International Research Journal of Pharmacy and Medical Sciences
ISSN (Online): 2581-3277

Chronic Kidney Disease in Metabolic Syndrome

Kayumov N.U.[1], Mukhamedova M.G.[2]
[1]Tashkent Pediatric Medical Institute, Tashkent, Uzbekistan
[2]Tashkent Postgraduate Medical Institute, Tashkent, Uzbekistan

***Abstract*—*The importance of prevention and treatment of chronic kidney disease (CKD) is caused not only by the development of chronic renal failure, which determines the patient's prognosis, but primarily by the risk of adverse outcomes of cardiovascular complications of kidney involvement in the pathological process and the development of the cardiorenal continuum. Metabolic syndrome (MS) is pathogenetically associated with the development of CKD and is an independent predictor of it. A direct correlation between the prevalence of CKD and MS diagnostic criteria and treatment options are shown in this article*.

***Keywords*—** *Metabolic syndrome, chronic kidney disease, microalbuminuria, glomerular filtration rate*.

I. INTRODUCTION

Metabolic syndrome (MS) is a combination of genetic, physiological, biochemical and clinical factors, manifestation which is the development of insulin resistance, dyslipidemia, visceral obesity, hypertension, hypercoagulable state, endothelial dysfunction, hyperuricemia. High relevance of learning MS is due to its significant prevalence throughout the world. About each fourth or fifth adult (depending by country and ethnic group) there is metabolic syndrome. Growth with age incidence. The proportion of people with MS among the population over 30 years old is 10–20%, while in the USA - 25% [1]. The average prevalence in the world among men and women - 24%. If before it was believed that MS is characteristic of older people, then in studies conducted American Diabetes Association (American Diabetes Association), shows an increase in incidence among young people aged 20-29 years [1].

It is estimated that by 2025 the number patients with this syndrome will be 300 million person. Therefore, the World Health Organization (WHO) considers the MS to be a global epidemic. Even 250 years ago, long before the MS description, Italian doctor Morgagni identified the connection between visceral obesity, arterial hypertension (AH), atherosclerosis, high levels uric acid in the blood and the frequency of respiratory diseases [2].

In 2009, to harmonize the criteria for metabolic syndrome, several international organizations, including IDF, American Heart Association / National Institute of Heart, Lung, and Blood, International Society Atherosclerosis, International Association for study of obesity, published a conclusion in which states that to confirm a diagnosis of MS, 3 or more of the five criteria [3]. Pathological conditions that are associated with metabolic syndrome (insulin resistance, obesity, dyslipidemia, arterial hypertension, hypercoagulation, inflammation, polycystic ovary, atherosclerosis) also include impaired renal function, which leads to chronic kidney disease (CKD). Among chronic noncommunicable diseases CKD takes special place, since it is widespread, is associated with deterioration of quality of life and high mortality. For many years, the relevance of the CKD problem has not received much attention. Only at the beginning of the 21st century after receiving data from large randomized studies (NHANES and others), which showed a high incidence of CKD in populations, researchers began to intensively deal with this issue. Scientific research recent years suggest that kidney damage can be considered as one of the manifestations of MS [4]. The presence of MS increases the likelihood the development of CKD in patients older than 20 years 2.6 times, moreover, it increases with the increase in the number of MS criteria. The authors conducted a study with the inclusion of more than 6,000 patients, in which studied the relationship of MS and CKD (Third National Health and Nutrition Examination Survey - NHANES III), as a result, it was demonstrated that metabolic syndrome is an independent factor risk of CKD. In patients with two, three, four and five criteria MS, compared with patients with one criterion of MS or without them at all, the likelihood of developing CKD was respectively 2.21; 3.38; 4.23 and 5.85 [4]. M. Kurella et al. [5] with A survey of 10,096 middle-aged people found that with MS, which lasts more than nine years, there is an increase in the risk of developing CKD by about 50%. They analyzed the relationship between glomerular velocity filtration (GFR) and metabolic syndrome with using the multiple regression model.

Due to the widespread use of antihypertensive therapy in recent years there has been a decrease in such severe cardiovascular complications of hypertension as cerebral stroke and myocardial infarction, but there has been a steady increase in the incidence of terminal chronic renal failure (CRF). In this regard, the American Nephrologists established the Kidney Disease Outcomes Quality Initiative Quality Initiative for the Treatment of Kidney Disease, which has developed terminology, classification, diagnosis and approaches to CKD therapy [6]. In accordance with these recommendations, CKD is understood to mean any kidney damage that can progress to terminal CRF.

