

**CARDIOVASCULAR BIOMARKERS IN CHRONIC KIDNEY DISEASE**

## BIOHEMIJSKI MARKERI KARDIOVASKULARNIH BOLESTI U HRONIČNOJ BOLESTI BUBREGA

Mirjana Đerić, Velibor S. Čabarkapa

Center for Laboratory Medicine, Clinical Center of Vojvodina, Novi Sad, Serbia

**Summary:** Cardiovascular morbidity and mortality are markedly increased in chronic renal failure patients. Although it cannot be regarded as a cardiovascular disease risk equivalent, kidney dysfunction is considered an independent predictor of increased cardiovascular risk that increases with deteriorating kidney function. The association is a very complex one, and the term cardiorenal syndrome is now widely used. Cardiovascular disease in chronic kidney disease patients usually manifests as ischemic heart disease (in the form of angina, acute coronary syndrome or sudden cardiac death), cerebrovascular disease, peripheral vascular disease, and congestive heart failure. Vascular disease includes atherosclerosis and vascular calcifications, and cardiomyopathy comprises left ventricular hypertrophy, cardiac fibrosis and left ventricular systolic and diastolic dysfunction. In addition to the well-established traditional risk factors such as hypertension, hyperlipidemia, insulin resistance and diabetes mellitus, the association is supported by synergistic action of non-traditional risk factors such as excessive calcium-phosphorus load, hyperparathyroidism, anemia, hemodynamic overload, malnutrition, inflammation, hyperhomocysteinemia, altered nitric oxide synthase and increased oxidative stress. This paper summarizes the current understanding of the significance of specific uremic retention solutes, natriuretic peptides, biochemical markers of disorders in calcium-phosphorus homeostasis, systemic inflammation, oxidative stress, and dyslipidemia.

**Keywords:** chronic renal failure, cardiovascular disease, biochemical markers

**Kratak sadržaj:** Kod pacijenata sa hroničnim oboljenjem bubrega, kardiovaskularni morbiditet i mortalitet su značajno povišeni. Iako se ne može smatrati ekvivalentom rizika za kardiovaskularne bolesti, veruje se da je bubrežna insuficijencija nezavisni prediktor povećanog kardiovaskularnog rizika i da se taj rizik povećava sa slabljenjem bubrežne funkcije. Ova udruženost je veoma kompleksna i danas se široko koristi termin kardiorenalni sindrom. Kardiovaskularna bolest u hroničnoj bolesti bubrega obično se ispoljava kao ishemijska bolest srca (u obliku angine, akutnog koronarnog sindroma ili nagle srčane smrti), cerebrovaskularna bolest, periferna vaskularna bolest i kongestivna bolest srca. Vaskularna bolest obuhvata aterosklerozu i vaskularne kalcifikacije, dok kardiomiopatija obuhvata hipertrofiju leve komore, kardijalnu fibrozu i sistolnu i dijasolnu disfunkciju leve komore. Pored dobro poznatih tradicionalnih faktora rizika kao što su hipertenzija, dislipidemija, insulinska rezistencija i diabetes mellitus, u osnovi ove udruženosti je i sinergističko delovanje netradicionalnih faktora rizika kao što su povećanje odnosa kalcijum-fosfor, hiperparatireoidizam, anemija, hemodinamsko opterećenje, pothranjenost, zapaljenje, hiperhomocisteinemija, izmenjena sinteza azot-monoksida i povećan oksidativni stres. U radu se razmatraju dosadašnja saznanja o značaju pojedinih uremijskih toksina, natriuretičkih peptida, biohemijskih markera poremećaja u homeostazi kalcijuma i fosfora, sistemske inflamacije, oksidativnog stresa i dislipidemije.

**Ključne reči:** hronična bubrežna insuficijencija, kardiovaskularna bolest, biohemijski markeri

**Introduction**

Kidney dysfunction is nowadays considered an independent predictor of an increased cardiovascular (CV) risk that increases with deteriorating kidney function. CV mortality thus accounts for almost one half, and sudden cardiac death for almost one quarter of mortality in end-stage renal disease (ESRD) (1, 2).

