiovascular risk in patients treated by PD. As outlined above, cardiovascular risk in these patients is multifactorial and difficult to analyze, and the methodology used runs the risk of incurring bias that could obscure its true causes. Hypervolemia, hypoalbuminemia and mitral calcification are in fact present in patients with chronic kidney disease before dialysis as well as in those undergoing HD, and so it cannot be inferred from this study that they are related to the technique itself. Furthermore, the fact that valve calcification was diagnosed at the beginning of the study means that a link cannot be established with PD. It thus remains to be seen to what extent PD contributes to the development or worsening of mitral calcification, independently of its contribution to the increased incidence of cardiovascular events and mortality in this population.

Conflicts of interest

The author has no conflicts of interest to declare.

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