ISSN 1561-6274. Nephrology. 2005. Volume 9. №3.

УДК 616.12+616.613]-092-084

A.V. Smirnov, V.A. Dobronravov, I.G. Kayukov

CARDIORENAL CONTINUUM, PATHOGENETICAL GROUNDS OF PREVENTIVE NEPHROLOGY

Department of Propaedeutics of Internal Diseases, Nephrology Research Institute, Pavlov First Saint Petersburg State Medical University, Russia

Keywords: chronic kidney disease, cardiovascular disease, risk factors, cardiorenal continuum

The present stage of medical science is distinguished by the preventative orientation of most major studies. Traditionally, this orientation has primarily been dominant in cardiology and oncology, by which example the notions of the epidemiology of noncommunicable diseases and risk factors, as well as primary, secondary and tertiary prevention, have been historically progressed. For a long time, extending up to today, nephrology was considered a narrow speciality. Prevention was understood in terms of a slowdown in the progression rate of renal failure in patients with a known renal disease and thedirection of nephro- (or, more correctly, reno-protection)was developed according to this understanding. Thanks to numerous studies carried out both by foreign and Russian authors, risk factors associated with more rapid formation of glomerulo- and tubulointerstitial sclerosis in individuals with diagnosed kidney disease were identified. Based on the analysis of literature and our own data, we presented a classification of risk factors for the progression of renal failure in one of our previous works (Fig. 1) [1].

Let us emphasise once again that the question concerns patients having established renal diagnosis: glomerulonephritis, pyelo- and interstitial nephritis, polycystic kidney disease, diabetic nephropathy and others. It is easy to see that the majority of potentially modifiable risk factors for the progression of renal diseases are widespread in the general population. These are associated with a greater frequency of atherosclerosis formation, and are therefore related to cardiovascular risk factors. The question is to what extent these risk factors can be associated with impaired renal function in persons without primary renal pathology. Paradoxical as it may seem, this issue only came under the purview of nephrology fairly recently. The only exception to this was, perhaps, arterial hypertension; even here, it is necessary to supply caveats. Thus, the point of view was initially formed that only severe, uncontrolled hypertension can lead to the development of glomerulosclerosis, azotaemia and the death of patients from renal failure [2]. In recent years, the attention of researchers has been attracted to an evaluation of the renal function of patients having mild forms of essential hypertension against the background of adequate hypotensive therapy [3]. The progress of research in this direction was largely promoted by the world community's acceptance of the chronic kidney disease (CKD) concept proposed by the US National Kidney Foundation at the beginning of the millennium [4]. We recall that chronic kidney disease is "the presence of kidney damage or a decrease in the level of kidney function for three months or more, regardless of the diagnosis" [5]. Thus, the introduction of the supranosological concept has allowed, first, the information about the prevalence of renal dysfunction in the population to be obtained, and, secondly, the attention of the medical community to be focused on the preservation of kidney function not only in primary renal pathology, but also for other diseases where the kidneys are the target organ. The recently completed HOT (Hypertension Optimal Treatment Study) and INSIGHT (Intervention as a goal in Hypertension Treatment) large-scale studies revealed that the initial decrease in renal function (creatinine clearance <60 ml/min, corresponding to the 3rd stage of CKD, see Table 1) in patients withadequately-treated essential hypertensionwas observed in 13 – 30% of cases [6, 7]. In one of thecombined cohort studies, it was shown that even "high normal arterialpressure" is associated with a high risk ofCKD development [8]. At present, it can be consideredasproven that hypertensionof any degree is the leading risk factorof the development of terminal renal failure. For example, in the United States, hypertensivenephropathy is the second most frequent cause ofterminal renal failure;here, the detection frequency of new cases increased by 50% from 1990 to 2001 amounting to

89 per 1 million population [9]. Contemporary data indicate that microalbuminuria(MAU) is the earliest sign of damage to the glomerularbarrier affiliated with essential hypertensionand diabetes, occurring long before the decline of the glomerular filtration rate (GFR) [10]. Microalbuminuria,i.e. the urinary excretion of minimal amounts ofalbumin (within the limits of 30-300 mg/day),can be detected only using special investigation methods. The usual biochemical methodsof proteinuria evaluation areunsubstantiated in these cases.

