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Одним из последних изученных веществ, синтезируемых адипоцитами, является многофункциональный гормон лептин, участвующий в регуляции потребления пищи, процессах энергообмена, ряде нейроэндокринных функций и обладающий периферическими эффектами. Нарушение секреции и действия лептина при ожирении может быть ведущим фактором в развитии инсулинорезистентности (ИР), нарушении метаболизма липидов и глюкозы. При этом гиперлептинемия, лептинорезистентность являются биомаркером ожирения.
Ключевые слова: лептин, функции, ожирение, лептинорезистентность.

ОРТИҚЧА ВАЗН ПАТОГЕНИЗИДА ЛЕПТИН АХАМЯТИНИНГ ЗАМОНАВИЙ ЖИХАТЛАРИ

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Сўнги ўрганилган моддалардан бири бу, адипацитлар тамонидан синтез қилинадиган, овқат қабул қилиш, энергия алмашинуви, бир қатор нейроэндокрин функциялар ва перифирик таъсирга эга кўп функционал, лептин гормонидир. Семизликда лептин секрецияси ва таъсирининг бузилиши инсулинга булган қаршиликнинг пайдо бўлишида, липидлар ва глюкоза метаболизими бузилишида етакчи омил бўлиши мумкин. Айни холатларда гиперлептинемия, лептинрезистентлик семиришнинг биомаркери хисобланади.
Калит сўзлар: лептин, функция, семизлик, лептинорезистентлик.

MODERN ASPECTS OF THE IMPORTANCE OF LEPTIN IN THE PATHOGENESIS OF OBESITY.

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One of the last studied substances synthesized by adipocytes is the multifunctional hormone leptin, which is involved in the regulation of food intake, energy metabolism, a number of neuroendocrine functions, and has peripheral effects. Violation of the secretion and action of leptin in obesity can be a leading factor in the development of insulin resistance (IR), impaired lipid and glucose metabolism. In this case, hyperleptinemia, leptin resistance are a biomarker of obesity
Key words: leptin, functions, obesity, leptin resistance

Modern aspects of the importance of leptin in the pathogenesis of obesity.

The first studies anticipating the discovery of leptin were conducted more than half a century ago when G. Kennedy proposed his “theory of lipostat” [1]. She said that information on the mass of adipose tissue in the body constantly enters the hypothalamus. The carrier of this information is an unknown factor circulating in the blood. The hypothalamus, receiving information from the blood, delivers impulses to the parts of the brain responsible for changes in appetite. The G. Hervey study [2] on parabiotic cross-circulating rats was even closer to the discovery of leptin. Blood coming from an experimental rat (with destroyed nuclei of the hypothalamus) in a healthy animal caused a feeling of satiety, leading to a decrease in food intake and sharp weight loss. At the same time, the operated rat developed hyperphagia and obesity. It was suggested that the blood of a rat with a damaged hypothalamus contains a factor that, when ingested in a healthy animal, causes anorexia and weight loss. The most convincing data on the involvement of an unknown blood factor in the regulation of eating behavior were obtained after isolating the special genetic lines of obese ob / ob and db / db mice [3, 4]. These animals, in addition to being overweight, were characterized by hyperphagia, hypodynamia,

reduced energy metabolism, increased lipid deposition in adipose tissue and the development of type II diabetes mellitus, which was caused by a recessive mutation. In cross circulation of ordinary and ob / ob mice, a decrease in food intake, an increase in energy metabolism, and a decrease in energy reserves in mutant animals (ob / ob) were observed; any changes in normal mice were absent. The data obtained allowed us to conclude that a humoral factor that stimulates energy metabolism circulates in the blood of healthy animals. The humoral factor is absent (or its content is significantly lower) in the blood of ob / ob mice, so they are obese, type II diabetes and infertility. The first report on the discovery of the obesity (ob) gene using positional cloning was published in 1994 by Y. Zhang et al. [5]. Artificial yeast chromosomes were used for positional cloning. The protein was given the name "leptin" from the Greek word "leptos" (thin) and the definition was formulated: the expression product of the ob gene, leptin, is a hormone that is secreted by adipocytes into the blood in varying amounts and controls the mass of adipose tissue by stimulating lipid metabolism in the body.

The structure of leptin.

Leptin is a monomeric protein (according to various sources, containing 145, 146 or 167 amino acid residues), which is expressed almost exclusively by adipocytes. The molecular weight is 16 kDa. In spatial structure, it belongs to the group of alphahelical proteins, which also includes growth hormones, prolactin and cytokines.

Fig1 http://sci-lib.com/article515.html. 4 antiparallel α-helices (A, B, C, D) with an ascending-descending connection are connected by one short (BC) and two long (AB and CD) loops. Leptin has two conserved cysteine residues (one in the CD loop and the C-terminal residue), which form a disulfide bridge connecting the CD loop to the C-terminal part of the D helix (Fig. 3). The disulfide bridge is crucial for its structural stability, secretory and biological activity. Also, these structural characteristics resemble those found generally in cytokines: granulocyte-colony stimulating factor (G-CSF) and interleukin6 (IL-6), so that leptin is classified as a long-chain cytokine.

The overwhelming amount of leptin is secreted by white adipose tissue (subcutaneous fat), and in a small amount by brown adipose tissue (internal fat) [7, 8]. Adipocytes secrete leptin into the blood in direct proportion to the mass of adipose tissue and nutritional status [9]. The expression and secretion of leptin is also regulated by a variety of other factors. The formation of leptin increases under the influence of insulin, glucocorticoids, TNF-a, estrogens, and decreases through ßS-adrenergic activity, androgens, free fatty acids, growth hormone, ghrelin [10].

Reception and signal reception. In 1995 and 1996 leptin receptors have been identified [11-13]. They are members of the class 1 cytokine receptor superfamily and are characterized by expression both in the central nervous system and on the periphery [14]. Three different receptor variants have been identified: ─ Soluble leptin receptor;

─ A membrane-bound leptin receptor that has a short intracellular domain and is not capable of transducing a hormonal signal;

─ A membrane-bound receptor that has a long intracellular domain and is capable of transmitting a hormonal signal.

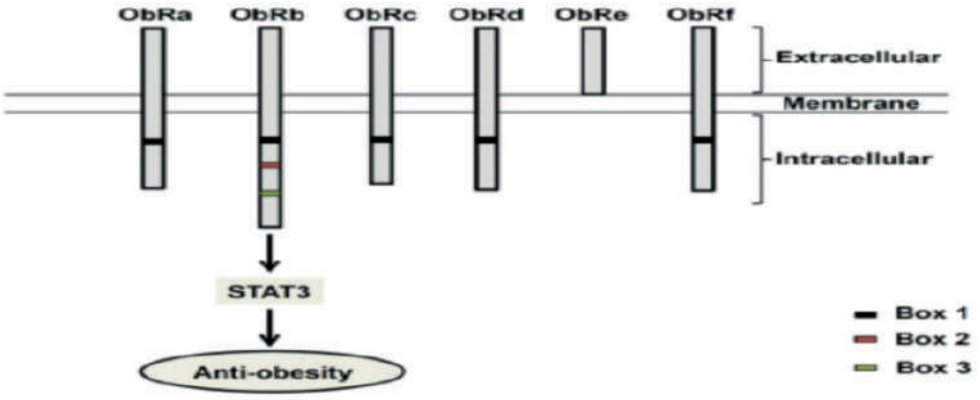

Fig2 http://sci-lib.com/article515.html.

The structure of various isoforms of leptin receptors. In organs, leptin binds to specific receptors (ob-R) [12]. So far, at least 6 isoforms of leptin receptors (ob-Ra, ob-Rb, ob-Rc, ob-Rd, ob-Re, ob-Rf) have been identified [13,14]. obRf, obRa, obRc, obRf belong to short forms, and obRe is soluble. (Journal of Environmental Earth and Energy Study (JEEES) No. 2 (2019) DOI: 10.5281 / zeno-

do.3328788) The structure of various isoforms of leptin receptors. In organs, leptin binds to specific receptors (ob-R) [12]. So far, at least 6 isoforms of leptin receptors (ob-Ra, ob-Rb, ob-Rc, ob-Rd, ob-Re, ob-Rf) have been identified [13,14]. obRf, obRa, obRc, obRf belong to short forms, and obRe is soluble. (Journal of Environmental Earth and Energy Study (JEEES) No. 2 (2019) DOI: 10.5281 / zenodo.3328788)

Fully functional is the only elongated form of ob-Rb, precisely through which leptin acts [10]. In humans and animals, ob-Rb receptors have been found in the hypothalamus, adrenal glands, pancreas, and adipose tissue. This form of the leptin receptor with a long cytoplasmic domain is most actively expressed in the hypothalamus and is found mainly in the arcuate nucleus (ARC) and the ventromedial nucleus (VMH), as well as in the paraventricular nucleus (PVN), lateral hypothalamus (LH), and ventral premillary nucleus (PMv) and dorsomedial nucleus (DMN). The mechanism of signal transduction of cytokine receptors includes activation of tyrosine kinases associated with the receptor, phosphorylation of the receptor by these kinases with the formation of landing sites for a number of protein effectors, and phosphorylation of some of them with the same tyrosine kinases. The functions of the remaining short isoforms are still not precisely defined [15]. Of the various short leptin receptor isoforms, ob-Ra has been better studied. The highest concentration of the receptor is noted in the kidneys (in the mesangium and blood vessels), which can have far-reaching consequences in the development of nephrosclerosis. [16, 17]. Leptin receptors interact with intracellular messengers, namely mitogen-activated protein kinase (MAP), insulin receptor substrate (IRS-1 and IRS-2), Yanus kinase (YAK), nitric oxide (NO) and signal transducer and transcription activation factor (STAT)) [fifteen]. Close interaction was found between signal transduction of leptin and insulin or between hyperleptinemia and hyperinsulinemia [17].

Effects, functions and connections of leptin. Various biological effects of leptin are manifested through its binding to receptors on neurons. The hormone causes a decrease in appetite by binding to receptors on the hypothalamic neurons, in which a-melanostimulating hormone (a-MSH) and neuropeptide Y are neurotransmitters [17]. α-MSH is synthesized as a precursor of proopiomelanocortin (POMK), from which it is released after proteolytic cleavage. In addition to a-MSH, ACTH and p-endorphin are formed from POMK. Currently, five different a-MSH receptors have been discovered: MK1-P, MK2-R, MK3-P, MK4-P and MK5-P [17]. The MK1-P gene is expressed only in melanocytes of the skin, and its binding to MSH stimulates pigmentation of the skin and hair color. The MK2-P gene manifests itself mainly in the adrenal cortex, being a conductor of the biological action of ACTH (stimulates the production of corticosteroids), the MK3-P gene in the hypothalamus and stomach, the MK4-P gene in the hypothalamus and MK5-P in almost all tissues, in including in the kidneys [18]. Leptin inhibits the expression of the neuropeptide Y gene in neurons of the hypothalamus. Increased food intake caused by neuropeptide Y is inhibited by leptin. Thus, leptin not only reduces the synthesis of neuropeptide Y, but also inhibits its physiological effect. Another mediator of the action of leptin is melanin-concentrating hormone (MCH). The action of MCH is the opposite of the effect of a-MSH. MKT causes increased appetite and food intake [18]. The next mediator of the biological effect of leptin is CART (cocaine amphetamine regulated transcript), the content of which increases after the animals are injected with cocaine and amphetamine. Leptin stimulates the expression of the CART gene and causes an increase in the content of CART mRNA in the hypothalamus [18]. Experiments on the introduction of CART into the ventricle of the rat brain revealed a reduced food intake stimulated by neuropeptide Y [18]. Thus, leptin can both stimulate appetite by suppressing gene expression and biosynthesis of neuropeptide Y and MCH, and reduce food intake through activation of POMK (MSH) and CART gene expression in neurons [18]. A series of mutations of the leptin genes (ob / ob mouse line) and its receptors (db / db mouse line, Zucker rat line, fa mutation) have been described; mutations are accompanied by similar symptoms - obesity, hyperphagia, decreased energy metabolism (hypothermia, reduced oxygen consumption) and physical activity, tissue resistance to insulin with hyperinsulinemia and hyperglycemia. Mutations of leptin and its receptor are the cause of a small proportion of human obesity cases. In addition to regulating the energy balance, leptin mediates neuroendocrine adaptation to starvation, in particular, changes in reproductive and thyroid functions. Leptin is a permissive factor in relation to puberty. Summarizing the functions of leptin, the following can be noted:

- Anorexigenic effect
- Inhibition of eating behavior and decreased activity of the appetite center
- Stimulation of energy metabolism

