

**FACTORS OF INFLAMMATION IN PATIENTS WITH ARTERIAL HYPERTENSION AND DIABETES MELLITUS**

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Abstract

The aim of the study was to study the relationship between indicators of subclinical inflammation and the degree of organ disorders in patients with isolated arterial hypertension (AH) and in combination with diabetes mellitus (DM). 49 patients were examined, 26 of them with isolated hypertension and 46 with hypertension in combination with diabetes, comparable in gender, age and office blood pressure (BP). The daily monitoring indicators were evaluated blood pressure, left ventricular myocardial hypertrophy, endothelial function. The activity of subclinical inflammation was assessed by blood concentrations of interleukines (IL1a, IL6, IL8, IL10), tumor necrosis factor alpha (TNF α) and C-reactive protein (hsCRP). The presence of insulin resistance and the degree of compensation for diabetes mellitus were assessed. Patients with hypertension in combination with DM have higher rates of SMAD and greater manifestations organ lesions, compared with patients with isolated hypertension. Patients with DM are characterized by greater activity of inflammatory processes. The processes of subclinical inflammation are responsible for both the degree of increase in blood pressure, and for the formation of organ lesions. Indicators of insulin resistance correlate with the concentration of the main markers of inflammation.

Keywords: arterial hypertension; diabetes mellitus; inflammation; metabolic syndrome.

Introduction

Arterial hypertension (AH) is the most common non-communicable disease and is the most important risk factor for major cardiovascular diseases (CVD) – myocardial infarction and cerebral stroke, mainly determining the high mortality rate in our country. If, in general, the general population prevalence of hypertension in Uzbekistan is 40%, then in patients with diabetes mellitus (DM) the frequency of detection of hypertension is 2-3 times higher than the general population - 80-90%. The association of DM and AH leads to an extremely rapid development of lesions as small vessels of the kidneys and retina, as well as large vessels of the heart, brain, peripheral vessels of the lower extremities. The combination of diabetes and hypertension in one patient increases the risk of coronary heart disease (CHD) by 2-4 times, stroke by 2-3 times, complete loss of vision by 10-25 times, uremia by 15-20 times, gangrene of the lower extremities by 20 times. Over the past decades, a large amount of data has been obtained on various links in the pathogenesis of hypertension. Research in recent years suggests that one of the mechanisms responsible for subclinical inflammation stands for organ lesions in hypertension. According to the literature, signs of a non-specific inflammatory process can be traced from the earliest stages of the development of damage to the vessel wall and in the early stages of hypertension. However,



data on the relationship between inflammatory markers and blood pressure (BP) are contradictory. In addition, there is still no convincing clinical data on the role of subclinical lesions in the development of organ lesions in patients with hypertension in combination with diabetes. The aim of the study was to identify the relationship between the indicators of subclinical inflammation and the degree of organ disorders in patients with isolated AH and in combination with DM.

MATERIALS AND METHODS OF RESEARCH

49 people were included in the study. The main group consisted of 26 patients with hypertension associated with type 2 diabetes aged 42 to 64 years, the average age was 51.1 years (47.6 54.2) and 23 patients with isolated hypertension without carbohydrate metabolism disorders, the average age was 49.3 years (46.7 52.4), $p=0.064$. During the initial examination, age, gender, height, body weight, blood pressure and heart rate, criteria for the diagnosis of essential arterial hypertension and type 2 diabetes mellitus, length of service, the fact of smoking were taken into account, treatment of hypertension and type 2 diabetes was analyzed currently and during the last year, concomitant diseases. The groups were comparable in all clinical and anamnestic parameters. Antihypertensive therapy was represented by angiotensin converting enzyme inhibitors (93.9 %); angiotensin II receptor blockers (6.1 %); thiazide-like diuretics (77.6%); beta blockers (36.7%). In the group of patients with Patients with hypertension associated with type 2 diabetes received metformin as a hypoglycemic therapy (100%) and sulfonylurea preparations (59.6%). Before the patient was included in the study, based on the examination data, his compliance with the inclusion criteria was determined.

