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Specific Characteristics of Clinical and Laboratory Changes in the Course of Arterial Hypertension Against the Background of Diabetes

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ABSTRACT

Arterial hypertension (AH) is one of the leading problems in cardiology, determining the structure of cardiovascular morbidity and mortality [1,2]. Prevalence of hypertension among adults. Increasing levels of systolic (SBP) and diastolic (DBP) blood pressure (BP) are associated with a higher risk of cardiovascular events [5].

In rare cases, hypertension is the only disease, but more often there are cases of its combination with a number of other pathologies. But if in a number of other patients this combination is random, caused by a simple coincidence, then in other cases there is a commonality of pathogenetic processes, the interdependence of the changes that occur that affect the prognosis of patients, management tactics and the effectiveness of therapy. Among such combinations, the presence of hypertension in diabetes mellitus (DM) is of greatest importance [4,6]. Hypertension is one of the most significant risk factors in the development and progression of diabetic micro- and macroangiopathies. According to epidemiological studies, when diabetes and hypertension are combined, the risk of developing fatal ischemic heart disease increases by 3–5 times, stroke by 3–4 times, complete loss of vision by 10–20 times, uremia by 20–25 times, gangrene of the lower extremities – 20 times [9].

Most patients with diabetes have elevated blood pressure levels, which is one of the main risk factors for cardiovascular and cerebrovascular diseases. Hypertension, as well as hemodynamic and metabolic disorders typical for this disease, play a sad role in the development and progression of micro- and macrovascular complications of diabetes. Diabetes mellitus (DM) and arterial hypertension (AH) are mutually aggravating diseases that accelerate damage to target organs such as the heart, kidneys, brain and retinal vessels, and great vessels [3]. Hypertension, in combination with metabolic disorders inherent in diabetes, accelerates the development of coronary heart disease (CHD), heart and kidney failure, cerebral complications, peripheral vascular diseases, and creates an increased risk of complications, disability and premature death in patients.

According to the Framingham study, severe cardiovascular complications with a combination of hypertension and diabetes are observed 5 times more often, the mortality rate from cardiovascular complications is 2.5–7.2 times higher, and when clinical symptoms of nephropathy appear, it is 37 times higher than in comparable age groups of the general population [5]. In the cardiovascular risk stratification system, the presence of diabetes mellitus in hypertensive patients allows them to be classified as a very high-risk group [12].

In people suffering from diabetes, elevated blood pressure values are observed 2 times more often compared to patients with other diagnoses [14]. According to various authors, the frequency of detection of hypertension among patients with diabetes ranges from 16.5 to 75% [9]. In European countries, the

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frequency of detection of hypertension is 10–30% in type 1 diabetes, 30–60% in type 2 diabetes, and 20–40% in individuals with IGT.

Epidemiology

In patients with diabetes, the frequency of hypertension is 2 times higher than the general population, amounting to 10–30% in patients with type 1 diabetes, 60–80% in patients with type 2 diabetes, and 20–40% in individuals with IGT [15]. In patients with type 1 diabetes, the appearance of hypertension, as a rule, indicates the development of renal failure (RF) and its frequency increases as the severity of kidney damage increases. According to the Endocrinological Research Center of the Russian Academy of Medical Sciences, with a diabetes duration of an average of 10 years, the frequency of hypertension in type 1 diabetes is 10% in persons without kidney pathology, normoalbuminuria (NAU), 20% in patients at the stage of microalbuminuria (MAU), 50 -70% - at the stage of protenuria (PU) and 70-100% at the stage of chronic renal failure [4].

The higher prevalence of hypertension even in the initial stage of nephropathy indicates that in type 2 diabetes, hypertension often precedes carbohydrate metabolism disorders and is detected in 50% of patients already at the onset of diabetes. This is due to the fact that the development of hypertension and type 2 diabetes is based on a common metabolic defect - insulin resistance (IR), which can clinically debut with an increase in blood pressure levels, only later leading to impaired carbohydrate metabolism]. The combination of these pathological changes is called metabolic syndrome or insulin resistance syndrome. Later, the hypothesis about the interrelated origin of diabetes and hypertension was confirmed in many studies, the largest of which is ARIC (The Atherosclerosis Risk in Communities). This study was conducted in the United States and included 12,550 individuals aged 45 to 64 years without diabetes. After 6 years, the incidence of new cases of type 2 diabetes was assessed [11]. It turned out that in people with hypertension (according to the criterion of blood pressure >140/90 mm Hg), the incidence of de novo type 2 diabetes was 2.43 times higher than in normotensive patients. The conducted studies confirm the close relationship between the development of type 2 diabetes and hypertension.