– Activation of the heat production center
– Fat utilization and weight loss
– Induction of onset and increase in puberty
– Maintenance of reproductive function
– Stimulation of secretion of GNRG, LH and FS Regulation of thyroid function
– Adaptation of thyroid function to starvation
– Decreased synthesis and secretion of NPY in the brain
– Stimulated synthesis and secretion of KRH
– Stimulated secretion of ghrelin
– Stimulated secretion of adiponectin
– Decreased secretion of insulin

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Leptin, obesity and leptin resistance. Obesity - excessive deposition of triglycerides in adipocytes - increases the risk of death of a person of reproductive age (20-50 years) by 50%. Obesity contributes to the development of cardiovascular diseases, diabetes mellitus, cholelithiasis, liver cirrhosis, endometrial and breast cancer (due to the increased aromatization of androgens into estrogens in adipocytes). The leptin content in human blood increases in parallel with the increase in adipose tissue mass [19]. The hormone concentration after puberty is 2-3 times higher in women than in men [20]. In fertile age, the content of leptin in men decreases and increases in women due to the more pronounced inhibitory effect of androgens on the synthesis of leptin than stimulating estrogen [21, 22]. In addition, the concentration of leptin in the blood is influenced by a higher content of total body fat in women than in men [22]. Subcutaneous adipocytes produce twice as much leptin per cell than intra-abdominal cells, possibly due in part to a larger volume of subcutaneous than visceral adipocytes [22]. The decrease in leptin production occurs 18-24 hours after the restriction of food intake [19]. Such changes can be mediated by a decrease in the plasma concentration of insulin and an increase in the concentration of epinephrine. Insulin increases the expression of the leptin gene, while catecholamines decrease it [23]. The concentration of circulating leptin can vary significantly among individuals with the same mass of fat, which may be due to exposure to the expression of the hormone (leptin) insulin, glucocorticoids, and sex hormones [24]. When fasting, the level of leptin in the blood plasma decreases. This decline is usually combined with adaptive physiological responses to starvation in the form of increased appetite and reduced energy expenditure. Such reactions were observed in mice with leptin deficiency and in people with severe obesity. It should be noted that therapy with small doses of leptin led to a decrease in hyperphagia and weight loss in experimental animals. In contrast, the usual (not associated with genetic defects) forms of obesity were characterized by an increased content of circulating leptin. Neither endogenously high levels of leptin, nor therapeutic measures with the introduction of exogenous leptin had an effect on reducing the amount of fat in the body. It has been suggested that this is due to the development of leptin resistance [6]. It became known that the existing increase in the level of hypothalamic BFBZ (a cytokine signal suppressor) can be considered as a molecular mediator of acquired leptin resistance [25, 26]. BOSBZ inhibits signaling to the leptin receptor and other receptors of the cytokine family by suppressing the activity of LHC2 (hence, BTAT activation) [25]. One of the first was established the function of leptin by its effect on energy metabolism, food intake and energy expenditure associated with the action of the hormone in the hypothalamus. Over time, it was found that the action of leptin is much more diverse. In addition to the central nervous system, it acts on the pancreas, kidneys, immune and sympathetic nervous systems, affects angiogenesis, hematopoiesis and, most likely, tumor growth, and also, apparently, takes part in the processes of fetal development, stimulates growth bones and their density [21]. Analyzing the literary data on the “interrelationship” of leptin and overweight, one cannot but touch upon the fact of leptin resistance, which often takes place in this condition. Although leptin is considered a hormone that counteracts obesity, in this condition hyperleptinemia is often observed, as a possible consequence of the development of leptin resistance. At the same time, some authors believe that due to the insignificant penetration of leptin through the blood-brain barrier, hyperleptinemia is not able to efficiently transmit the signal to the central nervous system in order to sufficiently initiate feedback suppression of leptin signals [28]. An increase in plasma leptin levels and pronounced resistance to leptin and insulin develops only after three days of overfeeding animals [27]. In contrast, fasting for several days induced a 10% reduction in body weight in combination with a 53% reduction in plasma leptin [29]. Decreased leptin levels can be a survival reaction to minimize

energy expenditure during weight loss. Therefore, a decrease in plasma leptin levels may indicate a key mechanism for short-term adaptation to starvation or to a situation associated with starvation [27]. As already emphasized, hyperphagia and increased leptin levels along with increased insulin are common signs of obesity. But at the same time, leptin itself is a powerful inhibitor of food intake and suggests a decrease in insulin levels by suppressing its secretion and better spending [30]. One gets the impression that leptin does not perform its function as a metabolic hormone that limits excess weight gain. However, it is seen that in fact leptin cannot achieve this goal with hyperleptinemia and leptin resistance. An original explanation of this problem was proposed by A. Mark et al. [thirty]. Researchers have proposed an explanation of this phenomenon from the perspective of the concept of "selective leptin resistance," which is based on the preservation of the sympathic stimulating effect of leptin, despite resistance to food intake (satiety) and the ability of the hormone to reduce body weight [30]. If selective leptin resistance occurs in obese people, then leptin can contribute to excessive sympathetic activity and hypertension, despite resistance to its metabolic effects. However, due to what mechanisms this occurs, is unknown. More research is needed to resolve this issue.

1. Kennedy G. The role of depot fat in the hypothalamic control of food intake in the rat. Proc R Soc London 1953;140:578-592
2. Hervey G. The effects of lesions in the hypothalamus in parabiotic rats. J Physiol 1959;145:338-352
3. Coleman G, Hummel K. Effects of parabiosis of normal with genetically diabetic mice. Am J Physiol 1969;217:1298-1304
4. Coleman G. Effects of parabiosis with diabetes and normal mice. Diabetologia 1973;9: 294 298
5. Zhang Y, Proenca R, Maffei M et al. Positional cloning of the mouse obese gene and its human homologue. Nature 1995;372:425-432
6. Kershaw ES, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89(6):2548 2556
7. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. Endocr Rev 2000;21:697-738
8. Fain JN, Madan AK, Hiler ML et al. Comparison of the release of adipokines by adipose tissue, adipose tissue matrix, and adipocytes from visceral and subcutaneous abdominal adipose tissue of obese humans. Endocrinology 2004;145:2273-2282
9. Wiecek A, Kokot F, Chudek J, Adamczak M. The adipose tissue – a novel endocrine organ of interest to the nephrologists. Nephrol Dial Transplant 2002;17(2):191-195
10. Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes Relat Metab Disord 2002;26:1407-1433
11. Tartaglia LA, Dembski M, Weng X et al. Identification and expression cloning of a leptin receptor, OBR. Cell 1995;83:1263-1271
12. Chen H, Charlat O, Tartaglia LA et al. Evidence that the diabetes gene encodes the leptin receptor: identification of a mutation in the leptin receptor gene in db/db mice. Cell 1996;84:491-495
13. Lee GH, Proenca R, Montez JM et al. Abnormal splicing of the leptin receptor in diabetic mice. Nature 1996;379:632-635
14. Bjorback C, Kahn BB. Leptin signaling in the central nervous system and the periphery. Recent Prog Horm Res 2004;59:305-331
15. Le Cava A, Alviggi C, Matarese G. Unraveling the multiple roles of leptin in inflammation and autoimmunity. J Mol Med 2004;82(1):4-11
16. Serradeil Le Gal C, Raufaste D, Brossard G et al. Characterization and localization of leptin receptors in the rat kidney. FEBS Lett 1997;404:185-191
17. Wolf G, Hamann A, Han DC et al. Leptin stimulates proliferation and TGFI expression in renal glomerular endothelial cells: potential role in glomerulosclerosis. Kidney Int 1999;56(3):860-872
18. Панков ЮА. Лептин – новый гормон в эндокринологии. Успехи физиологических наук 2003;34(2):3-20
19. Zeibel RL. The role of leptin in the control of body weight. Nutrition Reviews 2002;60 (10, pt2):s15-19
20. Rosenbaum M, Nicolson M, Hirsch J et al. Effects of gender, body composition, and menopause on plasma concentrations of leptin. J Clin Endocrinol Metab 1996;81:3424 3427

21. Horlick M, Rosenbaum M, Nicolson M et al. Effect of puberty on the relationship between circulating leptin and body composition. J Clin Endocrinol Metab 2000;85:25092518
22. Harmelen VV, Reynisdottir S, Eriksson P et al. Leptin secretion from subcutaneous and visceral adipose tissue in women. Diabetes 1998;47:913917
23. Ahima RS, Flier JS. Leptin. Annu Rev Physiol 2000;62:413437
24. Rosenbaum M, Pietrobelli A, Vasselli J et al. Sexual dimorphism in circulating leptin concentrations is not accounted for by dimorphism in adipose tissue distribution. Int J Obes 2001;25:13651371
25. Bjorback C, Elmquist JK, Frantz JD et al. Identification of SOCS3 as a potential mediator of central leptin resistance. Mol Cell 1998;1:619625
26. Flier JS. Obesity wars: molecular progress confronts an expanding epidemic. Cell 2004;116:337350
27. Wang J, Obici S, Morgan K et al. Overfeeding rapidly induces leptin and insulin resistance. Diabetes 2001;50:2786 2791
28. Bjorback C, ElHaschimi K, Frantz JD, Flier JS. The role of SOCS3 in leptin signaling and leptin resistance. J Biol Chem 1999;274:3005930065
29. Boden G. Role of fatty acids in the pathogenesis of insulin resistance and NIDDM. Diabetes 1997;46:310
30. Wang J, Liu R, Liu L et al. The effect of leptin on Lep expression is tissuespecific and nutritionally regulated. Nature Med 1999;5:895899

МАРКЕРЫ СОСУДИСТЫХ ОСЛОЖНЕНИЙ САХАРНОГО ДИАБЕТА 2 ТИПА: ВЫБОР ОПТИМАЛЬНОЙ ТЕРАПИИ

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Аннотация: Сахарный диабет одно из самых распространенных неинфекционных заболеваний в мире что обусловлено хроническим течением, сохраняющимися темпами роста числа больных и высокой инвалидности. По данным экспертов ВОЗ заболеваемость СД носит характер эпидемии и каждым годом количество больных увеличивается на 5–7%, и на сегодняшний день их численность составляет от 2 до 4% всего населения земного шара. Общее число больных СД в мире в настоящее время составляет 230 млн. человек, а к 2025 году число их достигнет 380 миллионов человек. Сахарный диабет 2типа остается ведущей проблемой современной эндокринологии во всем мире который ассоциируется с высоким риском развития микро и макрососудистых осложнений, ухудшением качества и сокращением продолжительности жизни пациентов. На момент постановки диагноза СД 2 типа 10–15% пациентов уже имеют ту или иную форму диабетической ретинопатии и ранние признаки диабетической нефропатии. А также у больных СД 2 регистрируется ишемическая болезнь сердца, риск развития острого инфаркта миокарда, риск мозгового инсульта чаще чем в общей популяции. Ключевая причина формирования микро и макрососудистых осложнений у больных СД является выраженная хроническая гипергликемия приводящая к изменению свойств сосудистой стенки - эндотелиальной дисфункции.

Ключевые слова: гипергликемия, эндотелиальная дисфункция, биомаркеры сосудистых осложнений.

MARKERS OF VASCULAR COMPLICATIONS TYPE 2 DIABETES MELLITUS: CHOICE OF OPTIMAL THERAPY

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Abstract: Diabetes mellitus is one of the most common noncommunicable diseases in the world due to chronic conditions, persistent rates of increase in the number of patients and high disability. According to WHO experts, the incidence of DM is an epidemic and every year the number of patients increases by 5-7%, and today their number is between 2 and 4% of the total population of the world. The total number of DM patients in the world now stands at 230 million, and by 2025 the number will reach 380 million. Type 2 diabetes remains the leading problem of modern endocrinology worldwide, which is associated with a high risk of micro and macrovascular complications, deterioration of quality and shortening of life expectancy of patients. At the time of diagnosis of type 2 DM 10-15% of patients already have some form of diabetic retinopathy and early signs of diabetic nephropathy. As well as in patients with type 2 DM recorded coronary heart disease, the risk of acute myocardial infarction, the risk of cerebral stroke more often than in the general population. The key cause of the formation of micro and macrovascular complications in patients with DM is the pronounced chronic hyperglycemia leading to a change in the properties of the vascular wall - endothelial dysfunction.

Keywords: hyperglycemia, endothelial dysfunction, biomarkers of vascular complications.