According to the results of large multicentre studies, it turned out that MAU is detected in 20-30% of patients with arterial hypertension (PREVEND, LIFE), in 25-40% of patients with diabetes I or IItype (AUSDIAB, DEMAND) and even in 5-7% of members of a conditionally healthy population(PREVEND, HAND, AUSDIAB) [11]. The development ofMAU is associated with virtually all components ofmetabolic syndrome [12] and is observedin the process of tobacco smoking [13]. It is believed that MAU reflects the presence of the generalisedendothelial dysfunction in the body, underlying both increases in the risk of atherosclerosis occurrence and progression, and kidney damage with the development of renal failure [17]. Currently, the question concerning to what extentmicroalbuminuria in the general populationreflects the risk of CKD formation, including the stageof renal failure, is under intensive study. Thus, arterial hypertension and microalbuminuria (proteinuria) can be simultaneously considered both as risk factors for cardiovascular pathology and for chronickidney disease. A similar situation can be tracedin relation to other risk factors thathave not been correlated with renal pathology for a long time. Epidemiological studiesindicate that obesity or excess body weight (body mass index> 30 kg/m^2) determine the high risk of cardiovascular morbidity and mortality in the general population [15, 16]. In recent years, it has been determinedthat obesity is an independent risk factor predicting the development of terminal renal failure in the general population [17]. Of course, the population significanceof obesityregarding cardiovascular andrenal pathologies is determined in many ways by the states associated with it, such as type 2 diabetes mellitus, arterialhypertension and dyslipoproteinemia[18]. Nevertheless, the development of specific nephropathy at obesity (a special form of focal-segmentary glomerulosclerosis)is possible in the absence of above states, and its incidence has increased by 10 times for the last 15 years [19].The data of numerous experimentalstudies connectthe development of glomerulosclerosiswith obesity with nephron hyperfiltration [20]. Perhaps, this explains the presence of the positive correlation between the body mass index and GFR, revealed in epidemiological studies [21]. On the other hand, therapeutic

