Atherosclerosis

Ethiology

Atherosclerosis is chronic disease, acompanied by damage of arterial wall and disturbance of metabolism. Some times integrity of atherosclerotic plague may disturb (due to less amount of collagen, inflammation, hemodynamic pressure). In this case blood contacts with the elements of plague. This sitimulates mechanism of tromb formation. Thrombocytar, wall, oclusive thrombi may form. Atherothrombosis is main cause of death and disability due to atherosclerosis. Clinical signs of atherothrombosis are ischemia and necrosis. Main clinical signs of atherothrombosis are acute coronary syndrome (myocardial infarction) and ischemic disorders of cerebral blood circulation (ischemic stroke).

There are some risck factors participate in the development of atherosclerosis: hypercholesterolemia, hypertony, obesity, smoking,chronic stress, diabetes mellitus, hypodynamy, dislipoproteinemia, ets.

Hypercholesterolemia is connected with excessive intake of cholesterol with food, excessive synthesis of cholesterol in the body, disturbance excretion of cholesterol with bile, decreasing of assumulation of cholesterol by peripheral tissues.

The amount of total cholesterol > 300 gr in the body. Also >1 gr cholesterol is synthesized in the liver. Cholesterol oxidized to the bile acids and throgth the intestines excretes from the body. Oxidation of cholesterol occurs in the liver. Cholesterol mainly in the content of LDLP and VLDLP (60-70% of complex ethers), 30-40% in free form in blood plasma. Free cholesterol is structural component of cell, ethterificated cholesterol is metabolic active product for synthesis of hormones of adrenal cortex, surfaktant.

Hypercholesterolemia is risck factor for coronary atherosclerosis. Primary and secondary hypercholesterolemia is distinguished. Primary hypercholesterolemia are: familiarly homo- and heterozygous primary hypercholesterolemia, familiarly combined hyperlipidemia, polygenic hypercholesterolemia. Secondary hypercholesterolemia is observed during hepatic disease accompanied by intra and extrahepatic cholestasis, renal (glomerulonephritis, nephrotic syndrome, chronic renal failure) disease, malignant tumors of pancreas and prostate, gout, hypertension disease, hypotireosis, chronic alcoholism, diabetes mellitus, I type glucogenosis, obesity.

Lipid indicies of plasma are the followings:

|  |  |  |
| --- | --- | --- |
| Plasma lipids | mmol/l | mg/dl |
| Total cholesterol | <5.0 | <190 |
| Cholesteron of LDLP | <3.0 | <115 |
| Cholesterol of HDLP | ≥1.0 (men), ≥1.2 (women) | ≥40 (men), ≥ 46 (women) |
| Triglicerides | <1.7 | <150 |

Classification of hypercholesterolemia:

|  |  |  |
| --- | --- | --- |
| Level of character | Total cholesterol mmol/l | Cholesterol of LDLP, mmol/l |
| Optimal | <5.0 | <3.0 |
| Moderate level | 5.0-5.9 | 3.0-3.9 |
| High level | ≥6.0 | ≥4.0 |

Hypocholesterolemia is observed during starvation, malabsorption syndrome, chronic heart failure, hypertireosis, acute infectious diseases, acute pancreatitis, tuberculosis, pneumonia, functional insufficiency of liver,ets.

Determined that, decreasing concentration of cholesterol in the blood also may lead to increasing of death during cardio-vascular diseases. So, main risck factor for ischemic disease of the heart is arterial hypertension. This leads to damage of endothelium of arteries. Decreasing amount of cholesterol in the blood does not accompanied by active regeneration and reparation of damage endothelial membrane. This leads to increasing of permeability of vasvular wall. Result in atherogenic lipoproteins pass to the intimae and lead to development of atherosclerosis.

In laboratary practice for determination of cholesterol of LDLP uses Fridvald formula. For this determine the level of cholesterol, cholesterol of HDLP, triglyserides in plasma. If we know the concentration of trigliserides, we can know the level of cholesterol of VLDLP. For this the concentration of trigliserides (mmol/l) divided into 2.2.

Cholesterol of LDLP = Cholesterol – (cholesterol of HDLP + cholesterol of VLDLP)

Due to atherogenic cofficient we can determine the type of dislipoproteinemia.

AC = Cholesterol – cholesterol of HDLP : cholesterol of HDLP

Atherogenic cofficient in norm is 2-3 .

There is clinical diagnostic significance of cholesterol of HDLP. For determination of α-cholesterol (cholesterol of HDLP) the blood must taken on an empty stomach in the morning. Decreasing concentration of cholesterol of HDLP increases risck for ischemic diseases of the heart. Decreasing of α-cholesterol up to 0.13 mmol/l (0.91- 0.78 mmol/l in norm) 3 times increases risck for ischemic diseases of the heart. ≤ 0.52 mmol/l of α-cholesterol and increasing of atherogenic cofficient mostly is observed during alymentary obesity.

Hypodynamy and smoking leads to decreasing of α-cholesterol. During atherosclerosis, myocardial infarction, diabetes mellitus, acute hepatitis, renal diseases, acute bacterial and viral infections the concentration of α-cholesterol severe decreases. During physical work, ander action of esterogens concentration of α-cholesterol increases.

Dislipoproteinemia is change of percentage of different types of lipoproteins. Predominance of atherogenic lipoproteins on antiatherogenic lipoproteins lead to decreasing colloid stability of atherogenic lipoproteins. That is why atherogenic lipoproteins pass to the vascular wall and accumulate their as lipid spots.

There are severel types of lipoproteins are distinguished. They are: chylomicrons, VLDLP, LDLP, MDLP, HDLP. Density of lipoproteins depend on the amount of triglicerides. If the amount of triglicerides more, it means dencity of lipoproteins is lower and against. If density is lower, it means atherogenicity is higher. So, HDLP is antiaterogenic, LDLP,VLDLP and MDLP are aterogenic lipoproteins.

In the content of HDLP (α-LP) is about 40-50% of protein, 27-30% of phospholipids, 3-8% of triglicerides, 2-3% of free cholesterol and 14-20% of cholesterol esthers. Apoproteins of HDLP (A, CII, E) is synthesized in the liver, in the wall of small intestines. There are many receptors on the surface of smooth muscular cells and fibroblasts for apoproteins of HDLP. When apoproteins of HDLP bind with that receptors, excess amount of cholesterol from cells transport to the liver in the content of HDLP. That is why, HDLP are antiatherogenic lipoproteins. Density of HDLP is 1.064-1.210 gr/ml.

In the content of VLDLP (pre-β-LP) is about 8-12% of protein, 10-12% of free cholesterol, 18-20% of phospholipids, 3-6% of cholesterol esthers, 50% of triacylglicerides. They form in the liver and a little amount of them are synthesized in the mucous membrane of intestines. Main function its transport of endogenous tryacylglicerides from liver to the cells. They have C, E və B100 apoproteins. Under action of lipoproteinlipase and lecitincholesterolacyltransferase the VLDLP are destructed and triglycerides exit and the amount of relative cholesterol increases in the contentent of them. At first VLDP convert into MDLP, then LDLP. Triglicerides accumulate in the adipocytes and are used as energy in sckeletal muscles. Density of VLDLP is 0.960-1.006 gr/ml.

İn the content of LDLP (β-LP) is about 24-31% of free cholesterol, 16-28% of esterificated cholesterol, 7-11% of triglicerydes, 30% of phospholipids, 20–25% of protein. On the surface of them only B100 apoprotein. About 70% of LDLP bind with the receptors on hepatocytes, which sensitive to their apoproteins. On the surface of smooth muscular cells of arterial wall and reticuloendothelial cells have low affin receptors for apoproteins of LDLP. When the concentration of β-lipoproteinlərins increases in the blood the synthesis of receptors on the surface of the hepatocytes for apoproteins of LDLP decreases. Result in LDLP accumulate in cells with low affin receptors. That is why, LDLP are atherogenic. Density of LDLP is 1.020-1.064 gr/ml.