Address for correspondence:

Mirjana Đerić  
Hajduk Veljkova 1-9, 21000 Novi Sad  
Tel/Fax.: +38121529148  
e-mail: mirjanadjeric@gmail.com

The interaction between the heart and the kidneys is a complex one. Cardiovascular disease (CVD) in chronic kidney disease (CKD) patients usually manifests as ischemic heart disease, cerebrovascular disease, peripheral vascular disease and congestive heart failure. Vascular disease comprises atherosclerosis and vascular calcifications, whereas cardiomyopathy comprises left ventricular hypertrophy, cardiac fibrosis and left ventricular systolic and diastolic dysfunction (2–4).

Chronic kidney disease causes hypertension, dyslipidemia, insulin resistance and eventually diabetes mellitus (5), and is associated with non-traditional risk factors such as excessive calcium-phosphorus load, hyperparathyroidism, anemia, hemodynamic overload, malnutrition, inflammation, hyperhomocysteinemia, altered nitric oxide (NO) synthase, and increased oxidative stress (1, 4).

### Uremic retention solutes

Uremic retention is a complex problem that involves progressive retention of a large number of components that are normally excreted through healthy kidneys and are difficult to remove by dialysis. The components are called retention solutes, or uremic toxins, considering their unfavorable effects on biological functions. The biological activity and clinical role of particular uremic toxins is not directly dependent on their concentrations; urea and creatinine, the most widely used markers of uremic retention that have high serum concentrations, have a relatively limited biological activity (6). Protein-bound compounds have recently been identified as the toxins playing a major part in the development of vascular lesions in CKD.

In the group of *phenols*, *p*-cresol, a product of phenylalanine and tyrosine metabolism circulating mainly in the form of conjugated *p*-cresylsulphate, has been shown in clinical studies to predict CV mortality in hemodialysis patients (7), which has been associated with increased oxidative burst activity. Phenylacetic acid, a degradation product of the phenylalanine metabolism, may also contribute to oxidative stress in CKD patients through different effects on the regulation of nitric oxide synthase (8).

*Polyamines*, mostly intracellular organic cations (spermine, spermidine and putrescine) produced by L-arginine catabolism, have also been found to exhibit toxic effects on vascular cells in renal failure patients (9).

Among *indoles*, tryptophan degradation metabolites, kynurenines show an independent and significant association with endothelial dysfunction in ESRD patients (10). The vascular toxins include indoxyl sulphate, which acts mainly via pro-oxidant mechanisms (11) and is possibly involved in vascular remodeling (12).

As regards *advanced glycation end-products* (AGE), the major effect of protein glycation in uremia is loss of clearance of glycation free adducts. It is assumed that they return to vascular cells and impair their function, thus likely contributing to increased CV risk. The changes in plasma levels of glycation adduct residues of proteins are mostly moderate, since they are not removed directly through the kidneys (13). Increased AGE formation in uremia may be a result of impaired receptors for AGE (RAGE) by the S100A12. Moreover, an independent association of this uremic toxin with carotid intimal media thickness in ESRD has been suggested, and its role is likely a pro-inflammatory one (14). The dicarbonyl proteome is likely a mediator in glycation damage in uremia. Elevated levels of dicarbonyl glycation agents in patients on dialysis, the so-called dicarbonyl stress, result from the changes in their endogenous production, alterations in the activity of enzymes involved in anti-glycation defense and their decreased clearance (13). Endothelial dysfunction, increased atherogenicity of LDL and proinflammatory activity of AGEs may associate protein glycation with an increased risk of CVD in ESRD patients (8, 13)

*Asymmetric dimethylarginine* (ADMA), a free water-soluble low molecular weight solute and a catabolite of proteins containing methylated arginine residue, causes endothelial dysfunction by direct and indirect effects on NO activity, and is now considered a strong marker of atherosclerosis and a predictor of mortality and CVD complications in CKD and ESRD (11). Increased ADMA in uremia may be induced by increased enzymatic synthesis or reduced enzymatic degradation (15).