ҚАНДЛИ ДИАБЕТ 2 ТУРИ ҚОН ТОМИР АСОРАТЛАРИ МАРКЕРЛАРИ: ОПТИМАЛ ТЕРАПИЯ ТАНЛОВИ.

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Аннотация: Қаедли диабет сурункали кечиши, беморлар сонининг ўсиш сўратлари давом этиши ва ногиронликнинг юфори даражаси туфайли дунёдаги энг кенг тарқалган юфумсиз касалликлардан биридир. БДССТ мутахасисларининг фикрига кўра, қандли диабет билан касалланиш эпидемик характерга эга ва хар йили беморлар сони дунё ахолисининг 5-7% гача кўпаймокда ва бугунги кунда уларнинг сони дунё ахолисининг 2 дан 4 % гачадир. Хозирги кунда дунёда диабетга чалинган беморларнинг умумий сони 230 милион кишини ташкил этади ва 2025 йилга келиб уларнинг сони 380 миллионга етади. Қандли диабет 2-тури бутун дунёда замонавий эндокринологиянинг етакчи муаммоси бўлиб қолмоқда, бу микро ва макроваскуляр асоратларнинг юқори хавфи, беморлар хаёт сифатининг йомонлашуви ва умир кўриш давомийлигининг пасайиши билан боғлиқ. Қандли диабет 2-тури ташхиси қўйилганда, беморларнинг 10-15% да диабетик ретинопатиянинг баъзи шакиллари ёки диабетик нефропатиянинг эрта белгилари намоён булади. Шунингдек ҚД 2-турида беморларда юрак ишемик касаллиги, ўткир миокард инфаркти ривожланиш хавфи, бош мия инсульти хавфи умумий популяцияга нисбатан кўпроқ аниқланади. ҚД билан оғриган беморларда микро ва макроваскуляр асоратлар пайдо бўлишининг асосий сабаби бу оғир сурункали гипергликемия бўлиб, қон томир девори хусусиятларининг ўзгариши- эндотелиал дисфункцияга олиб келади.

Калит сўзлар: гипергликемия, эндотелиал дисфункция, кон томир асоратлари биомаркерлари.

Сахарный диабет 2 типа эпидемиология и патогенез. Сахарный диабет одно из самых распространенных неинфекционных заболеваний в мире. По данным экспертов ВОЗ заболеваемость СД носит характер эпидемии, охватывающей все экономически развитые страны. Общее число больных СД в мире в настоящее время составляет 230 млн. человек, а к 2025 году число их достигнет 380 миллионов человек. При этом доля больных с СД 2 типа составляет 85- 90%. Однако значительная часть случаев СД 2типа протекает без очевидных клинических симптомов и остается нераспознанным в течение длительного времени. Заболеваемость СД 2 значительно возрастает среди лиц 35-40 лет и старше, и достигает максимальных значений в возрастных категориях ≥ 60 лет [1]. С момента дебюта заболевания до установки диагноза и начала лечения у большого числа таких пациентов проходит около 10 лет. В результате, СД 2 типа выявляется уже на стадии тяжелых, необратимых поздних осложнений, которые могли бы быть успешно предотвращены при своевременном начале лечения. Сахарный диабет по своей природе гетерогенен, это не одно, а целая группа метаболических заболеваний, существенно различающихся по распространенности, этиологии, патогенезу и клиническим проявлениям. При СД нарушается не только углеводный, но и многие другие виды обмена веществ (жировой, белковый, минеральный и др.). Это приводит к распространенному поражению сосудов, периферических нервов, центральной нервной системы, а также патологическим изменениям практически во всех органах и тканях. При СД 2 типа, инсулинорезистентность является ключевым фактором патогенеза. Инсулинорезистентность (ИР) приводит к неспособности инсулинзависимых тканей поглощать глюкозу плазмы крови и нарушению синтеза гликогена в печени. Так же дисфункция β-клеток поджелудочной железы с дефектом секреции инсулина влияет на патогенез СД 2 типа. На фоне прогрессирующей дисфункции β-клеток преодоление ИР становится все менее достижимым, что в итоге приводит к появлению ключевого симптома - хронической гипергликемии. Позднее, уже на фоне неадекватной регуляции глюконеогенеза в печени возникает повышение гликемии натощак. Данный тип диабета возникает, главным

образом, на фоне избыточной массы тела и недостаточной физической активности. До недавнего времени диабет этого типа наблюдался лишь среди взрослых, однако в настоящее время он все чаще поражает детей и подростков.

Сахарный диабет 2 типа, эндотелиальная дисфункция и сосудистые осложнения. Эндотелиальная дисфункция как типовой патологический процесс является ключевым звеном в патогенезе многих заболеваний и их осложнений [2].Эндотелиальной дисфункции можно отразить в виде трёх взаимодополняющих процессов: смещение равновесия регуляторов-антагонистов, нарушение реципрокных взаимодействий в системах с обратной связью, образование метаболических и регуляторных «порочных кругов», изменяющих функциональное состояние эндотелиальных клеток, что приводит к нарушению функций тканей и органов [3]. СД 2 типа имеет особое значение в инициации и развитии эндотелиальной дисфункции. На ранних этапах развития СД 2 типа активизирует каскад изменений в сосудистой стенке, включающих нарастание оксидативного стресса, низкоинтенсивного воспаления и нарушения гемостаза, нарушающих нормальное функционирование эндотелия [4]. В настоящее время известны различные патофизиологические механизмы, реализующие атерогенные эффекты СД 2 типа. Одним из важнейших факторов, присущих СД независимо от типа, служит хроническая гипергликемия. Так, увеличение уровня гликированного гемоглобина на 1% ведет к увеличению риска ССО на 11-16% [5]. Установлено, что острая и хроническая гипергликемия способствует развитию эндотелиальной дисфункции и снижению биодоступности оксида азота, что приводит к увеличению лейкоцитарной адгезии к эндотелиальной сосудистой выстилке и трансмиграции иммунокомпетентных клеток в субинтимальное пространство [6,7]. С точки зрения иммуновоспалительного каскада гипергликемия, помимо активации лейкоцитарной адгезии, ведет также к активации клеток миелоидного ростка, в том числе макрофагов, которые являются ключевыми иммунокомпетентными клетками в развитии атеросклероза [8]. Роль хронической гипергликемии в развитии и прогрессировании микрососудистой осложнений и макроангиопатий была неоднократно и убедительно продемонстрирована в многоцентровых исследованиях. Было показано, что макроваскулярный риск возрастает уже на этапе формирования инсулинорезистентности еще до развития собственно диабета. Гипергликемия и ряд других факторов, оказывает повреждающее действие на сосудистую стенку на уровнях микро- и макроциркуляции [9]. Таким образом, эндотелиальная дисфункция является одним из ключевых связующих звеньев между атеросклерозом и сахарным диабетом 2 типа. Еще одним мощным, самостоятельным фактором риска формирования микро- и макрососудистых осложнений СД2 признаны атерогенные изменения липидного спектра крови. По разным данным частота дислипидемии среди пациентов с СД 2 типа составляет 72-85% [10]. Дислипидемия, которая отмечается по меньшей мере у половины больных с СД, является самостоятельным мощным фактором риска макроангиопатий. Наиболее характерные для диабета изменения липидного спектра крови это гипертриглицеридемия (ТГ), снижение уровня холестерина липопротеидов высокой плотности (ЛПВП-ХС), а также повышение холестерина липопротеидов очень низкой плотности (ЛПОНП-ХС) и холестерина липопротеидов низкой плотности (ЛПНП-ХС). Еще одной отличительной «диабетической» чертой является окислительная модификация ЛПНП-ХС частиц, которая облегчает их захват артериальной стенкой и тем самым способствует прогрессированию атеросклероза [11,12]. Многие исследователи считают артериальную гипертензию одним из наиболее значимых факторов риска, так как повышение АГ приводит к повреждению эндотелия током крови. Центральным звеном в патогенезе атерогенной дислипидемии, артериальной гипертензии и СД 2 типа является ИР и хроническая гипергликемия. При СД 2 типа развитие артериальной гипертензии и дислипидемии в 50–70% случаев предшествует нарушениям углеводного обмена.

Биомаркеры сосудистых осложненийМаркеры воспаления и повреждения эндотелия. Гибель клеток сопровождается развитием воспалительной реакции с выбросом провоспалительных и компенсаторно, противовоспалительных медиаторов. Наиболее изученными белками острой фазы воспаления в настоящее время являются С-реактивный белок (СРБ), интерлейкин-6 (ИЛ-6), фактор некроза опухоли альфа (ФНО-α) и ряд других белков. С-реактивный белок – это гликопротеин, вырабатываемый печенью под действием противовоспалительных цитокинов (интерлейкина-1, фактора некроза опухолей – альфа и в особенности интерлейкина-6) и относящийся к белкам острой фазы воспаления. Повышенный уровень СРБ, отражает активность воспаления во внутренней оболочке сосудов и является достоверным признаком

атеросклероза. Некоторые исследования указывают на то, что пациенты с повышенным СРБ и нормальными ЛПНП имеют больший риск развития сердечно-сосудистых заболеваний, чем пациенты с нормальным СРБ и высокими ЛПНП. Относительно повышенный уровень СРБ даже при нормальном уровне холестерина у практически здоровых лиц позволяет прогнозировать риск возникновения гипертонической болезни, инфаркта миокарда, инсульта, внезапной сердечной смерти, сахарного диабета 2-го типа и облитерирующего атеросклероза периферических сосудов. Интерлейкин-6 относится к семейству цитокинов с молекулярной массой 26 кДа и реализует свое действие в различных тканях . ИЛ 6, принимает активное участие в регуляции сосудистого воспаления, развитии и прогрессировании атеросклеротического поражения сосудов. Предполагают, что увеличение уровня ИЛ 6 более адекватно, чем повышение концентрации СРБ, отражает риск множественного атеросклеротического поражения коронарных артерий [13]. ИЛ 6 является предиктором эндотелиальной активации и дисфункции. P.H. Dessein и соавт [14]. ФНО-α является внеклеточным белком, который синтезируется моноцитами и макрофагами. Гиперпродукцией цитокинов, в том числе ФНО-α, связано увеличение риска развития атеросклероза и ассоциируемых с ним сосудистых осложнений [15]. ФНО-α приводит к эндотелий-зависимой вазодилятации и инициирует воспаление в сосудистой стенке [16]. Проатерогенный эффект собственно ФНО-α включает промоцию миграции лейкоцитов к эндотелию, увеличение синтеза молекул адгезии и хемоатрактанта, увеличение капиллярной проходимости [17]. В опыте на крысах былопоказано, что под действием цитокина происходят активация НАД(Ф)Н-оксидазы с последующим производством О2 и блокирование активации NO-синтетазы в эндотелии, что также вносит свой вклад в развитие его дисфункции [18]. Проспективное популяционное исследование EPIC (Prospective Investigation into Cancer and Nutrition Potsdam Study) засвидетельствовало, что повышение сывороточных уровней провоспалительных цитокинов, ФНО-α, интерлейкина-1 (ИЛ-1) и ИЛ-6 увеличивает риск развития и является важным фактором в патогенезе сахарного диабета 2-го типа (СД 2) [19]. Как известно клетки жировой ткани вырабатывает адипоцитокинов, помимо этого продуцируют и белки, преимущественно синтезируемые макрофагами, в том числе ФНО-α. Кроме того, при ожирении в жировой ткани локализуются не только адипоцитокины, но и скапливаются макрофаги, которые, вероятно, могут вносить существенный «вклад» в синтез провоспалительных цитокинов и поддержание хронического системного воспаления[20]. Адипонектин- обладает противовоспалительным и антиатерогенным действием. Низкие концентрации адипонектина приводят к ИР, АГ и эндотелиальной дисфункции. Адипонектин в сосудистом русле циркулирует в виде многомеров с различной молекулярной массой. Существует 2 вида рецепторов к адипонектину: 1 тип рецептора расположены в мышцах и эндотелиальных клетках, а рецепторы 2 типа – в печени. Так же в отличие от других адипокинов, уровень адипонектина обратно пропорционален количеству жировой ткани в организме. В эндо-телиоцитах человека имеются рецепторы к адипонектину. Дефицит данных рецепторов сопровождается снижением продукции NO и фосфорилирования NO-синтетазы (eNOS), вызывая вазодилатацию. Было выявлено, что адипонектин стимулирует продукцию NO эндотелиальными клетками аорты крупного рогатого скота, мышей, пупочной вены человека [21]. Высокомолекулярные формы адипонектина подавляют апоптоз эндотелиоцитов. Таким образом, гипер-адипонектинемия оказывает протективный эффект на сосудистый эндотелий. Адипонектин снижает накопление липидов в макрофагах и подавляет ихтрансформацию в пенистые клетки. Кроме того, адипонектин подавляет стимулированную окисленными липопротеидами пролиферацию клеток [22]. Так же, он снижает привлечение моноцитов к сосудистой стенке, подавляя экспрессию молекул адгезии эндотелиоцитами. Лептин -оказывает влияние на атерогенез, неоангиогенез и тромбогенез [23], стимулирует сосудистое воспаление, оксидативный стресс, гипертрофию гладкомышечных клеток (ГМК) сосудов, тем самым принимая участие в патогенезе СД 2 типа, артериальной гипертонии (АГ), ИБС и их осложнений. Доказано, что лептин стимулирует активность липопротеинлипазы, увеличивает накопление холестерина липопротеидов низкой плотности (ХСЛПНП) в пенистых клетках, способствуя быстрому формированию атеросклеротической бляшки, особенно при наличии гипергликемии. В нескольких исследованиях продемон-стрирована обратная связь между концентрацией лептина в плазме крови и уровнем холестерина липопротеидов высокой плотности (ХС ЛПВП) и аполипопротеина А, обладающих антисклеротическим действием. Кроме того, при гипергликемии лептин замедляет выведение холестерина из сосудистого русла, уменьшает концентрацию ХС ЛПВП, таким образом,