Chylomicrons are big lipoprotein particles. In the content of them about 3-8% of phospholipids, 2-4% of cholesterol esthers, 2% of free cholesterol, 1-2% of protein and 86-94% of triclicerides. There are B 48, A, C, E apoproteinlərs on the surface of chylomicrons. Chylomicrones form as a result of absorption of exogenous cholesterol and triacylglycerides in intestinal wall, then pass to the lymphatic vessels and transport to the blood. Density of chylomicrons is < 0.960 gr/ml.

Apoprotein metabolism between chylomicrones and HDLP occurs in the blood. Part of A apoprotein of chylomicrons replaced by C və E apoproteins of HDLP. Chylomicrons under action of lipoproteinlipase of blood capillaries of fatty tissue, myocardium, sckeletal muscles are destructed and result in a large amount of triglycerides split from them, free fatty acids and glycerin forms. In this case from chylomicrons release residual component, which rich with cholesterol esthers and transport to the liver. Part of residual component uses for synthesis of bile acids and part of them uses for synthesis VLDLP in the liver. Residual component of chylomicrons is atherogenic.

Catabolism of chylomicrons is important for pulmonary tissue. Becouse chylomicrons participate in the synthesis of surfanktant phospholipids and activation of alveolar macrophages.

Lipoprotein (a)- is atherogenic lipoprotein particle, density is 1.051-1.082 gr/ml. There is apoprotein (a) protein in the content of lipoprotein (a). Apoprotein (a) is glycoprotein and consist from domens like pasminogen. LP (a) binds throm with vascular wall, which reach with LP (a) and participate in atherothrombogenesis. LP (a) is about 1-1000 qr/ml. Increasing concentration of Lp (a) leads to atherosclerosis. Increasing of LP(a) is genetic pathology. LP (a) is independent biochemical marker of atherosclerosis.

In clinic labortary practice for division of lipoproteins into classes use electrophoretic methods. During electrophoresis of lipoproteins in agaroza HDLP binds with α-qlobulin fraction. That is why, they are called α-lipoproteins. Mobility of LDLP match with β-qlobulin fraction. That is why they are called β-lipoproteins. Fraction of VLDLP more than β-lipoproteins. That is why, they are called pre-β-lipoproteins. Chylomicrons are every time in start during electrophoresis. If the concentration of MDLP higher, in this case β-fraction becomes more.

For transport of cholesterol 2 classes of lipoproteins have significant: HDLP (transport cholesterol from the celll), LDLP (transport cholesterol to the cells). For transport of triglycerides has significant of VLDLP (they trasport endogenous triglicerides from liver to the cell) and chylomicrons (they trasport exogenous triglicerides brom intestines).

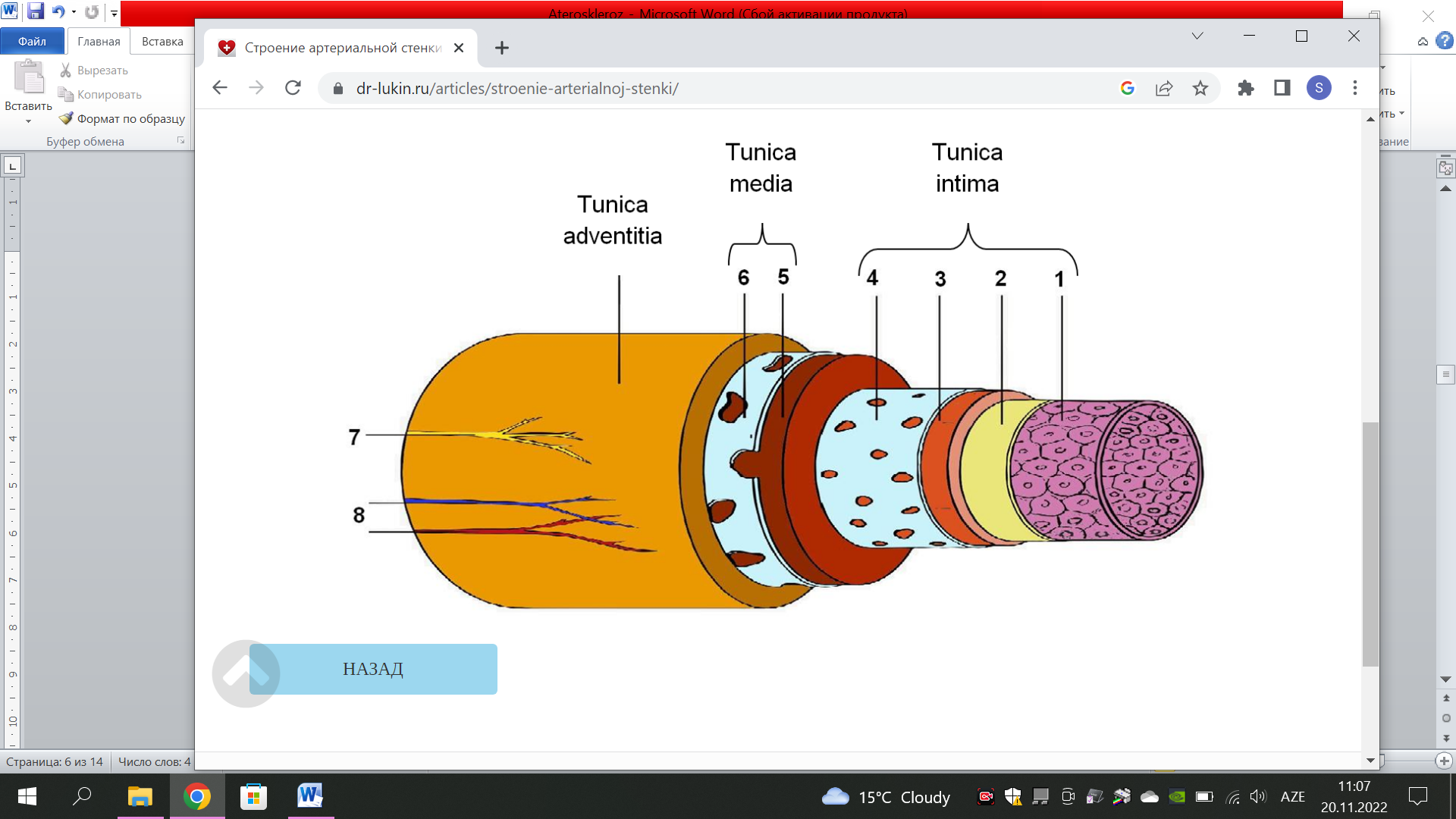
Pathogenesis of atherosclerosis

The arterial wall consist from 3 layers:

I. Tunica intima

II. Tunica media.

III.Tunica adventitia



Atherosclerosis starts with damage of endothelium. Vascular endothelium possesses antitrombocytar (intact endothelial cells of vascular wall prevent contact of thrombocytes with subendothelial layer), anticoagulant (thrombomodulin receptors on the surface of endothelial cells bind with thrombin and inactivates its; heparin-like substances bind with antithrombin III and inactivates thrombin) and fibrinolitic (t-PA synthesized in endothelial cells) activity. Increasing of lipoproteins rich with cholesterol in the blood, local hemodynamic disorders, smoking, infections, excess amount of homosystein in the blood, arterial hypertension may lead to damage of endothelium. All these factors lead to thinning and destruction of glycocalix on the surface of endothelial cells, dilation of endothelial qap and edema subendothelial layer. Damage of endoliam leads to loss its abilities and result in endothelium possesses thrombogenic and adhesiviness. On the surface of phospholipid layer of thrombocytes has 1α və IIα of glykoprotein receptors. These receptors for binding of collagen of subendothial layer. So, damage of endothium leads to adhesion of thrombocyte with subendothelial layer.

Endothial layer is wery narrow in norm and lipoproteins can not pass throgh this gaps. Some substances (cathecholamins, angiotensin II, serotonin, endotelin, ets.), also hypercholesterolemia, hypertension, smoking lead to damage of endothelial cells and endothelial qaps are dilated. Result in LDLP pass to the intima.