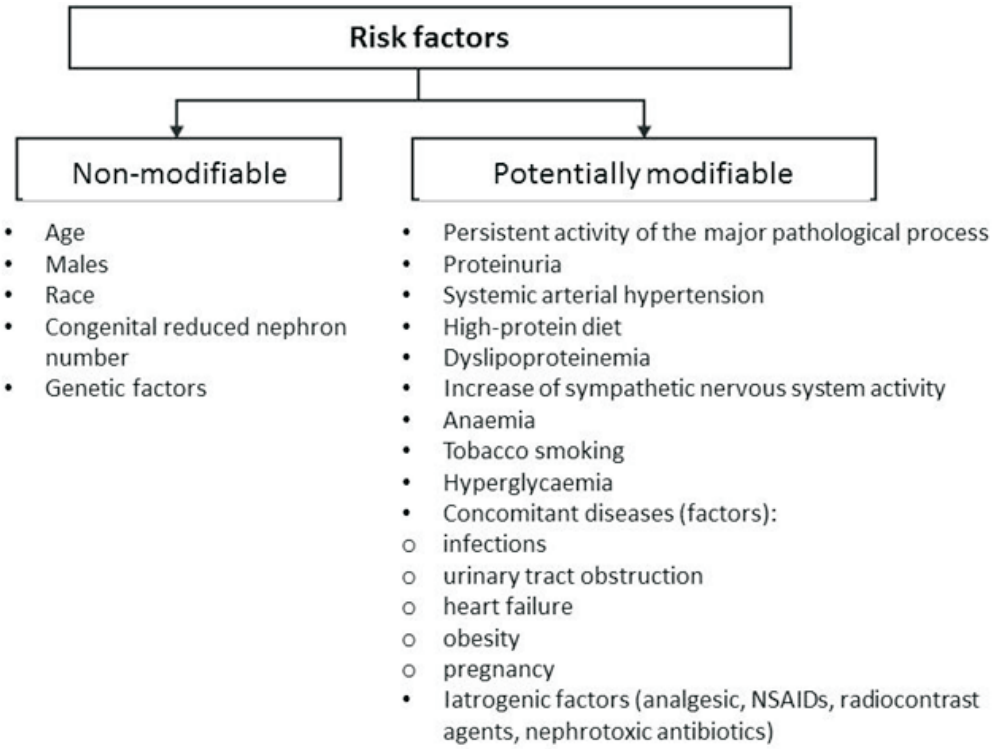

Fig. 1. Risk factors for the progression of chronic kidney diseases.

measures aimed at reducing body weight lead to a normalisation of GFR [18, 21].

Tobacco smoking and dyslipoproteinemia, which are classic risk factors for cardiovascularpathology, are also associated with a high incidence of CKD in the general population.Epidemiological studies indicate that smoking is a dose-dependent risk factor of GFR reduction and the occurrence of microalbuminuria [22]. Moreover, smoking is associatedwith more severe impairment of the kidney functionin the male portion of the population [23]. It is known that hyperlipidemiaworsens the prognosis of any kidney disease and thathypolipidemic therapy (mainlystatins) contributes to the preservation of kidney function [24]. However, the attention of researchershas only recently been drawn to the connectionbetween dyslipoproteinemia and the functionalstate of kidneys in persons not having a primary organicrenal pathology. In epidemiological studiesit was found that hypercholesterolemia [25], hypertriglyceridemia [26] and lowvalues of high-density lipoprotein cholesterol (HDL-C) [25] are independent predictorsof a decrease in renal function in the general population of conditionallyhealthy people. During anexamination of 8,592 people aged from 28 to 75 years old (PREVEND study:prevention of renal and vascular end-stage disease), a negative correlation was found between blood triglyceride levels and creatinine clearance;by contrast, the cholesterol /high-density lipoprotein cholesterol ratiowas positively correlated with renal function [21]. The obtained data allow the dyslipoproteinemia to be considered as an isolated risk factor for chronic kidney diseasewith a high degree of probability.

The experience of preventive cardiology clearly demonstrates that the likelihood of cardiovascular disease increases dramatically in caseswhere a combination of different risk factors occurs. The most typical example confirming this thesis is metabolic syndrome, which attracts the attention of researchers not only because it precedes diabetes mellitus of the second type, but also because it multiplies the risk of developing cardiovascular pathology [27]. At present, two classifications of metabolic syndrome have become widespread: one is that proposed by the US National Cholesterol Education Program (Table 2), while the other, more extended, is that defined by the World Health Organisation (Table 3). As can be seen, many of the previously described risk factors are part of the metabolic syndrome, with abdominal obesity taking a key position. There are several reasons for this. Firstly, abdominal obesity is more closely associated with a decrease in glomerular filtration rate [28]; secondly, abdominal fat tissue is the main site of production of cytokines that determine the formation of endothelial dysfunction [29]. And, thirdly, with intra-abdominal obesity, the production of adiponectin and adipocyte hormone decreases, which have anti-inflammatory effects [18, 29]. The prevalence of CKD estimated by the GFR reduction (<60 ml/min) and microalbuminuria increases proportionally to an increase in the number of risk factors that make up the metabolic syndrome. Thus, the prevalence of CKD (GFR <60 ml/min) in the general population in-

Table 1

Classification of chronic kidney disease
(*NKF K/DOQI GUIDELINES*)

Stage	Description	GFR (ml/min)
0	Risk factors	>90
1	Kidney damage with normal or elevated GFR	>90
2	Mild GFR reduction	60-89
3	Moderate GFR reduction	30-59
4	Severe GFR reduction	15-29
5	Chronic Renal Failure	<15

Table 2

Clinical criteria for metabolic syndrome according to ATP III (Adult Treatment Panel) [27]

