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Biomarkers in Chronic Kidney Disease - The Linkage Between Inflammation, Ventricular Dysfunction and Overhydration

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1. Introduction

Since 1970s several studies have shown a significant prevalence of cardiovascular disease (CVD) among patients with end-stage renal disease (Linder et al., 1974). Among patients treated by hemodialysis and peritoneal dialysis, the prevalence of CVD is approximately 40%. Even after stratification by age, sex, race, and diabetes, CVD mortality in chronic kidney disease (CKD) patients is 10 to 20 times higher than in the general population (Foley et al., 1998). End-stage-renal-disease patients often have a high prevalence of cardiovascular risk factors as hypertension, diabetes and dyslipemia. Nevertheless, previous studies have shown that the high prevalence of CVD in hemodialysis patients is only partly explained by traditional risk factors (Cheung et al., 2000). Non-traditional risk factors have been emerged in the last decade. One of this non-traditional risk factor is C-reactive protein (CRP).

In this chapter, it is tried to explain the results of several studies supporting an association between inflammation (measured by high levels of CRP), left-ventricular dysfunction and volume overload among patients with CKD and how volume overload, which is present at the very early stages of CKD, could be the main underlying factor contributing to the worse CV prognosis among these patients.

2. Inflammation (C-reactive protein) in patients with chronic kidney disease: prevalence and prognostic factor

CRP is considered the prototypical acute-phase reactant in man. Plasma CRP is produced by hepatocytes although other sites of local CRP synthesis have been suggested.

The plasma half-life of CRP is about 19 hours and is constant under all conditions of health and disease, so that the sole determinant of circulating CRP concentration is the synthesis rate, which thus directly reflects the intensity of the pathological process stimulating CRP production. In most disease, the circulating value of CRP reflects ongoing inflammation and/or tissue damage much more accurately than other laboratory parameters of the acute-phase response. The CRP concentration is thus a very useful nonspecific biochemical marker of inflammation, measurement of which contributes importantly to screening for organic disease, monitoring of the response to treatment of inflammation and infection and detection of intercurrent infection (Pepys et al., 2003).

Elevated CRP levels have been described in a significant proportion of end-stage-renal-disease patients on hemodialysis or peritoneal dialysis (Arici et al., 2001). About one-third of patients with chronic renal failure have serum CRP concentration > 10 mg/l (Owen et al., 1998). In healthy men, high CRP level has been identified as a risk factor for cardiovascular disease (Ridker et al., 2001). As occurs in the general population, prospective studies point to a correlation between CRP plasma levels and overall and cardio-vascular mortality also in end-stage-renal disease patients (Arici et al., 2001; Ikizler et al., 1999; Noh et al., 1998; Owen et al., 1998; Panichi et al., 2008; Wang et al., 2009; Yeun et al. 2000; Zimmermann et al., 1999).

3. Inflammation and anemia

In dialysis patients, inflammation expressed by high levels of CRP is also associated with low blood hemoglobin and/or resistance to erythropoiesis-stimulating agents (Barany et al., 1997; Bradbury et al., 2009; Gunnel et al., 1999; Owen et al., 1998). This has been attributed to the inhibition of erythropoietin secretion by pro-inflammatory cytokines. Inflammation also contributes to anemia by inducing functional iron deficiency probably blocking the delivery of iron from the reticuloendothelial cells to the hemathopoietic cells. Cytokines may also induce ferritin synthesis directly or by increasing iron uptake into hepatocytes. The increase in ferritin synthesis by hepatocytes and reticuloendothelial cells underlies in the iron storage pool during inflammation. Thus, inflammation among patients with CKD can contribute to anemia and impaired response to erythropoietin. Erythropoietin resistance by itself has been associated with higher short-term mortality in CKD patients (López-Gómez et al., 2008).

4. Inflammation and malnutrition

High concentration of acute phase protein is correlated with low serum albumin in malnourished hemodialysis patients (Kaysen et al., 1997; Qureshi et al., 1998). Low serum albumin concentrations are highly associated with increased mortality risk in patients with renal replacement therapy (Lowrie et al., 1990). Hypoalbuminemia has been traditionally been assumed to result from inadequate protein and calorie intake. However, albumin is a negative acute-phase protein. The synthesis of this protein decreases during inflammation independently of nutritional state. Albumin concentration in dialysis patients is negatively correlated with levels of positive acute-phase protein. Moreover, inflammation and malnutrition data has been associated with the presence of atherosclerotic carotid plaques (Stenvinkel et al., 1999) describing the so called MIA (malnutrition-inflammation-atherosclerosis) syndrome in patients with advanced renal failure.