усугубляет дислипидемию у пациентов с СД 2 типа [24]. В ряде исследований доказано, что лептин стимулирует секрецию фактора некроза опухоли-α (ФНО-α), интерлейкинов 2 и 6 (ИЛ-2, ИЛ-6) и других цитокинов, увеличивает синтез и накопление свободных радикалов, а также продукцию этого протеина моноцитами, вызывающего их миграцию и адгезию на сосудистую стенку [25]. Лептин стимулирует выработку трансформирующего фактора роста (TGF-β) эндотелиальными клетками, стимулирующего выработку ингибитора активатора плазминогена (PAI-I), тем самым потенцируя атеротромбоз [26] В физиологических концентрациях лептин стимулирует синтез СРБ в гепатоцитах [27], также показа на положительная корреляция лептина и СРБ.

GDF-15 роль в патогенезе СД 2 типа. GDF-15 принадлежит к суперсемейству трансформирующих факторов роста бета (TGFβ), который экспрессируется в низких концентрациях в большинстве органов и активируется из-за повреждения органов: печень, почки, сердце и легкие. Основные функции GDF-15 в регулировании воспалительных путей и участие в регуляции апоптоза, восстановления и роста клеток, которые являются биологическими процессами, наблюдаемыми при сердечно-сосудистых и неопластических заболеваниях. Это вызванный стрессом цитокин, который также выделяется макрофагами, гладкомышечными клетками сосудов, кардиомиоцитами, адипоцитами и эндотелиальными клетками после повреждения тканей, аноксии и реакций провоспалительных цитокинов. GDF-15 играет роль эндокринного фактора, если присутствует в кровотоке [28]. GDF-15 высоко экспрессируется в ответ на различные виды цитокинов и факторов роста, таких как интерлейкин-1 (ИЛ-1), ФНО-α, ангиотензин II и TGF-β. GDF-15 продуцируется в форме пропептида. N-конец отщепляется и высвобождается в виде дисульфидно-связанной димерной активной формы белка [29]. Прямой молекулярной биологической мишенью GDF-15 является белок p53, который индуцируется окислительным стрессом и оказывает антиапоптотическое действие на клетки-мишени. Этот эффект тесно связан с фактором транскрипции 3, активирующим белок выживания (ATF3), который негативно регулируется экспрессией белка p53. Таким образом, GDF15 ингибирует N-концевую киназу c-Jun, промотор смерти, связанный с Bcl-2, и рецептор эпидермального фактора роста, а также активирует различные внутриклеточные сигнальные пути, например Smad, эндотелиальную синтазу оксида азота (eNO), фосфоинозитид-3-киназу и серин / треонинкиназа. Конечным результатом этой взаимосвязи является подавление как фактора некроза опухоли альфа, так и синтеза ИЛ-6. Адипоцитокины у лиц с ожирением могут способствовать активации p53 в жировой ткани и приводить к инсулинорезистентности и СД2. Пока неясно, зависит ли проапоптотическая способность GDF-15 от типа тканей. В целом, GDF15 может действовать как защитный, антиапоптотический, иногда и проапоптотический фактор, при этом способствует росту ткани, созреванию и дифференцировке различных клеток. GDF-15 может быть независимым маркером сердечно-сосудистой дисфункции и сердечно-сосудистых заболеваний у пожилых. В популяции СД2 уровень GDF-15 в сыворотке положительно ассоциировался с индексом массы тела, телесным жиром, уровнем глюкозы натощак, гликированным гемоглобином, индексом инсулинорезистентности, соотношением талии к росту, возрастом, артериальным давлением, триглицеридами, креатинином, глюкозой, СРБ, диабетической нефропатии, анемии [30]. GDF15– один из маркеров эндотелиальной дисфункции, ухудшения эхокардиографической систолической функции левого желудочка [31] и заболевания периферических артерий [32]. GDF15 защищает сердце от повреждения и является биомаркером, отражающим воспаление и окислительный стресс, но не фактором патогенеза ССЗ. Плазменные уровни GDF15 сильно зависят от динамического вклада несердечных тканей и отражают риск сердечной недостаточности как следствие других основных заболеваний, таких как метаболический синдром [33].

Профилактика новых инновационных препаратов при сосудистых осложнений СД 2 типа. Одной из глобальных проблем мирового здравоохранения считается стремительное увеличение распространенности сахарного диабета (СД) 2 типа. Системные сосудистые осложнения признаны самыми опасными последствиями заболевания. Поэтому снижение риска развития микро и макро сосудистых осложнений СД 2 типа является важной терапевтической целью. Новые инновационные сахароснижающие препараты, к которым преимущественно относятся агонисты рецепторов глюкагоноподобного пептида 1 (арГПП-1), ингибиторы дипептидилпептидазы 4 (иДПП-4) и ингибиторы натрий-глюкозного котранспортера 2 (иНГЛТ-2) способны управлять не только гликемией, но и другими факторами сердечно-сосудистого риска.

Которые являются самыми распространенными факторами риска развития макрососудистых осложнений при СД 2 типа признаны ожирение, дислипидемия, артериальная гипертензия. Среди инновационных сахароснижающих препаратов занимают агонисты рецепторов ГПП-1. В среднем лекарственные средства из данной группы понижают уровень HbA1c на 1–1,5%[34] Кроме сахароснижающего действия арГПП-1 обладают множеством негликемических плейотропных эффектов. За счет ингибирования моторики желудка и подавления аппетита они способствуют снижению веса[35]. Помимо влияния на уровень HbA1c, и веса ученные оценили положительные кардиоваскулярные действия. арГПП-1 снижают содержание общего ХС, ЛПНП, триглицеридов и увеличивают уровень ЛПВП, влияниет на эндотелиальную дисфункцию и окислительный стресс (улучшение микроциркуляции, увеличение синтеза NO, подавление окисления ЛПНП); антигипертензивное действие (нормализация АД в нескольких исследованиях арГПП-1, не зависящая от динамики массы тела и гликемии); антиатеросклеротический эффект (уменьшение размеров атеросклеротических бляшек, торможение пролиферации гладкомышечных клеток сосудов). В алгоритме многих зарубежных стран ингибиторы НГЛТ-2 рекомендованы как приоритетные при наличии у пациентов сердечной недостаточности, а арГПП-1 – при преобладании признаков атеросклеротического сердечно-сосудистого процесса. Согласно последним рекомендациям, пациентам с диабетом Ингибиторы натрий-глюкозного котранспортера 2-го типа (иНГЛТ-2) представляют собой группу сахароснижающих препаратов с принципиально новым механизмом действия, которая заключается в блокировании SGLT2- глюкозо-натриевого транспортного белка, расположенного в почечных канальцах и обеспечивающего реабсорбцию организмом глюкозы. Длительный прием указанных препаратов сопровождается уменьшением массы тела на 2–3 кг вследствие утилизации жиров в качестве источника энергии и потери 200–300 ккал/сут с мочой. Ингибиторы НГЛТ-2, как правило, повышают уровень ЛПНП; уменшает уровня маркеров воспаления и окислительного стресса, способствующих прогрессированию атеросклероза это важно учитывать, поскольку пациенты с СД находятся в зоне повышенного риска сердечно-сосудистых заболеваний [36]. Ингибиторы дипептидилпептидазы-4 (ДПП-4)- новая группа сахароснижающих препаратов, механизм действия которых основан на инкретиновом эффекте. Инкретинами являются глюкозозависимый инсулинотропный полипептид (ГИП) и глюкагоноподобный пептид-1 (ГПП-1). Они играют роль в инсулиновом ответе на прием пищи, стимулируют высвобождение инсулина бета-клетками и угнетают продукцию глюкагона альфа-клетками поджелудочной железы в ответ на повышение глюкозы крови. Так же повышают концентрацию инсулина, способствуя утилизации глюкозы периферическими тканями; уменьшают высвобождение глюкозы печенью, стимулируют высвобождение инсулина бета-клетками и угнетают продукцию глюкагона альфа-клетками поджелудочной железы в ответ на повышение глюкозы крови. Повышают концентрацию инсулина способствуя утилизации глюкозы периферическими тканями, уменьшают высвобождение глюкозы печенью. Секреция фермента дипептидилпептидазы-4 тесно связанно с повышением концентрации глюкозы в эндотелиальных клетках микрососудистого русло. Таким образам ингибирование фермента глиптинами повышает не только антигипергликемический но и ангиопротекторный эффект.

Литература:

1. https://www.who.int/ru/news-room/fact-sheets/detail/diabetes
2. Курапова М.В., Низямова А.Р., Ромашева Е.П., Давыдкин И.Л. Эндотелиальная дисфункция у больных хронической болезнью почек // Известия Самар. науч. центра РАН. — 2013. — Т. 15, №3–6. — С. 1823– 1826. [Kurapova M.V., Nizyamova A.R., Romasheva E.P., Davydkin I.L. Endothelian dysfunction at patients with kidneys chronic disease. Izvestiya Samarskogo nauchnogo tsentra Rossiyskoy akademii nauk. 2013; 15 (3–6): 1823–1826. (In Russ.)] 7. Лупи
3. Петрищев Н.Н. Патогенетическое значение дисфункции // Омск. науч. вестн. — 2005. — №13 (1). — С. 20–22. [Petrishchev N.N. Pathogenic meaning of the dysfunction.
4. Sena, C.M. Endothelial dysfunction — A major mediator of diabetic vascular disease / C.M. Sena, A.M. Pereira, R. Seiça // Biochimica et Biophysica Acta. – 2013. – Vol. 1832. – P. 2216–2231.
5. Low Wang, C. Clinical Update: Cardiovascular Disease in Diabetes Mellitus Atherosclerotic Cardiovascular Disease and Heart Failure in Type 2 Diabetes Mellitus – Mechanisms, Management, and Clinical Considerations / C. Low Wang, C.N. Hess, W.R. Hiatt [et al.] // Circulation. – 2016. – Vol. 133, Is. 24. – P. 2429-2502.