Risk factors	Value
Combination of any three risk factors	
- Abdominal obesity	
- waist circumference	
Men	>102 cm
Women	>88 cm
- Level of triglycerides	>150 mg/dl (1.7 mmol/l)
- level of high-density lipoprotein cholesterol (HDL-C)	
Men	<40 mg/dl (1.03 mmol/l)
Women	<50 mg/dl (1.29 mmol/l)
- Arterial pressure	≥130/≥85 mm Hg.
- Fasting blood glucose level	≥110 mg/dl (6.1 mmol/l)

Table 3

Clinical criteria for metabolic syndrome according to WHO [27]

• Insulin resistance, determined by the presence of at least oneof the following criteria: - Type 2 diabetes mellitus - High fasting glucose level - Impaired tolerance to glucose - Hyperinsulinemia in patients with euglycemia
• The presence of at least two risk factors from the following: • Taking antihypertensive drugs and / or high blood pressure (≥ 140 mm Hg systolic or ≥ 90 mm Hg diastolic) • Blood plasma triglyceride level ≥ 150 mg/dl (≥ 1.7 mmol/l) • The level of HDL-C < 35 mg/dl (0.9 mmol/l) in men and <39 mg/dl (1.0 mmol/l) in women • Body mass index (BMI)> 30 kg/m^2 and / or the ratio of the waist circumference to thigh circumference > 0.9 in men and > 0.85 in women • Excretion of albumin with urine *> 20 mg/min or albumin/creatinine ratio in urine ≥30 mg/g

Note: * – microalbuminuria

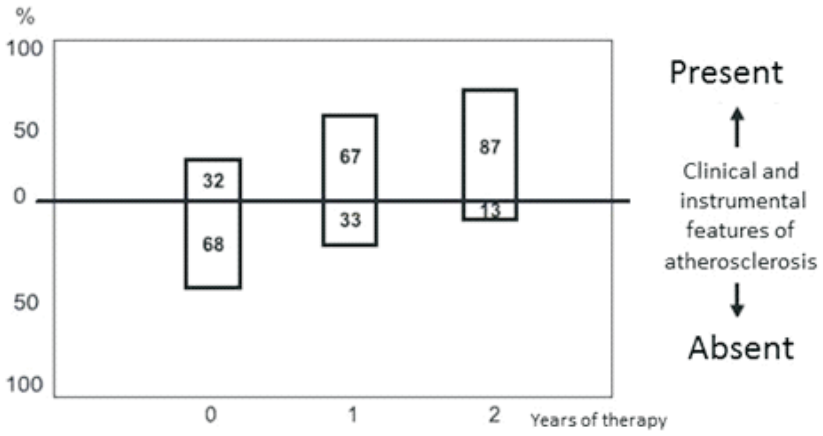

Fig. 2. Atherogenesis in patients on haemodialysis (own data, n = 76)

creased from 0.9% in the case of a single risk factor to 9.2% if all five signs of metabolic syndrome were present. Accordingly, the prevalence of microalbuminuria increased from 4.9% to 20.1% [30].

Thus, most of the currently known cardiovascular risk factors are also risk factors for CKD. In this regard, today's relevant issue is the primary prevention of CKD in people with cardiovascular pathology. The very formulation of such a question does not give rise to any particular objections,whether to nephrologists or to cardiologists, since it completely coincides with classical medical views concerning the kidney as a target organ, at least in arterial hypertension, as well as in other vascular pathologies. However, with such a statement of the question, we involuntarily assign a passive role to the kidney in the cardiovascular continuum [3], subconsciously considering it a "victim of circumstances". It is difficult to agree with this, since the scientific data in recent years, including that derived from large-scale research, allow for an inverse

