EDITORIAL

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Early Development and Rapid Progression of Atherosclerosis in Patients with Chronic Kidney Disease

Wczesny rozwój i szybka progresja miażdżycy u pacjentów z przewlekłą chorobą nerek

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Abstract

Chronic kidney disease (CKD) is an important risk factor for cardiovascular disease, due mostly to premature development and accelerated course of atherosclerosis. Apart form traditional risk factors influencing the development of atherosclerosis in general population, the role of the factors associated with endothelial damage, the oxidative stress-altered lipoprotein structure and function and chronic inflammation was recently characterized. It was suggested that activation of local renin-angiotensin system, increased oxidative stress and production of pro-inflammatory cytokines like interleukin-6 (Il-6) and tumor necrosis factor-α (TNF-α) are probable candidates to play a key role in early stages of CKD. Persistent microalbuminuria and proteinuria are independent risk factors for progression of both renal injury and vascular disease. As kidney function impairment progresses in the course of CKD, the prevalence and magnitude of several non-traditional risk factors for atherosclerosis, such as oxidative stress, endothelial dysfunction, chronic inflammation, accumulation of advanced glycation end-products and other toxic metabolites and vascular calcification increase. In patients with renal failure low serum levels of cholesterol, homocysteine, low blood pressure and malnutrition are associated with increased cardiovascular morbidity and mortality and it was suggested that development of the malnutrition, inflammation, atherosclerosis (MIA) syndrome is involved in the "reverse epidemiology" of cardiovascular complications in patients with end-stage renal disease (**Adv Clin Exp Med 2006, 15, 2, 227–232**).

Key words: chronic kidney disease, atherosclerosis, oxidative stress, inflammation, cardiovascular disease.

Chronic kidney disease (CKD) is defined as kidney damage, as confirmed by kidney biopsy or markers of damage, or glomerular filtration rate (GFR) < 60 ml/min/1.73 m^2 for ≥ 3 months [1]. Markers of kidney damage include microalbuminuria, proteinuria, abnormalities on urine dipstick or sediment examination, or abnormalities on imaging studies of the kidneys. GFR can be estimated from prediction equations based on serum creatinine and other variables, including age, sex, race and body size [1]. The stage of CKD is based on the level of GFR as presented in Table 1.

It was established that CKD is a risk factor for cardiovascular disease [2–4], caused by premature development and accelerated course of atherosclerotic vascular changes in the prevalent number of patients. Early development and rapid progression of atherosclerosis in patients with CKD constitute the main difference when compared to general population.

Both humoral and mechanical factors, modulated by genetic influences, predispose to atheromatous vascular lesions. Among the humoral factors, the role of these associated with endothelial damage, the oxidative stress-altered lipoprotein structure and function, and microinflammation have been recently considered as involved in early vascular injury in CKD [5]. There are multiple mechanisms whereby the inflammatory response can alter the vascular endothelium [6, 7], blood lipids [8, 9] and plasma protein composition in such a way as to favor vascular injury.

Table 1. Stages of CKD

Tabela 1. Stadia przewlekłej choroby nerek

Stage (Stadium)	Description (Opis)	GFR* (ml/min/1.73 m^2)
1	Kidney damage with normal or ↑ GFR (Uszkodzenie nerek z prawidłowym lub ↑ GFR)	≥ 90
2	Kidney damage with mild ↓ GFR (Uszkodzenie nerek z niewielkim lub ↓ GFR)	60–89
3	Moderate ↓ GFR (Umiarkowany GFR)	30–59
4	Severe ↓ GFR (Nasilony GFR)	15–29
5	Kidney failure (Niewydolność nerek)	< 15 or dialysis (< 15 lub dializowanie)

* GFR – glomerular filtration rate.

* GFR – filtracja kłębuszkowa.