In summary, inflammation is high prevalent among patients with chronic kidney disease and predicts anemia, malnutrition and CV death. An intriguing question is whether CRP is just a sensitive marker of systemic inflammation or actively contributes to the development and progression of atherosclerotic lesions and, therefore, to the CV damage. Some authors have demonstrated CRP content inside the atherosclerotic lesions, suggesting the active participation in the inflammatory process (Zhang et al., 1999) what hints that inflammation could be the cause rather than the consequence of CV damage. Based on the bad prognosis of patients with markers of inflammation, it is important to try to know the possible causes of inflammation in this population in order to prevent morbidity and mortality.

5. Possible causes of inflammation

The causes of inflammation in patients with CKD patients remained unclear over time. Several studies have attempted to address the question as to whether some factors related to the dialysis technique by itself could induce the inflammatory response. Activation of monocytes with the subsequent enhanced release of inflammatory cytokines can be caused by membrane-induced complement activation, by direct cell-membrane interaction and by dialysis fluids containing endotoxins (Carracedo et al., 2006; Honkanen et al., 1991; Kerr et al., 2007; Schouten et al. 2000). However, a similar prevalence of inflammation has been described in patients with advanced renal failure not yet on dialysis (Ortega et al., 2002; Panichi et al., 2002; Stenvinkel et al., 1999). An inverse correlation between CRP levels and clearance of creatinine has been observed (Panichi et al., 2002); thus, CRP levels increase as renal function declines. This finding suggests the possibility of a decreased renal clearance of CRP as a cause of an activated acute-phase response in patients with chronic kidney disease. Another possibility could be that uremia by itself could be the cause of inflammation among these patients. However, in another study performed in pre-dialysis patients with a more homogeneous clearance of creatinine (Ortega et al., 2002), a non-normal distribution of CRP levels were detected. That means that only a group of patients with advanced renal failure shows high levels of CRP, whereas other patients with the same degree of renal insufficiency have even normal CRP values. Hence, it seems that uremia by itself is not the unique cause of inflammation. Probably, inflammation could be related to some factors, frequently associated with renal failure, which can worsen with the worsening of renal function. In this study (Ortega et al., 2002), CRP levels were higher in those patients with a previous history of CVD. Comparing with patients with normal CRP levels at baseline, patients with higher levels maintained significant higher levels on follow-up. This group of inflamed patients showed during the study period persistently lower serum albumin, lower blood hemoglobin, needed higher doses of erythropoietin stimulating agents and showed higher hospitalization rate (table 1).

	Group I (CRP>6 mg/dL) <i>n</i> = 23	Group II (CRP<6 mg/dL) <i>n</i> = 43	<i>P</i> value
CRP (mg/L)*	21.6 (12.9 - 32.6)	2 (2 - 4.6)	0.00001
Albumin (g/dL)	3.5 ± 0.4	3.8 ± 0.4	0.017
Hemoglobin (g/dL)	11.6 ± 1.1	12.2 ± 0.8	0.045
Epo (IU/kg/week)	67 ± 32	43 ± 20	0.025
Hemoglobin/Epo	0.19 ± 0.08	0.32 ± 0.13	0.004
Hospitalization (n)	0.52 ± 0.8	0.03 ± 0.19	0.004

Table 1. Comparison of the evolution of analytical and clinical data between patients with high (Group I) or low (Group II) CRP levels at baseline. Mean ± standard deviation.
*Median (interquartile range).