*Cystatin C*, a small 13 kD protein, is a cysteine proteinase inhibitor produced constantly by all nucleated cells, mostly unrelated to renal function. It is filtered freely in renal glomeruli and reabsorbed and catabolized in proximal tubules. It is considered a marker of primarily mildly to modestly impaired renal function. Its increased plasma concentrations have been found to predict the presence and severity of CVD in mild renal impairment, hence it could be an early marker of vascular risk (16). It has been suggested that cystatin C may directly contribute to atherogenesis by affecting arterial extracellular matrix remodeling (17).

*Leptin*, a 16 kD protein and a product of the obese (*ob*) gene, exhibits numerous potentially atherogenic, thrombogenic and angiogenic effects on cardiovascular homeostasis. It has been shown in numerous studies to be an independent risk factor for clinical atherosclerosis. Furthermore, plasma leptin correlates with some markers of subclinical atherosclerosis in renal failure patients (11, 12, 18). Its increase in CKD is due not only to a decreased glomerular filtration rate, but also to decreased catabolism in renal parenchymal cells and increased synthesis influenced by immunological and metabolic

factors, primarily insulin and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) (19). However, due to pleiotropy of leptin's actions and its possible functional role in several clinical manifestations associated with renal failure, primarily related to energy metabolism, it is still unclear whether uremic patients are sensitive or resistant to some of leptin's actions (18).

In addition, many other uremic toxins such as uric acid, dinucleoside polyphosphates,  $\beta$ 2-microglobulin, interleukin-18 (IL-18), IL-1 $\beta$ , TNF- $\alpha$  and angiotensin-II have been implicated in the development of endothelial dysfunction and initiation and progression of atherosclerosis as a chronic inflammation condition, primarily by acting proinflammatory and increasing oxidative stress (8, 11). Proinflammatory cytokines basically represent secondary uremic toxins, since their expression is initially triggered by the uremic condition and the retention occurs due to loss of renal clearance.

Parathormone (PTH), phosphate, homocysteine and natriuretic peptides, which could also be classified under uremic toxins, have specific characteristics and hence will be described separately.

### Hyperhomocysteinemia

Homocysteine (Hcy), a 13 kD sulfur-containing amino acid, is produced by the methionine metabolism and metabolized through the remethylation and transsulfuration pathways. In hemodialysis and kidney failure patients, there are complex changes in the sulfur-amino acid metabolism. Although a decreased Hcy catabolism as a result of chronic uremia and impaired tubular cells has been suggested, renal function described as creatinine clearance is the strongest determinant for total Hcy (20).

Most major clinical studies in the general population and in CKD patients have found hyperhomocysteinemia to be an independent cardiovascular risk factor. However, this has been contradicted in a majority of secondary preventive intervention studies, suggesting that Hcy is only an associated marker. As a potential candidate, S-adenosylhomocysteine (AdoHcy), a potent competitive methyltransferase inhibitor that is itself a predictor of CVD and whose increased intracellular concentration is associated with hyperhomocysteinemia, has been suggested. In CKD and uremia, hyperhomocysteinemia and high levels of intracellular AdoHcy are associated with inhibition of DNA methyltransferases and altered gene expression. Furthermore, since plasmatic homocysteine is almost completely protein-bound, it is possible that homocysteine toxicity originates from protein homocysteinylolation that may contribute to structural and functional alterations at the molecular and cellular level. However, there is strong evidence about direct atherogenic and thrombogenic potentials of Hcy (21, 22).

### Natriuretic peptides

The family of *natriuretic peptides*, in particular BNP (B-type), and its precursor NT-proBNP (N-terminal pro-B-type), are reliable biomarkers of increased myocyte stress, whose diagnostic and prognostic value has been established within the CVD spectrum. These regulatory peptides are secreted from myocytes in response to volume and pressure overload. However, their prognostic value in CKD could be diminished by the fact that their clearance, like other small molecular weight proteins, is dependent on renal function (23). A recent prospective study has shown, however, that despite the inverse association of BNP and NT-proBNP with glomerular filtration rate, an independent predictor of their serum concentrations is cardiac production (24). NT-proBNP has been shown a better predictor of early mortality in the renal-dialysis population, compared with troponin T (TnT), which is primarily predictive of later mortality (25).