Activation of local renin-angiotensin system within the kidneys has been suggested to be the adaptative response to kidney injury and loss of renal mass [10]. Angiotensin II clearly plays a role in altering endothelial function and promotes oxidative injury of the vasculature and is a likely candidate to play a key role in early stages of CKD. The hypertrophic and proliferative effects of angiotensin II on mesangial cells and vascular smooth muscle cells are mediated by oxidants generated from nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase family enzymes (now referred to as Nox). The superoxide produced from Nox isoenzymes (expressed in mesangial cells, adventitial fibroblasts, smooth muscle cells of the resistance arteries, endothelial cells and leukocytes) can rapidly scavenge the nitric oxide (NO) and impair its vasodilatory functions. Reactive oxygen species, such as superoxide and hydrogen peroxide act also as direct signaling molecules regulating cellular hypertrophy, proliferation, cell migration and indirectly exerting pathological effects in the vasculature by oxidative modification of lipids and proteins. Furthermore, angiotensin II induces interleukin-6 (Il-6) synthesis through a lipogenase-mediated mechanism and thus can directly augment inflammation [11]. Il-6 has been implicated as an atherogenic cytokine both in patients with CKD and in subjects without kidney function impairment [12]. Il-6 is secreted from fibroblasts, adipocytes, monocytes, and endothelial cells. Unlike most cytokines, which

exert their effects via local paracrine/autocrine mechanism, Il-6 reaches significant concentrations in the circulation, and its effects are more systematic, including stimulation of C-reactive protein (CRP) production by the liver, increased blood viscosity and increased platelet activity. The monocytes activated by Il-6 contribute to the deposition of fibrinogen in the vessel wall. In the supernatants from Il-6 activated endothelial cells in culture, the soluble forms of the adhesion molecules ICAM-1, VCAM-1, and E-selectin have been detected [13]. On the basis of the "response to injury" hypothesis, atherosclerosis parallels the inflammatory process, and one of the primary events in both is the adhesion of circulating monocytes to endothelial cells [14]. Local accumulation of leukocytes in the vascular wall is initialized by marginalization and roling of the leukocytes along the epithelium, a process mediated by the selectins, this is followed by the attachment to endothelial cells and transmigration into the intimal spaces, a process mediated by the adhesive molecules expressed in activated endothelium [15]. It was demonstrated that plasma levels of ICAM-1 and E-selectin may serve as molecular markers for atherosclerosis and the development of coronary heart disease (CHD). All these data suggest that increased Il-6 production, induced, at least partly, by the activation of R-A system in CKD patients is a major modulator of atherosclerotic vascular injury. Moreover, stimulation of vascular smooth muscle cells with Il-6 results in up-regulation of AT1 receptor mRNA synthesis in vitro and increased vascular angiotensin II type 1 (AT1) receptor expression *in vivo*, and is associated with enhanced vascular superoxide production and impaired endothelium-dependent vasodilation [12]. The role of local increase of the angiotensin II activity and oxidants produced by Nox enzymes early in the course of CKD is not well documented in humans and requires further investigation. It was demonstrated, however, that both early CKD and atherosclerosis are associated with endothelial dysfunction and subclinical inflammation.

Microalbuminuria, an early and reversible sign of kidney damage, is considered a marker of endothelial damage and the indicator of generalized increase of vascular permeability [16]. Both, persistent microalbuminuria and proteinuria are independent risk factors for progression of renal injury and for vascular disease in diabetic and non-diabetic patients [17]. In the majority of patients with CKD either persistent microalbuminuria or proteinuria develop early in the course of the disease, and are additional risk factors for vascular disease, reflecting general injury to the vascular endothelium, which is not present in general pop-

ulation. When proteinuria is of the nephrotic range, there are alterations in plasma protein and lipoprotein composition that are themselves associated with progression of atherosclerosis.