In summary, at this point we know that inflammation is high prevalent among patients with CKD, that the prevalence is higher among patients with associated CVD, that inflammation tends to increase with the decline of renal function but that only about one third of patients with advance renal function shows persistently high levels of inflammatory

markers. Thus, we could argue that uremia by itself is not the cause of inflammation. It seems that another factor, usually associated with uremia and which usually worsens with the decline of renal function could be the responsible of inflammation in patients with CKD. In the past decade, it has been observed that circulating inflammatory cytokines are elevated in patients with chronic heart failure (Levin et al., 1990) and it has been suggested that cytokines can be in part responsible for cardiac disease progression in these patients (Seta et al., 1996). Some authors have detected elevated plasma levels of endotoxins and cytokines during the acute phase of heart failure and that normalization of endotoxins and cytokines concentration can be achieved using intensive diuretic treatment (Niebauer et al. 1999, Peschel et al. 2003). The authors hypothesized that during acute cardiac decompensation, acute mesenteric venous congestion with subsequently altered gut permeability for endotoxins would lead to translocation of these materials into the circulation inducing the inflammatory response. Thus, the authors highlight that inflammation could be the consequence, rather than the cause of heart failure.

6. Association between inflammation, overhydratation and cardiac disease: B-type natriuretic peptide

Cardiac disease is high prevalent among patients with CKD (Foley et al., 1995; Hayashi et al., 2006; Levin et al., 1996; Zocali et al., 2004). The typical feature of uremic cardiomyopathy is left ventricular diastolic dysfunction related to left ventricular hypertrophy and left ventricular fibrosis (Ahmed et al., 2007; Losi et al., 2010; Mark et al., 2006). Left ventricular hypertrophy is particularly highly prevalent in end-stage renal disease patients because of hypertension, hyperparathyroidism and increased volume. However, myocardial fibrosis is a specific finding among patients with CKD comparing with patients with isolated hypertension as revealed autopsy studies (Sharer et al., 1999). Probably, volume overload could be a main cause of myocardial fibrosis among these patients as volume overload can produce mechanical stress on the ventricular wall and it has been demonstrated that mechanical factors can induce the activation of the fibroblasts of the myocardium synthesizing the extracellular matrix (MacKenna et al., 2000). Volume overload is present very early in the course of CKD and is the consequence of the inability of the insufficient kidney to eliminate the excess of water and salt. Usually, the increase in extracellular water in the very early course of CKD is modest and may easily be underestimated by clinical examination and can only be proved by accurate measurement of body water volume, as with bioimpedance. Extracellular water excess increases when glomerular filtration rate declines and has emerged as an independent factor in the structural cardiac damage, as a direct relation between extracellular water excess and left ventricular mass has been demonstrated as well as with left ventricular data of diastolic dysfunction (Essig et al., 2008). The authors also highlighted that cardiac remodeling was present at the very early stages of CKD. Over time, structural myocardial alterations progress, leading to diastolic dysfunction. The central disturbance in diastolic dysfunction involves abnormalities in myocardial relaxation and ventricular compliance (Martos et al., 2007). Thus, in order to complete ventricular filling and achieve a sufficient end-diastolic volume, which will provide adequate stroke volume, the left ventricle needs filling pressure higher than normal. Diastolic dysfunction, in fact, means that the left ventricle fills at higher pressure. Echocardiographic data of diastolic dysfunction are the most frequent findings among patients with CKD (Hayashi et al., 2006).

Based on the association between inflammation and heart failure in the general population and as myocardial dysfunction is high prevalent among patients with CKD, several authors tried to find an association between inflammation and cardiac disease also in this population. Furthermore, this hypothesis could explain why only some patients (those with more ventricular damage) show high levels of CRP, whereas other patients with similar clearance of creatinine (those with less cardiac disease) could present even normal values of CRP.

Some authors (Ates et al., 2005; Kim et al., 2005) have observed an association between CRP and left ventricular hypertrophy or dysfunction among patients with CKD. However, most authors have employed in their studies the measurement of a biochemical marker of ventricular dysfunction such as B-type natriuretic peptide.

B-type natriuretic peptide (BNP) is a cardiac neurohormone specifically secreted from cardiac ventricles in response to an increased left-ventricular wall tension (Maeda et al., 1998). When end-diastolic filling pressure is increased (related to ventricular dysfunction, hypervolemia or both conditions), the release of BNP is induced. BNP is a potent natriuretic peptide by enhancing renal sodium excretion, reducing so the intravascular volume and, therefore, the end-diastolic volume and pressure. BNP is a strong predictor of systolic and diastolic abnormalities and is a powerful marker for prognosis and risk stratification in the setting of heart failure (Tabbibizar et al., 2002). In the general population, a cut point of about 100 pg/ml can discriminate patients with heart failure from patients without it.

