BEST JOURNAL OF INNOVATION IN SCIENCE, RESEARCH AND DEVELOPMENT
ISSN: 2835-3579
Volume:2 Issue:11|2023
www.bjisrd.com

Treatment of Patients with Cardiorenal Syndrome Due to Chronic Kidney Disease

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***SUMMARY*:** *Chronic kidney disease (CKD) significantly increases cardiovascular morbidity and mortality, especially in patients with diabetes mellitus. Despite the fact that over the past two decades, cardiovascular mortality in the general population has significantly decreased, the mutually aggravating progressive course of this complication and the high percentage of development of end-stage renal failure require new approaches to early diagnosis, development of prevention methods and timely treatment from the standpoint of evidence-based medicine.*

Key words: *chronic kidney disease, diabetic nephropathy, cardiorenal syndrome, natriuretic peptides.*

Recent years have been marked by a dramatic increase in the number of patients with diabetes mellitus (DM) and chronic kidney disease (CKD) worldwide. Diabetes mellitus (DM) and chronic kidney disease (CKD) are two very topical diseases that are inevitably linked and have been not only a medical but also a socio-economic problem for several generations in recent years. Diabetes mellitus (DM) is a widespread disease. The number of diabetes patients in the world is 140 million, and according to World Health Organization statistics this category of patients will increase to 300 million by 2025. Chronic kidney disease (CKD) affects 10-16% of adults in Asia, USA, Australia and Europe and is a global public health problem [4] (Levey AS, et al. 2010). It increases the risk of overall mortality and cardiovascular disease, and the possibility of progression to terminal renal failure [1]. According to the KDOQI guidelines of the 2002 protocols, CKD is defined as renal damage assessed by albumin loss and decreased glomerular filtration rate (GFR), which underlies its subdivision into stages (5).

According to the World Health Report 2000 Global Burden Disease (GBD) project kidney and urinary tract diseases cause approximately 850000 deaths annually and provide 15010167 permanent disability, ranking only 12th as a cause of death and 17th as a cause of permanent disability. However,

there is good reason to believe that the true prevalence and incidence of chronic kidney disease is at least several times underestimated (18).

The increasing incidence of CKD is steadily increasing the number of patients in need of CKD. According to the literature, by the end of the last century, about one million people worldwide were receiving some form of dialysis treatment, and the number of patients receiving this therapy at the start was about a quarter of a million per year. Organisational and financial problems have become serious for many countries around the world, even for the highly developed ones.

The term CKD summarises diseases in which there is renal damage or a decrease in glomerular filtration rate (GFR) of less than 60 ml/min/1.73 m2, persisting for more than three months, regardless of the primary diagnosis. CKD is very relevant to patients with diabetes, given the importance and need for unification of approaches to the diagnosis, treatment and prevention of renal pathology, especially in cases of minimal severity and the difficult-to-define nature of the disease. In making the diagnosis of CKD, the importance of identifying risk factors for the development and progression of chronic renal disease must be considered. When these factors are taken into account and their significance and modifiability are assessed, primary and secondary prevention of chronic kidney disease can be effectively implemented. A number of factors can have a significant influence on the development and progression of chronic kidney disease, irrespective of the population. These include the prevalence of some infections, the use of certain medications, alcohol and smoking, environmental conditions, climate, dietary habits and traditions, genetic characteristics of the population, etc. [6,11]. Most interestingly, however, many of the factors associated with the development of renal dysfunction are also 'traditional' cardiovascular risk factors, including arterial hypertension (AH), diabetes mellitus (DM) and others.

In diabetes, renal pathology can be diverse (in particular diabetic glomerulosclerosis, urinary tract infection, chronic glomerulonephritis, drug-induced nephritis, atherosclerotic renal artery stenosis, tubulointerstitial fibrosis, etc.). They have different mechanisms of development, which affect the dynamics of progression, the choice of treatment, is a particular problem for diabetic patients, because their frequent combination is mutually aggravating.

Diabetic nephropathy (DN) is a specific kidney damage in patients with diabetes in which nodular or diffuse glomerulosclerosis is observed, leading to the development of terminal renal failure (TRF), requiring renal replacement therapy (RRT) such as dialysis or kidney transplantation (2).