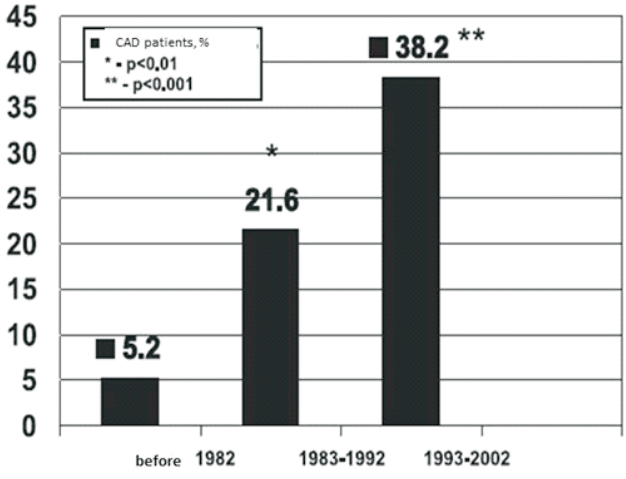

Fig. 3. The proportion of patients with coronary artery disease by the time of dialysis initiation in different years (own data).

relationship, i.e. the influence of renal pathology on the frequency of cardiovascular diseases.

The connection of renal pathology and cardiovascular diseases was first noticed in 1974, when A. Lindner et al. [31] reported that more than 50% of deaths in patients on haemodialysis were due to cardiovascular complications, based on atherosclerotic vascular lesions. Modern data suggest that almost 45% of deaths in this population of patients are caused by cardiovascular diseases, 20% of them being acute myocardial infarction [32]. The risk of death due to cardiovascular disease in haemodialysis patients is 10-30 times higher than in the general population [33]. The data given can indicate the acceleration of atherogenesis processes in patients receiving haemodialysis therapy. According to our information, the detection frequency of clinical and instrumental signs of atherosclerosis for 2 years of haemodialysis increases from 32 to 87% [34] (Fig. 2). It is believed that this may be caused by dyslipoproteinemia, oxidative and inflammatory stresses, changes in haemodynamics and other factors related in some way to uraemia or to the haemodialysis procedure itself [34, 35].

In the case of terminal renal failure, two processes coexist: atherosclerosis and arteriosclerosis, the latter being caused by both hemodynamic (anaemia, arterial hypertension), and metabolic factors (vascular calcification, the impact of parathyroid hormone, homocysteine and asymmetric dimethylarginine, etc.), directly related to uraemia itself [35]. It is not accidental that before the initiation of the renal replacement therapy for terminal renal failure, coronary artery disease (CAD) is diagnosed in 38.2% of cases (Fig. 3), congestive heart failure is detected in 40% of the patients, and a stroke or transient ischemic attack is present in the anamnesis of 10% of the patients [36].

Congestive heart failure and terminal renal failure have such close pathogenetic connections that their coexistence has been referred to as a severe cardiorenal syndrome [37]. The high incidence of cardiovascular disease in patients with terminal renal insufficiency attracted the attention of researchers to the problem of cardiovascular disease in patients with CKD in the early stages, i.e. with moderately reduced values of GFR (in the range of 50-60 ml/min), when the level of serum creatinine is normal or slightly elevated.

In one of the largest studies (Cardiovascular Heart Study) it was found that among people of 65 years and older a moderate decrease in kidney function was accompanied by an increase in the prevalence of hypertension (from 36% to 55%), CAD (from 13% to 26%), and cardiac Insufficiency (from 3% to 8%). In this case, both general and de novo cardiovascular morbidity increased [38]. In another large-scale ARIC study (Atherosclerosis Risk in Communities), which included persons aged 45-64 years, the presence of CKD was associated with an increase in the prevalence of coronary artery disease (from 4.4% to 11%), cerebrovascular disease (from 4.4% up to 10%) and diabetes mellitus (from 13% to 24%) [39]. The results of a prospective large-scale population study conducted in the Danish city of Hoorn showed that in people aged 50 to 75 years, the risk of cardiovascular mortality increased by 26% for every 5 ml/min reduction in GFR. This corresponds to an almost twofold increase in mortality from cardiovascular disease with a basal GFR reduction of 20 ml/min [40]. An even more impressive effect of kidney function on the prognosis was observed in individuals with initial cardiovascular pathology and left ventricular dysfunction (Table 4) [41-44]. In all four large-scale studies, the reduction in GFR below 60 ml/min was associated with a high mortality rate due to cardiovascular complications; this did not depend on other concomitant diseases or factors [44]. Moderate reduction in renal function (GFR <70 ml/min) in persons with acute coronary syndrome, regardless of the ST segment location, is associated with a higher incidence of mortality and recurrent myocardial infarction at the 30th and 180th day of surveying [45]. In individuals with unstable stenocardia or with acute myocardial infarction, a decrease in renal function is a predictor of left ventricular heart failure and cardiac death [46]. The question of the relationship between renal function and cardiovascular pathology is currently being intensively studied, but already-available data allow for a prediction of the presence of a reliable feedback between the GFR values and the risk of