6. Perkins, J.M. Acute effects of hyperinsulinemia and hyperglycemia on vascular inflammatory biomarkers and endothelial function in overweight and obese humans / J.M. Perkins, N.G. Joy, D.B. Tate // Am. J. Physiol Endocrinol Metab. – 2015. – Vol. 309. – P. E168–E176.
7. Smolock, A.R. Protein kinase C upregulates intercellular adhesion molecule-1 and leukocyte-endothelium interactions in hyperglycemia via activation of endothelial expressed calpain / A.R. Smolock, G. Mishra, K. Eguchi [et al.] //Arterioscler Thromb Vasc Biol. – 2011. – Vol. 31. – P. 289–296.
8. Nishizawa, T. Diabetic vascular disease and the potential role of macrophage glucose metabolism / T. Nishizawa, K.E. Bornfeldt // Ann. Med. – 2012. – Vol. 44. – P. 555–563.
9. Ceriello, A. Point: postprandial glucose levels are a clinically important treatment target / A. Ceriello // Diabetes Care. – 2010. – Vol. 33. – P. 1905–1907.
10. Vergès, B. Pathophysiology of diabetic dyslipidaemia: where are we? / B. Vergès // Diabetologia. – 2015. – Vol. 58 (5). – P. 886–899.
11. National Diabetes Statistics, 2011 [Электронный ресурс] - The NationalDiabetes Information Clearinghouse (NDIC).Режимдоступа:http://www.talkondiabetes.org/docsTOD/DM_Statistics_2011.pdf
12. Демидова, Т.Ю. Сосудистые осложнения сахарного диабета 2 типа за гранью гликемического контроля / Т.Ю. Демидова // Сахарный диабет. — 2010. — № 3.— С. 111—116.
13. Kuo L.T., Yang N.I., Cherng W.J. Serum interleukin-6 levels, not genotype, correlate with coronary plaque complexity. Int Heart J 2008;49(4):391–402.
14. . Dessein P.H., Joffe B.I. Suppression of circulating interleukin-6 concentrations is associated with decreased endothelial activation in rheumatoid arthritis. Clin Exp Rheumatol 2006;24(2):161–7.
15. Насонов Е.Л. Иммунологические маркеры атероклероза. Тер. архив, 2002, 5, 80-5.
16. Chia S., Quadan M., Newton R. et al. Intra-arterial tumor necrosis factor-alpha impairs endothelialdependent dilatation in humans. Arterioscler. Thromb. Vasc. Biol., 2003, 23, 695-701.
17. Libby P., Ridker P.M., Maseri A. Inflammation and atherosclerosis. Circulation, 2002, 105, 1135-43.
18. Dessein P.H., Joffe B.I. Suppression of circulating interleukin-6 concentrations is associated with decreased endothelial activation in rheumatoid arthritis. Clin Exp Rheumatol 2006;24(2):161–7.
19. Spranger J., Kroke A., Mohlig M. et al. Inflammatory Cytokines and the Risk to Develop Type 2 Diabetes. Results of the Prospective Population-Based European Prospective Investigation into Cancer and Nutrition(EPIC)-Potsdam Study. Diabetes, 2003, 52, 812-7
20. Weisberg S.P., McCann D., Desai M. et al. Obesity is associated with macrophage accumulation in adipose tissue. J. Clin. Invest., 2003, 112, 1796-1808.
21. Ouchi N, Ohishi M, Kihara S, et al. Fssociation of hypoadiponectinemia with impaired vasoreactivity // Hypertension2003; 42: 231-234.
22. Iwashima Y, Katsuya T, Ishikawa K, et al. Hypoadiponectinemia is an Independent Risk Factor for Hypertension // Hypertension 2004; 43: 1318-1323.
23. Beltowski J. Leptin and atherosclerosis // Atherosclerosis 2006; 189: 47–60.
24. Lundasen T, Liao W, Angelin B, et al. Leptin induces the hepatic high density lipoprotein receptor scavenger receptor B type I (SRBI)but not cholesterol 7_-hydroxylase (Cyp7a1) in leptin deficient (ob/ob) mice // J Biol Chem 2003; 278: 43224–43228.
25. Yamagishi SI, Edelstein D, Du XL, et al. Leptin induces mitochondrial superoxide production and monocyte chemoattractant protein-1 expression in aortic endothelial cells by increasing fatty acid oxidation via protein kinase A // J Biol Chem 2001; 276: 25096–25100.
26. Wolf G, Hamann A, Han DC, et al. Leptin stimulates proliferation and TGF-beta expression in renal glomerular endothelial cells: potential role in glomerulosclerosis // Kidney Int 1999; 56: 860–872.
27. Chen K, Li F, Li J, et al. Induction of leptin resistance through direct interaction of C-reactive protein with leptin // Nat Med 2006; 12: 425–432.
28. N.Ferrari, U.Pfeffer, R. Dell'Eva, C. Ambrosini, D. M. Noonan, and A. Albini, "The transforming growth factor-β family members bone morphogenetic protein-2 and macrophage inhibitory cytokine-1 as mediators of the antiangiogenic activity of N-(4-hydroxyphenyl) retinamide," Clinical Cancer Research, pp. 4610–4619, 2005
29. Фоли П.У, Стегеманн Б, Рамачандран С, Праудлер А. и др. (2009) Фактор дифференциации роста-15 позволяет прогнозировать смертность и заболеваемость после сердечной ресин-

хронизирующей терапии.
30. Lind L. Wallentin L. Kempf T. Tapken N. Quint A. (2009) Growth differentiation factor-15 is an independent marker of cardiovascular dysfunction and disease in the elderly: results of a prospective study of the vascular network in the elderly in Uppsala (PIVUS). Eur Heart J 30: 2346-2353.
31. Stenemo M, Nowak C, Byberg L et al. Circulating proteins as predictors of incident heart failure in the elderly. Eur J Heart Fail. 2018;20(1):55–62. doi: 10.1002/ejhf.980.
32. Jirak P, Mirna M, Wernly B et al. Analysis of novel cardiovascular biomarkers in patients with peripheral artery disease (PAD). Minerva Med. 2018 Apr 12. doi: 10.23736/S0026–4806.18.05628–8.
33. Du W, Piek A, Schouten EM et al. Plasma levels of heart failure biomarkers are primarily a reflection of extracardiac production. Theranostics.2018;8(15):4155–4169. doi: 10.7150/thno.26055.
34. George C., Byun A., Howard-Thompson A. New injectable agents for the treatment of type 2 diabetes part 2-glucagon-like peptide-1 (GLP-1) agonists. Am. J. Med. 2018; 131(11): 1304–6. DOI: 10.1016/j.amjmed.2018.05.04
35. Hinnen D. Glucagon-like peptide 1 receptor agonists for type 2 diabetes. Diabetes Spectr. 2017; 30(3): 202–10. DOI: 10.2337/ds16-0026
36. Nauck M.A., Del Prato S., Meier J.J. et al. Dapagliflozin Versus Glipizide as Add-on Therapy in Patients With Type 2 Diabetes Who Have Inadequate Glycemic Control With Metformin: A randomized, 52-week, double-blind, active-controlled noninferiority trial // Diabetes Care. – 2011. – Vol. 34, №9. – P. 2015-2022.

CLINICAL AND HISTOCHEMICAL CHARACTERISTICS OF PATIENTS WITH BENIGN DYSPLASIA OF THE MAMMARY GLANDS

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Purpose: study the features of the clinical and histological characteristics of women with hyperprolactinemia.

Materials and methods: We have studied 106 women aged 21 to 68 years (average age 44,5) with histologically confirmed breast lesions. All 106 patients underwent a clinical examination, which included the study of complaints, anamnesis, palpation of the mammary glands, as well as histological examination. Because of this goal, the patients were checked by the immunochemiluminescence assay in RSSPMCE named after academician Y. H. Turakulov under the leadership on the level of prolactin, estradiol, thyroid-stimulating hormone, free thyroxine, and ultrasound diagnostics of the mammary glands. All patients were consulted by mammologists, and all patients underwent MRI of the hypothalamic pituitary region.

Results: According to the tasks, 110 women underwent the puncture biopsy of the mammary glands and in 102 cases (main group) (92.7%) benign a dysplasia of the mammary glands was found, and in 8 cases (7.2%) malignant lesions were revealed, which made up the comparison group. The average prolactin level ranged from 70 to 120 ng / ml (with a norm of 1 to 27 ng / ml). Among the benign dysplasia of mammary glands, fibroadenoma predominated in 51 patients (50%), cystic mastopathy was in 15 patients (14.7), and fibrocystic mastopathy in 36 patients, which corresponds to (35.2%). Most cases out of the 51 of fibroadenoma were noted between the ages of 30 and 40. In 26 (50.9%) cases out of 51 cases of fibroadenomas, , the formation was localized in the left mammary gland, in the right mammary gland in 17 patients (36.1%) and bilateral fibroadenoma of the mammary glands were in 8 cases (17.02%). It should be noted that the majority of cases (69.6%) of fibroadenoma were located in the upper outer quadrant.

Conclusion: The role of prolactin in benign dysplasia, as well as in human breast cancer, is now becoming more and more clearly defined. Epidemiological data clearly shows that both pre- and post-menopausal women with high serum prolactin levels have a significantly increased risk of developing these diseases. Thus, self-diagnosis primarily depends on the woman herself, on her vigilance and conscientious attitude towards preventive examinations, and contemporary methods of medical diagnostics allows to identify all breast diseases at an early stage.

Key words: benign dysplasia of the mammary glands., hyperprolactinemia, fibroadenoma, fibrocystic mastopathy.

КЛИНИКО-ГИСТОХИМИЧЕСКАЯ ХАРАКТЕРИСТИКА ПАЦИЕНТОК С ДИСГОРМОНАЛЬНОЙ ДИСПЛАЗИИ МОЛОЧНЫХ ЖЕЛЕЗ

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Цель исследования: изучить особенности клинико-гистологической характеристики женщин с гиперпролактинемией.

Материал и методы исследования: Мы изучили 106 женщин в возрасте от 21 года до 68 лет (средний возраст составил 44,5 лет) с гистологически подтвержденным поражением молочной железы. Все 106 пациенток были подвергнуты клиническому обследованию, которое включало изучение жалоб, анамнеза, производилась пальпация молочных желез, а также гистологическому исследованию в городском онкологическом диспансере. В силу поставленной цели пациентам в РСНПМЦЭ имени Я. Х. Туракулова методом ИХЛА был

проверен уровень пролактина, эстрадиола, тиреотропного гормона, тироксина свободного а также была проведена ультразвуковая диагностика молочных желез. Все пациенты были проконсультированы врачами маммологами, по необходимости- онкомаммологами, а также все пациенты проходили магнитно-резонансную терапию гипоталамо-гипофизарной области.

Результаты: Согласно поставленным задачам 110 женщин были подвергнуты пункционной биопсии молочных желез и в 102 случая (основная группа) (92,7%) обнаружилась доброкачественная дисплазия молочных желез, а в 8 случаях (7,2%) выявлены злокачественные поражения, которую составили группу сравнения. Средний уровень пролактина колебался от 70 до 120нг/мл (при норме от 1 до 27 нг/мл). Среди ДДМЖ в большинстве преобладала фиброаденома у 51 пациента (50%), кистозная мастопатия была у 15 пациентов (14,7), и фиброзно-кистозная мастопатия у 36 пациенток, что соответствует (35,2%). Из 51 случая фиброаденомы, большинство случаев были отмечены в возрасте от 30 до 40 лет. Из 51 случая фиброаденом- в 26 (50,9%) случаев образования локализовались в левой молочной железе, в правой молочной железе у 17 пациенток (36,1%) и двусторонняя фиброаденома молочных желез были в 8 случаях (17,02%). Следует отметить, что большинство случаев (69,6%) фиброаденома располагалась в верхнем внешнем квадранте.

Выводы: Роль пролактина в доброкачественной дисплазии, а также в раке молочной железы человека в настоящее время становится все более четко определенной. Эпидемиологические данные ясно показывают, что у женщин как до, так и после менопаузы с высоким уровнем пролактина в сыворотке крови значительно повышен риск развития данных заболеваний. Таким образом, самодиагностика прежде всего зависит от самой женщины, от ее бдительности и сознательного отношения к профилактическим осмотрам, а современные методы медицинской диагностики позволяют выявить все заболевания молочной железы на ранней стадии.

Ключевые слова: дисгормональная дисплазия молочных желез, гиперпролактинемия, фиброаденома, фиброзно-кистозная мастопатия.

КЎКРАК БЕЗЛАРИ ДИСГОРМОНАЛ ДИСПЛАЗИЯЛИ БЕМОРЛАРНИ КЛИНИК-ГИСТОКИМЁВИЙ ХУСУСИЯТЛАРИ

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Тадқиқот мақсади: гиперпролактинемияли аёлларни клиник-гистокимёвий хусусиятларини ургани ш.

Материал ва услублар: Биз 21 ёшдан 68 ёшгача (ўртача ёш 44,5 ёшни ташкил қилди) бўлган кўкрак безлари зарарланиши гистологик тасдиқланган 106 та аёлларни ўргандик. Барча 106 бемор шикоят, анамнез, кўкрак безлари пальпацияси хамда шахар онкология диспансерида гистологик текширув каби клиник текширувлардан ўтган. Қўйилган мақсад асосида беморлар академик Ё.Х. Тўрақулов номидаги РИЭИАТМда ИХЛА усули ёрдамида пролактин, эстрадиоа, тиреотроп гормон, эркин тироксин миқдорлари текширилди хамда кўкрак безлари ультратовуш ташхисоти ўтказилди. Барча беморлар маммолог шифокорлар томонидан, зарур холларда онкомаммологлар томонидан консультация қилинган хамда барча пациентларда гипоталамо-гипофизар сохаси магнит резонанс томографияси ўтказилган.

