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CHANGES OF MARKERS OF ENDOTHELIAL DYSFUNCTION IN PATIENTS WITH VARIOUS TYPES OF HYPERTENSION UNDER THE THERAPY

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Abstracts. Background: *The multifactorial influence determines the complexity of the medical correction of high blood pressure in patients with CKD.*
Methods: *Plasma S-nitrozotiols, von Willebrand factor (vWF) levels were measured at start of the study t and in the end.*
Aim: *the assessment of the impact of antihypertensive therapy on markers of endothelial dysfunction in patients with hypertension only and in patients with high blood pressure comorbid with chronic kidney disease.*
Results: *It was found that therapy with lisinopril the vWF content decreased in 10.5 % ($p<0.01$) .After the treatment with candesartan the level of vWF decreased in 8.61 % ($p < 0.05$). Under the influence of lisinopril nitric oxide increased in 7.69 %, and reached in average 0,143 ± 0,04 mmol / l. After the treatment by candesartan the level of nitric oxide increased in 11.1 %, reaching an average of 0,16 ± 0,04 mmol / l.*
Conclusions: *The positive influence of renin-angiothensin-aldosteron system modulators on endothelial function was established in patients with different variants of hypertension.*
Key words*: hypertension, endothelial dysfunction, chronic kidney disease.*

The primary determinants of progression of arterial hypertension (AH) in the patients with chronic kidney disease (CKD) are an excess of sodium and water in the body, activation of the renin-angiotensin-aldosterone and sympathetic-adrenal systems, increased endothelial synthesis of vasoconstrictive substances, bivalent ions and parathyroid hormone. [1] The age over 50 years, hypertriglyceridemia, proteinuria and diabetes are among independent factors of progression of hypertension [2]. This multifactorial influence determines the complexity of the medical correction of high blood pressure in patients with CKD.

Hypertension is characterized by the development of functional changes in the endothelium, thrombogenicity of vascular wall; inflammatory reactions, vascular reactivity to vasoconsticting and vasodilating substances [3].

Von Willebrand factor and nitric oxide, which is formed from L-arginine, plays a role of particular importance for the assessment of endothelial function. It was demonstrated a direct correlation between the level of nitric oxide metabolites, blood pressure (BP) and increased cardiovascular morbidity and mortality, that means - endothelial damage was identified as one of the main risk factor for cardiovascular disease and as the subject of therapeutic interventions [4,5,].

In experimental and clinical studies (EUCLID, REIN, BRILLIANT) was demonstrated the ability of angiotensin-converting enzyme (ACE) inhibitors to cause significant antihypertensive and antiproteinuric effects, that is, to provide cardio-and renoprotection by restoring endothelial function [6].

At the same time the results of other randomized controlled trials have shown that angiotensin-receptor-blockers (ARBs) (losartan, termisartan, irbesartan, candesartan, eprosartan) can also provide renoprotective and antihypertensive effects, which are not less effective than ACE inhibitors, causing correcting impact on glomerular filtration rate and proteinuritic function [7]. Nephroprotective effect of ARB II was studied mainly for losartan and irbesartan.

The study IRMA and IDNT showed that irbesartan reduced the degree of microalbuminuria and the risk of ESRD mortality. The study RENAAL demonstrated nephroprotective effect of losartan in patients with diabetes mellitus type 2. MARVAL, DROP, SMART trials, which included patients with diabetic microalbuminuria, evidenced the nephroprotective effect of valsartan [8]. In addition, there is no exact evidence of any particular drug or class preferred for the treatment of hypertension in patients with CKD. There is no clear data about what medicine is more effective in normalization of endothelial function in such cohort of patients.

There is a modern data which supports the idea of development of endothelial dysfunction while disease progression - endothelium-dependent vasodilation (EDVD) becomes reduced and content of endothelin-1 is being increased [9].

Based on the fact that the degree of endothelial dysfunction is important for the formation of this pathology, the development of the best management for endothelial function is an important clinical challenge.

Purpose - a comparative assessment of the impact of therapy with candesartan or lisinopril on indicators of endothelial dysfunction in CKD patients with hypertension.