Depending on the duration of the disease, the incidence of DN can be assumed, with a maximum peak between 15 and 20 years of diabetes. Diabetic kidney damage may occur in 40% of diabetic patients with diabetes. The development of this complication cannot always be explained by poor glycaemic or blood pressure (BP) control alone (8).

The earliest sign of renal damage in diabetes is the detection of microalbuminuria, which directly influences the further progression of diabetic nephropathy. As proteinuria develops, DN progresses to chronic renal failure. 5-10% of DN cases end in end-stage renal failure [18], which accounts for 1.5-3% of mortality in type 2 diabetes mellitus patients [6]. All stages of DN are associated with cardiovascular disease. The onset of DN leads to a 5-8-fold increase in mortality in these patients compared to the general population. Cardiovascular disease is still the leading cause of death in type 2 DM patients who do not survive to the terminal stage of renal failure (1).

Recent studies have described the association of GFR and albuminuria with clinical outcome in subjects in the general population, suggesting that threshold values of GFR (<60 mL/min/1.73m2) and

AF are risk factors for increased mortality. The data of epidemiological studies with the examination of more than 65000 patients support the point of view about AF as a "biomarker" of adverse outcome even in patients with intact renal function. This suggests that AF should be included as a biomarker of both risk and progression of renal dysfunction. According to large-scale multicenter studies, MAU has been found to be detected in 20-30% of individuals with arterial hypertension (PREVEND, LIFE), in 25-40% of patients with diabetes type I or II (AUSDIAB, DEMAND), and even in 5-7% of the general population of conditionally healthy individuals (PREVEND, HAND, AUSDIAB) [13]. The development of IAH is associated with almost all components of the metabolic syndrome and is noted in tobacco smoking. Scientists suggest that IAH demonstrates the presence of generalized endothelial dysfunction in the body, underlying both increased risk of atherosclerosis initiation and progression, and renal damage with further development of renal failure. The extent to which microalbuminuria in the general population reflects the risk of CKD, including renal failure, is currently under intensive investigation. The detection of MAU in patients is a warning sign and may provide a basis for renoprotective and cardioprotective measures [6].

Diabetic nephropathy (DN), a specific kidney damage in diabetes, is not currently classified as a fatal complication of DM, as it is preventable.

According to the concept of CKD, the stage of renal disease is assessed by a renal FFR value, which is recognised as the most representative of the number and total amount of nephron work, including non-excretory functions (Table 1).

Table 1

CKD stages by GFR level

Stage	Definition	GFR (ml/min/1.73m2)
1	High and optimum	>90
2	Slightly reduced	60-89
3a	Moderately reduced	45-59
3b	Substantially reduced	30-44
4	Severely reduced	15-29
5	Terminal renal failure	<15

Recent studies have separated cardiovascular and renal risks within Stage 3 CKD (3a - GFR 45-59 ml/min/1.73 m2 and 3b - GFR 30-44 ml/min/1.73 m2 respectively). This is supported by data on depopulation of patients with renal dysfunction due to cardiovascular events and relatively low renal mortality due to modern STD technologies.

In clinical practice, simple methods for calculating creatinine clearance without daily urine collection (Cockcroft-Gault, MDRD, CKD-EPI formulas) can be widely used to calculate aFC. The CKD-EPI formula correlates better with data obtained by reference methods, which makes it recommended for outpatient practice. The index can be calculated automatically using calculators [8].

Thus, creatinine and rCG estimation should become routine practice to assess cardiovascular risk, choose therapy and management tactics, preserve health and quality of life of patients [1].

In 2009-2011, an accurate method - CKD-EPI formula - was developed, which is the most optimal method for outpatient practice at the moment.

Table 2

Variants of the CKD-EPI formula for calculating rSKF (depending on race, sex and creatinine concentration)

Race	Gender	Serum creatinine concentration mg/100ml (SCr)	Formula
The white race	Women's	≤ 0,7	$144\times(0,993)^{age}\times(SCr/0,7)^{-0,328}$
The white race	Women's	≥ 0,7	$144\times(0,993)^{age}\times(SCr/0,7)^{-1,210}$
The white race	Men's	≤0,9	$141\times(0,993)^{age}\times(SCr/0,9)^{-0,412}$
The white race	Men's	≥ 0,9	$141\times(0,993)^{age}\times(SCr/0,9)^{-1,210}$