The increase in the prevalence of CKD is largely due to the high prevalence of hypertension, and the increased incidence of type 2 diabetes, and obesity, as well as the overall increase in life expectancy. Currently, there is also no doubt not only the existence of the renal continuum, but also its simultaneous and unidirectional progression with the cardiovascular continuum. However, many factors associated with renal

Kayumov N.U. and Mukhamedova M.G., "Chronic kidney disease in metabolic syndrome," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 2, Issue 2, pp. 9-11, 2019.

dysfunction are at the same time "traditional" cardiovascular risk factors, among them are hypertension, diabetes, dyslipidemia, and obesity, which are components of MS [7].

Recent studies have shown that kidney damage can now be considered as one of the manifestations of MS. Insulin resistance, being an integral component of MS, is interrelated with renal dysfunction. Sit D. et al. conducted a study aimed at identifying the prevalence of insulin resistance in patients with CKD not receiving dialysis, not suffering from diabetes and obesity. The study involved 89 patients (42 men and 47 women), the control group consisted of 30 healthy volunteers. Patients with diabetes and obesity were excluded from the study. HOMA-IR (i.e., the prevalence of insulin resistance), determined by the formula: HOMA-IR = fasting insulin level IU / ml нат fasting glucose (mmol / l) / 22.5, was significantly higher in patients with 4th at the CKD stage than in the control group ($p < 0.001$), its increase was also observed as the GFR decreased. In addition, a correlation was found between insulin resistance and parameters such as age, body mass index, calcium / phosphorus ratio, C-reactive protein levels, intact parathyroid hormone (iPTH), albumin, creatinine clearance, hemoglobin, and HDL-C [8] .

The presence of MS increases the likelihood of developing CKD in patients older than 20 years by 2.6 times, and this probability increases as the number of components of MS increases. In patients with two, three, four and five MS criteria, compared with patients with no or one MS criterion, the probability of developing CKD was 2.21, 3.38, 4.23 and 5.85, respectively [8].

Due to the high prevalence of chronic kidney disease in the population, currently more and more attention is paid to the initial stages of kidney damage. According to modern data, the first stage of kidney damage is hyperfiltration, ie, an increase in GFR over 110 ml / min / 1.73 m2, associated with an increase in pressure on the glomeruli and, as a consequence, their hyperfunction due to a violation of the autoregulation of glomerular arteriole. In turn, hyperfiltration leads to the development of MAU, and therefore is a marker of metabolic risk [9].

Thus, there is an obvious need for early detection of metabolic and cardiovascular risk factors in the population and, accordingly, early onset of drug treatment at the stages of subclinical kidney damage, including during hyperfiltration, with drugs capable of reducing intraglomerular hypertension even at normal blood pressure levels. The ability to prevent the progression of CKD in patients with MS and elevated blood pressure largely depends on the timely initiation of antihypertensive therapy and maintaining the target level of blood pressure.

When choosing antihypertensive therapy, it should be remembered that there are several mechanisms for the implementation of the nephroprotective effect: adequate reduction of blood pressure; preventing the development and / or reduction of glomerular hypertension; suppression of hypertrophic and proliferative processes in the glomerulus; improvement of endothelial dysfunction; reduction of proteinuria as an independent factor in the progression of nephropathy.

However, the steady growth of CRF in the world in patients with cardiovascular diseases indicates a lack of effectiveness of nephroprotection, which may be due to the late onset of antihypertensive therapy, after the formation of irreversible structural changes in the kidneys; inadequate control of hypertension; a relative increase in the proportion of renal complications of hypertension with a decrease in mortality from stroke and myocardial infarction; the presence of various metabolic disorders, including hyperlipidemia, insulin resistance and hyperuricemia; underestimation of the role of genetic susceptibility to the development of nephropathy; violations in the blood coagulation system; the presence of concomitant atherosclerotic lesions of the renal arteries.

