

CARDIOVASCULAR RISK AND VASCULAR ALTERATIONS IN CHRONIC KIDNEY DISEASE

Adalbert Schiller

REZUMAT

Boala cronică de rinichi (BCR) este un concept nou în nefrologie introdus de grupul de lucru Kidney Disease Outcome Quality Initiative (K/DOQI) al National Kidney Foundation în anul 2002 cu scopul de a evalua patologia renală cronică independent de etiologie. Numeroase date sugerează faptul că BCR, așa cum a fost ea definită de K/DOQI, este factor favorizant al bolii cardiovasculare datorită prevalenței crescute a factorilor de risc (clasici și specifici) din cursul BCR. În același timp disfuncția endotelială pronunțată evidentă la bolnavii cu BCR contribuie la dezvoltarea bolii cardiovasculare. Date experimentale și clinice recente sugerează ideea că în cursul BCR se dezvoltă o patologie micro și macrovasculară cu anumite caracteristici particulare (proces aterosclerotic accelerat însoțit de calcificări extensive, remodelare arteriolară pronunțată și deficit de angiogeneză) care stă la baza morbidității și mortalității cardiovasculare crescute la bolnavii renali cronici.

Cuvinte cheie: boală cronică de rinichi, boală cardiovasculară, disfuncție endotelială, alterări vasculare

ABSTRACT

The concept of chronic kidney disease (CKD) was introduced in nephrology in 2002 by the National Kidney Foundation work group, The Kidney Disease Outcome Quality Initiative (K/DOQI) with the net intention to evaluate clinical problems related to renal failure regardless of etiology. Available data suggest the fact that CKD is a risk factor for the development of cardiovascular disease due to high prevalence of classical and specific risk factors present in CKD. In the mean time a severe endothelial dysfunction present in CKD contributes to the development of cardiovascular disease. Experimental and clinical data tend to prove that in CKD patients vascular alterations have a particular pattern (accelerated atherosclerosis with extensive calcifications, marked arteriolar remodeling, and deficient angiogenesis) involved in the high cardiovascular morbidity and mortality.

Key Words: chronic kidney disease, cardiovascular disease, endothelial dysfunction, vascular alterations

CHRONIC KIDNEY DISEASE - A NEW CONCEPT IN NEPHROLOGY

Kidney diseases have several common characteristics: in many cases the etiology is unknown, chronic evolution to renal failure is common, and failing renal function often evolves with severe extra-renal complications, hence the need for a general concept to include all renal diseases regardless of etiology. In 2002, The National Kidney Foundation

(NKF) through The Kidney Disease Outcome Quality Initiative Group (K/DOQI) introduced the concept of **chronic kidney disease** (CKD).¹ According to K/DOQI defining chronic kidney disease and classifying its stages of severity would provide a common language for communication among patients, investigators and providers, and a framework for developing a new approach to improve the treatment of chronic kidney disease.

The K/DOQI Group has defined CKD as:

- **Kidney damage for ≥ 3 months**, as defined by structural or functional abnormalities of the kidney, with or without decreased GFR, manifested by either: a. **pathological abnormalities**; or b. **markers of kidney damage**, including abnormalities in the composition of blood or urine, or abnormalities in imaging tests.

- **GFR (glomerular filtration rate) <60 mL/min/1.73m² for 3 months, with or without kidney damage.**

Department of Nephrology, Victor Babes University of Medicine and Pharmacy, Timisoara

Correspondence to:
Adalbert Schiller, 2 Mehadia Str., Timisoara, Romania, Tel: +40 256 202563,
Mobile: +40724554072
Email: timisoaraschiller@yahoo.com

Received for publication: Jul. 04, 2005. Revised: Mar. 13, 2006.

Under these conditions the severity stages of CKD have been defined as:

- Stage 1: Kidney damage with normal or increased GFR (GFR > 90 ml/min/1.73m²);
- Stage 2: Kidney damage with mild reduction of GFR (GFR 60-89 ml/min/1.73m²);
- Stage 3: Moderate reduction of GFR (GFR 30-59 ml/min/1.73m²);
- Stage 4: Severe reduction of GFR (GFR 15-29 ml/min/1.73m²);
- Stage 5: Kidney failure (GFR < 15 ml/min/1.73m² or dialysis).