As kidney function impairment progresses in the course of CKD, the serum levels of Il-6 and other inflammatory biomarkers increase. The relationship between renal function and circulating Il-6, CRP, and tumor necrosis factor-α (TNF-$α_1$, which is another pro-inflammatory cytokine) has been demonstrated, indicating that the kidney play a role in the clearance of pro-inflammatory cytokines [18]. Although decreased elimination may be a major cause of elevated levels of pro-inflammatory cytokines in patients with impaired kidney function, increased generation also may play a role. The fluid overload, congestive heart failure (CHF), preexisting cardiovascular disease, various persistent infections, visceral adiposity and several variations within the genes encoding cytokines, may contribute to increased serum levels of pro-inflammatory cytokines [18]. The patients with slightly elevated serum creatinine levels > 1.5 mg/dl in men and > 1.3 mg/dl in women (which corresponds approximately to the stage 3 of CKD) had significantly increased levels of not only Il-6 but also CRP and fibrinogen, as well as increased levels of some clothing factors including factor VIIc, factor VIIIc, plasmin-antiplasmin complex and D-dimer, suggesting that even mild renal function impairment is associated with and possibly causes inflammation and vascular injury [19]. It was also demonstrated that serum creatinine level alone was an independent risk factor for cardiovascular mortality and morbidity, consistent with the hypothesis that the impairment of renal function *per se* may be an important risk factor for vascular disease [20]. This risk factor is not commonly present in the general population, although about 10% of low- and 30% of high-risk cardiovascular disease populations have mild renal insufficiency [21]. Mild renal insufficiency is now being regarded as independent cardiovascular risk factor of a similar (or even larger) magnitude than traditional risk factors, such as diabetes mellitus and hypertension [22].

There are several mechanisms by which renal insufficiency *per se* may mediate an accelerated atherogenic process. The prevalence and magnitude of a number of non-traditional risk factors for atherosclerosis such as oxidative stress, endothelial dysfunction, inflammation, accumulation of the advanced glycation end-products (AGEs) and several toxic nitrogen metabolites, as well as vascular calcification increase as renal function deteriorates [22]. The coexistence of these non-traditional cardiovascular risk factors with the tradi-

tional ones, such as hypertension, dyslipidemia, hyperhomocysteinemia and others results in accelerated course of atherosclerosis in patients with CKD.

The association between inflammation, reflected by the elevated levels of pro-inflammatory cytokines (Il-6, TNF-α), CRP, decreased concentrations of anti-inflammatory cytokines like Il-10 and the atherosclerotic cardiovascular disease is well documented in patients with renal failure (stage 5 of CKD). Several lines of evidence suggest that the balance between pro- and anti-inflammatory cytokines moved toward pro-inflammatory profile may contribute to the atherogenic process *per se* [22, 23] in patients with advanced stages of CKD, but it cannot be ruled out that the association between chronic inflammation and cardiovascular disease may be indirect, as other factors known to mediate atherosclerosis, such as endothelial dysfunction, increased oxidative stress and insulin resistance are all strongly associated with inflammation [22]. It should be also considered, that the acute-phase response is, at least partly, an epiphemenon reflecting established atherosclerotic disease [22]. Nevertheless, it was demonstrated that elevated Il-6 levels have been associated with progression of carotid atherosclerosis in patients with end stage renal disease (ESRD) [24], which confirmed independent pro-atherogenic properties of Il-6.

In patient with CKD, particularly in these with renal failure and end stage renal disease (ESRD), the level of asymmetric dimethylarginine (ADMA), an endogenous inhibitor of NO-synthase, is significantly increased, due to reduced excretion by the kidneys and the oxidative stress which decreases the activity of enzyme involved in the metabolism of ADMA: diethyl-diamino-hydrolase. Raised plasma concentration of ADMA may impair blood flow, accelerate atherogenesis and is associated with increased carotid intima media thickness, left ventricular hypertrophy, and cardiac remodeling [25, 26]. The accumulation of ADMA in CKD represents one of the numerous non-traditional (uremia-related) risk factors for atherosclerosis, which are not present in general population (Table 2).