BNP is increased among patients with CKD and an inverse correlation between BNP levels and glomerular filtration rate has been observed (McCullough et al., 2003). This increased BNP level among these patients is in part related to the decreased renal clearance as well as the accompanying increased intravascular volume which is usually present in these patients. However, values above a cut-point reflect ventricular dysfunction and predict heart failure also among patients with CKD. In general, as CKD stage advances, a higher cut point of BNP is implied. BNP levels higher than 500 pg/ml usually predict heart failure even in patients with renal failure. Diastolic dysfunction is the most frequent cardiac disease among patients with CKD. In this setting, a small increment in end-diastolic volume lead to an exaggerated increase in diastolic pressure (Mandinov et al., 2000), inducing the release of natriuretic peptide. Probably, this pathophysiological mechanism partly explains the high levels of BNP detected among patients with CKD. In fact, several studies have observed an association between natriuretic peptide levels and echocardiographic data of left ventricular hypertrophy and dysfunction among patients with CKD (Guo et al., 2009; Paniagua et al., 2010; Zocali et al., 2001). Natriuretic peptide levels among patients with CKD predict death, as it occurs in patients with heart failure and normal renal function. Otherwise, some authors (Jacobs et al., 2010) have demonstrated a direct correlation between extracellular water, measured by bioelectrical impedance, and natriuretic peptide in CKD patients, explaining how volume overload can increase end-diastolic volume and, therefore, end-diastolic pressure favoring the release of BNP. Probably both mechanisms, volume overload and myocardial damage, both high prevalent among patients with CKD, could explained the high levels of natriuretic peptides detected in this population.

NT-proBNP is the amino-terminal peptide fragment of the precursor of BNP and shows a close correlation to BNP (Masson et al., 2002). A non-normal distribution of NT-proBNP levels was observed among patients with advanced renal failure, as previously observed

with CRP (Ortega et al., 2004). Newly, it means that only a group of patients with advanced renal failure shows high levels of natriuretic peptides, whereas other patients with similar creatinine clearance show even normal values. This finding probably reflects the presence of a mixed population among patients with advanced CKD with a group of patients with more severe cardiac disease whereas other patients can achieve the end-stage disease phase with less myocardial damage. But most importantly, a strong correlation between NT-proBNP and CRP levels is found (figure 1), suggesting an association between left-ventricular filling pressure and inflammation among patients with CKD.