Table 4

Effect of kidney function on the incidence of cardiovascular complications in individuals with left ventricular dysfunction

Study,	Year	Number of patients	The ratio of risks of cardiovascular complications for every 10 ml / min of GFR reduction
SOLVD	2001	6635	1,1
TRACE	2002	6252	1,2
SAVE	2003	2184	1,5
VALIANT	2003	14527	1,1

Note: SOLVD - The Studies of Left Ventricular Disfunction; TRACE - TRAndolapryl Cardiac Evaluation; SAVE - Survival And Ventricular Enlargement; VALIANT - VALsartanIn Acute myocardial INfarcTion.

cardiovascular diseases or their complications [47]. As was mentioned earlier, cardiovascular pathology in CKD is represented by two processes that mutually stimulate each other: atherosclerosis and arteriosclerosis of vessels [35].

There are several reasons for discussing atherogenesis in CKD. First, the number of traditional risk factors for atherosclerosis increases with decreasing kidney function. This pertains, first of all, to arterial hypertension, dyslipoproteinemia, albuminuria [44], which, with renal insufficiency, acquire their own characteristics. Thus, in the genesis of arterial hypertension, the volume overload factor, which contributes to vascular remodelling, begins to play an increasingly important role, which in turn is accompanied by an increase in postload on the myocardium of the left ventricle (due to loss of vascular elasticity) causing its hypertrophy [35]. The decrease in the elastic properties of the vessels (also determined by concomitant calcification) leads to a violation of their damping properties, which is instrumentally evaluated by an increase in the pulse wave propagation velocity [44]. Regardless of the level of AP and the influence of other traditional risk factors, a negative correlation was found between the GFR level and the pulse wave propagation rate when examining 1290 patients with essential arterial hypertension and the initial stages of CKD [48]. Thus an increase in the pulse wave propagation rate is a predictor of cardiovascular complications [49]. The increase in pulse pressure is also pathogenetically associated with the violation of the damper properties of blood vessels. This phenomenon is often recorded in the late stages of CKD and is an independent predictor of cardiovascular mortality [50].

At the very first stages of CKD (↓ GFR up to 60 ml/min), specific shifts appear in the lipid and lipoprotein spectra of blood plasma. In such a situation, the

level of α – HDL cholesterol decreases, the concentration of triglycerides increases and the level of intermediate-density lipoprotein and oxidised forms of low-density lipoproteins (o-LDL) of increased atherogenic activity increases in blood plasma [51,52]. As the kidney function further decreases (III-IV stage of CKD), the symptoms of systemic inflammation and oxidative stress appear [34], which, in turn, lead to protein-energy deficiency and a decrease in cholesterol synthesis. At these very stages of CKD normo- and hypocholesterolemia are recorded; however, despite this, the processes of atherogenesis continue to progress due to the high concentration of o-LDL [51, 52]. Albuminuria increases with progression of CKD, and its association with cardiovascular pathology becomes even more close and obvious [44].