In the above definitions the markers of kidney damage are: albuminuria (proteinuria), abnormalities in the urine sediment (hematuria, leukocyteuria) and abnormalities on imaging investigations (ultrasound, IV urography, CT scan, MRI).

Detection of proteinuria (albuminuria) should be performed using standard urine dipsticks i.e. albumin specific dipsticks and, for quantitative measurements, protein-to-creatinine ratio or albumin-to-creatinine ratio in untimed ("spot") urine samples should be used.

The level of GFR should be estimated from prediction equations: MDRD (Modification of Diet in Renal Disease) Study equations for adults and Schwartz or Counahan-Barratt equations for children.

The MDRD Study 4 equation:²

$$\text{GFR (ml/min/1.73m}^2\text{)} = 186 \times \text{SCr} - 1.154 \times \text{Age} - 0.203 \times 0.742 \text{ (if female)} \times 1.210 \text{ (if African-American)}$$

The Counahan-Barratt equation:³

$$\text{GFR (ml/min/1.73m}^2\text{)} = (0.43 \times \text{Length}) / \text{SCr}$$

The K/DOQI group has also defined the potential risk factors for development of chronic kidney disease. These risk factors have been classified into clinical factors (diabetes, hypertension, systemic infections, urinary tract infections, urinary stones, lower urinary tract obstruction, neoplasia, family history of CKD, recovery from acute renal failure, reduction of kidney mass, exposure to certain drugs, low birth weight) and sociodemographic factors (old age, ethnic minority groups - African Americans, American Indians, Hispanic, Asian or Pacific Islanders, low income/education, exposure to chemical or environmental agents).

Data which highlight the dimensions of the problem are offered by The Third National Health and Nutrition Examination Survey (NHANES III), The

United States Renal Data System (USRDS) and the AUSDIAB study.^{4,6} For example, out of a population of 122 million adults (>20 years of age), 5.9% are in CKD stage 1; 4% in CKD stage 2; 4.3% in CKD stage 3; 0.2% in CKD stage 4 and 0.1% in CKD stage 5.^{4,5} If we take into account the persons at risk of developing CKD (K/DOQI data for The United States) (about 7% of the general population with diabetes mellitus, 24% with hypertension, 16% over the age of 60, 5% ingesting non-steroidal anti-inflammatory drugs on a daily basis, and so on), then the seriousness of the problem becomes apparent.¹

The above data reveals that the number of patients with CKD stage 5 is more than 20 times smaller than the number of patients with CKD stage 3. The very high mortality rate among patients with CKD accounts for the difference.

CHRONIC KIDNEY DISEASE - A RISK FACTOR IN CARDIOVASCULAR DISEASE

In the United States, The Hypertension Detection and Follow-up Program (HDFP-1989), having investigated more than 11,000 persons (less than 16% diabetics) evidenced that in subjects with serum creatinine higher than 1.7 mg/dl, 58% of deaths were due to CVD.⁷ These data are further supported by The British Regional Heart Study (7,000 subjects, less than 2% diabetics).¹ It seems that the mortality rate from cardiovascular disease (CVD) (i.e. coronary artery disease, cardiac failure, left ventricular hypertrophy, peripheral artery disease, cerebrovascular disease) is 15 times higher in patients with end stage renal failure than in the general population.⁸ In fact, in CKD patients, cardiovascular disease mortality is more likely to occur than the development of kidney failure (in the HDFP trial 19% of deaths were attributable to end stage renal failure vs. 58% attributable to CVD; in the Framingham study 198 patients with elevated serum creatinine died, while only 10 died in end stage renal failure).⁹

At the same time, existing data suggests that the prevalence of CVD is elevated in patients with CKD, irrespective of stage (early or late) and is increasing with the severity of the CKD.¹⁰

The high prevalence of CVD in CKD is attributable to at least two alarming conditions:

1. The prevalence of classical risk factors for CVD (hypertension, elevated LDL cholesterol, low HDL cholesterol, diabetes) is significantly higher in CKD patients than in the general population.

