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Features of Clinical and Laboratory Changes in Arterial Hypertension on the Background of Diabetes Mellitus

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Abstract: Arterial hypertension (AH) is one of the leading problems of cardiology that determine the structure of cardiovascular morbidity and mortality [13]. Prevalence of hypertension in the adult population.

Increased levelsof systolic (SBP) and diastolic (DBP) arterial pressure (BP) are associated with a higherким risk of cardiovascular events [7].

In rare cases, hypertension is the only disease, but more often it is combined with a number of other pathologies. But if in some other patients this combination is random, caused by a simple coincidence, then in other cases there is a commonality of pathogenetic processes, the interdependenceof emerging changes that affect the prognosisof patients, management tactics andthe effectiveness oftherapy. Among such combinations, the presence of hypertension in diabetes mellitus (DM) is of the greatest importance [12]. Hypertension is one of the most significant risk factors in the development and progressionof diabetic micro-and macroangiopathies. According to epidemiological studies, when DM and hypertension are combined, the risk of fatal CHD increases 3-5 times, stroke – 3-4 times, complete vision loss – 10-20 times, uremia –20- 25 times, gangrene of the lower extremities -20 times [9].

The majority of DM patients have elevated blood pressure, which is one of thec- main risk factors for cardiovascular and cerebrovascular diseases. Hypertension, as well as для typical hemodynamicand metabolic disorders, play a sad role in the development and progression of micro-and macrovascular complications of diabetes.Diabetes mellitus (DM) and arterialhypertension (AH) are emutually aggravatingdiseases that acceleratedamage to target organs such, as the heart, kidneys, brain and retinal vessels, and major vessels [3]. Hypertension in combination withmetabolic disorders inherent in diabetes accelerates the development of coronary heart disease (CHD), heart and kidney failure, brain complications, peripheral vascular diseases, and creates an increased risk of complications, disability, and premature death in patients.

According to the Fr Hemingham study,severe cardiovascular complications in combination with hypertension and diabetes areobserved 5 times more often, the death rate from cardiovascular complications is 2.5- 7.2 times higher, and when clinical symptoms ofnephropathy appear– в , it is 37 times higher than in comparable age groups of the general population [1]. In the system of cardiovascular risk stratification, the presence of diabetes mellitus in patients with hypertension allows them to be classified as a very high risk group [2].

In individuals with DM, elevated BP values are observed 2 times more often than in patients with-other diagnoses [11-4]. According to various authors, the frequency of detection of

hypertension among patients with DM ranges from 16.5 to 75 % [9].

In Europe, the detection rate of hypertension is10-30 % in СД type 1 diabetes, 30-60 % – in СД type2 diabetes, and 20-40 % – in people with HTG.

Epidemiology

In patients with DM, the frequency of hypertension is 2 times higher than in the general population, accounting for 10-30 % in patients with type 1 diabetes, 60-80 % – in patients with type 2 diabetes, and 20-40 % in those with HTG [11-5]. In patients with type 1 diabetes, the appearance, of hypertension usually indicates the developmentof renal insufficiency (PI) and its frequency increases as the severity поражения of kidney damage increases. According to the Endocrinological Research Center of the Russian Academy of Medical Sciences, with an average duration of DM of 10 years, the frequency of hypertension in СД type 1 diabetes is 10 % in people without kidney pathology normo albuminuria (NAU), 20% – in patients на with microalbuminuria (MAU), 50-70% in patients with protenuria (PU), and 70-100% in patients with non – renal pathology. at the stageof CRF [4].

The higher prevalence of hypertension even in theinitial stage of nephropathy indicates that in type 2 diabetes, hypertension often precedes a violation of carbon-water metabolism and in 50% of patients is detected already at the onset of diabetes. This is due to the fact that в the development of hypertension and type 2 diabetes is based on a general metabolic defect - insulin resistance (IR), which clinically canmake its debut with an increase in blood pressure, only later leading to a violation of carbohydrate metabolism]. The combination of thesepathological changes is called metabolic syndrome or insulinresistance syndrome. Later, the hypothesis of the interrelated origin of DM and hypertension wasconfirmed in many studies, the largest of which is ARIC (The Atherosclerosis Risk in Communities). Thisstudy was conducted in the United States and included 12 12,550 individuals aged 45 до 45-64 years without diabetes. After 6 years , the incidence of new cases of type 2 diabeteswas assessed [1-1]. It turned out that in patientswith hypertension (BP>140/90 mm Hg), the frequency of de novo type 2 diabetes novo was 2.43 times higher than in normotensive patients. The conducted studies confirm a close relationship between the development СД of type 2 diabetes and hypertension.