Monocytes circulate freely in the blood in norm and do not tach with endothelial cells. Damage of endothelial cells leads to formation of adhesive molecules on them. That is why, monocytes and T-lymphocytes at first sticks to the endothelium and then by diapedesis pass through the endothelial qaps. Monocytes release free raducals. These radicals oxidise LDLP. Oxidised lipoproteins more active involve monocytes and they synthesized free radicals. So, vicious circle develops. Converted into macrophages the monocytes absorb LDLP and convert into foam cells. During accumulation of excess amount of lipoproteins in arterial wall foam cells overload by lipids, they accumulate on the intima and undergo apoptosis. In this case cholesterol esthers and cholesterol cristals release. This prosess leads to local accumulation of cholesterol in intima and leads to formation of lipid spots, then lipid strips and atherosclerotic plague. Foam cells, also is reserve for superoxide anion of oxygen and metalloproteinase of matrix. These factors participate in proggresivation of atherosclerotic damage.

The smooth muscular cells located in tunica media in norm. Ander action of chemoatractants they migrate to the intima. These chemoatractants synthesized to the responce of modificated LDLP from endothelial cells, macrophages. Then smooth muscular cells ander action of fibroblast growth factors, TNF and IL-1- prolipherate. They possess new properties: synthesize collagen, elastin, glucoseaminglicans. These substance is base for connective tissue of atherosclerotic plague.

In atheroma during atherogenesis occurs both prolipheration and apoptosis of smooth muscular cells. This process occurs ander action of proinflammatory cytocines of cytotoxic T-lymphocytes. Th1 secrete proinflamatory cytokines (IL-1, IFN-γ, TNF-α). These cytocines activate endotheliocytes, macrophages, stimulate formation of proteolytic enzymes and lead to inflammation. Th2 synthesized antiinflammatory cytocines. These substances provide prolipheration of smooth muscular cells, formation of fibrosis and strengthen of healing processes.

Clinical picture of atherosclerosis

Atherosclerosis may develop in early ages, prolonged term continues without any symptoms and does not recognises during routine examinations. Main serious changes develop in coronary and cerebral vessels. This may lead to acute coronary syndrome, heart failure, stroke. Atheroma of hand arteries leads to decreasing blood flow. Sometimes this is called occlusive disease of peripheral arterirs.

Clinical manifestation of atherosclerosis is different. This depend on the level of damage, localisation and the amount of arteries involving to the pathological processes. There are some clinical signs, which can be easily detected during examination of patient. There are following external signs of predisposition to atherosclerosis:

* Perceptible and premature aging
* Disperancy between the age and appearance of the patient
* Premature graying of hair in the head and anterior part of the thorax (in men) of the patient
* Xantoma and xantelesms (yellow lipid spots in tendom and in eyelid)

Sometimes, in the area of atherosclerotic plague sudden stops the blood flow, the vessels may rupture, or thrombi may forms in the vessels. That is why 60% of cases the main symptom of atherosclerosis is acute coronary syndrome and sudden death. Thrombosis in certain organs (heart,brain, intestines, kidneys, extremites) may leads to ischemia and necrosis.

If atherosclerotic stenotic changes in the arteries develops gradually (without thrombi), in this case clinical picture is in the form of chronic ischemia of organ.

* If the vessels of the heart is involved to the process chronic ischemic disease may manifest itseleves as angina pectoris of tension or painless ischemia of myocardium. Sometimes early manifestation of prolonged term chronic ischemia of myocardium may be cardiomegaly or severe cardiac insufficiency.
* Chronic ischemia of cerebral vessels may manifest itselves as dissiness, noise in the head and ears, severe disturbance of memory, sleepylessness. Prolonged and rapid developing ischemia of cerebral vessels may lead to vascular nature dementia and cachectia. During atherosclerosis of brain vessels in auscultation of carotid artery heard noice. It is physical sign. But this phenomenon is not often happening. During stenosis of aortal orrifice also, may heard noice in carotid artery.
* Chronic obliterated atherosclerosis of lower extremities arteries may manifest itselves as numbness, weakness, ant walk sensation in the legs. Main characteristic symptom is pain in the calf muscles during walking and limp. Due to pain the patient stops his walking. In severe cases may develop coolness in the leg, loss of hair in men and trophic disorders in the foot. During examination determine decreasing of pulsation or absence of pulsation in the arteries of lower extremities.
* During atherosclerosis of bifurcation of aorta is determined chronic obstraction of bifurcation of aorta. For this following symptoms are characteristic: limp, coolness in extremities, numbness, loss of hair, atrophy in the calf and thigh muscles, disturbance growth of toe nails, impotention in men, decreasing of skin temperature, absence of pulsation in the lower extremities arteries, ulcer and necrosis in the toes and leg, systolic murmur in the femoral artery, ets. Atherosclerosis of thorathic and abdominal aorta may lead to aneurism. Atherosclerosis is systemic disease, that is why in one patient may observe chronic ischemic signs of several organs.

All diaqnostic methods of atherosclerosis are divided into 3 groups:

**I group-** laboratory- instrumental method: determination of different markers/risk factors of atherosclerosis. For this is necessary determination of following indicies:

* Total analysis of the blood
* Total analysis of urine
* Total cholesterol
* LDLP
* HDLP
* VLDLP
* Triglycerides
* PTİ
* Glycozylated hemoglobin

- C-reaktive protein

* Homosistein

Determination methods of total cholesterol are: chemical (direct or indirect calorymetry, turbidimetry, fluoimetry), physico-chemical (chromatography, polyarimetria) and enzymatic.

Determination of the amount of cholesterol due to calorimetry is based on the following reactions:

1) Liberman- Burchardt- in this case cholesterol reacts with vinegar anhydrite, concentrated sulphate acid and leads to turquoise-green color of solution.

2) Kaliani-Zlatsc- Zaka- cholesterol + Fe chloride, or vinegar or sulphate acid.This leads to red color of solution.

Calorymetry is divided into direct and indirect. During direct method color reaction is performed by blood plasma. During indirect method at first plasma lipids is removed by organic solution, then conducts Liberman-Burchardt reaction.

Enzymatic method is spesific. For reaction is required less blood plasma (5 mkl) and aggressive luquid does not require. The base of enzymatic method: by participation of cholinesterase occurs hydrolysis of cholesterol esthers and forms free cholesterol. This by participation of cholesteroloxidase oxidises with air oxygen and hydrogen peroxide forms. By participation of peroxidase hydrogen peroxide oxidise chromogenic substrates and colored solution forms. Intencity of color is proportional to the concentration of cholesterol.

One of the determined indicies during atherosclerosis is homosystein.Homosystein is amino-acid and intermediate product of metionin and systin amino-acids.It is risck factor for the development and proggresivation of atherosclerosis, thrombosis of artery and veins, ischemia and infarctus of different organs.Concentration of homosystein is 9.1-10.0 mkmol/l. in norm. During functional disorders of kidneys, deficiency of B6, B12, folic acid, malabsorbtion syndrome, intake of metotrexate, methylprednisolon, peroralcontraceptives, teophillin, diuretics, hypolipidemic preparations, excessive intake of coffe, alcohol increases concentration of homosystein in the blood.

**C-reactive-protein-** is spesific marker of inflammation, acute fase protein, risck factor for the development of cardio-vascular pathologies. 6-12 hours after infectious processes or diffuse damage of tissues concentration of C-reactive protein increases in the blood.

Concentration of C-reactive protein is 0-5 mg/l.in the blood in norm. During infectious-inflammatory processes, rheumatoid arthritis, ulcerative colitis, myocardial infarction, necrosis, metastasized tumors, trauma, pregnancy, COVİD-19 viral pneumonia, systemic lupus erythematosis concentration of C-reactive protein increases in the blood.