Натижалар: Қўйилган топшириқ асосида 110 та аёлда кўкрак безлари пункцион биопсияси ўтказилган ва шулардан 102 холатда (асосий гурух) (92,7%) кўкрак безлари яхши сифатли дисплазияси аниқланган, 8 холатда (7,2%) эса ёмон сифатли зарарланиши аниқланган (солиштирма гурух). Пролактин ўртача миқдори 70 дан ё120 нг/мл гача (нормада 1 дан 27 нг/мл гача). ЯДКБ лар орасида 51 беморда (50%) фиброаденома, кистоз мастопатия 15 та беморда (14,7%) ва фиброз-кистоз мастопатия 36 беморда (35,2%) аниқланди. Фиброаденомали 51 та беморлар асосан 30-40 ёшда бўлган ва 26 (50,9%) холатда хосила чап кукракда, 17 (36,1%) холатда ўнг кўкракда ва икки томонлама фиброаденома 8 (17,02%) холатда аниқланди.

Хулоса: Пролактиннинг яхши сифатли дисплазия хамда кўкрак бези ракидаги ўрни хозирги вақтда кўпроқ ўрганилмоқда. Эпидемиологик маълумотлар шуни кўрсатадики, аёлларда менопауза ва менопаузадан кейинги даврда пролактин миқдорининг юқорилиги ушбу касаллик ривожланиш хавфини оширади. Шундай қилиб, ўз-ўзига ташхис қўйиш аввалambор аёлнинг ўзига, унинг эътиборига ва профилактик кўрикдан ўтиб туришига боғлиқ, замонавий тиббий ташхис усуллари эса кўкрак безлари барча касалликларини эрта босқичларида аниқлай олади.

Калит сўзлар: кўкрак безлари дисгормонал дисплазияси, гиперпролактинемия, фиброаденома, фиброз-кистоз мастопатия

Introduction: Recently, one of the frequent complaints that we hear from women of all age groups is discomfort and pain in the mammary glands. One category of women pays a lot of attention to it. They ask to make an additional examination. While others try to be treated with folk remedies, or do not pay attention to it at all. Unfortunately, a fairly large group of women considers the temporary pain of mammary glands to be natural and for a long time they do not go to the specialist, thereby aggravating their condition. Benign breast diseases present to be a heterogeneous group and include abnormalities, epithelial and stromal proliferation, inflammatory lesions, and neoplasms. Benign breast lesions deserve attention because of their high distribution, their impact on women life, and because of the cancer potential of some histological types (5). Mastopathy or disharmonic dysplasia of the mammary glands is a fibrocystic disease, characterized by a defection of the ratio of epithelial and connective tissue components, a wide range of proliferative and regressive changes in breast tissue. The frequency of mastopathy of the general population of women is 30-45%, and 50-60% of the population of women with gynecological diseases. It is known that mastopathy relates to benign, but patients with mastopathy are considered as a high risk group of the cancer occurrence. Since, according to data of the literature, breast cancer (BC) occurs 3-5 times oftener with the benign breast diseases and 30-40 times oftener with some forms of nodular mastopathy (5). The mammary glands are the first to form among all glands of ectodermal origin already on the sixth week of gestation. The development of the girls begins at the age of 8-10 years and is realized mainly due to the supporting and peri glandular stroma. (8) The growth of the parenchyma is activated in the second phase of puberty, after menarche, when the proliferation of the alveolar and ductal epithelium increases. The beginning of the growth of the mammary glands marks the beginning of puberty, and the assessment of their development as a secondary sex characteristic is mandatory for a pediatrician, gynecologist, endocrinologist, as well as all specialists, who provide therapeutic and prophylactic care to adolescent girls (1,2). A woman's mammary glands are like a "mirror of the endocrine system" and closely depends on the level of hormones, among which prolactin plays a huge role. The prolactin effect on the mammary gland consists in the effect on the growth of the gland, initiation and stimulation of milk secretion (6,7). Under the influence of prolactin, the development of ducts of the primary ductal system and the onset of mammary gland development and the prolactin secretion of girls are being determined at the age of 4-7 and 9-11. In puberty, the prolactin secretion increases again, the ducts of the mammary gland lengthen and become branched, forming the glandular lobules. During pregnancy, under the influence of prolactin, the number of alveoli, lobules, ducts increases, the size of the glands increases, and it reaches full morphological maturity (4). The role of prolactin in the pathogenesis of benign breast dysplasia (BPD) is extremely important: on the one hand, an increase of the hormone level can only be a marker of central disturbances in the reproductive function regulation system, on the other hand, its excess has a direct stimulating effect on the development of proliferative processes in the mammary glands, realized by increasing the content of estradiol receptors in breast tissue, increasing the sensitivity of cells to the action of estradiol, as well as accelerating the growth of epithelial cells, leading to the development of benign dysplasia of the mammary glands. (8). According to various studies, the development of hyperplastic processes in the mammary glands ranges from 38% to 52% of patients with hyperprolactinemia. The X-ray characteristics of the state of the mammary glands in hyperprolactinemia differs depending on the origin of hyperprolactinemia - organic (micro- and macroadenomas of the pituitary gland) or functional. Thus, in most cases, benign dysplasia of the mammary glands**.** is a hormone-dependent pathology, and the treatment of the disease, the prevention of breast cancer should begin with the therapy of the base endocrine disease (9).

Materials and methods: We have studied 106 women aged 21 to 68 years (average age 44,5) with histologically confirmed breast lesions. All 106 patients underwent a clinical examination, which included the study of complaints, anamnesis, palpation of the mammary glands, as well as histological

examination at the city oncological dispensary under the leadership of Gulrukh Kamilzhanovna. Because of this goal, the patients was carried out at the Republican Specialized Center of Endocrinology named after Y. Kh. Turakulov on the level of prolactin, estradiol, TSH, free thyroxine, by the by the immunochemiluminescence assay under the guidance of Saodat Khozhaakbarovna, and ultrasound diagnostics of the mammary glands (ultrasound doctor Rasulova Muniz). All patients were consulted by mammologists, and all patients underwent MRI of the hypothalamic pituitary region.

Results and discussions: According to the tasks, 110 women underwent the puncture biopsy of the mammary glands and in 102 cases (main group) (92.7%) benign a dysplasia of the mammary glands was found, and in 8 cases (7.2%) malignant lesions were revealed, which made up the comparison group. The average prolactin level ranged from 70 to 120 ng / ml (with a norm of 1 to 27 ng / ml). Among benign dysplasia of mammary glands, fibroadenoma predominated in 51 patients (50%), cystic mastopathy was in 15 patients (14.7), and fibrocystic mastopathy in 36 patients, which corresponds to (35.2%). Of the 51 cases of fibroadenoma, most cases were noted between the ages of 30 and 40. Out of 51 cases of fibroadenomas, in 26 (50.9%) cases, the formation was localized in the left mammary gland, in the right mammary gland in 17 patients (36.1%) and bilateral fibroadenoma of the mammary glands were in 8 cases (17.02%). It should be noted that the majority of cases (69.6%) of fibroadenoma were located in the upper outer quadrant. Out of the 102 cases, 70 patients (68.6%) did not complain of breast tenderness in everyday life. In the remaining 32 patients, mastodynia was the leading complaint both on palpation and independently.

In the comparison group, which was consisted of 4 (3.9%) women, who had a benign phylloid tumor. These patients were 21-30 years old (2 cases), 51-60 years old (1 case) and 31-40 years old (1 case). The youngest woman was 26 years old, and the oldest was 58 years old. 3 lesions were found in the right breast and 1 in the left. Overall, the tumor size was 5 to 10 cm in diameter. Microscopically, these formations were characterized by stromal hyperplasia and elongated clefts of the epithelial cover. The hypercellular stroma consisted of spindle-shaped cells without pleomorphism, which were located perpendicular to the lining epithelium in the subepithelial regions of leaf-like structures.

Out of the 102 benign breast lesions, 15 (14.7%) had fibrocystic disease, which were distributed so: in the 3rd decade - 9 patients (60%), and 6 patients (40%) of the 4th decade, while the right breast was affected in 8 (53.3%) patients, and the left - in 7 (46.6%) patients. The microscopic picture consisted of cyst formations, fibrosis, epithelial hyperplasia with chronic inflammation. In our study, we found 1 case of sclerosing adenosis, which accounted for 1% of all benign lesions in a 47-year-old woman who had a small, mobile tumor in her left mammary gland, which was microscopically composed of dense fibrous connective tissue. In 3 cases (2.9%) benign lesions of the mammary glands turned out to be granulomatous mastitis, and was observed in women mainly at the age of 30 years.

Thus, benign dysplasia of the mammary glands is a common pathology of the mammary glands. Self-palpation of the mammary glands and health education of women from school age are very important for the early treatment with a doctor, what will further contribute to the timely provision of care to patients. Benign dysplasia of the mammary glands is most often observed in the age group from 20 to 40 years old. Fibroadenoma is the most common benign breast disease. Most patients do not have any complaints of discomfort or acute pain in the mammary glands. Histopathology plays an important role in the diagnosis, outcome and prognosis of benign breast disease. By comparing clinical data, mammography and ultrasound data, histopathological examination led to early diagnosis of benign breast diseases.

The incidence of benign breast diseases begins to rise in the 2nd decade and peaks in the 3rd or 4th decades comparing to the malignant lesions. Fibroadenoma (46.07%) was the most common lesion among benign breast lesions. Fibroadenomas are more common at the age of 30 (50.9%), mainly affecting the left mammary gland. Self-diagnosis primarily depends on the woman herself, on her vigilance and conscientious attitude towards preventive examinations, and modern methods of medical diagnostics make it possible to identify all breast diseases at an early stage, and, therefore, to preserve to the woman not only health, but also beauty.

Conclusion:

1. Among BMD, in the majority cases the fibroadenoma prevailed in 51 patients (50%), and out of 51 cases of fibroadenoma, the most were noted between the ages of 30 and 40 years.

2. Out of 51 cases of fibroadenomas, mainly in 26 patients (50.9%), the formations were localized in the left mammary gland. Here it should be noted that the most cases (69.6%) of fibroadenomas were located in the upper outer quadrant.

3. Out of the 102 cases, 70 patients (68.6%) did not complain at all about the breast pain in everyday life.

References:

1. Jacobs A, Abou-Dakn M, Becker K, et al. S3-Leitlinie „Therapie entzündlicher Brusterkrankungen in der Stillzeit“ Senologie - Zeitschrift für Mammadiagnostik und -therapie. 2014;11:50–56.

2. Lee SJ, Trikha S, Moy L, et al. ACR Appropriateness Criteria evaluation of nipple discharge. J Am Coll Radiol: JACR. 2017;14:138–153

3. Mansel R.E., Webster D.J.T., Sweetland H.M. Breast pain and nodularity // Benign Disorders and Diseases of the Breast. Philadelphia : Elsevier, 2009. P. 107–139.

4. Orr B, Kelley JL 3rd. Benign breast diseases: evaluation and management. Clin Obstet Gynecol. 2016;59:710–726

5. Андреева Е.Н., Хамошина М.Б., Руднева О.Д. Пролактин и молочные железы: норма и патология // Гинекология. 2012. Т. 14, № 6. С. 12–16.

6. Балан В.Е. Коррекция различных состояний, обусловленных гиперпролактинемией, растительными препаратами // Consilium Medicum. 2007. Т. 9, № 6. С. 80–84. 11.

8. Веропотвелян П. Н., Веропотвелян Н.П., Бондаренко А.А. Влияние пролактина на состояние молочных желез // Мед. аспекты здоровья женщины. 2011. № 3/1(43). С. 29–37. 12.

9. Гуркин Ю. А. Гинекология подростков: руководство для врачей. — СПб.: Фолиант, 2000. — 574 с.

10. Сергеева Н.И., Дзеранова Л.К., Меских Е.В. Участие пролактина в формировании фиброзно-кистозной мастопатии. Пролактин и нормопролактинемическая галакторея // Акуш. и гин. 2005. № 2. С. 13–15.