### Alteration in calcium-phosphorus homeostasis

As a result of hyperphosphatemia and a high prevalence of nutritional vitamin D deficiency in patients with renal dysfunction, CKD patients have hyperparathyroidism and higher calcium-phosphorus product that necessarily lead to bone remodeling and soft tissue and vascular calcifications. Along with extensive and marked atherosclerotic intimal calcifications, there are present medial types of calcifications (Monckeberg's calcinosis). The systemic disease of mineral and bone metabolism in uremic patients is termed Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD) (12, 26, 27).

It has been clearly established that the presence of arterial calcification is a predictor of increased mortality and CV death in ESRD patients (1, 2). Hyperphosphatemia is an independent risk factor for vascular calcifications and CV events, and mortality risk increases with elevated serum phosphorus levels and calcium-phosphorus product (26, 27). In addition, some epidemiological and *in vitro* studies seem to corroborate the stimulatory effect of PTH on cardiac fibrosis and its negative effect on left ventricular myocardial function and cardiac hypertrophy in uremic patients (26, 28).

In addition to these pro-calcific factors, the progression of mineralization depends also on inhibitory factors such as fetuin-A, pyrophosphate, osteopontin, osteoprotegerin, and  $\gamma$ -carboxyglutamic acid protein. Recent data suggests that serum fetuin-A (alpha2-Heremans Schmid glycoprotein; AHGS), a circulating calcium inhibitor *in vivo* and a negative acute phase protein, may be a significant mediator of vascular calcification in patients with ESRD, as well as an inflammatory predictor of overall and CV mortality, even more potent than C-reactive protein (CRP) (29).

## Systemic inflammation

Chronic systemic inflammation is a constituent part of CKD because of a range of factors interplaying in the predialysis and especially in the dialysis stage, such as reduced cytokine clearance, uremic retention solutes, oxidative stress, atherosclerosis per se, different non-verified infections, membranous bioincompatibility and exposure to endotoxins (8, 30). CKD is virtually a condition of chronic low-grade inflammation, termed para-inflammation, subclinical inflammation, or micro-inflammation, and inflammation has been well-established as one of the most potent non-traditional risk factors for CVD and atherosclerosis (4).

Among the circulating inflammation markers, C reactive protein (CRP) is the most important as a strong and independent indicator of vascular risk in ESRD patients. A strong association between plasma CRP levels and all-cause and cardiovascular mortality in renal patients was established already in early studies (31, 32). CRP is an acute-phase reactant synthesized in the liver in response to proinflammatory cytokines IL-1, IL-6 and TNF- $\alpha$ , which are all also significantly increased in ESRD and predict mortality (23). Interleukin-6 has recently been found to be a much more reliable predictor not only of CVD and mortality, but also of malnutrition in ESRD (33). In addition, CRP correlates with many other acute phase reactants that are potent CV risk factors (1, 34). CRP has been shown to have numerous proatherogenic, prothrombotic and proliferative characteristics and play a possible causal role in different stages of atherogenesis (34, 35). Unfortunately, it lacks specificity (4, 23).

Monocytes and monocyte-derived macrophages are inflammation components directly involved in the atherosclerotic plaque pathogenesis. CKD is characterized by a domination of monocytes with a high level of expression of the surface molecules CD14 and CD16 (CD14<sup>++</sup>CD16<sup>++</sup> monocytes) and angiotensin conversion enzyme (ACE) on their surface, which may be associated with increased oxidative stress in the plaque. The presence of large numbers of these proinflammatory tissue-aggressive monocytes has been found to be a strong predictor of mortality in hemodialysis patients and a prospective CVD marker (36).