**Glycosylated hemoglobin-** is binding form of hemoglobin with glucose. Consentration of glycosylated hemoglobin does not depend on intake of food and the time of analysis allows to evaluate state of hyperglycemy last 4-8 days. When concentration of fetal hemoglobin is higher, in this case may be pseudo positive result. Concentration of glycosylated hemoglobin is 4-6 % of total hemoglobin. During diabetes mellitus (1 and 2 type, latent type) increases concentration of glycosylated hemoglobinin the blood. Increasing concentration of glycosylated hemoglobin in the blood leads to development of atherosclerosis. During loss of blood, hemorrhagic anemia concentration of glycosylated hemoglobin decreases in the blood.

Evaluation the level of glucose in the blood due to glycosylated hemoglobin

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| HbA1c | 4.0 | 4.5 | 5.0 | 5.5 | 6.0 | 6.5 | 7.0 | 7.5 | 8.0 | 8.5 | 9 |
| Glucose | 2.6 | 3.6 | 4.4 | 5.4 | 6.3 | 7.2 | 8.2 | 9.1 | 10.0 | 11.0 | 11.9 |

One of the main biomarkers of atherosclerosis is phospholipase A2 associated with lipoprotein **(Lp-FLA2).** The amount of this substance is connected with lipid disorders, inflammatory processes and endothelial dysfunction**.** These disorders participate in pathogenesis of atherosclerosis.Lp-FLA2 transports with connection of LDLP, a little amount (20%) of this substance transports with connection of HDLP in the blood. There are 2 source of Lp-FLA2  in the content of atherosclerotic plague of human: in intima they binds with HDLP, again synthrsizing in inflammatory cells. Lp-FLA2 is marker forcardio-vascular diseases.

By instrumental methods determines endothelial dysfunction. Usually, invasive angiography is used. Acetylcholine is injected into coronary artery and reaction of intact arteries by angiography is evaluated: healthy vessels are dilated under action of acetylcholine, in the vessels with endothelial dysfunction occur spasm. One of the non-invasive method is creating of ischemia by dosed compression to the upper extremities. After ischemia dilated level of brachial artery determined by ultrasound examination.

* **II group-** instrumental methods discovering ischemia developing as a result of atherosclerosis:
* During load tests (velergometr, tredmil) to the patient the ECG is recorded. İn this case ischemic changes may occur in ST segment. By spesific load tests the level of ischemia determines by Echo-cardiography and radioisotop methods. For determination of atherosclerosis in the arteries of lower extreminites is used ankle-brachial index. In the base of this method is determination difference of systolic pressure between upper and lower extremities. In classic variant arterial pressure by palpator-auscultative method, registration of blood flow determines by Dopler US examination.
* **III group-** visual examination of atherosclerosis. Prolonged time narrowing part of artery determined by angiography. Contrast solution is injected into artery and by X-ray determined narrowing area. It is expensive and invasive method and do not satisfi for early determination atherosclerotic plague and exentric nodes. That is why to the angiography added intravascular ultrasound examination. It means, by ultrasound examination looking to the intravascular area, the content and amount of nodes determined. It is also invasive method.

For diagnosis atherosclerosis of peripheral and extracranial cerebral vessels ulktrasound examination uses. Thichen of intima-media in carotid artery determine. In norm this index is 0.6-0.8 mm. > 1mm of this index is sign of thichening of that layer and atherosclerosis.

Atherosclerosis may be result of accumulation of Ca in coronary vessels. In this case during X-ray examination of thorathic organs determined calcinosis of big arteries. But to confirm the diagnosis and evaluation of quantitative indicies of calcinosis uses CT.

For determination the level of severity of atherosclerosis uses MRT, agioscophy, thermography, spectroscophy.

Arterial hypertension

Arterial hypertension- is stable increasing of systolic arterial pressure more than 140 mm.Hg. and distolic arterial pressure more than 90 mm.Hg. About 30-40% of aged peaple suffer by AH.

Etiology

According to the etiology primary and secondary arterial hypertension are distinguished. Primary is called hypertension disease, secondary (symptomatic) develops as a result of patholopgies in different organ and systems. Secondary type is 5-10% of arterial hypertension.

Following risk factors participate in the developmwnt of hypertension disease:

* hypodunamy
* excess intake of NaCl
* smooking
* obecity
* alcoholism
* stress
* age
* hereditary predisposition

**Pathogenesis**

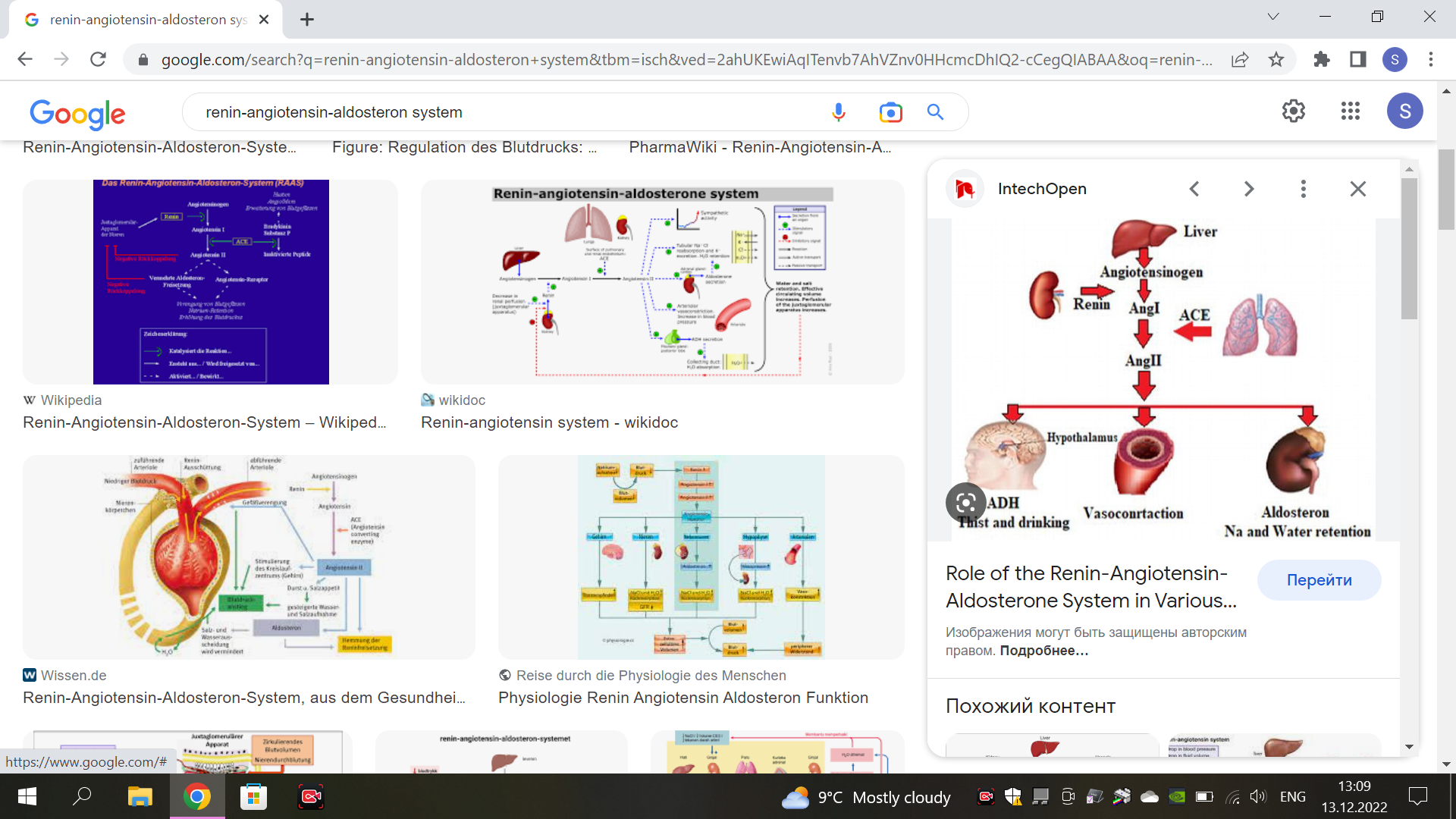
Arterial hypertension develops due to complex interreletion of several factors (surrounding,hereditary, neuro-humoral). The level of AH is determined by systolic volume and general peripheral vascular resistance. Development of AH is connected with interreletion of following factors:

1) due to spasm of peripheral vessels increasing of peripheral vascular resistance

2) due to intensive work of the heart or increasing volume of intracellular fluid increasing of cardiac output

3) both increasing of cardiac output and peripheral vascular resistance increasing of arterial pressure

In the base of pathogenesis of arterial hypertension takes part formation of pathological dominance focus in the CNS due to prolonged term psycoemothional tension. From dominance focus impulses pass to the sympato-adrenal system and from medulla part of adrenal gland release a lott of catecholamins to the blood.Cathecholamins excite β1 receptors in the heart and tachycardia develops. Tachycardia leads to increasing of cardiac output and result in arterial pressure increases. Cathecholamins lead to spasm of afferent arterioles of kidneys and result in ischemia develops in juxstaglomerular apparatus. Hypoxia stimulates systhesis of renin. Renin acts to the angiotensinogen and release angiotensin I. The in the pulmonary capillaries under action of convertase from angiotensin I forms angiotensin II. From angiotensin II by participation of angiotensinase forms angiotensin III. Angiotensin II leads to narrowing of arterioles and result in arterial pressure increases, also acts to the glomerular part of adrenal cortex and stimulates secretion of aldosteron. Angiotensin III only stimulates secretion of aldosteron. Aldosteron increases reabsorbtion of Na+ and increases secretion of H+ and K+ ions from distal tubules of kidneys. Increasing concentration of Na+ ions in the blood leads to increasingof osmotic pressure of the blood and irritation of osmoreceptors. Impulses throwth the osmoreceptors pass to the hypothalamus and release vasopressin.Vasopressin increases reabsorption of water from distal and convoluted tubules of kidneys. Also in high concentration vasopressin acts to the V1 receptors of the vessels and result in intracellular amount of Ca 2+ ions increases. This leads to spasm in the smooth muscular cells of the vessels and result in peripheral vascular resistance increases. So, activation of renin-angiotensin-aldosteron-vasopressin system leads to delay water and Na+ in the body, hypervolemy, increasing of peripheral vascular resistance and increasing of arterial pressure.



Development of hyperrenin arterial hypertony is connected with disturbance of feedback mechanism. It means, increasing concentration of renin by feedback mechanism does not accompany by decreasing secretion of renin. Hyperreninemia usually is observed in renovascular hypertension. 25% of people suffering with hypertension disease is observed increasing concentration of renin in the blood. 20% of patient the concentration of renin in the blood may lower than norm. Severe form of hypertension disease usuallly accompanied by increasing of concentration of renin in the blood. Activity of kinin system decreases in that patients. Prostaglandin A and E synthesized in the medulla part of kidneys and in the cells of distal tubules synthesized kinins. Currently determined that prostaglandins may synthesized in all cells. They are depressor factors. Prostaglandin A ais physiological antoganist of angiotensin II, prostaglandin E increases intrarenal local hemodynamics. Kinins dilates arterioles and lead to decreasing of peripheral vascular resistance.

So, in the pathogenesis of hypertension disease paralel participate activation of sympato-adrenal system, change of morphological structure of the vessels and insufficiency of depressor mechanisms.

**Classification of arterial hypertension**

A/H is classificated by level of increasing of arterial pressure, by stages of hypertension disease and risck of development of cardio-vascular complications.

Classification level of arterial pressure in the people high than 18 age

|  |  |  |
| --- | --- | --- |
| Category | Systolic AP, mm.Hg. | Diastolic AP, mm.Hg. |
| Optimal | <120 | <80 |
| Normal | <130 | <85 |
| High normal | 130-139 | 85-89 |
| I level AH | 140-159 | 90-99 |
| II level AH | 160-179 | 100-109 |
| III level AH | >180 | >110 |
| Special form: | >140 | <90 |

Stages of hypertension disease:

|  |  |
| --- | --- |
| I | Minor and unstable change of arterial pressure is observed, functional disturbances in the cardio-vascular system does not observed. |
| II | Stable change of arterial pressure and hypertrophy of left ventricle in the patient is observed. |
| III | Constant high pressure, changes in the heart, kidneys, eyes, brain is observed. |

The stages of hypertension disease is determined due to “subkcinical damage of turget organs”. The term of “Subclinical damage of turget organs” is changes of turget organs which determine by labortary and instrumental methods. These changes by adeguate antihypertensive therapy may be reversible or partially reversible.

The indicies of “subclinical damage of target organs” are the followings:

**ECG signs:**

* Hypertrophy of left ventricle
* Sockolov -Layon index (Sv1 + Rv5/ Rv6 ) > 38 mm

**EXO -signs:**

-Mass index of myocardium of left ventricle - ≥ 125 gr/m2 in men, ≥ 110 gr/m2 in women

-Thichen of the wall of carotid artery (thichen of “intima-media” complex >0.9 mm)

-Velocity of pulce wave between carotid and femoral artery >12 m/s

-Ankle-brachial index- <0.9

**Changes in the blood:**

-Minor increasing level of kreatinin in the blood: 115-133 mkmol/l for men, 107-124 mkmol/l- for women

- ≥7.0 mmol/l of glucoe in plasma on an empty stomach

- ≥ 11.0 mmol/l of glucose in the plasma after sugar stress test

* **Changes in the kidneys:**
* Decreasing of glomerular filtration < 60 ml/min./1.73 m2
* Microalbuminuria: 30-300 mg/ daily or ≥22 mg/gr for men, ≥31 mg/gr for women albumin/creatinin in urine

**Target organs for arterial hypertension are followings:**

* heart
* kidneys
* vessels
* brain

**Complications that develop during arterial hypertony are divided into 4 groups:**

* **I. Cardiac:**

a) early atherosclerosis of coronary vessels

b) acute heart failure on the back round of hypertonic crisis

* **II. Vascular:**

a) disturbance of vision (up to blindness)

b) early atherosclerosis of cerebral vessels

c) functional and organic disturbances of cerebral blood circulation

* **III. Kidney:**

a) hypertonic nefroangiosclerosis

b) chronic insufficiency of kidney

* **IV. Aortic:**

a) bulging aneurism of aorta

**Changes in the heart in arterial hertension**

Risk factors participating in the development of complication in the heart during arterial hypertension are the followings:

* The level of systolic and diastolic arterial pressure
* The level of pulce pressure
* Age (men- ≥ 55 , women- ≥ 65 )
* Smooking
* Dislipoproteinemia:

- Total cholesterol - >5.0 mmol/l

- Cholesterol of LDLP - >3.0 mmol/l

- Cholesterol of HDLP - <1.0 mmol/l (in men), <1.2 mmol/l (in women)

- Triglycerides - >1.70 mmol/l

* Glucose of the plasma on an empty stomach - 5.6- 6.9 mmol/l
* Unusual glucose tolerance test
* Abdominal obesity: waistline- > 102 sm for men, > 88 sm for women.
* Early cardio-vascular diseases in family analysis (in men - <55 age, in women -<65 age)

Subclinic damage of the heart during arterial hypertension is hypertrophy of left ventricle. Hypertrophy of left ventricle is risck factor for heart failure, ischemic diseases of the heart, sudden death and rhythm disorders of ventricles.

During hypertension disease both tonogen and myogen dilatation of left ventricle is observed. That is why the peak accent of the heart directs to the left, and in late stages also to the down. Hypertrophy of left ventricle, then dilatation of its and decreasing of contractibility develops. At the first stage of disease there is not any changes in auscultation. Sometimes may be systolic murmur in apex of the heart. It is index of relative insufficiency of the heart. When aortal atherosclerosis develops in the next stages of the disease accent of II ton in aorta and rude systolic murmur occurs. It heard in left part of sternum nearly to the subclavicularis pit. Development of galop rhytm means severe distrofic changes in myocardium.