FUNCTIONAL STATE OF THE HYPOTHALAMIC-PITUITARY-ADRENAL AXIS IN OPERATED WOMEN PATIENTS WITH CUSHING'S SYNDROME AFTER SURGICAL TREATMENT

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Health of the Republic of Uzbekistan named after Acad. Y.H. Turakulov

Summary

Under the supervision of employees of the Department of Neuroendocrinology and Neurosurgery of the RSSPMC of Endocrinology of MoH of RUZ in the Republic of Uzbekistan and in the Republic of Karakalpakstan regarding Cushing's Syndrome, from 2000 to the present, 163 patients of child-bearing age are registered. The average age was 27.58 ± 3.4 years (17 to 49 years). The duration of the disease averaged 4.2 ± 0.2 years. 20 healthy women of the corresponding age made up the control group. All female patients with CS registered since 2000 (deceased are not included) were distributed according to etiology as follows: 1 g. - patients with ACTH-dependent CS– 130 (79.7%), 2 g. - with ACTH-independent CS - 30 (18.4%) and group 3 - patients with ACTH-ectopic CS - 3 (1.8%).

Before treatment, women with CS in group 1 showed a significant increase in the basal values of ACTH, cortisol, prolactin against the background of hyperandrogenemia and ovarian failure ($p < 0.05$). In patients with CS of groups 2 and 3, against the background of a significant increase in basal values of cortisol, prolactin, hyperandrogenemia ($p < 0.05$), an insignificant decrease in estradiol and progesterone was observed ($p > 0.05$).

Patients with CS with surgical treatment in groups 1, 2 after 1 month following the operation showed normalization of ACTH and cortisol levels, and after 6 months the condition remained almost the same, $p < 0.05$.

A year after surgical treatment, we established normal levels of blood hormones - ACTH, LH, FSH, cortisol, prolactin in patients of all three groups.

Key words: cushing's syndrome, ACTH-dependent, ACTH-independent, ACTH-ectopic, hypothalamic-pituitary-adrenal axis, surgical treatment.

«ФУНКЦИОНАЛЬНОЕ СОСТОЯНИЕ ГИПОТАЛАМО-ГИПОФИЗАРНО-НАДПОЧЕЧНИКОВОЙ ОСИ У ОПЕРИРОВАННЫХ ЖЕНЩИН С СИНДРОМОМ КУШИНГА ЧЕРЕЗ 1, 3, 6 МЕСЯЦЕВ ПОСЛЕ ХИРУРГИЧЕСКОГО ЛЕЧЕНИЯ»

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Под руководством сотрудников отдела нейроэндокринологии и нейрохирургии РГППМК эндокринологии МЗ РУз по Республике Узбекистан и Республике Каракалпакстан по поводу синдрома Кушинга, с 2000 года по настоящее время зарегистрировано 163 пациента детородного возраста. Средний возраст составил 27,58 ± 3,4 года (от 17 до 49 лет). Длительность заболевания в среднем составила 4,2 ± 0,2 года. 20 здоровых женщин соответствующего возраста составили контрольную группу. Все пациенты женского пола с СК, зарегистрированными с 2000 года (умершие не включены), были распределены по этиологии следующим образом: 1 г. - пациенты с АКТГ-зависимой CS– 130 (79,7%), 2 г. - с АКТГ-независимой КС - 30 (18,4%) и 3-й группой - пациенты с АКТГ-эктопической КС - 3 (1,8%).

До лечения у женщин с КС в 1-й группе наблюдалось значительное увеличение базальных значений АКТГ, кортизола, пролактина на фоне гиперандрогенемии и недостаточности яичников ($p < 0,05$). У пациентов с КС групп 2 и 3 на фоне значительного увеличения базальных значений кортизола, пролактина, гиперандрогенемии ($p < 0,05$) наблюдалось незначительное снижение эстрадиола и прогестерона ($p > 0,05$).

У пациентов с ХС с хирургическим лечением в группах 1, 2 через 1 месяц после операции отмечалась нормализация уровня АКТГ и кортизола, а через 6 месяцев состояние оставалось практически таким же, $p < 0,05$.

Через год после хирургического лечения мы установили нормальный уровень гормонов

крови - АКТГ, ЛГ, ФСГ, кортизол, пролактин у пациентов всех трех групп.

Ключевые слова: синдром Кушинга, АКТГ-зависимый, АКТГ-независимый, АКТГ-эктопический, гипоталамо-гипофизарно-надпочечниковая ось, хирургическое лечение**.**

«JARROHLIK DAVOLASHDAN KEYIN 1, 3, 6 OYLIK KUSHING SINDROMI BO'LGAN OPERATSIYA QILINGAN AYOLLARDA GIPOTALAMUS-GIPOFIZ-ADRENAL O'QNING FUNKTSIONAL HOLATI».

Xalimova Z.Yu., Irgasheva O. B.

O'zbekiston Respublikasi va Qoraqalpog'iston Respublikasida O'zR Sog'liqni saqlash vazirligi Endokrinologiya RSSPMC Neyroendokrinologiya va neyroxirurgiya bo'limi xodimlarining nazorati ostida Kushing sindromi bo'yicha 2000 yildan hozirgi kungacha 163 ta tug'ish yoshidagi bemorlar ro'yxatga olingan. O'rtacha yosh 27,58 ± 3,4 yoshni tashkil etdi (17 dan 49 yoshgacha). Kasallikning davomiyligi o'rtacha 4,2 ± 0,2 yilni tashkil etdi. Nazorat guruhini tegishli yoshdagi 20 sog'lom ayol tashkil etdi. 2000 yildan beri ro'yxatga olingan CS kasalligi bo'lgan ayollarning barchasi (marhumlar kiritilmaydi) etiologiyaga qarab quyidagicha taqsimlandi: 1 g. - ACTHga bog'liq bo'lgan CS - 130 (79,7%), 2 g. - ACTH mustaqil CS bilan - 30 (18,4%) va 3-guruh - ACTH-ektopik CS bilan og'rigan bemorlar - 3 (1,8%).

Davolanishdan oldin, 1-guruhdagi CS bilan og'rigan ayollar giperandrogenemiya va tuxumdonlar etishmovchiligi fonida ACTH, kortizol, prolaktinning bazal qiymatlarining sezilarli darajada oshganligini ko'rsatdilar ($p < 0.05$). 2 va 3 guruhdagi CS bilan og'rigan bemorlarda kortizol, prolaktin, giperandrogenemiyaning bazal qiymatlarining sezilarli darajada oshishi fonida ($p < 0.05$), estradiol va progesteronning ahamiyatsiz pasayishi kuzatildi (0,05-bet).

Jarrohlik yo'li bilan davolangan 1, 2 guruhlardagi CS bilan og'rigan bemorlar operatsiyadan keyingi 1 oydan keyin ACTH va kortizol darajasining normallashganligini ko'rsatdilar va 6 oydan keyin ahvoli deyarli o'zgarmadi, $p < 0.05$.

Jarrohlik davolashdan bir yil o'tgach, biz har uch guruhdagi bemorlarda qon gormonlari - ACTH, LH, FSH, kortizol, prolaktin miqdorini aniqladik.

Kalit so'zlari: Kushing sindromi, AKTG-bog'liq, AKTG-bog'liqmas, AKTG-ektopik, gipotalamus-gipofizar-buyrak usti bezi, jarrohlik davo.

Thematic justification. Back in 1989, Manusharova R.A. was one of the first to provide data on the functional state of the HPA axis system in 119 women with Cushing's syndrome in the active stage, the stage of stable clinical remission, and after total adrenalectomy. It was established that the most significant changes in the ratio of hormones of the pituitary gland, adrenal glands, and uterus were found in the active stage of the disease, which lead to the Menstrual disorder as a hypomenstrual syndrome, polycystic ovarian degeneration and infertility. In a state of stable remission after treatment and after adrenalectomy, it was found that the hypothalamic-pituitary-adrenal relationships are gradually restored, leading to the restoration of the menstrual cycle and fertility [11].

In 1957 Magiakou MA, Mastorakos G., Webste E. were among the first to show that HPA axis and the female reproductive system are interconnected and exhibit complex relationships, HPA axis has a mainly inhibitory effect on the reproductive axis with using corticotropin-releasing hormone (CRH) and CRH-induced propiomelanocortin peptides that inhibit the secretion of gonadoliberins in the hypothalamus, and with glucocorticoids that inhibit the secretion of LH, as well as estrogen and progesterone. Estrogen-targeted tissues, such as the endometrium, are resistant to the gonadal steroid. These effects of the HPA axis are responsible for the "hypothalamic" amenorrhea of stress, depression and eating disorders, as well as for hypogonadism due to Cushing's syndrome . Conversely, estrogens directly stimulate the CRH gene, contributing to significant hypercorticism and the predominance of depressive, anxiety and eating disorders in women. It is interesting that some components of the HPA axis and their receptors are present in reproductive tissues, such as ovarian and endometrial CRH, can participate in inflammatory processes of the ovary, that is, in ovulation and luteolysis, as well as in implantation and the menstrual cycle. Finally, hypercorticism in the second half of pregnancy can be explained by a high level of plasma CRH in the placenta. This hypercorticism causes transient suppression of the adrenal glands in the postpartum period, which may explain postpartum depression

and autoimmune phenomena of this period [12].

Then in 1998, Chrousos GP, Torpy DJ, Gold P W. described how the HPA axis exerts a deep, multi-level inhibitory effect on the female reproductive system. Corticotropin releasing hormone (CRH) and CRH-induced proopiomelanocortin peptides inhibit the secretion of the hypothalamic gonadotropin releasing hormone, while glucocorticoids inhibit the production of pituitary LH and estrogen and progesterone by the ovaries and make target tissue resistant. Thus, the HPA axis is responsible for "hypothalamic" amenorrhea of stress, which is also observed with melancholic depression, malnutrition, eating disorders, chronic active alcoholism, chronic excessive physical exertion and hypogonadism of Cushing's syndrome [6].

Sexual disorders caused in most cases by the development of hypogonadism induced by hypercortisolism are detected in 60% of men and 80% of women. In men, spermatogenesis is impaired, emasculation phenomena are detected with a decrease in the size of the genital organs, a decrease in libido and potency. In women, the generative function and the menstrual cycle are violated, up to persistent amenorrhea, primary and secondary infertility [1-5].

Ovarian changes in Cushing's syndrome are characterized in most cases as involutive-atrophic and are manifested by moderate sclerosis of the protein coat and cortical layer, a decrease in the number of primordial follicles. In Cushing's syndrome, a number of observations reveal sclerocystic ovarian degeneration, sometimes with a significant increase in their size. The latter suggests the possibility of a combination of Cushing's syndrome with polycystic ovary syndrome, which is confirmed to a certain extent by the nature of changes in the endometrium [6-12].

The restoration of menstrual function in women and potency in men according to the observations of a number of authors [13, 14] occur in most patients with Cushing's syndrome already in the first 3 months of remission. Repeated violation of sexual function indicates a relapse of the disease, and in women, a possible pregnancy. A sharp increase in prolactin levels in the blood does not serve as a prognostic criterion for the development of ACTH-ZSC relapse, but may indicate pregnancy [15-18]. Consequently, the normalization of sexual function involves a remission of the disease, while its repeated violation indicates another relapse of ACTH-ZSC or ACTH-NSK.

All of the above was the reason for the present study.

The objective of the study was to study the functional state of the hypothalamic-pituitary-adrenal axis (HPA) in operated women patients with CS 1, 3, 6 months after treatment.

Material and research methods. Under the supervision of employees of the Department of Neuroendocrinology and Neurosurgery of the RSSPMC of Endocrinology of MOH of the Republic of Uzbekistan and RKK, regarding Cushing's Syndrome, from 2000 to the present, only 308 patients with various forms of CS are registered, 95 of them are men and 213 are women. The average age was 27.58 ± 3.4 years (from 17 to 49 years). The duration of the disease averaged 4.2 ± 0.2 years. 20 healthy women of the corresponding age made up the control group. Table 1 shows the number of patients with Cushing's syndrome in Uzbekistan according to the etiological factor among men and women, including those who died. As can be seen from table 1, women predominated, which corresponds to the literature.

Table 1.

The number of patients with Cushing's syndrome in Uzbekistan by etiological factor among men and women, including the dead

Types of Cushing's syndrome	Men	Women	Total
ACTH-ZSC	80	169	249
ACTH-NSK	12	40	52
ACTH-ESK	3	4	7
Total	95	213	308

Note: ACTH-ZSK - ACTH-dependent SK, ACTH-NSK - ACTH independent SK, ACTH-ESK - ACTH-atropic SK

Next, we divided the patients depending on reproductive age into 2 groups: 1st group of reproductive age (from 18 to 35) and 2nd group of non-reproductive age <35 years).