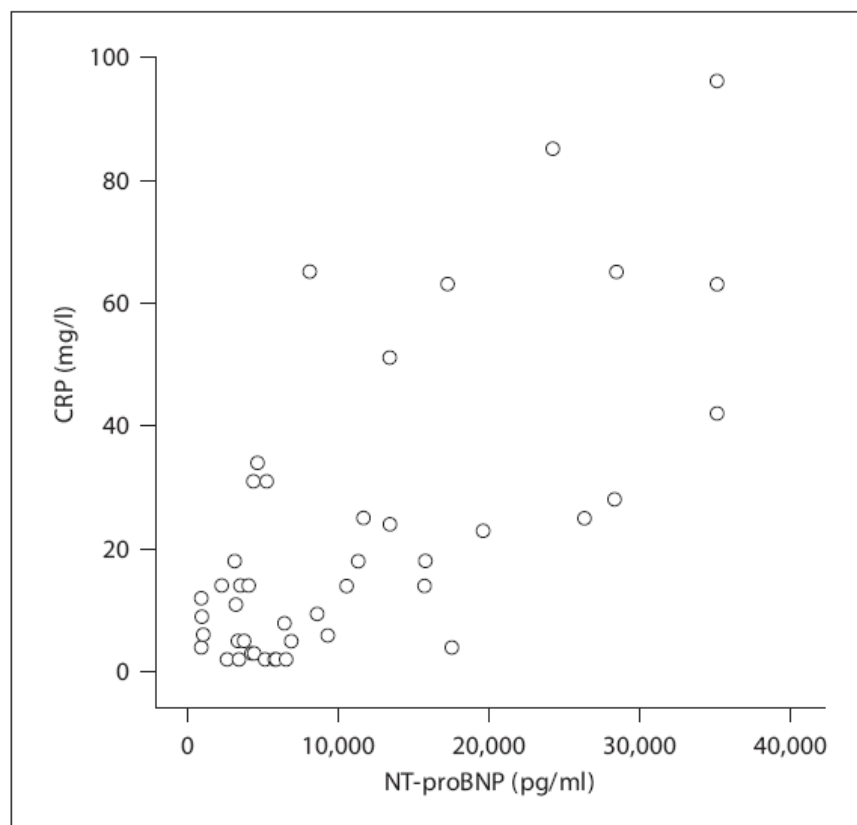


Fig. 1. Regression graph demonstrating the correlation between NT-proBNP and C-reactive protein values at baseline ($r: 0.7$; $p < 0.001$)

This association between left-ventricular filling pressure and inflammation among CKD patients has been confirmed in subsequent years (Guo et al., 2009; Jacobs et al., 2010; Paniagua et al., 2010). Otherwise, the same studies and other authors (Booth et al., 2010) observed a relationship between cardiac and inflammatory biomarkers and volume overload. An association between volume overload and inflammation had been previously observed among patients on peritoneal dialysis (Woodrow, 2006). Overhydration by itself has emerged as an independent predictor on mortality in chronic hemodialysis patients (Wizemann et al., 2009).

Thus, all these findings show the complex relation between overhydration, malnutrition, inflammation and cardiac biomarkers in CKD patients. Although CRP can actively

participate in the atherosclerotic process inducing CV damage, it has also been suggested that inflammation among patients with CKD could be the consequence, rather than the cause, of an increased left-ventricular filling pressure, related to ventricular dysfunction, hypervolemia or both conditions (Ortega, 2005).

The complex relation between ventricular dysfunction, overhydration and inflammation highlights the importance of strict volume control in patients with CKD. Usually, ventricular dysfunction progress over time. In an interesting longitudinal study performed in hemodialysis patients, a progressive deterioration of left ventricular filling pressure (an index of diastolic dysfunction) was observed in parallel with the progression of left ventricular hypertrophy and a progressive increment in levels of NT-proBNP (Kim et al., 2011). Thus, these results suggest that diastolic dysfunction progress over time among patients with chronic kidney disease. In another longitudinal study performed in hemodialysis patients (Ortega et al., 2009), the effect of strict volume control on the evolution of cardiac biomarker levels over time was analyzed. In this study, the strategy of strict volume control permitted the stabilization of cardiac biomarker levels over time, suggesting that this strategy may prevent further progression of left ventricular hypertrophy, cardiac fibrosis and diastolic dysfunction. Patients with higher biomarker levels at baseline, probably those with more severe myocardial damage, were the most benefited as NT-proBNP levels could even be reduced over time (figure 2). In these high risk patients, continuous prevention of fluid overload diminished the inflammatory parameters on follow-up, confirming the importance of volume control for preventing inflammation in dialysis patients (figure 3).