There is not changes in ECG in I stage of the disease. In II and III stages the signs of hypertrophy of left ventricle determine: electric axis of the heart directs to the left, high amplitude of R wave in I standart abduction, amplitide of QRS complex in V5-V6 apduction increases. Characteric depression in ST segment and deformation of T wave determine. Main ECG index of hypertrophy of left ventricle is Sokolov-Layon index.

During ECHO-cardiography evaluate both mass index of left ventricle and diastolic disfunction of left ventricle. The wall of left ventricle becomes thichen, active myorelaxation disturbs. This leads to distolic disfunction of left ventricle.

In I stage of disease during X-ray examination of heart and large vessels there are not changes. In late stages of the disease typical signs of left ventricle determine (the top of the heart is rounded, seperated from the dome of diaphragm), aorta dilates, aortal window is enlarged, atherosclerosis is observed.

On the basck round of adeguate antihypertensive terapy in some parts of patients hypertrophy of left ventricle may regress, but it regiures long time teraphy.

**Chanhes in the kidneys**

During arterial hypertension increasing of intracapillary pressure in glomeruli, then ischemia its leads to development of local glomerulosclerosis.Glomerulosclerosis is accompanied by decreasing of filtration rate in glomeruli and increasing of creatinin in plasma. Endothelial dysfunction in glomerular apparatus leads to increasing permeability of glomerular membrane. This leads to microalbuminuria and proteinuria.

For evaluation of functional state of kidney during arterial hypertension filtration rate of glomeruli and the level of creatinin in the plasma determine. Also, microalbuminuria, proteinuria, albumin/creatinin ratio is evaluated.

**Changes in the vessels**

Microcirculatory changes during arterial hypertension may be functional and organic character. Disturbance of microcirculation during arterial hypertension leads to increasing of peripheral vascular resistance. Index of microcirculatory disorders during arterial hypertention are the following:

* Hypertrophy of vascular wall
* Decreasing of capillary net
* Local spasm of arterioles
* Congestion in venules
* Decreasing intensity of blood circulation in metabolic vessels

Disturbance of microcirculation accompanies bu metabolic and functional disorders in the organs. In the vessels with midle diameter hypertrophy of smooth muscular layer and increasing of wall/lumen ratio is observed. For evaluation of the state of midle vessels is used USM. In this case the thichen of intimae-meadia in bifurcation area determine. Increasing of this index is risck factor for myocardial infarction and cerebrovascular complications. > 0.9 mm means damage of carotid artery, >1.3 mm – means development of atherosclerotic plug.

>12 m/s of pulce wave distribution speed means arterial rigidlity and the sign of damage of turget organs. (distribution of pulce speed between carotid-femoral artery).

Ankle-brachial index is marker of occlusive damage arteries of lower extremities. This index is determined by ratio between systolic A/P in artery of lower extremity and systolic A/P of brachial artery (a.dorsalis pedis və ya a. tibialis posterior). 0.9-1.3 in norm. Increasing of this index is observed during atherosclerosis.

**Changes in the brain**

Damage of brain during AH manifest itselves by demencia, stroke, transitory ischemich attacs. Increasing of A/P leads to lipohyalinosis of small intracerebral arteries, then hypertrophy and occlusion them. This leads to development of hypoperfusion of white matter in the periventricular area of brain, ischemic damage and locunar infarct. These symptoms determine by MRT.

Transitory ischemic attacs is episods of vascular nature local serebral disfunction. Sudden occurs and sudden stops, continues about several minutes.

During A/H risck for ischemic and hemorrhagic stroke is higher. 80% cases develops ischemic stroke. Ischemic stroke develops as a result of stenosis, embolia or trombosis of arteries. (in situ). Coma during ischemic stroke develops gradually. Dizziness, motor, sensation, speech disorders is observed in the patients. Then disturbance of conscioussness and completly loss of consciousness, decreasing of arterial pressure, superficial respiration, paleness of skin and mucous membrane, loss of reflexes develops.

Lipohyalinosis of smal intracerebral arteries leads to rupture of microaneurism and intracerebral hemorrhages develops. Hemorrhagic stroke sudden develops and patient losses consciousness. Skin and mucous membrane in red color, vissible vessels dilate and pulsation determine in them, the eyeballs loss reaction to the light, arterial hypertension, respiratory disorders, hypo and areflexia, pathological reflexes may observe.

**Changes in the eyes**

There are not changes in the vessels of ocular fundus in the I stage of A/H. Sometimes maybe spasm in the vessels of retina. In the II and III stages acute changes determine in the vessels of ocular fundus: narrowing lumen of arterioles, thicken their wall determine. Thichened arterioles press to the veins (Salyus-Qunna symptom), sclerosis of arterioles develops, may be hemorrhages. Edema of retina, sometomes retinal disinsection and blindness develops.

**Clinical manifestation and diaqnosis of arterial hypertension**

Clinical picture of A/H is non-spesific. There are not complaints sometimes despite to the high pressure during primary arterial hypertension. Mostly the patients complaince from severe headache,. Headache continues several hours and may result in vomiting. During disease may be tinnitus, black points, brights in front of eyes, tachycardia, weakness.Myocardial infarction may develops in the patients with unchanged coronary vessels during A/H. It is connected with increasing the work of heart due to resistance.

According to the character of proggression and duration the course of hypertension disease is divided into 2 types:

**a)** benign type

b) malignant type( 0.1-0.2 % of hypertension disease).

**For malignant type characteristic:**

1) Rapid proggression of disease

2) Constant high level of A/P (220/130-140 mm.Hg.)

3) Early development of changes in organs and vessels

4) Therapevtic measures are non-effective.

5) Rapid development of death (after 1-2 years of symptoms)

During malignant is observed edema of retina and visiual nerves, hemorrhages. Mostly hypertonic encefalophathy, disturbance of cerebral blood circulation develops. Artheriosclerosis and arterionecrosis of renal vessels leads to insufficiency of kidneys. Acute albuminuria with moderate hematuria and silinduria, proggressive decreasing of glomeruli filtration and disturbance of concentration function of kidney is observed. Presence of leukocyturia is manifestation of joining of infection of urinary tracts or pyelonefritis.

For benign type characteristic:

1) Slowly proggression

2) Periodic remission and relapce

3) Effective drug therapy

4) Complications develop in late stage of the disease

**Hypertension disease may complicated by hypertonic crisis.** Hypertonic crisis –is characterised by high level of systolic and diastolic pressure and deepens of clinical signs in turget organs.This case reguires emergensy measures. **There are** 3 variants of hypertonic crisis are distinguished:

I. Neuro-vegetative

II. Water-electrolyte

III. Hypertensive encefalophathy (convultive form)

**Classification of hypertonic crisis:**

* Complicated crisis.This case reguires emergency therapevtic measures. In this case may occur fatal damage in turget organs: stroke, myocardial infarction, cardiac, renal insufficiency.
* Uncomplicated crisis. In this case there are not acute damage in turget organs.This type does not reguires emergency measures, but the doctor must decrease A/P/.

**Pathogenesis of hypertonic crisis**

In the base of hypertonic crisis participate neuro-humoral mechanisms. Activation of sympatoadrenal system leads to hyperstimulation of RAAS. This leads to development of visious circle. Excess releasing of catecholamins, angiotensin II, vasopressin and insufficiency of endogenous vasodilatators (No, prostacyclin) leads to increasing of peripheral vascular resistance. Next increasing of A/P leads to damage of endotelium of vessels. Result in permeability of vessels increases and perivascular edema develops. Loss of fibrinolytic activity, activation of thrombocytar and couagulation cascade lead to DIVC syndrome.

