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Review

Cardiac Biomarker NTproBNP in Chronic Kidney Disease - A Brief Review

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REZUMAT

Biomarker cardiac NTproBNP în insuficienta renală cronică - o scurtă trecere în revistă

Afecțiunile cardiovasculare reprezintă o cauză importantă de morbiditate și mortalitate la pacienții cu insuficiență renală cronică, în special la bolnavii cu boală cronică de rinichi (BCR) stadiul terminal. Studii clinice și experimentale aprofundate au urmărit identificarea de markeri utili în confirmarea precoce a afectării cardiace la acest grup populațional. În ultimii ani, o deosebită considerație a fost acordată rolului peptidelor natriuretice, în special NTproBNP (N-terminal probrain type natriuretic peptide); s-a observat faptul că acest peptid prezintă valori ridicate din stadii incipiente ale BCR, creștere a cărei semnificație nu a fost pe deplin elucidată, reprezentând încă un subiect de controversă. Astfel, articolul de față parcurge succint aspecte edificatorii de actualitate referitoare la rolul NTproBNP în BCR.

Cuvinte cheie: boală cronică de rinichi, afecțiuni cardiovasculare, NTproBNP

ABSTRACT

Cardiovascular disease (CVD) is the principal cause of morbidity and mortality in chronic kidney disease (CKD) and end-stage renal disease (ESRD). Extensive researches have been conducted in order to identify markers for early cardiac involvement in CKD. Cardiac biomarker N-terminal probrain type natriuretic peptide (NTproBNP) increases early in the course of CKD, but the significance of this increment is still a matter of debate. The present article briefly reviews the present data concerning NTproBNP in CKD.

Key words: chronic kidney disease, cardiovascular disease, NTproBNP

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INTRODUCTION

Chronic kidney disease (CKD) is a worldwide health problem [1,2] affecting between 7 – 10% of young individuals (30 – 64 years old) in Europe [2] and approximately 10 – 18% of the population in the USA [3]. In 2013, in Romania, the prevalence of CKD was approximately 13.1%, meaning about 1,900,000 persons, and 13,899 patients were on chronic dialysis [4].

CKD is associated with increased cardiovascular morbidity, even from early stages [5-8]. Decreased glomerular filtration rate (GFR) is a strong predictor of cardiovascular events, even in the absence of other cardiac risk factors [9]. Risk for cardiovascular disease in CKD patients is 10 – 30 times higher than in non-CKD individuals and mortality from cardiovascular diseases (CVD) accounts for approximately 50% from all causes of death in dialysis population [6,10,11,12]. Predisposing features for developing CVD in CKD patients include both traditional and nontraditional – uremia associated – factors [11,12].

Early detection of CVD in the CKD population is a subject of numerous researches and several biomarkers have been studied in order to detect early alterations of cardiac function in CKD. The present article reviews data on cardiac biomarker N-terminal probrain type natriuretic peptide (NTproBNP), a marker which is increased in CKD and is associated with progression of CKD and/or with prediction of cardiovascular events.

Natriuretic peptides

Natriuretic peptides are polypeptide hormones synthesized in the heart secondary to distention of the cardiac walls (wall stretch), which occurs during plasma volume expansion [13-16]. Atrial natriuretic peptide (ANP) is synthesized in the atria secondary to atrial distension, while brain natriuretic peptide (BNP) is produced mainly in the cardiac ventricles, but also in the atria [13-16].

In the kidney, the natriuretic peptides ANP and BNP have vascular and tubular actions [13-17]. They induce afferent arteriolar vasodilation, thereby promoting increased filtration [13-17]. Additionally, they inhibit the release of renin and the actions of angiotensin II that normally promote reabsorption of sodium in the proximal tubules and they also directly inhibit sodium reabsorption in the medullary collecting duct [13-17]. This way, these natriuretic peptides increase natriuresis and diuresis [13-17]. Several researches attribute BNP the ability to protect against remodelling fibrosis in cardiac failure [13,14,16].

C-type natriuretic peptide (CNP) is synthesized in endothelial cells and influences local blood flow and the vascular tone [14,16].

Natriuretic peptides have been studied especially as biomarkers in cardiac diseases where increased serum levels are associated with poor prognosis, degree of left ventricular dysfunction, and congestive cardiac failure [18-22].