Despite the strong evidential base, it is not possible to explain the accelerated development of atherosclerosis in CKD solely from the perspective of traditional risk factors. First, the prevalence of cardiovascular diseases and their incidence in CKD are much higher than would be expected from the impact of traditional risk factors [44]. Secondly, the initial stages of CKD are accompanied by an increase in the incidence of cardiovascular disease, regardless of the effect of traditional risk factors, which allows the CKD itself to be regarded as the cause of the accelerated development of atherosclerosis. The latter circumstance, apparently, is explained by those metabolic shifts that accompany the decrease in renal function and which provide the predominance of other risk factors for atherogenesis in CKD, called non-traditional in cardiology such as systemic inflammation, oxidative stress, anaemia and hyperhomocysteinemia [53].

For the first time, the attention of researchers to the problem of systemic inflammation in patients with terminal renal insufficiency was attracted to the example of patients receiving haemodialysis treatment. It turned out that the level of C-reactive protein (CRP) in the blood plasma exceeded the upper limit of normal values in 35-46% of patients on haemodialysis [34, 54, 55]. This is explained by two reasons. First, in haemodialysis, there is direct contact between the peripheral mononuclear cells and the synthetic material of dialysis membranes and blood lines, which leads to their activation and an increase in the synthesis of proinflammatory cytokines [56]. Secondly, endotoxins and the fragments of bacterial lipopolysaccharides contained in the dialysis solution can enter the blood flow and stimulate macrophages to synthesise proinflammatory cytokines (IL-1, IL-6, TNF-α) in some haemodialysis methods as a result of reverse diffusion or even filtration [57]. In response to contact with proinflammatory cytokines, hepatocytes synthesise acute phase proteins, including CRP [57]. The signs of systemic inflammation are noted in patients with CKD at earlier stages, long before the initiation of RRT [58]. The reason for this can be a decrease in the clearance of proinflammatory molecules, the accumulation of the final products of glycosylation in the body (especially in diabetes mellitus), which in turn initiate inflammation [59]. In addition, the very process of progression of glomerulo- and tubulointerstitial sclerosis is ultimately an immunocompetent inflammatory reaction [14]. In addition, a high percentage of co-morbidities in CKD, including of infectious etiology, should be considered.

In the earliest observations it was shown that CRP is a predictor of adverse outcomes with stable and unstable stenocardia [60]. Further, in most epidemiological studies, the role of CRP as a predictor of acute myocardial infarction, stroke, and peripheral vascular thrombosis afflicted with atherosclerosis was proven [14].

C-reactive protein acts not only as a marker or predictor of atherosclerosis complications, but also directly participates in its pathogenesis. Thus, CRP is included in the atheroma, facilitates the diffusion and binding of LDL by macrophages in the vascular wall, leads to the development of an unstable state of atherosclerotic plaque, thereby provoking the thrombosis of the vessels [61]. In a recently completed, large-scale multicentre MDRD study (the Modification of Diet in Renal Disease) in people with an initial stage of CKD (GFR <60 ml/min), high CRP values were observed; the relative risk of developing cardiovascular complications was 1.73 times higher than in patients with preserved GFR and normal CRP levels [58].

It should be also considered that systemic inflammation is accompanied by changes in protein metabolism, leading to an increase in protein catabolism in the body and ultimately to protein deficiency, which is often detected in CKD. Its main feature is hypoalbuminemia, which is a predictor of lethal outcomes in patients with CKD, especially with haemodialysis [62].

Oxidative stress has direct connection with systemic inflammation, which is understood as a violation of the balance between pro- and antioxidants. There is an increase in blood prooxidant substances generated by activated (including inflammation) neutrophils in patients with CKD, beginning with the early stages [63]. Oxidative damage of LDL and endotheliocytes initiates and promotes the progression of the atherosclerotic process [64].

Anaemia is another important risk factor for cardiovascular complications, both in patients with CKD and in patients with chronic heart failure [65]. For every 1% of reduction in haematocrit in CKD, the risk of mortality is increased by 3% [41]. Anaemia in CKD causes hypertrophy and dilatation of the left ventricle, participating in the processes of vascular remodelling and promoting the progression of sclerosis of renal tissue [41, 65].