Etiology and pathogenesis

The most commoncauses of hypertension in type 1 diabetes mellitus are:

1. Diabetic nephropathy – 80 %.
2. Essential hypertension (systolicand diastolic) – 10 %.
3. Isolated systolic hypertension ––– 5-10 %.
4. Other endocrine pathology ––– 1-3 %.

The main causes of hypertension in СД type 2 diabetes are:

1. Гипертоническая Hypertension ––– 30-35 %.
2. Isolated systolic hypertension ––– 40-45 %.
3. Diabetic nephropathy ––– 15-20 %.
4. Renovascular hypertension and ischemic kidney – disease – 5-10 %.
5. Other endocrine pathology ––– 1-3 %.

That is, the main cause of hypertension in type 1 diabetes can be considered diabetic kidney damage, in type 2 diabetes – hypertension and isolated systolic hypertension [15].

Hypertension in DMcan also be induced by heavy alcohol consumption or by taking certain medicationsthat increase blood pressure, including. glucocorticoidsand contraceptives.

Pathogenesis of hypertension in СД type 2 diabetes

Синдром Insulin resistance syndrome (IR). Hypertension in type 2 diabetes is a component of the IR syndrome (or metabolic syndrome) described in 1988 г. by G. M. Reaven [8]. The term "metabolic syndrome" currently includes type 2 diabetes (or HTH), hypertension, dyslipidemia (mainly – hypertriglyceremia), abdominal obesity, hyperuricemia, MAU, and increased blood levels ofprocoagulants (fibrinogen, an inhibitor of plasminogen activator 1). All these conditions can be a consequence of reduced sensitivityof peripheral tissues to insulin, i.e. IR [11]. The latter also occurs in other pathological or physiologicalconditions that are not included in theconcept of metabolic syndrome: polycystic ovaries, CRF, infections, glucocorticoid therapy,pregnancy, and aging.

The prevalence of IR was studied in a largepopulation study conducted in Italy [6], which included 888 people aged от 40 to 79 years. When analyzing IR by the NOMA method, it was found that it occurs in such syndromesand diseases as in essential hypertension (BP□< 160/95 mm Hg) - in 58 %; in hyperuricemia (serum uric acid content > 416 mmol/ l y in men and > 387 mmol/l y in women) in – 63% of patients with hypertriglyceridemia (TG > 2.85 mmol/ L) - 84 %; in 88 % of patients with low HDL cholesterol (< 0.9 mmol/L in men and < 1.0н- in women); in 66 % of patients with HTG; in 84 % of patients with type DM 2 (when it was diagnosed according to the criteria: fasting glycemia > 7.8 mmol/ l and 2 hours after glucose loading > 11.1 mmol/l); in 10 % of individuals without metabolicdisorders.

When type 2 diabetes (or HTG) was combined with dyslipidemia, hyperuricemia , and hypertension, т. i.e. , with the main componentsof the metabolic syndrome, the frequency of IR detection was 95 %. This suggests that IR is indeed the leading mechanism for the development of metabolic syndrome ИР [6].

The role of IR in the development of type 2 diabetes. Peripheral tissue IR underlies the development of type 2 diabetes. Peripheral tissue IR precedes the development of type 2 diabetes and can be detected in the closest relatives of patients with type 2 diabetes who do not have carbohydrate metabolism disorders. For a longtime, IR is compensatedby excessive production of insulinby παγχρεατιχ β-cells (hyperinsulinemia), which increasescarbohydrate metabolism in the norm. Hyperinsulinemia is equated with markersof IR and is considered a harbinger of type 2 diabetes. Subsequently, whenthe degree of IR increases, the cells stop coping with the increased glucose load, which leads to a gradual depletion of insulin secretory ability and clinical manifestation of diabetes. First of all, the 1st phase of insulin secretion (rapid) in response to food load suffers, the 2nd phase(basal insulin secretion phase) also begins to decrease. The developed hyperglycemia further increases the IR of peripheral tissues and suppresses the insulin secretory function □□T-cells. Thismechanism is called *glucose toxicity* [8].