All patients had their blood pressure measured using the Korotkov method. Daily blood pressure monitoring (SMAD) was performed by the automatic outpatient daily monitoring system BPLab MnSDP 2. Echocardiography was performed in two-dimensional scanning mode on a Hitachi-2000 device. The mass left ventricular myocardium (LVMH) was calculated according to the formula proposed by R. Devereux and N. Reichek. The determination of the MMLJ index (MMLJ) was carried out according to the formula: $MMLJ = MMLJ / S$, where S is the surface area of the body (g/m^2). Ultrasound color dopplerography of the brachial artery it was carried out according to the standard procedure proposed by Hitachi, on a Sony 2500 device with a 7 MHz ultrasound vascular sensor in the morning, on an empty stomach, up to 10 o'clock.

All patients underwent a standard biochemical blood test to determine the concentration of glucose in venous blood. The concentration of interleukins (IL 1 α , IL 6, IL 8, IL10), tumor necrosis factor alpha (TNF α), highly sensitive C-reactive protein (hsCRP) and immunoreactive insulin was determined by solid-phase enzyme immunoassay using standard reagents on the CHEM WELL 2910 (C) apparatus. The concentration of glycated hemoglobin in venous blood was determined by the method of low-pressure cation exchange chromatography "DiaSTAT". Microalbuminuria (UIA) it was determined by turbidimetry on a biochemical autoanalyzer "Siemens". The Homa formula was used to assess insulin resistance: $\text{Nome index} = \text{fasting insulin} \times \text{fasting glucose} / 22.5$. The Homa index value of more than 2.7 indicated the presence of insulin resistance. The data was processed using the STATISTICA 8.0 application software package. The sample was checked for the correct distribution. Due to the fact that the sample was different from normal distribution, nonparametric statistical methods were used. The average values and standard deviations were calculated. The results are presented in the form of $M \pm \sigma$ and $Me \pm Q$. The difference in indicators



in the two groups was assessed using the Mann Whitney criterion. Spearman correlation analysis was used to identify the relationship between the studied values. Differences and correlations were considered significant at $p < 0.05$. In all statistical analysis procedures, the significance level of p was assumed to be 0.05.

THE RESULTS AND THEIR DISCUSSION

As a result of comparative analysis, there were no significant differences in the main clinical and anamnestic parameters between patients in the group of isolated hypertension and in combination with type 2 diabetes. However, in patients with hypertension in combination with type 2 diabetes, compared with patients with isolated hypertension, significantly higher values of triglycerides in blood plasma were revealed – 1.37 mmol/l (0.94-1.71) and 1.6 mmol/l (1.16- 1.89), respectively ($p = 0.017$). Despite the absence of differences in the indicators of office blood pressure measurement, when comparing the indicators SMAD in patients with arterial hypertension in combination with type 2 diabetes mellitus, compared with patients with isolated hypertension, significantly higher diastolic blood pressure (DBP) was detected both during the daytime and at night. In addition, in the group of patients with hypertension associated with type 2 diabetes, a predominance of patients with the types of circadian rhythm "non dipper" (67.1%) and "night peaker" (18.2%) was revealed, compared with the group of patients with isolated hypertension (52.6% and 5.3%, respectively; $p < 0.005$ and $p < 0.005$). Patients with dipper circadian rhythm prevailed in the group of patients with isolated hypertension (42.1% and 31.1%; $p < 0.005$). There were no patients with an over-dipper circadian rhythm in any of the groups. It is known that the types of daily blood pressure curve "non-dipper" and "night-peaker", characterized by the lack of sufficient reduction in blood pressure at night, are associated with a higher risk of death from cardiovascular diseases, unlike the "dipper" type. In patients with hypertension, who do not have a sufficient nocturnal decrease in systolic blood pressure (SAD) and DAD, the course of the disease is less favorable due to the greater likelihood and severity of damage to target organs and a higher incidence of complications of hypertension. Yeo Shin et al. demonstrated that patients with hypertension who do not there is an overnight decrease in SAD and DAD, and they have twice the percentage of cardiovascular complications.