2. In CKD, nontraditional CVD risk factors are also present (extra-cellular fluid overload, proteinuria, decreased GFR, abnormal calcium and phosphorus metabolism, anemia, malnutrition, inflammation, oxidative stress, elevated homocystein levels, high rennin-angiotensin activity, uremic toxins and so on).¹

The above data suggests that, indeed, CKD represents a risk factor for the development of CVD.¹¹

CVD, and above all coronary artery disease, has specific features in CKD. The mortality rate is higher than in the general population, but only 20-30% of it is attributable to acute myocardial infarction.¹² In fact, the one year mortality after acute myocardial infarction is significantly higher as compared to the general population: 10% in the general population, 15% in DM, 55.4% in chronic renal failure patients and 62.3% in DM patients with chronic renal failure.^{10,13} The prevalence of coronary X syndrome is significantly higher in patients with chronic renal failure (CRF) and the coronary perfusion reserve in non obstructed areas is considerably lower.¹⁴

It is possible that these problems are related to a marked endothelial dysfunction due to increased number of risk factors, classical and CKD-related and to several recently demonstrated vascular alterations.

ENDOTHELIUM DYSFUNCTION IN CKD

The endothelium is a very large and complex organ placed between the circulating blood and the wall of the blood vessels. It reacts to a large number of stimuli (pressure, shear stress, hormones, vasoactive substances) by releasing agents that modulate vasomotor function, inflammation and hemostasis. The endothelium is also involved in the maintenance of fluid balance, angio and mito genesis and vascular permeability.¹⁵ The vasomotor agents released by the endothelium are represented by: vasodilators – nitric oxide (NO), prostacyclin, C-type natriuretic peptide; and vasoconstrictors - endothelin-1, angiotensin II, thromboxane A₂, reactive oxygen species (ROS).¹⁶ The inflammation modulators released by the endothelium are represented by NO, ICAM-1, VCAM-1, E-selectin, NF- κ B and the hemostasis modulators by plasminogen activator, tissue factor inhibitor, von Willebrand factor, NO, prostacyclin, thromboxane A₂, PAI-1, fibrinogen.¹⁵

NO plays a key role in the endothelium function, generating vasodilatation and anti-aggregant effects on platelets, inhibiting growth and inflammation.

Reduced NO has been reported in the presence of

impaired endothelial function. Reduced NO synthesis may result from reduced availability of its substrate, L-arginine, and or reduced endothelial NO synthase (eNOS) activity (related to endogenous and exogenous inhibitors, and the decoupling of the enzyme by ROS). Also the bioavailability of NO may be reduced by many factors: ROS, inflammation, advanced glycation end products (AGE) (in diabetes mellitus) and so on.

In CKD, but especially in renal failure, endothelium function is altered by many factors which affect NO synthesis and its bioavailability. Oxidative excess (excess of ROS) generated by NAD (P)H, xantinioxidase, mitochondria, etc., seems to have a central role in this process. ROS reduce the bioavailability of NO by quenching NO, reduce tetrahydrobiopterin (BH₄-cofactor of eNOS) and so decouple eNOS. Decoupled eNOS enhance the synthesis of ROS.¹⁷ The activity of eNOS is also diminished in CRF by increased asymmetric dimethyl arginine (ADMA) levels (endogenous inhibitor of eNOS) due to reduced renal clearance and homocysteine excess.¹⁸ On the other hand, excess of ROS initiates inflammation by upregulating ICAM-1, VCAM-1, MCP-1 expression (thus inducing CRP synthesis).¹⁹ ROS excess is also involved in initiation of apoptosis of endothelial cells, and in a particular form of apoptosis called anoikis.²⁰

Endothelial dysfunction assessed by endothelium-dependent vasodilatation, ICAM-1, VCAM-1, CRP, and, recently by ADMA levels seems to be associated with poor cardiovascular prognosis.¹⁵

VASCULAR ALTERATIONS IN CKD

The high prevalence of coronary atheroma is well documented in CKD.²¹ It seems that the thickening of the intima and media and the calcification of the media of the arteries are significant in CKD, but the dominant lesion is represented by the thickening of the media. Although plaque area is comparable in renal patients and controls, the residual lumen is significantly lower in CKD patients. At the same time the prevalence of heavily calcified plaques is significantly higher in uremic patients.²² The prevalence of heavily calcified plaques and the coronary mortality rate of CKD patients are related to hyperphosphatemia, hypercalcemia and over suppressed PTH.²³ The high tendency to calcification of the coronary plaques explains the poor outcome of PTCA in CKD patients (1 year reocclusion rate is 70% as compared to 20% in nonuremic patients).²⁴