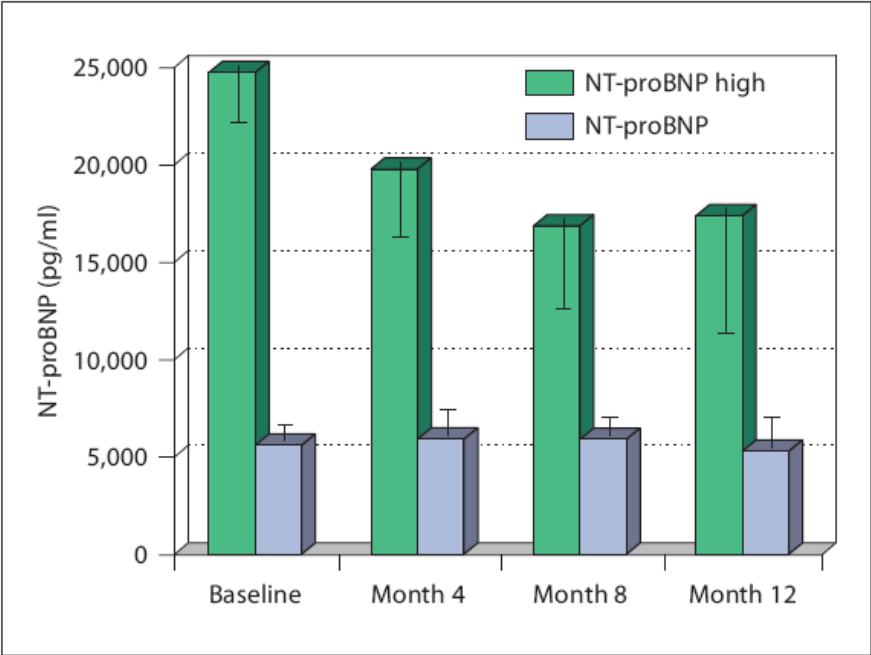


Fig. 2. Evolution over time of NT-proBNP values among patients distributed in high quartile at baseline (NT-proBNP high) and those distributed in other basal quartiles (NT-proBNP). Data expressed as mean \pm standard error.

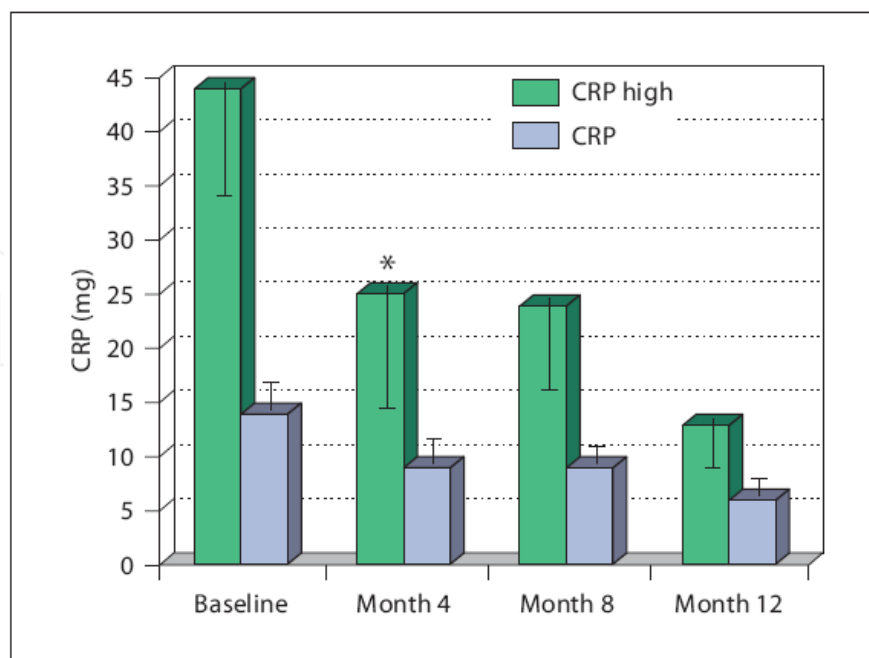


Fig. 3. Evolution over time of CRP values among patients distributed in high quartile at baseline (CRP high) and those distributed in other basal quartiles (CRP). * $p < 0.05$ vs baseline levels. Data expressed as mean \pm standard error.

7. Other cardiac biomarkers: Troponin T

Cardiac troponins are regulatory proteins within the myocardium that are released into the circulation when damage to the cardiomyocyte has occurred. Therefore, serum troponin is an exquisitely sensitive marker of myocardial injury during the acute coronary syndrome and is necessary for establishing the diagnosis of myocardial infarction (Daubert et al., 2010).

Cardiac troponins control the calcium-mediated interaction of actin and myosin, which results in contraction and relaxation of striated muscle. The troponin complex is made up to three subunits: troponin C, troponin I and troponin T. Troponin C is expressed by cells in both cardiac and skeletal muscle. In contrast, troponin I and T are unique to cardiac muscle. Among patients with acute coronary syndrome, cardiac troponin has not only diagnostic value, but yield prognostic information as well. It has been proven to be a potent independent indicator of recurrent ischemic events and an estimate for the risk of death among patients presenting with acute coronary syndrome (Heidenreich et al., 2001).