Left ventricular hypertrophy is the main structural change of the heart and one of the early criteria for target organ damage, and echocardiography is the most sensitive method of its assessment. Although the relationship between LVMH and cardiovascular risk is continuous, the generally accepted criteria for diagnosing left ventricular hypertrophy are LVMH values of more than 125 g/m^2 in men and 110 g/m^2 in women. As a result of the study, significantly higher values of MMLH and LVMH were revealed in patients with arterial hypertension in combination with type 2 diabetes mellitus, compared with patients with isolated hypertension, with comparable indicators of contractility and diastolic function of the left ventricular myocardium. Thus, with isolated hypertension, the LVH was 169.2 g/m^2 , and with hypertension in combination with DM – 184.3 g/m^2 ($p < 0.001$).

In addition, patients with hypertension and DM also differed in more pronounced endothelial dysfunction, manifested by lower values of the endothelium-dependent vasodilation index (EDVD), less sensitivity of the arteries to the shear stress. Thus, in patients of comparable gender and age, the presence of diabetes mellitus increases the severity of hypertension. With equal values of office indicators of blood pressure and heart rate, conducting SMAD allows us to assert that



patients with hypertension in combination with DM have higher rates of DAD, especially at night, and also more often demonstrate pathological daily indices HELL of "non dipper" and "night peaker". As a result, in patients with hypertension in combination with DM, this is manifested by high values of LVH and endothelial dysfunction, manifested by lower values of the ESRD index, less sensitivity of the arteries to shear stress and a more significant MAU, compared with patients with isolated hypertension.

When analyzing the indicators characterizing the inflammation process in the analyzed groups of patients, it turned out that in patients with a combination of hypertension and diabetes Type 2 significantly higher values of proinflammatory markers were recorded: IL-6, TNF and CRP, compared with patients with isolated hypertension. Anti-inflammatory IL-10, on the contrary, showed significantly lower values in patients with hypertension in combination with DM, which suggests the insolvency of compensatory reactions in patients with DM. The indices of IL 1 α and IL 8 in the patients of the analyzed groups did not differ significantly. These facts indicate the important role of carbohydrate metabolism disorders in the activation of subclinical inflammation processes.

In patients with isolated hypertension, when conducting a correlation analysis between the indicators carbohydrate metabolism and inflammatory markers revealed direct correlations between the values of postprandial glycemia, on the one hand, and IL-6 and CRP, on the other ($r = 0.27$; $p = 0.016$ and $r = 0.38$; $p = 0.024$). CRP values also positively correlated with the values of glycated hemoglobin ($r = 0.28$; $p = 0.003$), IRI ($r = 0.09$; $p = 0.031$) and Homa index ($r = 0.54$; $p = 0.001$). Glycated hemoglobin and Homa index showed a positive association of average strength with TNF ($r = 0.32$; $p = 0.034$ and $r = 0.26$; $p = 0.033$). In the group of patients with hypertension associated with diabetes The 2 types of correlations described above have shown great strength and reliability. Thus, the correlation coefficient between IRI and CRP was 0.31 ($p = 0.001$), between IL-6 and the Homa index – 0.48 ($p = 0.001$), which suggests a common pathogenesis of insulin resistance and subclinical inflammation. In addition, in patients with hypertension In combination with DM, there was a positive correlation between IL-1 α , on the one hand, and indicators of lean glycemia and the Homa index, on the other ($r = 0.24$; $p = 0.012$ and $r = 0.43$; $p = 0.001$). An inverse correlation was found between IL-10 and the Homa index ($r = -0.28$; $p = 0.001$), indicating a negative relationship between insulin resistance and anti-inflammatory index. It should be emphasized that in patients with isolated hypertension, there were no such connections.