The concentrations of BNP in the myocardium is higher than that of ANP, and BNP is considered a marker of increased cardiac filling pressure more useful than ANP [23]. Therefore, BNP was investigated more intensely.

Before its activation, BNP is stored as a 108-amino acid polypeptide precursor (proBNP) in secretory granules in the cardiac ventricles [24,25]. As a result of myocardial stretching, proBNP is secreted into plasma and it is cleaved to a 32-peptide, biologically active hormone BNP and a 76-peptide, biologically inert N-terminal fragment (NTproBNP) [24,25]. Both fragments are produced in equal quantities [24,25]. BNP clearance from the circulation is performed by plasma endopeptidases; its plasmatic half-life is approximately 20 minutes [24-26]. NTproBNP is excreted mainly by the kidney and no receptor-mediated clearance of NTproBNP is known to occur; its plasmatic half-life is more prolonged than that of BNP (approximately 60 – 120 minutes) [24,25]. Plasma levels of NTproBNP are 3 – 5 times higher than BNP levels and in a blood sample, NTproBNP is stable a longer period than BNP [24,25].

NTproBNP in CKD

NTproBNP is increased in the CKD and ESRD population. The cause and significance of this increase is still a matter of debate.

Causes of high levels of NTproBNP in CKD

Numerous studies report high plasma levels of NTproBNP in CKD even in the absence of symptomatic cardiac failure [27-29]. However, some researches do not find a linear increase of NTproBNP parallel with the decrease of GFR and report, especially in late stages of CKD, an excessive increment of this hormone [30]. Moreover, these researches found that the urinary excretion fractions of NTproBNP did not correlate with GFR [27-30]. Thus, it was concluded that an increased production

of NTproBNP occurs as a result of occult, asymptomatic cardiac disease [27-30].

Lack of uniformity in increasing NTproBNP values may alter the interpretation of data in clinical practice [31,32]. Between and within individual variations of NTproBNP have been studied in an end-stage renal disease (ESRD) population on chronic hemodialysis [32]. The investigators revealed that there is a smaller within-individual variation, but a significant greater between-individual variation of NTproBNP, and they recommended caution when interpreting high levels of NTproBNP in this group of individuals [32].

The variability of NTproBNP increases also depending on the type of hemodialysis membranes; the clearance of NTproBNP is negligible in a low flux hemodialysis membrane, while, in high flux dialysis, a considerable decrease was noted and the investigators draw attention to the possibility to alter a myocardial infarction diagnosis in these latter patients [33].

Significance of increased NTproBNP in CKD and ESRD

Increase of NTproBNP has been proven to predict cardiovascular and all-causes mortality, in the absence of ischemia or cardiac failure [34-38]. However all these studies could not define an interval for predictive values for NTproBNP and most of them report the necessity to apply a cut-off threshold for patients without significant residual renal function [34-38]. Progression of CKD and extension of atherosclerosis was proven to correlate with the degree of NTproBNP increase in several studies, too [28,31,39-41].

The main debate regarding increase of NTproBNP in the CKD population is whether it is a marker of myocardial dysfunction or a marker of volume overload [28,31,40,41].

Extensive researches report that the elevation of NTproBNP in CKD or ESRD patients is a marker of cardiac dysfunction, measured by several imagistic investigations (angiography, CT, echocardiography, myocardial scintigraphy etc) [18,28,31,35,36,41,42]. Left ventricular hypertrophy, abnormal diastolic function or decreased left ventricular ejection fraction, coronary extensive atherosclerosis and vascular rigidity have been proven to correlate with high NTproBNP in many studies [18,28,31,35,36,41,42].

Other studies reveal a direct relationship between increase of NTproBNP and hypervolemia measured by different modalities (pressure in pulmonary artery, bioimpedance, left ventricular filling pressure or end-diastolic wall stress, left ventricular or left atrial dimensions) [28,31,37,38,43,44].

The ratio between extracellular water to total body water has been associated in some reports with increased NTproBNP in CKD patients, in the absence of volume overload, as it happens in malnutrition or chronic inflammation [28,31,44-46].

CONCLUSIONS

Potential usefulness of NTproBNP increase in CKD patients is still controversial. Further studies are needed not only to clarify whether it may serve as a cardiac biomarker in daily practice as it is used in the diagnosis of heart failure in non-CKD individuals, but also to elucidate the exact significance of this increase.

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