Persistently elevated cardiac troponin is frequently observed among asymptomatic patients with end-stage-renal-disease and is associated with increased mortality (Apple et al., 2002; de Fillipi et al., 2003; Ogi et al., 2001). There has been proposed several mechanisms for explaining the high levels of troponin among patients with CKD. Although troponin is a relative large molecule which is believed to be cleared by the reticuloendothelial system, more recent evidence suggest that troponin T is fragmented into molecules small enough to be renally excreted, which may partly explain the high prevalence of troponin T elevation in patients with renal failure (Diris et al., 2004).

Cardiac microinfarctions and arrhythmia have also been suggested as possible causes of elevations of troponin among patients with CKD.

More recently, it has been observed that CKD patients with high troponin T concentrations had clear evidence of myocardial dysfunction and raised left ventricular filling pressure (Sharma et al., 2006), supporting that volume and pressure overload can cause excessive ventricular wall tension with resultant myofibrillary damage or cardiomyocytes death (Horwich TB et al., 2003). In this way, a strong association between troponin T and NT-proBNP has been observed in hemodialysis patients (figure 4) (Ortega et al., 2009) and both troponin T and NT-proBNP levels has been observed to be higher in volume-overloaded CKD patients (Sommerer et al., 2007).

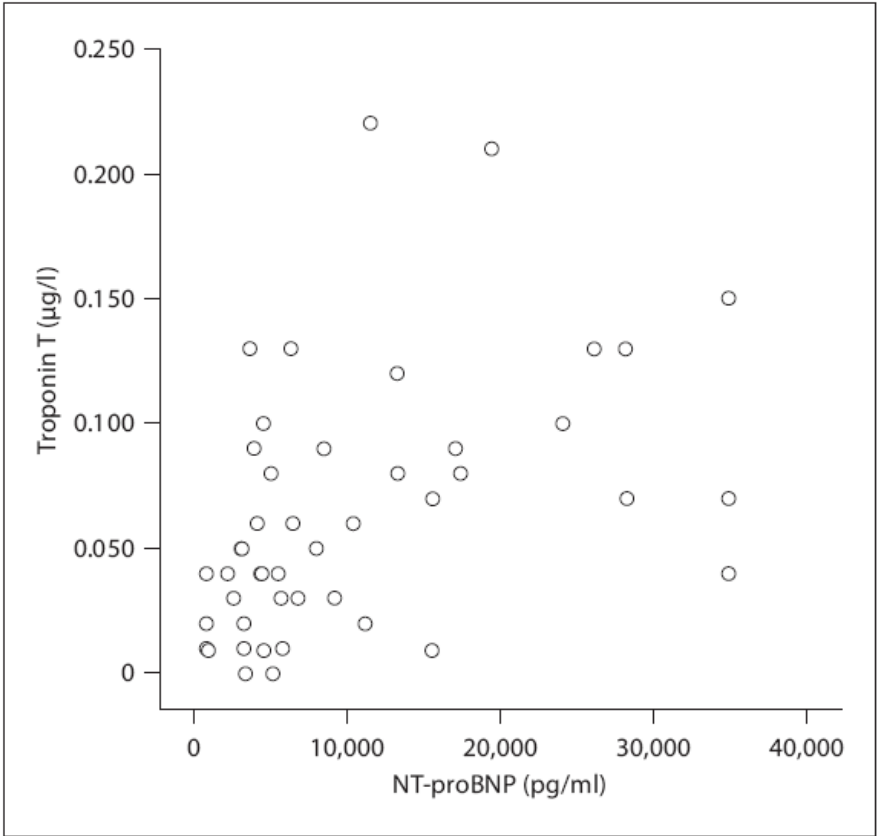


Fig. 4. Regression graph demonstrating the correlation between NT-proBNP and troponin T values at baseline ($r: 0.4$; $p= 0.002$)

Thus, it seems that the increased troponin T in a high proportion of patients with CKD could be related to myocardial injury induced by an increased left ventricular volume especially in those patients with diastolic dysfunction, in whom a small increase in end-diastolic volume produces an exaggerated increment in end-diastolic pressure with the subsequent myocardial damage. Furthermore, in hemodialysis patients, a strategy of strict volume control over time could significantly reduce the troponin T levels especially in those patients with higher biomarker levels at baseline, probably those with more severe myocardial dysfunction (figure 5) (Ortega et al., 2009).