**Dyfferential diaqnosis**

For diaqnosis of hypertension disease must be research all factors leading to the symptomatic arterial hypertension:

**Obstruktive night (ONA) syndrome** is observed in the patient with obesity and AH, often in men. Repeted night epizods of hypoxemia leads to acute neuro-humoral activation and increasing of AP. This case continues even after crisis. ONA syndrome is accompanied by daily sleepiness, wheezing during sleep, epizods stop of respiration. Diagnosis is based to polisomnography: monitoring of EEG, movement of eyes, muscular tonisity, movement of anterior part of thorax and abdomen, air flow through the respiratory tracts, saturation of blood with oxygen and itrathoratic pressure. Index of apnoe/ hypopnoe is quantitative index of apnoe anf hypopnoe. In healthy people may be 5 epizods of apnoe in hour, 5-20 is light, 20-40 moderate, >40 is severe level. Decreasing of body mass, avoid of smoking is complex of non-drug therapy of AH and ONA.

**Renoparenchymal AH** (during glomerulonephritis, diabetic nephropathy, polikistosis). In the base of this participates decreasing amount of functional nephrones. This leads to decreasing of glomerular filtration. Result in water and Na+ delayes in the body and hypervolemy develops. Observation of renal diseases in anamnesis, proteinuriya, silinduria, hematuria, leukocyteuria in urine analysis helps to clarification of diagnosis.

**Vazorenal AH.** In the base participates stenosis of renal artery. This leads to ischemia in the kidneys. Hypoperfusion of kidneys leads to activation of RAAS and AP increases. For clarification stenosis of renal artery is used arteriography of renal artery.

**Pheochromacytoma** is tumor developing from chromaffinic cells of adrenal glands and synthesizing of catecholamins.For diagnosis determined in daily plasma and urine the level of catecholamines. During pheochromavytoma the amount of epinephrin and norepinephrin in urine is > 200 mkg/day. In patients with chromacytoma sympoms when the amount of catecholamins increases little in the plasma (500-1000 pg/ml), for clarify the diagnosis is used clonidin test: during primary AH using of clonidin leads to decreasing concentration of norepinephrin in the plasma. Clonidin decreases physiological secretion of catecholamins, but does not act to the catecholamins synthesing by tumor.

**Primary hyperaldosteronism –** is tumor developing from glomerular part adrenal cortex. This tumor cells synthesize aldosteron. In the patients develops AH, hypernatriemia, hypokaliemia, metabolic alkalosis. For diaqnosis is used ratio concentration of aldosteron in plasma to the activity of renin of plasma. Aldosteron/PRA > 30 is index of hyperaldosteronis. High concentration both of renin and aldosteron in the plasma may be connected with stenosis of renal artery.

**Hypo and hyperthyreosis.** Characteristic signs of hypotireosis are: high diastolic arterial pressure, decreasing of systolic volume and carduiac output, diffuse edema.

Characteristic signs of hypertireosis are: tachycardia and increasing of cardiac output, normal or decreased diastolic pressure on the backround of increasing of systolic pressure. During hypertireosis increasing of diastolic pressure is the sign of another disease accompanied by AH or hypertension disease. In this case becidies clinical examinations, the thyroid gland also should be examine and hormonal status must be defined.

**Drug AH.** In the pathogenesis of this AH participate following factors:

* Vazoconstraction under action of sympatic stimulation or direct action to the smooth muscular cells of vessels.
* Increasing of viscocity of the blood
* Stimulation of RAAS
* Delay water and Na+
* Interaction with central regulatory mechanisms

**AH developing under action of alkohol.** Alcohol is risk factor for AH.Development of AH during excess intake of alcohol is connected with increasing activity of CNS, stimulation of adrenal glands by etanol and decreasing synthesis of prostacyclin.After intake of alkohol activates CNS, sympato-adrenal system and increases synthesis of catecholamins. Catecholamins activates RAAS. Diagnosis to anamnesis and chronic alkohol intocication. During excess intake of alkohol in laboratory analysis macrocytosis, increasing activity of γ-qlyutamyltranspeptidase is observed.

**Labortary –instrumental analysis during hypertension disease**

During uncomplicated cases doing simple analysis, that negate symptomatic A/H, risck factors and level of damage in turget organs determine. Complicated cases reguires special analysis.

Obsolute, dilated and deep analysis for determination of A/H:

|  |  |  |
| --- | --- | --- |
| Examination | Whoom  When doing | Description |
| Absolute | To all patients | -Glucose, total cholesterol, HDLP, LDLP, triglicerides in the plasma on an empty stomach.  -Creatinin, K+, uric acid in plasma, glomerular filtration rate  -Hemoglobin, hematocrit  -Microscopic analysis of urine sediment and determination of microalbuminuria  -ECG |
| Dilated | For the people with low and midle risck group | -EChO-ckardiography  -USM of carotid artery  -Quantitative and qualitative index of microalbuminuria  -Uncle-brachial index  -Examination of ocular fundus  -Glucose tolerance test (if the level of glucoese in plasma on an empty stomach > 5.6 mmol/l)  -Monitoring of A/P  -Speed of pulce wave |
| Deep | During suspicion to the secondary A/H | -Determination signs of damage of brain, heart, kidneys, vessels.  -During suspicion to the secondary A/H, anamnesis, physical examination, rutin examination:  -Determination of renin, aldosteron,glücocorticoid, catecholamins in the blood and urine  -arteriography;  -USM, CT anf MRT of kidneys, adrenal glands |

Laboratary-instrumental methods in A/H are the followings:

* General analysis of blood
* General analysis of urine
* Biochemical analysis of blood :

-Total cholesterol

-HDLP

-LDLP

- VLDLP

-triglicerides

- Protromin index

-PT

-Creatinin

-Fibrinogen

-Renin

-Angiotensin

-Aldosteron

* EKQ
* EChO
* X-ray examination of thoratic organs
* Examination of ocular fundus

In the III stage of hypertension disease due to chronic renal insufficiency may develops anemia.

* **General analysis of the blood:**

|  |  |
| --- | --- |
| **Indicies** | **Norm** |
| **Hematocrit** | 40-54%-in men, 36-42% in women |
| **MCHC-** | 30-48%. |
| **MCH** | 27-33 pgr. |
| **Hypersegmentation of neutrophiles** | Absent in norm |
| **Basophilic granularity of erythrocytes** | Absent in norm |
| **Kebot ring** | Absent in norm |
| **Reticulocytes** | 2.0-10 %. |
| **Macro və megalocytes** | Absent in norm |
| **Plasmatic cells** | Absent in norm |
| **Trombocytes** | 180-320 109/l. |
| **Color index** | 0.9-1.1 |
| **Erythropoietin** | 25-75 mED/ml |
| **MCV** | 80-96 femtolitrdir |
| **Jolli body** | Absent in norm |

**Percentage of different types of leukocytes:**

|  |  |
| --- | --- |
| **Types of leukocytes** | **Norm %** |
| Myelocytes | - |
| Metamyelocytes | - |
| Sticnuclear neutrophils | 1-5 |
| Segmented neutrophiles | 40-70 |
| Lymphocytes | 20-45 |
| Monocytes | 3-8 |
| Eosinophils | 1-5 |
| Basophils | 0-1 |
| Plasmocytes | - |

In III stage of disease due to chronic renal insufficiency may develops anemia.

**In biochemical analysis** of the blood in early stage of hypertension disease there are not changes. If atherosclerosis develops the concentration of cholesterol (α-cholesterol), triglicerides, β-lipoproteins may increases.

* **LDLP-** 1.3-3.5 mmol/l in norm in the blood

During II and III type of hyperlipemia, hypotireosis, diabetes mellitus, dislipidemia, nefrotic syndrom, acute porphiria, atherosclerosis LDLP increases in the blood. I,IV,V type of hyperlipidemia, hypertireosis, pancreatitis, steroid terapia, alkoholism, pregnancy LDLP decreases in the blood.

* **YSLP** –0.8-2.2 mmol/l. in norm in the blood

During obesity, hyperlipidemia HDLP increases in the blood. During Tanjer disease (cholesterol accumulates in the tissues, the amount of cholesterol in the blood decreases) HDLP decreases in the blood.