Etiology and pathogenesis

The most common causes of hypertension in type 1 diabetes mellitus:

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

The main reasons for the development of hypertension in type 2 diabetes:

1. 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 the development of hypertension in type 1 diabetes can be considered diabetic kidney disease, in type 2 diabetes – hypertension and isolated systolic hypertension [15].

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Hypertension in diabetes can also be induced by alcohol abuse or taking certain medications that increase blood pressure, incl. glucocorticoids, contraceptives.

Pathogenesis of hypertension in type 2 diabetes

Insulin resistance syndrome (IR). Hypertension in type 2 diabetes is a component of the IR syndrome (or metabolic syndrome), described in 1988 by G. M. Reaven [8]. The term "metabolic syndrome" currently combines type 2 diabetes (or IGT), hypertension, dyslipidemia (mainly hypertriglyceridemia), abdominal obesity, hyperuricemia, MAU and increased blood levels of procoagulants (fibrinogen, plasminogen activator inhibitor 1). All of these conditions may be a consequence of decreased sensitivity of peripheral tissues to insulin, i.e. IR [11]. The latter also occurs in other pathological or physiological conditions that are not included in the concept of metabolic syndrome: polycystic ovary syndrome, chronic renal failure, infections, glucocorticoid therapy, pregnancy, aging.

The prevalence of IR was studied in a large population-based study conducted in Italy [6], which included 888 people aged 40 to 79 years. When analyzing IR using the HOMA method, it was revealed that it occurs in such syndromes and diseases as essential hypertension (BP□160/95 mmHg) – in 58%; with hyperuricemia (uric acid in the blood serum > 416 μmol/l in men and > 387 μmol/l in women) – 63%; with hypertriglyceridemia (TG > 2.85 mmol/l) – 84%; in 88% of people with low levels of HDL cholesterol (<0.9 mmol/l in men and <1.0 in women); in 66% of people with IGT; in 84% of people with type 2 diabetes (when diagnosed according to the criteria: fasting glycemia > 7.8 mmol/l and 2 hours after a glucose load > 11.1 mmol/l); in 10% of people without metabolic disorders.

When type 2 diabetes (or IGT) was combined with dyslipidemia, hyperuricemia and hypertension, i.e. with the main components of the metabolic syndrome, the detection rate of IR was 95%. This indicates that, indeed, the leading mechanism for the development of metabolic syndrome is IR [6].

The role of IR in the development of type 2 diabetes. IR of peripheral tissues underlies the development of type 2 diabetes. IR of peripheral tissues precedes the development of type 2 diabetes and can be detected in close relatives of patients with type 2 diabetes who do not have carbohydrate metabolism disorders. Over the long term, IR is compensated by excess production of insulin by β-cells of the pancreas (hyperinsulinemia), which maintains normal carbohydrate metabolism. Hyperinsulinemia is equated to markers of IR and is considered a precursor of type 2 diabetes. Subsequently, as the degree of IR increases, the cells no longer cope with the increased glucose load, which leads to a gradual depletion of insulin secretory capacity and the clinical manifestation of diabetes. First of all, the 1st phase of insulin secretion (fast) suffers in response to a food load; the 2nd phase (phase of basal insulin secretion) also begins to decrease. The developed hyperglycemia further enhances the IR of peripheral tissues and suppresses the insulin secretory function of β-cells. This mechanism is called glucotoxicity [8].

In modern conditions, in countries with a high standard of living, characterized by physical inactivity and high-calorie nutrition, the IR mechanisms preserved in the genetic memory continue to "work" on energy accumulation, which leads to abdominal obesity, dyslipidemia, hypertension and, finally, 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 near future. Moreover, this connection can be traced both in obese patients and in individuals with normal body weight.