Recent experimental and clinical data suggest that in uremic patients a so-called “secondary stenosis” occurs behind tight coronary stenosis. It seems that

low blood flow in CKD patients triggers overshooting intimal proliferation. It has been suggested that abnormal synthesis and release of endothelin-1 (present in uremia) is the main cause of this alteration since, in experimental models, intimal proliferation was prevented by endothelin-1 type A receptor blockers.²⁵

For more than a decade it has been known that, due to vascular smooth muscle cell hypertrophy and polyploidy, myocardial arteriolar thickening and remodeling, occurs in hypertensive patients and in hypertensive animal models as well as in patients with the so-called coronary X syndrome.^{26,27} Uremic patients (post-mortem studies) and animal models with subtotal nephrectomy also develop myocardial arteriolar thickening. Proliferation and hypertrophy seem to be the dominant processes involved in this situation and the arteriolar changes are not dependent on hypertension. In uremic animal models endothelin receptor blockers and ACE-inhibitors prevented the arteriolar thickening.^{12,28} The clinical consequences of these arteriolar changes are not very clear (except extremely severe stenosis). It has been suggested that these changes may contribute to the reduction of coronary perfusion reserve (perfusion after maximal vasodilatation with Persantin).¹²

Capillary abnormalities are also present in CKD. In tissues undergoing hypertrophy new capillaries are formed through sprouting, branching and acquisition of pericytes. That is why the myocardial capillary density in hypertensive animal models with left ventricular hypertrophy is similar to the normotensive ones. In subtotally nephrectomised animals with left ventricular hypertrophy, the capillary density in the left ventricle is significantly lower.¹² Similar findings have been demonstrated in hemodialized patients when compared to hypertensive patients without renal failure, and to controls.²⁹ It seems that capillary growth does not keep pace with cardiomyocyte growth in uremia. As a consequence, the oxygen diffusion distance increases by 25% and so, under conditions of hypoxia or ischemia, the cardiomyocyte is exposed to the risk of hypoxic damage.¹² It seems that in uremia, on a functional level, by this mechanism, a certain degree of ischemic cardiomyopathy occurs.

Recent data suggest the fact that impaired angiogenesis is generalized and can be demonstrated in the kidney too. Uremia-associated loss of the microvasculature in the kidney correlates directly with the development of glomerular and tubulointerstitial scarring. It seems that impaired angiogenesis is related to the alteration of the balance between angiogenic (vascular endothelial growth factor) and antiangiogenic

(thrombospondin 1) factors induced by macrophage-associated cytokines (interleukin-1 β) and vasoactive mediators (endothelin-1 and angiotensin II).³⁰ Pro angiogenesis interventions (using erythropoietin, VEGF and so on) may stabilize renal function and slow histologic progression in CKD patients and also may ameliorate cardiac prognosis. In the same time, it is worth mentioning that angiogenic stimulation may also increase the risk of tumors and of retinal angiogenesis in diabetic subjects.³¹

Hopefully, in the years to come, new therapy solutions will improve the survival rate of CKD patients. Given the existing data, it is reasonable to believe that the treatment of endothelial dysfunction will play a central role in these therapy solutions.