In modern conditions in countries with a high standard of living characterized by inactivity and high-calorie nutrition, the mechanisms of IR preserved in genetic memory continue to " work" onenergy accumulation, which leads to abdominalobesity, dyslipidemia, hypertension and,finally, СД type 2 diabetes.

The role of IR in the development of hypertension. The relationship between hyperinsulinemia (a marker of IR) and essential hypertension is so strong that with a high concentration of plasma insulin in a patient , it is possible to predict the development of hypertension in the nearfuture. Moreover, this relationshipcan be traced both in obese patients and in people with normal body weight.

Insulin promotes activation of the sympathetic nervous system, increases the reabsorption of Na and fluid in the renal tubules, intracellular- accumulation of Na and Ca, and insulin as a mitogenic factor activates the proliferation of vascular smoothmuscle cells, which leads to thickening of the vessel wall.

Stimulation of the sympathetic nervous system (SNS). The ability ofinsulin to activate SNS was establishedin the 1980s, when studieson- healthy volunteers showed that prolonged insulin

infusion causes a dose dependent increase in the level of norepinephrine by approximately 1.5-2 times [6]. In patients with type 2 diabetes, a 45-minute insulin infusion(under the conditions of a euglycemic hyperinsulinemic clamp) increased the concentration of norepinephrine in the arterialblood by 64 %. Maximal SNA stimulation is observed in patientswith IR, hyperinsulinemia и ожи, and obesity, in whom additional insulin infusion does not lead to even greater SNA activation. The study by K. D. Ward [8] demonstrated a direct relationship between the concentration of insulin in the blood, the level of blood pressure, and the excretion of norepinephrine in the urine, which once again confirmsthe undoubted pathogenetic relationshipbetween the activity of SNS, hyperinsulinemia, and hypertension.

The mechanism of influence of insulin on the SNA is not completely clear.It is suggested that insulin canactivate the SNS by direct action onthe central nervous system, passing through the blood-brain barrier в to theperi обл-ventricular area of the hypothalamus, where,by binding to its receptors on the surface of neurons- , it blocks the activity of the parasympathetic nervous system and, on the contrary, activates the SNS [10].

G. M. Reaven, thefounder of IR syndrome, suggested that when the SNSis overactivated under conditions of hyperglycemiaa- , glucose metabolism in the hypothalamic nuclei may be increased, which inhibits the transmission of blocking impulses to the sympathetic centers of the medulla oblongata

Mediatedactivationof the central nervous system by the inclusion of a baroreceptor response to vasodilation and hypotension caused by insulin is also possible.

Stimulation of the SNS in hyperinsulinemia pois accompaniedby an increase in cardiac output,an increase in OPSS, which inevitably leads to anincrease in blood pressure.At the same time, a decrease in the activity of the para sympatheticsystem caused by hyperinsulinemia, increases the heart rate.

Increased Na and water reabsorption. Insulin has a direct effecton the proximal tubules of renal nephrons, increasing the reabsorption of Na and fluid. In addition to anti-natriuresis , insulin causes tanticaliuresisand anti- uricosuria[12]. Under the conditions of a euglycemic hyperinsulinemic clamp, the excreted Na fraction decreases by 20-30 % in healthy volunteers and by 40-50 % in patients with type 2 diabetes. As a result, the volume of circulatoryy- fluid increases , which leads to an increase in cardiac output. Apparently, the Na and water-retaining effect is associated with the occurrence of edema y in individuals with СД type 1 diabetes at the beginning of insulin therapy (insulin edema) [7].

Thickening of the vascular wall. The mitogenic propertiesof insulin were discovered long ago in a seriesc- of experimental studies by R. W. Stout in 1970-1990 [13], where it was shown that insulin stimulates cell growth, proliferation, and migrationof vascular smooth muscle cells, leading to thickeningof their walls.