The presence of DN is an important independent risk factor for the development of cardiovascular disease in CKD. A population-based study in Alberta, Canada, which included 1.3 million patients hospitalised and followed up for 48 months, demonstrated the significance of CKD combined with diabetes for myocardial infarction (MI), comparable to prior MI. The risk of overall mortality, including in the first 30 days after MI, was highest in the group of patients with DM and CKD. According to USRDS 2013, there are significant differences in the incidence of cardiovascular events in patients with and without CKD, regardless of age. The results of the ACCOMPLISH, ALTITUDE, SHARP, ADVANCE, ROADMAP, CARRESSHF and some other studies have recognized CKD as an independent risk factor for cardiovascular disease (CVD) and the equivalent of coronary heart disease (CHD) in terms of risk of complications. The classification of the cardiorenal relationship highlights type 4 (chronic nephrocardiac syndrome), reflecting the initiating role of chronic renal disease in reducing coronary function, developing left ventricular myocardial hypertrophy and increasing the risk of serious cardiovascular events through common haemodynamic, neurohormonal and immunobiochemical feedbacks. These relationships are very pronounced in DN. And also, in formation of inseparable pathogenetic interrelations between damages of kidneys and cardiovascular system it is necessary to mention activation of intrarenal renin-angiotensin-aldosterone system, natriuretic factors of different origin, etc. [4,6].

The presence of reduced renal function due to DN accelerates the formation of cardiovascular pathology, as it provides additional non-traditional risk factors for atherogenesis: albuminuria, systemic inflammation, anaemia, hyperparathyroidism, hyperphosphatemia, vitamin D deficiency and reduced ejection fraction (3). As renal dysfunction increases, there is a tendency for systolic cardiac dysfunction to progress (7). There is a clear need for cardiovascular screening in all patients with DM and DN. Patients with DM and CHD and heart failure should be treated for cardiac disease in full compliance with national and international guidelines, unless contraindicated (Table 3).

Table 3 Therapy strategy in patients with CKD and CVD

Recommendations	Class of recommendations	Level of evidence of evidence
Patients with CKD should be classified as at high risk of CVDs	I	A
The treatment of CHD in patients with COPD should be based on current recommendations in the absence of contraindications*	I	A
Antithrombotic therapy can the following is an example of an antithrombotic therapy risk of cardiovascular complications if there is no increased risk of bleeding*	II	B

Treatment of heart failure in CKD should be treated to the same extent, as in patients without CKD*.	II	A
For chest pain, patients with COPD should be treated in the same way as non-CBP patients	II	B

* the dose of medication needs to be adjusted to the GFR

Patients should be closely monitored during therapy, especially for heart failure, and their GFR and serum potassium levels should be monitored.

In patients with type 2 diabetes, kidney damage is multifactorial and more complex than in people with type I diabetes. Therapeutic management of diabetic nephropathy is based on a multiple risk-factor approach, and the aim is to slow down the progression or progression of the disease and reduce the increased risk of cardiovascular disease in this patient population. Achieving the best possible metabolic control, treating hypertension [<130/80 mmHg] and dyslipidaemia [LDL cholesterol <100 mg/dL] using drugs that block the renin-angiotensin-aldosterone system are effective strategies for preventing the development of microalbuminuria, delaying progression to later stages of nephropathy and reducing cardiovascular mortality in diabetic patients [11,12,13].

Until this time, there was no clear understanding of the role of RAAs in the development of diabetic kidney disease, no drugs capable of effectively blocking this system (IAPs) and no evidence to support the nephroprotective activity of these drugs. However, in clinical practice, IAPs have been widely used for this purpose. In addition to the clear advantages of IAP therapy, experience with their long-term use has shown a number of disadvantages that limit their use. IAPIs often cause dry cough, angioedema due to reduced breakdown of bradykinin and similar vasodilator metabolites. Long-term (more than 25 years) use of IAPPs has shown that in real clinical practice, only 50% of patients with DN develop nephroprotective effects of IAPP use. In some patients with DN, despite the use of IAPP, renal function continues to decrease progressively, even with satisfactory BP control. The reasons for insufficient effectiveness of IAPP (slippage phenomenon) may be due to the activity of alternative pathways of angiotensin II formation (controlled by chymase, cathepsin G, tonin etc), salt abuse and genetic factors. The causes, mechanisms, timing of the phenomenon as well as its clinical significance remain speculative and little reported in the literature. A more complete and selective blockade of the system can be provided by BRAs, which act as angiotensin II (AII) antagonists against AT 1 receptors, mediating the main cardiovascular and renal effects of RAAS activation while retaining the function of AT 2 receptors, providing an additional organoprotective effect [7].