## Oxidative stress

Oxidative stress is defined as a condition of imbalance between reactive oxygen species (ROS) production and endogenous antioxidant defense mechanisms.

As shown in a series of reports over the past years, renal patients live under particular pro-oxidative conditions. Increased oxidative stress in uremia results from an increased ROS production in

vascular and glomerular cells, leukocytes and renal interstitial cells, as well as from a loss of antioxidant activity (37, 38). It has been suggested that particularly the treatment of uremic patients with hemodialysis and peritoneal dialysis contributes to oxidative stress and decreased antioxidative defense mechanisms (39). Other reasons for ROS elevations are a high frequency of diabetes, chronic inflammation and excessive intake of parenteral iron (40, 41).

Oxidative stress leads to structural and/or functional impairments in cellular components such as DNA, proteins, carbohydrates and lipids, and therefore represents a significant cofactor contributing to endothelial dysfunction, inflammation, atherosclerosis and glomerulosclerosis (42, 43). The imbalance in ROS formation may have deep vascular deleterious effects, as well as affect the pathogenesis and progression of heart failure, since oxidative stress may damage cellular proteins and cause myocyte apoptosis and necrosis (44).

In chronic renal failure patients, markers of lipid peroxidation and markers of antioxidant defense have been associated with reduced endothelium-dependent vasodilatation, through regulation of NO bioavailability (4, 42). In hemodialysis patients, there is an increased production of oxidized low density lipoproteins (LDL), and autoantibody titer against oxLDL is a predictor of mortality in ESRD patients on vitamin supplementation. Increased LDL oxidation seen in uremic patients can play a significant role in atherogenesis via multiple pathophysiological mechanisms (31). Additionally, studies on effects of hemodialysis treatment on oxidative stress in ESRD have suggested that malondialdehyde (MDA) levels should be measured as a marker of oxidative damage of lipids and ALA-D ( $\delta$ -Aminolevulinatase) reactivation index as a marker of oxidative damage of thiol protein (39).

## Dyslipidemia

Dyslipidemia, a well-known traditional risk factor for premature atherosclerosis is found in 40–60% of CKD patients (45). It is characterized by accumulation of triglyceride-rich particles and decreased HDL-cholesterol concentrations, due to impaired triglyceride removal and/or increased triglyceride synthesis rate or VLDL apoB-100 overproduction (46). Cholesterol concentrations are typically similar to or lower than those in the general population (31, 43), but this pattern often conceals a highly abnormal lipid subfraction profile with a predominance of atherogenic small, dense LDL (sd LDL) and HDL particles (47). Furthermore, elevated serum Lp(a) concentrations have also been reported (48).

Although the Framingham Heart Study has shown that HDL-cholesterol and CKD have a synergistic effect on CVD risk (49), the prognostic value of dyslipidemia in CKD has not been confirmed

(34). Moreover, paradoxically, it was found that mortality was higher in patients with low cholesterol levels, which is likely attributable to the effects of associated factors such as malnutrition and higher levels of systemic inflammation (50). Dyslipidemia and inflammation are associated through several mechanisms and it is believed that they together may be responsible for premature atherosclerosis in renal disease. Even if dyslipidemia is not clearly associated with CVD in hemodialysis patients, it may act through the inflammatory process and thus accelerate atherosclerosis.

### Conclusion

Although it cannot be regarded as a CVD risk equivalent, CKD does represent a risk factor for CVD.

The association is a very complex one, and the term cardiorenal syndrome (CRS) is now widely used, albeit without a consistent or well-defined definition. In addition to the well-established traditional risk factors such as hypertension, dyslipidemia, insulin resistance and diabetes mellitus, the association is supported by an interplay of non-traditional risk factors such as excessive calcium-phosphorus load, hyperparathyroidism, anemia, hemodynamic overload, malnutrition, systemic inflammation, hyperhomocysteinemia, altered nitric oxide synthesis, and increased oxidative stress.

### Conflict of interest statement

The authors stated that there are no conflicts of interest regarding the publication of this article.

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