Insulin promotes the act Indirect activation of the central nervous system by the inclusion of a baroreceptor response to vasodilation and hypotension caused by insulin cannot also be excluded.

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Stimulation of the SNS during hyperinsulinemia is accompanied by an increase in cardiac output and an increase in peripheral vascular resistance, which inevitably leads to an increase in blood pressure. The simultaneous decrease in parasympathetic system activity caused by hyperinsulinemia increases heart rate.

Increased Na and water reabsorption. Insulin has a direct effect on the proximal tubules of the renal nephrons, increasing Na and fluid reabsorption. In addition to antinatriuresis, insulin causes antipotassiumuresis and antiuricosuria [12]. Under conditions of an 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 circulating fluid increases, which leads to an increase in cardiac output. Apparently, the occurrence of edema in people with type 1 diabetes at the beginning of insulin therapy (insulin edema) is associated with Na and the water-retaining effect [10].

Thickening of the walls of blood vessels. The mitogenic properties of insulin were discovered quite a long time ago in a series of experimental studies by R. W. Stout in 1970–1990 [13], where it was shown that insulin stimulates cell growth, proliferation and migration of vascular smooth muscle cells, leading to thickening of their walls.

Insulin can have a dual effect on the vascular endothelium, causing either dilation or spasm.

Despite the close relationship between IR and elevated blood pressure, not all individuals with essential hypertension have IR and hyperinsulinemia. According to the Brunneck Study, in 40% of patients with hypertension, plasma insulin concentration remains within normal values. It has been established that hypertension of other etiologies (renal, renovascular, primary hyperaldosteronism) is not associated with IR. Also, it was noted that not all individuals with IR develop hypertension [2]. It is assumed that a feedback relationship between IR and hypertension is possible, i.e., IR can develop secondarily with a long course of hypertension. This hypothesis is partly confirmed in the work of I. E. Chazova and V. B. Mychka, where a reliable relationship was established between the duration of hypertension and the severity of IR. 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 transports glucose into cells and produces NO. At the same time, AT I I stimulates the MAPK system, which is involved in the mitogenic and proliferative activity of insulin.

Thus, hyperactivity of the 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 can contribute to the development of IGT, and then type 2 diabetes.

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

Renin-angiotensin system in diabetes mellitus and arterial hypertension

Initial studies of the condition in diabetes assessed mainly the concentration of circulating components of the RAS: renin, AT II, aldosterone, etc. Very contradictory data were obtained on the activity of plasma renin and AT II in diabetes - from high to low values. Later, most scientists who conducted independent studies at different times re-established that diabetes, both type 1 and type 2, is most often characterized by low levels of renin in the blood plasma and is combined with the syndrome of hyporeninemic hypoaldosteronism. It was noted that the level of renin activity inversely correlates with the quality of glycemic control, assessed by the level of glycated hemoglobin HbA1c; The worse the diabetes compensation and the higher the HbA1c level, the higher the plasma renin activity. At the same time, the

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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 diabetes is associated with high activity of local renal AT II.

It has been established that the local renal concentration of AT II is 1000 times higher than its content in plasma. A similar local RAS was found in DM in cardiac tissue and vascular endothelium.

The pathogenic effect of AT II in diabetes is associated not only with its powerful vasoconstrictor effect, but also with proliferative, pro-oxidant and prothrombogenic activity.

The role of the RAS in the occurrence of diabetes

In recent years, it has been discovered that the active use of ACE inhibitors for the treatment of hypertension and vascular complications in diabetes is in some cases accompanied by hypoglycemic state and decreased IR. This was the reason for studying the role of AT II in the mechanisms regulating glycemic levels - the sensitivity of peripheral tissues to insulin and insulin secretion by the pancreas. The use of modern molecular biological technologies has made it possible 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 tyrosine phosphorylation of the IRS-1 and IRS-2 proteins. Next, IRS molecules activate PI-K, through which signal transmission and implementation of the metabolic and vasodilatory effects of insulin are carried out (glucose transport into cells, NO synthesis). 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 the activation of mitogenic and proliferative processes. Thus, AT II blocks the main metabolic effect of insulin - the transport of glucose into cells - and enhances the atherogenic effect of insulin. In other words, RAS hyperactivity is accompanied by increased IR.

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