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These neurohormones inhibit the secretion of aldosterone, renin and angiotensin II as well as the activation of the sympathetic nervous system. As natural antagonists of the sympathoadrenal and renin-angiotensin systems, vasopressin and aldosterone, NUPs induce peripheral vasodilation, increase diuresis, reduce arterial pressure, pre- and post-load, reduce endothelin synthesis and release, and weaken smooth muscle, cardiac, endothelial cell and fibroblast cardiac cell growth [9]. Studies conducted in the general population for more than 30 years have found an association between levels of these neurohumoral markers and renal and hepatic dysfunction, but above all with the prevalence of cardiovascular disease [15,18,19].

A new class of drugs, sacubitril/valsartan, have demonstrated efficacy in blocking the RAAS, and their effects on natriuretic peptides raise hopes for long-term nephroprotection in DM without the phenomenon of slippage.

For this purpose, the action of valsartan + sacubitril complex is mediated by a new mechanism, namely, by a simultaneous inhibition of neprilysin activity (neutral endopeptidase, NEP) by substance LBQ657 (active metabolite of sacubitril) and blockade of angiotensin II type 1 receptors (AT1) by valsartan, which is an angiotensin II receptor antagonist (ARA II). Complementary beneficial effects of sacubitril and valsartan on cardiac and renal outcomes in patients with heart failure are due to an increase in neprilysin cleavable peptides (such as natriuretic peptides (NPs) mediated by LBQ657, while the negative effects of angiotensin II are inhibited by valsartan. NPs activate membrane-bound guanylate cyclase-conjugated receptors, resulting in increased cGMP concentration causing symptoms of vasodilation, increased natriuresis and diuresis, increased FFR and renal blood flow, inhibition of renin and aldosterone release, reduced sympathetic activity, and antihypertrophic and antifibrotic effects. Valsartan, by selectively blocking AT1 receptors, suppresses the adverse effects of angiotensin II on cardiac and renal function and blocks angiotensin II-dependent aldosterone release. This prevents persistent activation of the RAAS, which causes vasoconstriction, renal sodium and water retention, activation of cell growth and proliferation, and subsequent remodelling of the CPS, exacerbating its dysfunction.

According to data from a large-scale clinical trial (PARADIGM-HF), the use of sacubitril + valsartan in patients with CHF statistically significantly reduced the risk of death due to cardiovascular disease or hospitalization due to acute heart failure (21.8% in the study drug group versus 26.5% in the enalapril group). The absolute risk reduction for cardiovascular death or hospitalization due to acute heart failure was 4.7% (3.1% for risk of cardiovascular death and 2.8% for primary hospitalization due to acute heart failure). The relative risk reduction compared with enalapril was 20%. The effect was noted early in the use of the drug and persisted throughout the study period. Both active ingredients contributed to the development of the effect. The incidence of sudden death, which was 45% of all cardiovascular deaths, was reduced by 20% in the study drug group compared to enalapril group (hazard ratio, HR) 0.8; p=0.0082). The incidence of contractility failure, which caused 26% of deaths due to cardiovascular disease, decreased 21% in the study drug group compared with the enalapril group (HR 0.79; p=0.0338).

The search for markers of early diagnosis of CKD in DM patients and methods of active intervention would prevent or delay the progression of renal function loss. Modern approaches of nephroprotection including means, such as sacubitril/valsartan, specifically affecting RAAS and natriuretic peptides, lead to improvement of cardiovascular function, increase of FFR in patients with DN.

Taking into account the above mentioned, studying the relationship between the degree of renal dysfunction and myocardial structural and functional characteristics, revealing pathogenetic mechanisms of CRF progression, controlling cardiovascular risk factors, as well as determining the effect of new pharmacotherapeutic approaches in treating this syndrome is an important clinical task of internal medicine.

Thus, it is clear that the combined treatment of sacubitril/valvsartan improves left ventricular systolic function. However, the effects of the combination drug in patients with CKD have not been sufficiently studied according to the literature, which has served to define the aim of this research work.

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