REFERENCES

1. The National Kidney Foundation, The Kidney Disease Outcome Quality Initiative (KDOQI). Clinical practice guidelines for chronic kidney disease. Evaluation, Classification and Stratification. 2002
2. Levey AS, Bosch JP, Lewis JB, et al. A more accurate method to estimate glomerular filtration rate from serum creatinine: A new prediction equation. Modification of Diet in Renal Disease Study Group. *Ann Intern Med* 1999;130:461-70.
3. Counahan R, Chantler C, Ghazali S, et al. Estimation of glomerular filtration rate from plasma creatinine concentration in children. *Arch Dis Child* 1976;51:875-8.
4. Jones CA, McQuillan GM, Kusek JW, et al. Serum creatinine levels in the US population: Third National Health and Nutrition Examination Survey. *Am J Kidney Dis* 1998;32:992-9.
5. US Renal Data System. USRDS 1998 Annual Data Report. National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases. Bethesda, MD, 1998
6. Chadban SJ. Diabetes and kidney damage: The AUSDIAB Study. WCN, Berlin, June 8-12, 2003
7. Shulman NB, Ford CE, Hall WD, et al. Prognostic value of serum creatinine and effect of treatment of hypertension on renal function. Results from the hypertension detection and follow-up program. The Hypertension Detection and Follow-up Program Cooperative Group. *Hypertension* 1989;13:180-93.
8. Foley RN, Parfrey PS, Sarnak MJ. Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 1998;32:112-9.
9. Cullerton BF, Larson MG, Wilson PW, et al. Cardiovascular disease and mortality in a community-based cohort with mild renal insufficiency. *Kidney Int* 1999;56:2214-9.
10. Jardine AG. Cardiovascular complications of renal disease. *Heart* 2001;86:459-66.
11. Rauscher M. Cardiovascular risk factor burden high in renal disease. *Mayo Clin Proc* 2005;80:1270-7.
12. Amann K, Ritz E. Microvascular disease - the Cinderella of uraemic heart disease. *Nephrol Dial Transplant* 2000;15:1493-503.
13. Herzog CA, Ma JZ, Collins AJ. Long-term outcome of dialysis patients in the United States with coronary revascularization procedures. *Kidney Int* 1999;56:324-32.
14. Depre C, Vanoverschelde JL, Melin JA, et al. Structural and metabolic correlates of the reversibility of chronic left ventricular ischemic dysfunction in humans. *Am J Physiol* 1995;268:H1265-75.
15. Endemann DE, Schiffrin EL. Endothelial dysfunction. *J Am Soc Nephrol* 2004;15:1983-92.
16. Verma S, Anderson TJ. Fundamentals of endothelial function for the clinical cardiologist. *Circulation* 2002;105:546-49.

17. Landmesser U, Dikalov S, Price SR. Oxidation of tetrahydrobiopterin leads to uncoupling of endothelial cell nitric oxide synthase in hypertension. *J Clin Invest* 2003;111:1201-9.
18. Nijveldt RJ, Teerlink T, Van Der Hoven B. Asymmetrical dimethyl-arginine (ADMA) in critically ill patients: High plasma ADMA concentration is an independent risk factor of ICU mortality. *Clin Nutr* 2003;22:23-30.
19. Szmítko PE, Wang CH, Weisel RD. New markers of inflammation and endothelial cell activation. *Circulation* 2003;108:1917-23.
20. Taniyama Y, Griendling KK. Reactive oxygen species in the vasculature. *Hypertension* 2003;42:1075-81.
21. Go AS, Chertow GM, Fan D, et al. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004;351:1296-306.
22. Franklin SS. Vascular compliance: Impact on cardiovascular and renal disease risk. *ASN Renal Week, San Diego, CA, November, 2003.*
23. Moe SM. Mineral and metal accumulation without changes in the "usual laboratory suspects". *ASN Renal Week, October, 2004.*
24. Herzog CA, Ma JZ, Collins AJ. Poor long-term survival after acute myocardial infarction among patients on long-term dialysis. *N Engl J Med* 1998;339:799-805.
25. Demuth K, Blacher J, Guérin AP, et al. Endothelin and cardiovascular remodelling in end-stage renal disease. *Nephrol Dial Transplant* 1998;13:375-83.
26. Schwartzkopff B, Motz W, Frenzel H, et al. Structural and functional alterations of the intramyocardial coronary arterioles in patients with arterial hypertension. *Circulation* 1993;88:993-1003.
27. Opherk D, Mall G, Zebe H, et al. Reduction of coronary reserve: a mechanism for angina pectoris in patients with arterial hypertension and normal coronary arteries. *Circulation* 1984;69:1-7.
28. Amann K, Neusüß R, Ritz E, et al. Changes of vascular architecture independent of blood pressure in experimental uremia. *Am J Hypertension* 1995;8:409-17.
29. Amann K, Breitbach M, Ritz E, et al. Myocyte/capillary mismatch in the heart of uremic patients. *J Am Soc Nephrol* 1997;9:1018-22.
30. Kang DH, Kanellis J, Hugo C, et al. Role of the microvascular endothelium in progressive renal disease. *J Am Soc Nephrol* 2002;13:806-16.
31. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. *Nat Med* 1995;1:27-31.