Insulin can act in two ways on the vascular endothelium, causing either their expansion or spasm.

Despite the close relationship between IR and elevated blood pressure, not all patients c with essential hypertension have IR and hyper insulinemia. According to the Brunneck Study, in 40% of patients with hypertension, the concentration of insulin in plasma remains within normal values. Hypertension of otheretiologies (renal, renovascular, primary hyperaldosteronism) is not associated with IR. It was also noted that not all individuals with IR develop hypertension [2]. It is assumed that an inverse relationship between IR and AH is also possible, i.e. IR may develop secondarily in the long-term course of hypertension. This hypothesisis partially confirmed in the work of I. E. Chazova and V. B. Mychka, where a reliable relationship between the duration of hypertension and the severity of IR is established. There is a pathophysiological explanation for this hypothesis: there is a relationship between RAS activity, blood pressure levels, and tissue sensitivity to insulin.

IRS-1 and IRS-2 associated with PI3-K), which implements glucose transport to cells and NO

production. At the same time, AT I I stimulates the MAPK systeminvolved in the mitogenic and insulin.

Thus, hyperactivity of RAS and AT II can cause tissue resistance to the antiatherogenic and hypotensive effects of insulin, as well as block the transport of glucose into cells, which cancontribute to the development of HTG, and then и СД type 2 diabetes.

It is obvious that essential hypertension in СД type 2 diabetes isa reflection of the general pathophysiological syndrome IR-the basis for the development of both type 2 diabetes and hypertension. At the same time, IR itself may be a consequence PAC, of ASD hyperactivity, which-maintains a high blood pressure level, or it may increase with this hyperactivity.

Renin-angiotensin system in diabetes mellitus and arterial hypertension

Initial studies of the state inDM mainly evaluated the concentrationof circulating componentsof RAS om: renin, AT II,aldosterone , etc. Very contradictorydata were obtained on the activity of plasma renin and AT II in DM – from high to low values. Later most scientist who conducted indepen dent studies at different times found that both type 1 and type 2 diabetes are most often characterizedby low renin levels in blood plasma and are combined with hyporeninemic hypoaldosteronism syndrome . It was noted that the level of renin activity is inversely correlated with the quality of glycemic control, estimated by the level of glycated hemoglobin HbA1c; the worse the compensation of diabetes and the higher the level of HbA1c, the higher the activity of plasma renin. At the same time, the level of circulating AT II did not correlate with the level of HbA1c and remained consistently high. Since AT II is an inhibitor of renal renin synthesis, the hyporeninemic state in DM is associated witha high activity of locally renal AT II.

It was found that the local renal concentrationof AT II is 1000 times higher than its content in plasma.Analogous local RAS was detectedжена in DM in ткани the heart tissue and vascular endothelium.

The pathogenic effects of AT II in DM are associated not only его with its powerful vasoconstrictor action, but also with its proliferative, pro-oxidant, and prothrombogenic activity.

The role of ASD in the development of DM

In recent years, it has been found that the active use of ACE inhibitors for the treatment of hypertension and vascular complications in DM in some cases is accompanied by a hypoglycemic state and a decrease in IR. This led to the study of the role of AT II in the mechanisms regulating the level of glycemia – the sensitivity of peripheral tissues to insulinand the secretion of insulin by the pancreas. The use of modern molecular biological technologies allowed us to establish that the post receptor signaling systems of AT II and insulin are closely interrelated. Insulin, after interacting with its receptors on the cell surface, induces tyrosinephosphorylation of IRS-1 and IRS-2 proteins. Further IRS molecules activate PI-K, through which signal transmission andrealization of the metabolic and vasodilating effects of insulin (glucose transport to cells, синтез NO synthesis) are carried out. AT II blocks the PI3-K – signaling pathway of insulin in vascular cells and other insulin-dependent tissues, while simultaneously stimulating another insulin signaling system (ras, raf, MEK, MAPK), leading to activation of mitogenicand proliferative processes. Thus, AT II blocks the main metabolic effect of insulin - glucose transport to cells - and enhances the atherogenic effect of insulin. In other words, ASD hyperactivity is accompanied by increased IR.

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