As the kidney function is impaired, the exchange of sulphur-containing amino acids and homocysteine is disrupted [66]. In patients with CKD, it has been established thatfor every 1 μmol increase in the concentration of homocysteine in the blood, the risk of vascular complications increases by 1% [66]. The mechanism of homocysteine involvement in vascular lesions and in atherogenesis with chronic renal failure has not been fully studied [53]. It is known that homocysteine promotes the proliferation of smooth muscle cells, initiates the formation of LDL oxidised forms, is accompanied by generalised endothelial dysfunction and activates thrombocytes and a coagulation cascade [66]. At present, due to the lack of scientific research on this topic, it is difficult to predict the results of the pharmacological effect on hyperhomocysteinemia in patients with CKD.

The analysis of the facts presented in this article allows the authors to approach the problem of cardiorenal interrelations more broadly, to bring it out of the rigid frameworks of treating cardiovascular diseases (heart failure, in particular) in terminal uraemia (cardio-renal syndrome). Obviously, the kidney is a multifunctional organ that cannot be considered only as a point of application of pathological influences (target organ). The relationship of the kidney with the pathology of the cardiovascular system is multifaceted and is often exacerbated by the feedback mechanism. The existence and functioning of feedback, in turn, support risk factors acting bi-directionally and giving the pathogenetic stability to the entire cardiorenal system (Fig. 4). The interdependence of the pathological processes of the cardiovascular system and the kidneys, as well as the clinical predictability of the end results, allows the cardio-renal relationships to be considered as a continuous chain of events constituting a peculiar vicious circle, i.e. as a cardiorenal continuum (Fig. 5). The disclosure of the role of risk factors opens the prospect of primary prevention of not only cardiovascular diseases, which has long been a clinical standard in cardiology, but also of chronic kidney disease itself. A deeper understanding of cardio-renal relationships will allow "therapeutic nihilism" to be overcome in patients, both in the initial stages of CKD, and for those receiving renal replacement therapy. Such an approach will improve survival, quality of life and reduce the cost of treatment for patients with various complications from both the kidneys and the cardiovascularsystem.

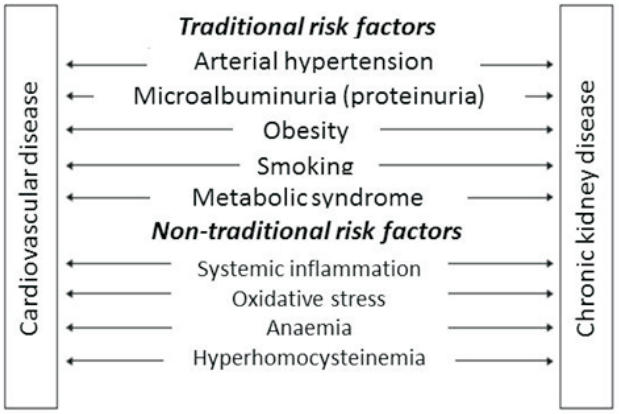

Fig. 4. The main risk factors for cardiovascular disease and chronic kidney disease.

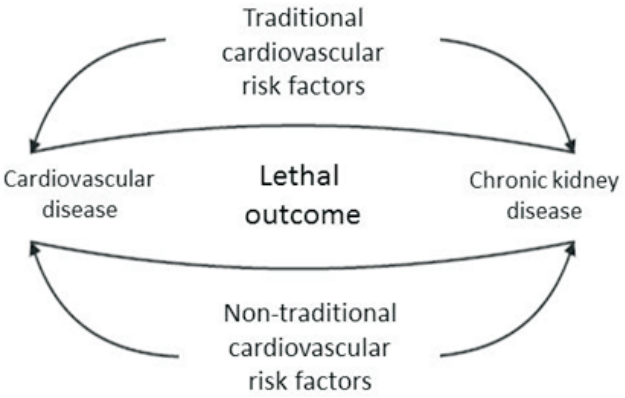

Fig. 5. Cardiorenal continuum.

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Received 18.06.2005.

The paper was translated by Thomas Al. Beavitt