Angiotensin-Converting Enzyme (ACE) Inhibitors

One of the major studies on the possibilities of nephroprotection in MS was the PREVEND study. Part of it was the PREVEND-IT study, which involved 864 patients with UIA - men and women aged 28 to 75 years (mean age 50.7 years), randomized into groups taking fosinopril 20 mg / day for four years or placebo, pravastatin 40 mg / day or placebo. One of the exclusion criteria was creatinine clearance less than 60% of normal values. A statistically significant decrease in urine albumin excretion in the group of patients who took fosinopril, compared with the control group, was noted already three months after the start of treatment and was 29.5%. This trend was recorded in the fosinopril group for all four years and by the end of the study it was 31.4% ($p < 0.05$) compared with the group of patients taking placebo. There were no significant changes in urine albumin excretion in the group of patients taking pravastatin and placebo [10].

Angiotensin II Receptor Blockers

Another class of antihypertensive drugs that affect the renin-angiotensin-aldosterone system (RAAS) are angiotensin II receptor blockers (ARBs). By carrying out a complete blockade of angiotensin II receptors, this class of drugs affects the RAAS more specifically than ACE inhibitors. In order to evaluate the antiproteinuric efficacy of ARBA in comparison with placebo, ACE inhibitors and other antihypertensive drugs, a meta-analysis was conducted of 49 randomized clinical trials in patients with diabetes and other renal pathology who had UIA and proteinuria. The results of the study showed that ARA monotherapy leads to a decrease in proteinuria in comparison with placebo and calcium antagonists (AK), regardless of its severity and causes. The antiproteinuric effect of ARB is comparable in strength to the effectiveness of an ACE inhibitor [11]. However, the only ARB with a proven nephroprotective effect at all stages of kidney damage, from MAU to CKD, is irbesartan [11].

Thus, the nephroprotective properties of ARB are not in doubt, moreover, apparently, the prescription of this group of antihypertensive therapy is justified not only in the early stages of kidney disease, but also at the stage of end-stage CRF.

Kayumov N.U. and Mukhamedova M.G., "Chronic kidney disease in metabolic syndrome," *International Research Journal of Pharmacy and Medical Sciences (IRJPMS)*, Volume 2, Issue 2, pp. 9-11, 2019.

Beta Blockers

Before the advent of modern high-selective beta-blockers (BAB), it was suggested that this group of drugs was incorrectly used as first-line drugs for treating hypertension, which was based on unfavorable morbidity and mortality data, a higher incidence of diabetes. However, experience with the use of highly selective BAB in large randomized clinical trials (bisoprolol, carvedilol, nebivolol) proved their metabolic neutrality. However, studies on the evaluation of the nephroprotective properties of BAB have been practically not conducted. The results of only one study were published on the evaluation of the effect of nebivolol on MAU in patients with hypertension and type 2 diabetes. In one study, 2,915 patients participated who were prescribed nebivolol as an additional therapy or a substitute for another class of antihypertensive drugs (with insufficient antihypertensive efficacy or the occurrence of undesirable side effects). At the end of the study, 62% of patients reached the target figures for blood pressure, while there was a significant decrease in the level of MAU from 133 ± 11.3 mg / day to 100 ± 8.5 mg / day ($p < 0.001$) [12].

Calcium Antagonists

The administration of AK to patients with CKD is due to their vasodilating properties and the ability to favorably influence endothelial function. Among AK, drugs of the dihydropyridine series (nifedipine, felodipine, amlodipine) and the non-dihydropyridine series (verapamil and diltiazem) are isolated. The nephroprotective properties of verapamil in combination with trandolapril were proven in a large randomized clinical trial involving 1204 patients with type 2 diabetes, hypertension and without MAU. The use of combination therapy with verapamil with trandolapril and monotherapy with trandolapril slowed the development of UIA 2.6 and 2.1 times, respectively [13].

Studies have shown that dihydropyridine AK, prescribed as monotherapy, were not effective enough in patients with diabetic and non-diabetic nephropathy, but their use in patients with CKD of any etiology is possible in combination with other antihypertensive drugs with nephroprotective effects, for example, in combination with an ACE inhibitor or aARB.

Diuretics

The need to use diuretics in the treatment of kidney disease is associated with an increase in extracellular fluid volume. In many studies using ACE inhibitors and ARBs, the need for diuretic prescription was due to the failure to achieve target blood pressure. Several studies showed that therapy based on the use of the thiazide-like diuretic Arifon retard is equivalent in terms of its nephroprotective properties (UIA level) in terms of the effectiveness of therapy based on prescribing ACE enalapril in patients with hypertension and type 2 diabetes.