Materials and Methods:

We examined 54 patients – 30 males (55.5 %) and 24 females (44.4 %) with age of 37 to 59 years (mean age 51,5 ± 6,4 years). The control group consisted of 20 healthy subjects (9 men and 11 women), comparable with the studied patients by age and sex.

Patients were divided into the following groups: 30 patients (55.5 %) with chronic kidney disease stages II-III and hypertension II stage, including 14 men and 16 women, the second group of 24 patients (44.4 %) patients with chronic kidney disease II-III stages without hypertension, including 11 men and 13 women. Patients were followed for 8 weeks.

Depending on the treatment, the patients were randomized into two groups. First subgroup consisted of 30 patients treated with basic therapy of lisinopril 10 mg/day. This subgroup included 9 (31.34 %) patients with CKD and hypertension, and 7 patients (23.88 %) with CKD without hypertension. The second subgroup consisted of 24 patients, which in addition to the primary therapy were assigned to use candesartan 32 mg/day. Inside this subgroup there were 12 (22.39 %) patients with CKD and hypertension, and 12 patients (22.39 %) with CKD only.

CKD diagnosis was established on the basis of various clinical and laboratory examinations. Inclusion criterias of patients in the study were that they have clinical signs of CKD, confirmed by results of additional tests. Patients with concomitant acute inflammatory, infectious disease, cancer, immune diseases and chronic diseases in the acute phase, rheumatic diseases were excluded. CKD stage was set on according to GFR formula Cockroft - Gault.

The study protocol was approved by the Ethics Review Committee. All clinical work was conducted in compliance with Good Clinical Practice Rules (GCP) (ICH E6). All subjects signed an informed

Assessment of endothelial function state was performed by von Willebrand factor (Sigma chemical Co, USA) ristomycin aggregometry method (Biola, Russia). In addition, endothelial function was evaluated by studying the dynamics of blood flow in the brachial artery during reactive hyperemia on the ultrasound scanner HD11XE (Philips, USA) using linear 7.5 MHz probe (resolution 0.01 mm) by D. Celermajer et al., 1992. Determination of S-nitrosothiols was performed spectrophotometrically by Marzinzing M., et al., 1997 in modification of Kovaleva O. N. et al., 2007 [10].

Results and discussion. All patients from the both groups were characterized by the development of endothelial dysfunction before the treatment. It was confirmed by increased levels of von Willebrand factor and nitric oxide reduction in comparison with the control. During comparative study of the nature of endothelial dysfunction in patients of groups I and II, we have found that levels of von Willebrand factor had more pronounced increasing in the blood in patients with CKD associated with hypertension.

Before the initiating treatment with lisinopril in CKD patients with hypertension the systolic blood pressure (SBP) was elevated in comparison with the control group by 29.4 %, and diastolic blood pressure (DBP) - by 25.85 %. Under the influence of lisinopril (Table) the SBP decreased by 16.81 % (from 161,9 ± 9,6 mm Hg to 135,1 ± 10,7 mmHg , $p < 0.05$) , and DBP - by 12.5 % (from 98,8 ± 6,5 mmHg to 86,4 ± 4,1 mm Hg.).

Before treatment with the candesartan SBP and DBP were also increased in CKD patients with hypertension in comparison with the control group at 31.15 % and 26.87 %. Under the influence of candesartan the systolic blood pressure decreased by 16.23 % from 164,9 ± 12,5 mmHg to 137,9 ± 11,7 mmHg ($p < 0.05$), and diastolic blood pressure by 11.95 % from 99,6 ± 5,3 mmHg to 87,7 ± 4,9 mmHg. Thus, the influence of candesartan and lisinopril on SBP and DBP decreasing was comparable.

It was found that on the background of lower blood pressure the contents of von Willebrand factor became decreased in patients of first subgroup. Thus, if the initial level of von Willebrand factor was increased in comparison with control by 43.32 % ($p < 0.01$) and averaged 158,37 ± 6,79%, against after 8 weeks of therapy with lisinopril the vWF content decreased by 10.5 % and averaged 141,75 ± 5,75% ($p < 0.01$) .