Thus, there is a close connection between indicators characterizing the activity of nonspecific inflammation processes (IL-6, TNF and CRP), and indicators of carbohydrate metabolism in patients with both isolated hypertension and hypertension in combination with diabetes. At the same time, in patients with hypertension in combination with diabetes, there are strong and reliable connections, which indicates the important role of carbohydrate metabolism disorders in the initiation and maintenance of subclinical inflammation. In addition, SMAD indicators also correlated with the main markers of subclinical inflammation. Thus, in patients with isolated hypertension, direct correlations were found between the indicators of minimum daily mean SAD, on the one hand, and such proinflammatory cytokines as IL-6 ($r = 0.17$; $p = 0.034$) and CRP ($r = 0.34$; $p = 0.017$), on the other. In the group of patients with AH associated with diabetes, these connections have strengthened. So, The indices of the minimum values of DBP and the average minimum blood pressure at night positively correlated with TNF ($r = 0.33$; $p = 0.02$ and $r = 0.39$;



$p = 0.009$), and the indices of the minimum values of nighttime DBP with CPP ($r = 0.36$; $p = 0.01$). The activity of subclinical inflammation turned out to be closely related to the manifestations of organ lesions. Thus, in patients with isolated hypertension, correlations of average strength between LVH and the level of IL-6 concentration ($r = 0.27$; $p = 0.016$) and CRP ($r = 0.24$; $p = 0.038$) were revealed, and in patients with hypertension associated with diabetes, these connections showed greater strength – $r = 0.54$ ($p = 0.021$) and $r = 0.60$ ($p = 0.08$), respectively. Similar patterns were also revealed in the correlation analysis between ESRD and MAU, on the one hand, and markers of inflammation, on the other. Thus, in patients with isolated hypertension, a direct correlation was found between EDVD and CRP ($r = 0.39$; $p = 0.046$), in patients with hypertension and DM, the level of EDVD and IL-6 concentration ($r = 0.29$; $p = 0.031$). Microalbuminuria, reflecting the processes of endothelial dysfunction, also had an association with inflammatory activity: in patients with isolated hypertension – IL 6 ($r = 0.19$; $p = 0.008$) and CRP ($r = 0.23$; $p = 0.038$). In the group of patients with hypertension associated with diabetes, these connections became stronger – $r = 0.35$ ($p = 0.018$) and $r = 0.72$ ($p = 0.029$), respectively.

When discussing the data presented in this study on the relationship of subclinical inflammation processes with the main manifestations of hypertension (increased blood pressure and organ changes), it should be remembered that there are several mechanisms explaining this the relationship. It has been proven that excessive activation of the renin-angiotensin-aldosterone system, in particular angiotensin II, causes not only such well-known effects as vasoconstriction, myocardial hypertrophy, proliferation of smooth muscle cells, activation of lipid peroxidation processes, but also the expression of proinflammatory molecules of the vascular wall, which leads to the accumulation of monocytes at the site of its damage. It is known that in endothelial cells, angiotensin II regulates the expression of intracellular adhesion molecules and E-selectin, which contributes to endothelial dysfunction.

It has been shown that the processes of nonspecific inflammation increase the permeability of albumin through the basement membrane of the glomerulus of the kidneys in response to an increase in blood pressure. In a large study of PREVENT in patients with hypertension, a positive relationship between CRP and MAU levels was established, which may be due to dysfunction of the glomerular endothelium and/or a violation of the processes of autoregulation of intraclobular pressure.

CONCLUSIONS

The data of this study demonstrate that patients with hypertension in combination with diabetes, even in the absence of differences in gender, age, office characteristics of blood pressure and heart rate, have higher rates of SMAD and greater manifestations of organ lesions. The processes of nonspecific inflammation are responsible for both the degree of increase in blood pressure and the formation of organ lesions, as evidenced by the correlations described above. In addition, it has been proven that insulin resistance, which can be reflected by the concentration of IRI and the Homa index correlates with the concentration of the main markers of inflammation, which indicates the commonality of the processes of insulin resistance and inflammation. Patients with DM are characterized by greater activity of inflammatory processes, which determines in this category of patients more pronounced organ lesions and an unfavorable prognosis for cardiovascular diseases.

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