* **VLDLP-** 0.13-1.0 mmol/l. in norm in the blood

During I və II type of hyperlipidemia and porphiria slight rice the amount of VLDLP in the blood. During alkoholism, hypotireosis, diabetes mellitus, dislipidemia, nefrotic syndrome, atherosclerosis, IV və V tip hiperlipiemiya, pregnancy, pankreatitis, steroid therapy the amount of VLDLP more increases in the blood.

* **Triglicerides**- normada qanda 0-1.71 mmol/l. in norm in the blood

During I type of familiarly hyperlipidemia, obesity, diabetes mellitus, hypotireosis, alkoholism, intake of peroral contraseptives, accumulation diseases (Qoshe,Niman-Pik), nefrotic syndrome, paraproteinemic hemoblastosis, drugs (esterogens, glucocorticosteroids), fatty dystrophy of the liver the amount of triglicerides increases in the blood. During hypertireosis the amount of triglicerides decreases in the blood.

* **Total lipids**- normada qanda 4.5-7.0 gr/l. in norm in the blood

3-4 hours after feeding, diabetes mellitus, atherosclerosis, nefrotic syndrome, biliar cirrhosis of the liver, acute hepatitis, hypotireosis, acute and chronic pancreatitis, alcoholism the amount of total lipids increases in the blood.

* **Total cholesterol-** 3.5-5.0 mmol/l in norm in the blood. During slight (moderate) level hypercholesterolemia the amount of total cholesterol is about 5.0-6.0 mmol/l, high level hypercholesterolemia >6.0 mmol/l. in the blood.

During atherosclerosis, hypotireosis, diabetes mellitus,familiarly hypercholesterolemia, cholestasis, disglobulinemia (paraproteinemic hemoblastosis), Ateroskleroz, hipotireoz, şəkərli diabet, ailəvi hiperxolesterinemiya, alimentar hiperxolesterinemiya, xolestaz, disqlobulinemiya (paraproteinemik hemoblastoz), systemic vasculitis, nefrotic syndrome, medicamentoz hypercholesterolemia, obesity the amount of total cholesterol increases in the blood.

During functional insufficiency of the liver, malabsorption syndrome the amount of total cholesterol decreases in the blood.

**Chilomicrons**- abcence in norm in the blood.

During I, III,V type hyperlipidemia, alcoholism, hypotireosis, diabetes mellitus, disglobulinemia, nefrotic syndrome, pancreatitis, steroid therapy the amount of chilomicrons increases in the blood.

**Protrombin time (PT)** 11-13.3 second in norm. During alcohol disease of the liver, DIVC syndrome, A hypervitaminosis, K hypovitaminosis, cancer of pancreas, hemorrhagic diseases of newborns, systemic disease of connective tissue, hemophilia, hemorrhagic fever, non-adeguate dose of antiagregants and anticoagulants PT increases.

During thrombosis, hypercoagulation, increasing activity of VII factor of coagulation PT decreases.

**Protrombin index**  80-120% in norm (percentage ratio of standart protrombin time to the protrombin time of patient). During DIVC syndrome, hemophilia, alcohol disease of the liver, parenchymal jaundice, intestinal disbacteriosis, K hypovitaminosis, hemorrhagic fever, systemic diseases of connective tissue, non-adeguate dose of antiagregants and anticoagulants protrombin index increses.

* **Creatinin** for evaluation of functional state of kidneys. Creatinin 80-120 mkmol/l. in norm in the blood. During obturation of urinary tracts, severe diabetes mellitus, hypertireosis, acromegaly, damage of the liver, hypofunction of adrenal glands the amount of creatinin increases in plasma. During decreasing of muscular mass,I and II trimestr of pregnance the amount of creatinin decreases in plasma.
* **Uric acid is** 214 - 488 mkmoll/ in plasma in norm. During gout, leukosis, renal insufficiency, acidosis, I trimestr of pregnancy, intake of food rich with purins, intake of thiazide diuretics concentration of uric acid increases in the blood.
* **K+** is one of the microelements participated in water-electrolite metabolism.Mainly in intracellular fluid. Concentration of K+ is regulated by kidneys, aldosteron, by Na-uretic factor is inhibited. Concentration of K+ in plasma is 3.3-5.3 mmol/l, in erythrocytes is 78-97 mmol/l, in urine is 80-100 mmol/l in norm. During renal insufficiency, massive damage of cells, intake of K+ containing preparations, poisoning with strichinin, hypocortisizm, bronchial asthma, anaphylactic shock, ets. Concentration of K+ increases in the plasma. During malabsorbtion, diarrhea, repeted vomiting, injection of insulin, ACTH, corticosteroids, hyperaldosteronism, damage of renal tubules, ets. Concentration of K+ decreases in the plasma.
* **Fibrinogen** is acute faze protein of inflammation, synthesized in the liver and under action thrombin converts into fibrin. Fibrinogen increases ESR. The amount of fibrinogen is 2.0-4.0 gr/l. in norm in the plasma.

During pregnancy, acute inflammation and infections, tyberculosis, necrosis of tissues, hypotireosis, myocardial infarction, burns, amiloidosis, diseases of the liver, malignant tumors, DIVC syndrome,systemic vasculitis, myeloma disease, COVID-19 the amoun of fibrinogen increases in the blood.

During diseases of kidneys, embolia with amniotic water, deficiency of C and B12 vitamines, polycythemia, afibrinogenemia, chronic myeloleukosis the amount of fibrinogen decreases in the blood.

* **Renin** 1.6-4.5 mkg/l hour in norm. During renovascular or nefrogenic hypertony, hyperaldosteronism, stenosis of renal artery, cirrhosis of the liver, hepatitis, cardiac insufficiency, insufficiency of adrenal cortex the amount of renin increases in the blood.
* During prymary hyperaldosteronism**,** damage of the parenchyma of the kidneys, mineralokorticoid synthesising malignant tumors of adrenal glands the amount of renin decreases in the blood.
* Angiotensin is oligopeptide hormone, leads to vasoconstraction and increasing of arterial pressure**,** stimulates synthesis of aldosteron from adrenal cortex. Angiotensin forms from angiotensinogen in the liver.
* **Aldosteron** normda 15-70 nmol/l in plasma, 4.5-17.7 mkg/ daily in urine.

Fizioloji olaraq aldosteronun yuxarı qalxmasına su çox qəbul etdikdə, fziki yük zamanı, duzsuz dieta zamanı, hamiləlikdə rast gəlinir.

During prymary hyperaldosteronism, secondary aldosteronism, hyperplasia of adrenal glands, cardiac insufficiency, cirrhosis of the liver, hepatitisrenovascular hypertony, hypertension disease the amount of aldosteron increases in the plasma.

During Addison disease, hypocortisizm, diabetes mellitus, acute alcohol intocication, Terner syndrome the amount of aldosteron decreases in plasma.

**Analysis of urine:** total analysis, Nechiporenko, Zimnitskiy tests, daily proteinuria, bacteriuria, gualitative changes of leukocytes determine. In I və II stages of arterial hypertension there are not observe changes in the urine. Periodic microhematuria, transitory albuminuria is observed during hypertonic crisis. In III stage moderate albuminuria (1 qr/l), slight hematuria may be observed. The special mass of urine during arterial hypertension is normal. Asotemia is not characteristic for arterial hypertension, but may develops in III stage. Asotemia usually is the result of chronic latent glomerulonephritis or pyelonephritis.

|  |  |
| --- | --- |
| **Indicies** | **Norm** |
| Ammonia in urine | 0.044 - 0.141 mmol/l. |
| Atypical cells | normada sidikdə olmur |
| Acetone in urine | normada olmur |
| Total protein | 0.033 gr/l-dən az olur. |
| Bilirubin | Does not observe in norm |
| Glucose | Does not observe, or a <0.3 gr/daily |
| Ketone bodiees | does not observe in norm |
| The amount of urine | 800-1500 ml. |
| Leukocytes | up to 5- in vision area |
| Special mass of urine | 1018-1025 gr/ml. |
| Reaction of urine | 5.0-7.5 |
| Color of urine | Transparent |
| Erythrocytes | Does not observe or single |