CKD patients with hypertension treated with candesartan were characterized by similar changes. Prior to the appointment of candesartan the levels of von Willebrand factor in patients averaged 165,57±6,57%, and were by 49.83 % higher than in the control group ($p < 0.01$). After the treatment with candesartan for 8 weeks the level of von Willebrand factor decreased by 8.61 % ($p < 0.05$) and averaged 151,33 ± 5,12% ($p < 0.05$).

The changes of other vasoactive substances in the patients' blood under the influence of treatment with either candesartan or lisinopril were characterized by the following. Content of nitric oxide (S- nitrosothiols) before the treatment with lisinopril was reduced by 40.91 % and averaged 0,13±0,038 mg / dL. After treatment, this index increased by 7.69 %, and reached an average of 0,143 ± 0,04 mmol / l. In the subgroup of patients treated with candesartan the initial level of nitric oxide (S-nitrosothiols) was also reduced compared with control group by 34.56 % , and averaged 0,144 ± 0,027 mmol / l ($p < 0.05$). After the treatment, it rose by 11.1 %, reaching an average of 0,16 ± 0,04 mmol / l.

The reduction of von Willebrand factor that was discovered under the influence of lisinopril and candesartan leads to reducing of vasospastic condition of the endothelium. However, increasing of nitric oxide (S-nitrosothiol) level, as indicator of the vasodilator mechanisms of cellular interactions is noteworthy. It can be regarded as a compensatory increased vasodilator activity in response to the reduced action of von Willebrand factor.

In patients with CKD without hypertension, in a subgroup with lisinopril therapy the same dynamics of changes in the content of von Willebrand factor and nitric oxide (S-nitrosothiols) was defined.

There was a decreasing of von Willebrand factor content after treatment with lisinopril at 7.73 % to an average of 143,27 ± 5,68% and increasing of nitric oxide (S-nitrosothiols) by 9.7% to an average of 0,147 ± 0,042 mg/liter.

In patients with CKD without hypertension the therapy with candesartan lead to lowering the level of von Willebrand factor compared to baseline of 8.91 % ($p < 0.05$), reaching an average of 148,24 ± 5,07% and an increasing in nitric oxide metabolites (Snitrosothiols) to 10.06% , an average of 0,164 ± 0,043 mg / dL.

We can assume that activity of vasoconstriction mechanisms is predominant in patients with chronic kidney disease and is associated with endothelial dysfunction on background of sympathetic nervous system activation [11, 12]. At the same time a failure of physiological mechanisms takes place caused by decrease in activity of nitric oxide. Effects of ACE inhibitor (lisinopril) and ARB II (candesartan) primarily aimed at the normalization of endothelial function, which was evidenced by decreasing the blood content of von Willebrand factor and increasing of nitric oxide formation.

As it is considered that the changes of the content of von Willebrand factor is biochemical marker of endothelial involvement in the processes of regulation of vascular tone, it can be argued that the CKD with hypertension is accompanied by a more significant increasing of the formation of constrictive factors and insufficient production of relaxing factor, that is proved by lowering content of S-nitrosothiols.

Significant reduction of von Willebrand factor under the influence of lisinopril in CKD with hypertension, confirms a greater impact of the ACE inhibitor on synthesis of von Willebrand factor. A more significant reduction of the vWF in the blood under the influence of lisinopril probably depends on the increased local formation of angiotensin II.

This confirms the position that one of the action mechanisms of the renin-angiotensin-aldosterone system modulators is the ability to improve the endothelial function and to reduce the content of von Willebrand factor in the blood.

Conclusions that can be made from the study:

1. The positive influence of renin-angiothensin-aldosteron system modulators such as lisinopril and candesartan on endothelial function was established that in patients with CKD associated with hypertension.
2. In the group of patients who were administered lisinopril more significant decreasing in the concentration of von Willebrand factor in the blood was determined, in comparison with candesartan.
3. The ACE inhibitor lisinopril can be considered as the drug of choice for the correction of endothelial dysfunction in chronic kidney disease with hypertension.

Further development of methods of medicamental influence on the degree of endothelial dysfunction seems to be promising and will improve the quality of treatment and possibly the prognosis of patients with CKD and hypertension.

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