In ESRD patients, in contrast to general population, extensive vascular calcification can be observed in the younger age groups. Abnormal phosphate and calcium metabolism in CKD resulting in increased calcium phosphate product is the most important factor in the development of cardio-vascular calcification in ESRD, but chronic inflammation may be also the significant promoter of vascular calcification [22]. Among the hemodialysis patients, these with low fetuin-A level, an important inhibitor of vascular calcification, down-regulated by inflammation, showed

Table 2. Amenable to intervention traditional and non-traditional (uremia related) risk factors for atherosclerosis

Tabela 2. Poddające się interwencji tradycyjne i nietradycyjne (zależne od mocznicy) czynniki ryzyka miażdżycy

Traditional (Tradycyjne)	Non-traditional – uremia related (Nietradycyjne – zależne od mocznicy)
Hypertension (Nadciśnienie) Dyslipidemia (Dyslipidemia) Diabetes mellitus (Cukrzyca) Smoking (Palenie tytoniu) Left ventricular hypertrophy (Przerost lewej komory) Hyperfibrinogenemia (Hiperfibrynogenemia) Hyperhomocysteinemia (Hiperhomocysteinemia) Menopause (Menopauza)	Endothelial dysfunction (Dysfunkcja śródbłonka) Oxidative stress (Stres oksydacyjny) Inflammation (Zapalenie) Wasting, hypoalbuminemia (Wyniszczenie, hipoalbuminemia) Advanced glycation end products (Końcowe produkty glikacji) ADMA (Asymetryczna dimetyloarginina) Prothrombotic factors (Czynniki prozakrzepowe) Abnormal divalent ion metabolism (Ca/P) (Zaburzony metabolizm jonów dwuwartościowych Ca/P) Anemia (Niedokrwistość)

significantly poorer survival than those with normal values [27]. It was also recently showed that hemodialysis patients with the signs of rapid progression of aortic calcification were not only more inflamed but also had elevated levels of osteoprotegerin [28].

There is also proof that atherosclerotic plaques in patients with renal failure differs from these in persons with normal kidney function. The coronary plaques in uremic patients are characterized by increased media thickness, infiltration and activation of macrophages and marked calcification. The most marked difference in comparison to persons demonstrating normal kidney function is not the size but rather composition of the plaque [29]. Heavily calcified and inflamed plaques may

contribute to the excessive cardiovascular risk in ESRD patients [22].

Other important difference between the patients with ESRD and general population was that whereas traditional risk factors, such as diabetes mellitus and smoking, were strongly associated with cardiovascular disease in patients on dialysis therapy as it was demonstrated in general population, neither serum total cholesterol nor systolic blood pressure (both important traditional risk factors) were associated with coronary artery disease [30]. In contrast to the well-known association between hypercholesterolemia, hypertension, hyperhomocysteinemia, obesity and poor outcome due to atherosclerotic cardiovascular complications in the general population, in patients with ESRD low, rather than high serum levels of cholesterol and homocysteine, low blood pressure and wasting were associated with increased cardiovascular morbidity and mortality [22]. The explanation of this phenomenon, referred to as "reverse epidemiology", may by partially related to the presence of the malnutrition (wasting), inflammation, atherosclerosis (MIA) syndrome, which develops in patients with advanced stages of CKD and is common in these with ESRD [31]. As increased release of inflammatory cytokines, such as Il-6 or TNF-α may suppress appetite, and cause muscle proteolysis, hypoalbuminemia and malnutrition and may be involved in the processes that lead to atherosclerosis, one of the important mechanisms for the development of cardiovascular disease and wasting in pre-dialysis and dialysis patients may be cytokine activation [22].

This short review summarizes some data indicating that although traditional risk factors, such as hypertension, diabetes mellitus, dyslipidemia and smoking are highly prevalent among patient with CKD they alone cannot explain the accelerated atherosclerosis in these patients. The prevalence and magnitude of the various non-traditional risk factors present in patients with CKD, but not in general population, such as chronic inflammation, oxidative stress, vascular calcification, AGEs, ADMA accumulation, vascular calcification increase as renal function declines and result in several differences in atherogenesis and cardiovascular risk between patients with CKD and general population.

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