II. CONCLUSION

In patients with metabolic syndrome in conditions of insulin resistance, in addition to traditional manifestations, there may be renal dysfunction, which at early stages manifest as a change in GFR, MAU and endothelial dysfunction. Drugs of choice in patients with MS when it is necessary to correct an increased level of blood pressure in terms of nephroprotective effects are ACE inhibitors and ARBs with metabolic neutral and organ-protective properties. Nephroprotective properties of antihypertensive drugs have been proven for patients with already clinically pronounced kidney damage.

REFERENCE

[1] A. Bener, M. Zirie, M. Musallam, Y. S. Khader, and A. O. Al-Hamaq, "Prevalence of metabolic syndrome according to adult treatment panel III and international diabetes federation criteria: A population-based study," *Metab. Syndr. Relat. Disord*., vol. 7, issue 3, pp. 221–229, 2009.

[2] S. O'Neill and L. O'Driscoll, "Metabolic syndrome: A closer look at the growing epidemic and its associated pathologies," *Obes. Rev*., vol. 16, issue 1, pp. 1–12, 2015.

[3] K. G. M. M. Alberti, P. Zimmet, and J. Shaw "The metabolic syndrome—A new worldwide definition," *Lancet*, vol. 366, issue 9491, pp. 1059–1062, 2005.

[4] Center for Disease Control and Prevention, National Center for Health Statistics. National Health and Nutrition Examination Survey. [Accessed May 19, 2016]; Available from http://www.cdc.gov/nchs/nhanes/about_nhanes.htm. Updated February 3 2014.

[5] M. Kurella, J. C. Lo, and G. M. Chertow, "Metabolic syndrome and the risk for chronic kidney disease among nondiabetic adults," *J Am Soc Nephrol*, vol. 16, issue 7, pp. 2134-2140, 2005.

[6] R. R. Kalyani, D. C. Rodriguez, H. C. Yeh, S. H. Golden, R. J. Thorpe, Jr, "Diabetes, race, and functional limitations in older U.S. men and women," *Diabetes Res Clin Pract*, vol. 108, pp. 390–397, 2015.

[7] J. Uzokov, B. Alyavi, S. Azizov, and S. Kamilova, "Influence of metabolic syndrome on renal function in patients with hypertension," *Journal of Hypertension*, vol. 36, e84, 2018.

[8] E. D. Poggio, X. Wang, T. Greene, F. Van Lente, and P. M. Hall "Performance of the modification of diet in renal disease and Cockcroft-Gault equations in the estimation of GFR in health and in chronic kidney disease," *J Am Soc Nephrol*, vol. 16, issue 2, pp. 459–466, 2005.

[9] I.-T. Lee, W.-J. Lee, C.-N. Huang, and W. H-H Sheu, "The association of low-grade inflammation, urinary albumin, and insulin resistance with metabolic syndrome in nondiabetic Taiwanese," *Metabolism: Clinical and Experimental*, vol. 56, issue 12, pp. 1708–1713, 2007.

[10] J. A. Abdelmalek, R. T. Gansevoort, H. J. Lambers Heerspink, J. H. Ix, and D. E. Rifkin, "Estimated albumin excretion rate versus urine albumin-creatinine ratio for the assessment of albuminuria: A diagnostic test study from the prevention of renal and vascular endstage disease (PREVEND) study," *Am J Kidney Dis*., vol. 63, issue 3, pp. 415–421, 2014.

[11] D. de Zeeuw, H. H. Parving, and R. H. Henning "Microalbuminuria as an early marker for cardiovascular disease," *J Am Soc Nephrol*, vol. 17, issue 8, pp. 2100–2105, 2006.

[12] K. Ayers, L. M. Byrne, A. DeMatteo, and N. J. Brown, "Differential effects of nebivolol and metoprolol on insulin sensitivity and plasminogen activator inhibitor in the metabolic syndrome," *Hypertension*, vol. 59, issue 4, pp. 893–898, 2012.

[13] P. Verdecchia, G. Reboldi, F. Angeli, R. Gattobigio, M. Bentivoglio, L. Thijs, J. A. Staessen, and C. Porcellati, "Angiotensin-converting enzyme inhibitors and calcium channel blockers for coronary heart disease and stroke prevention," *Hypertension*, vol. 46, issue 2, pp. 386–392, 2005.