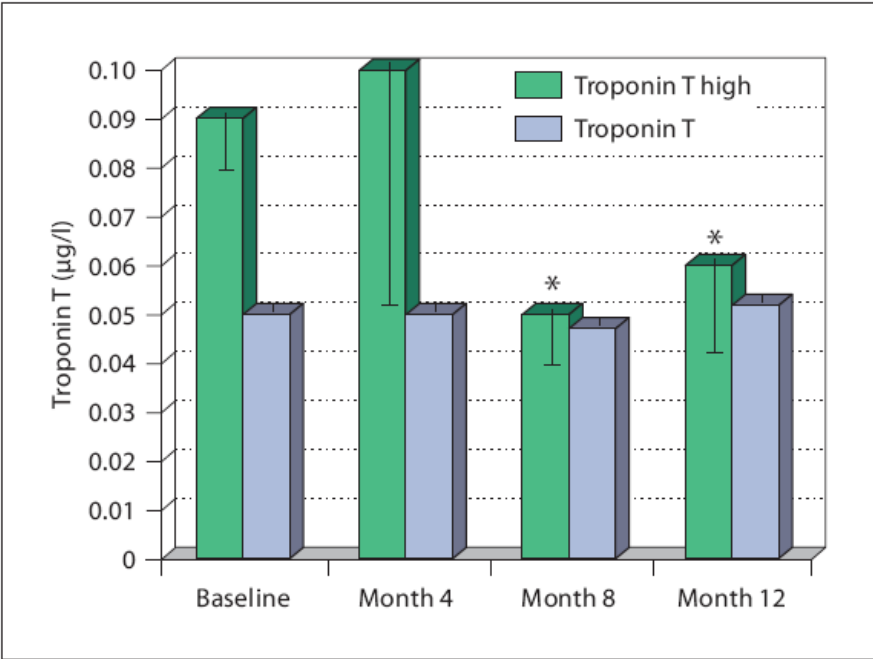


Fig. 5. Evolution over time of troponin T values among patients distributed in the high quartile at baseline (Troponin T high) vs those distributed in the other basal quartiles (Troponin T). * $p<0.05$ vs baseline levels. Data expressed as mean \pm standard error.

8. Summary and future perspectives

There is a complex association between ventricular dysfunction, cardiac biomarkers, malnutrition, inflammation and overhydration among patients with CKD, which could partly explain the high CV morbidity and mortality among these patients, comparing with the general population.

Probably, these alterations begin in the very early stages of CKD and volume overload could be an important underlying factor. The inability of the insufficient kidney for excreting water and salt induces an increase in extracellular volume, which may be underestimated in the early phases of CKD. Persistently volume overload can induce an increment in blood pressure, myocardial hypertrophy and myocardial fibrosis. Over time, diastolic dysfunction develops. In this setting, further small increments in end-diastolic volume produce an exaggerated increment in end-diastolic pressure favoring the release of BNP and also, myocardial damage and cardiac remodeling. During cardiac remodeling, death of cardiomyocytes is produced inducing a serum increment in troponins, and normal myocardium is progressively substituted by a fibrotic matrix, worsening so diastolic dysfunction. In this situation, systemic inflammation is produced by a yet non clear mechanism.

Thus, in this chapter, it is tried to highlight the importance of early intervention for controlling volume excess in the very early stages of CKD in order to prevent future cardiac dysfunction and inflammation, reducing so the bad CV prognosis of these patients.

It is noteworthy that at this early stage of CKD some patients can show normal plasma creatinine, especially older patients or patients with low muscle mass, but they may be subclinically overhydrated. A prescription of low sodium diet and the carefully use of diuretics at this phase of CKD could be the main tool for preventing volume overload and future CV damage.

9. References

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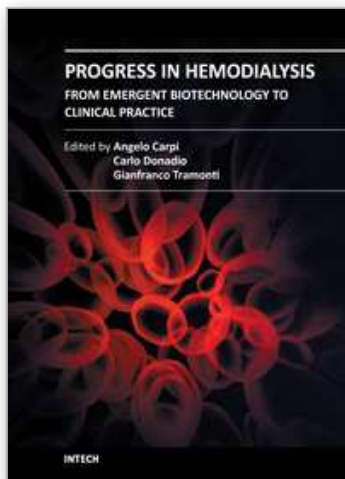
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