Table 2

The number of patients of reproductive age (age was considered from 18 to 35 years)

Types of Cushing's syndrome	Reproductive age			Non-reproductive age		
	men	women	total	men	women	Total
ACTH-ZSC	57	115	172	11	39	50
ACTH-NSK	7	35	42	2	5	7
ACTH-ESK	3	2	5	0	2	2
Total	67	153	220	13	45	58

To achieve our goals, we selected 153 women of reproductive age who underwent a complete examination, including general clinical, biochemical studies - a general analysis of blood, urine, blood sugar, lipid spectrum, blood electrolytes (potassium, sodium, chlorides, blood calcium), radioimmunological hormonal research methods blood (adreno-corticotron hormone (ACTH), prolactin, cortisol, estradiol, progesterone, free testosterone, small and large samples with dexamethasone, the rhythm of cortisol secretion), as well as instrumental studies - ECG, X-ray densitometry, ultrasound-genital organs. All patients underwent magnetic resonance imaging of the pituitary gland (MRI) and computed tomography (CT) scan of the adrenal gland. If necessary, an oral glucose tolerance test was performed.

According to the treatment, women were distributed as follows: TPA - 45%, AE - 28%, radiation therapy (RT) -% and drug therapy (MT) - 14%, and combination therapy (CT) - 13%.

All patients with CS received treatment in the Department of Neuroendocrinology and Neurosurgery of the RSSPMC of MoH, RUz named after Acad. Y.H. Turakulov. Transnasal pituitary adenomectomy (TPA) was performed primarily in 93 patients, of which secondary - in 15, a total of 108 TPAs (Prof. Powell M.P. (Great Britain, London), Doctor of Medicine Fayzullaev RB Doctor of Medicine, Makhkamov K.I. and Akbutaev A.M.). Adrenalectomy was performed in only 89 patients, including 10 patients with ACTH-ZSC (Prof. S. Ismailov).

The data obtained were processed using computer programs Microsoft Excel and STATISTICA_6 (136-140). The significance of differences in quantitative indicators (n> 12) was determined by the Wilcoxon method for unrelated ranges, to determine the reliability of small samples (n <12), the non-parametric randomization criterion for Fisher components for independent samples was used, for qualitative values, the exact Fisher-Irwin criterion was used. Differences between groups were considered statistically significant at P< 0,05.

The results of the study. According to the classification of the American Association of Endocrinologists from 2012, all 153 female patients of childbearing age with CS, registered since 2000 (the dead are not included), were distributed by etiology as follows: 1 gr. - patients with ACTH-dependent SC– 115 (75.2%), 2 g. - with ACTH-independent SC - 35 (22.9).

The main goal of treating patients with CS is to achieve remission. Since remission contributes to a decrease in the total mass of fat, it improves cardiovascular RF. It is proved that the level of K in the early postoperative period can be a criterion for predicting relapse of CS in the near and distant periods.

Table 3 shows the activity of the process of hypercorticism in various forms of the disease in women.

Table 3

Characterization of the condition of sick patients of fertile age with CS according to the register (n = 153)

Types of Cushing's syndrome	Active stage	remission	total
ACTH -ZSK	42	73	115
ACTH-NSK	5	30	35
ACTH-ESK	1	1	2
Total	48	105	153

Table 4 presents the functional state of the HPA axis, the levels of ACTH, cortisol and other plasma hormones in the operated patients before surgery and after 1, 3, 6 months following the treatment.

Thus, the analysis of hormonal parameters in patients with CS at the time of diagnosis of the dis-

ease in patients with ACTH-ZSK revealed the following: ACTH varied from 31.8 to 82.4 ng / ml and averaged 57.1 ± 2.99 pg / ml, indicating the apparent presence of ACTH-ZSK. It should be noted that a significant (p <0.01) increase in the level of ACTH was found in all 115 patients with ACTH-ZSK (82.4 ± 4.28), which dictated to us the need for additional visualization methods in order to search for an ectopic focus hypersecretion of ACTH. In patients with ACTH – NSK, ACTH levels remained normal or low and averaged 31.8 ± 0.52 pg / ml.

Table 4 presents the functional state of the HPA axis, the levels of ACTH, cortisol and other plasma hormones in the operated patients before surgery and after 1, 3, 6 months following the treatment.

Table 4

Functional state of the HPA axis, levels of ACTH, cortisol and other plasma hormones in operated women of childbearing age before surgery and 1, 3, 6 months after treatment

Groups	Indicators	Functional state of HPA axis			
		Before operation	After 1 month	After 3 months	After 6 months
1 group **N**=115	ACTH	82,4±4,3*	47,9±5,5*	52,6±4,3	42,2±3,7*
	Cortisol,	934,4±8,3*	436,7±21,3*	723,4±18,3*	545,6±18,7*
	Estradiol	0,14±0,02 *	0,34±0,06 *	0,44±0,04	1,4±0,03
	Progesterone	1,5±0,03 *	8,8±0,02 *	12,5±0,03	31,9±0,04
	Prolactin	17,6 ±0,5	4,6 ±0,3	3,8 ±0,3	3,6 ±0,4
	Fr. T	6,3±0,2*	4,2±0,3*	2,1±0,3*	0,2±0,04
2 group **N**=35	ACTH	51,8 ±0,5	43,4±4,3 *	46,1±3,2 *	47,9±4,6*
	Cortisol	846,5±14,6*	439,8±19,9*	327,6±16,3*	322,1±17,3*
	Estradiol	0,11±0,02*	0,37±0,06	0,35±0,04	1,1±0,03
	Progesterone	6,4±0,2*	10,6±0,3	13,9±0,7	27,6±0,6
	Prolactin	14,8 ±0,8	4,8 ±0,6	3,4 ±0,6	3,2 ±0,3
	Fr. T	7,3±0,3*	2,2±0,6*	0,8±0,04*	0,2±0,05
Control	ACTH pg / ml - up to 50 pg / ml		контроль	21,4 ±0,3	
	Cortisol - from 250 to 720 nmol / l in the morning			272,2 ± 2,3	
	Estradiol, nmol / L			1,3 ±0,3	
	Progesterone, nmol / L			24,5 ±3,2	
	Prolactin, ng / ml			4,2 ±0,4	
	free testosterone, pg/ml			0,3±0,02	

Note: * significance of differences compared with data before treatment, where * is P <0.05 difference with control, in dynamics, Fr. T - free testosterone

As can be seen from table 4, before treatment in women with CS in the 1st group, a significant increase in basal values of ACTH, cortisol, prolactin was observed against the background of hyperandrogenemia and ovarian failure (p <0.05). In patients with group 2 CS, against the background of a significant increase in basal values of cortisol (normal 250-720 nmol / l), prolactin (normal up to 5.7 ng / ml), hyperandrogenemia (normal 0.14-6.3 pg / ml), (p <0.05) there was an unreliable decrease in estradiol and progesterone (p> 0.05).

Thus, the analysis of hormonal parameters in patients with CS at the time of diagnosis of the disease in patients with ACTH-ZSK revealed the following: ACTH varied from 31.8 to 82.4 ng / ml and averaged 57.1 ± 2.99 pg / ml, indicating the apparent presence of ACTH-ZSK. It should be noted that a significant (p <0.01) increase in the level of ACTH was found in all 115 patients with ACTH-ZSK (82.4 ± 4.28), which dictated to us the need for additional visualization methods in order to search for an ectopic focus hypersecretion of ACTH. In patients with ACTH – NSK, ACTH levels remained normal or low and averaged 31.8 ± 0.52 pg / ml.

Table 3

Functional state of the HPA axis, levels of ACTH, cortisol and other plasma hormones in operated women of childbearing age before surgery and 1, 3, 6 months after treatment

Groups	Indicators	Functional state of HPA axis			
		Before operation	After 1 month	After 3 months	After 6 months
1 group N=115	ACTH	82,4±4,3*	47,9±5,5*	52,6±4,3	42,2±3,7*
	Cortisol	934,4±8,3*	436,7±21,3*	723,4±18,3*	545,6±18,7*
	Estradiol	0,14±0,02 *	0,34±0,06 *	0,44±0,04	1,4±0,03
	Progesterone	1,5±0,03 *	8,8±0,02 *	12,5±0,03	31,9±0,04
	Prolactin	17,6 ±0,5	4,6 ±0,3	3,8 ±0,3	3,6 ±0,4
	Св. T	6,3±0,2*	4,2±0,3*	2,1±0,3*	0,2±0,04
2 group N=35	ACTH	51,8 ±0,5	43,4±4,3 *	46,1±3,2 *	47,9±4,6*
	Cortisol	846,5±14,6*	439,8±19,9*	327,6±16,3*	322,1±17,3*
	Estradiol	0,11±0,02*	0,37±0,06	0,35±0,04	1,1±0,03
	Progesterone	6,4±0,2*	10,6±0,3	13,9±0,7	27,6±0,6
	Prolactin	14,8 ±0,8	4,8 ±0,6	3,4 ±0,6	3,2 ±0,3
	Fr. T	7,3±0,3*	2,2±0,6*	0,8±0,04*	0,2±0,05
control	ACTH pg / ml - up to 50 pg / ml		control	21,4 ±0,3	
	Cortisol - from 250 to 720 nmol / l in the morning			272,2 ± 2,3	
	Estradiol, nmol / L			1,3 ±0,3	
	Progesterone, nmol / L			24,5 ±3,2	
	Prolactin, ng / ml			4,2 ±0,4	
	free testosterone, pg/ml			0,3±0,02	

Note: * significance of differences compared with data before treatment, where * is P <0.05 difference with control, in dynamics, Fr. T - free testosterone

According to international standards, we investigated the rhythm of secretion of blood cortisol (C) and daily urine cortisol (DUC). In patients with ACTH - ZSK, despite significantly elevated levels of C, the rhythm of its secretion was maintained throughout the day, tending to decrease in the evening. At the same time, patients with adrenal or ectopic hypercorticism had an irregular rhythm with significantly high (p <0.01) C values at 18:00 - 1185 ± 67.8 nmol / L and 1132 ± 54.8 nmol / L and at 23:00 - 970.7 ± 27.3 and 1482 ± 46.9 nmol / L, respectively, compared with pituitary CS.

Against the background of Large sample with dexamethasone (BPD), blood cortisol levels in patients with ACTH - ZSk were suppressed by 61.3%, ACTH-NSA - 39.2 and ACTH-ESA 33.3%, that is, in patients of the last two groups there was no sufficient suppression of cortisol level, which indicates the presence of an autonomous focus of hypersecretion of cortisol or ACTH, the search for which we conducted in our subsequent stages of work.

So, we established hyperandrogenism and hypercortisolemia in all patients before treatment.

Next, we studied the functional state of the HPA axis, the levels of ACTH and plasma cortisol in the operated patients 1, 3, 6 months after treatment.

In patients of group 1, 1 month after TPA, normalization of ACTH, cortisol, prolactin, estradiol, progesterone and free testosterone levels in plasma was observed, and after 6 months this condition persisted, p <0.05.

In patients of group 2, 1 month after AE, normalization of ACTH, cortisol, prolactin, estradiol, progesterone and free testosterone levels in plasma was observed, and after 6 months the condition remained almost the same, p <0.05.

A year after surgical treatment, we also monitored the levels of blood hormones - LH, FSH, ACTH, cortisol, prolactin in patients in 2 groups.

A year after the operation, 2x from the 2nd group became pregnant. A year after transnasal hypophysectomy, 30 women out of 128 (23.07%) with ACTH-ZSK became pregnant by independence, which indicated the achievement of stable remission, while 13.7 (%) developed relapse. Of the 128 patients, 54 (%), in order to avoid provoking a relapse, SK refrained from planning pregnancy and

were on COCs. In 10 (%) with normal levels of cortisol (101.2 + 535.7 ng / mmol), the absence of clinical symptoms of relapse, as well as regular menstruation, pregnancy did not occur.

It was established that in 73 (63.4%) women with ACTH-ZSK, remission was achieved, in 42 (36.6%) patients in general, remission was not achieved. A high frequency of remission was found in patients with ACTH-NSK, which amounted to 30 (85.7%) cases, and only in 2 cases a relapse of the disease developed due to an unfavorable outcome with the development of metastases after surgery for adrenal carcinoma.

Как As evidenced by the research results of Narimova G.D., in 2018, remission was achieved in 71% of patients with CS in the Republic of Uzbekistan. Moreover, the smallest remission was observed in patients with ACTH – ZSK and amounted to 65.3%, which is consistent with the literature. (Halimova Z.Yu., Narimova G.D., Kurbaniyazova G. Reproductive health of women with Cushing's syndrome // Therapeutic Journal of Uzbekistan. - Tashkent, 2014. - No. 4. - P. 194.)

Summing up our study, I would like to emphasize that out of 115 patients with ACTH-ZSK, remission after (TPA) was achieved in 73 (63.4%) patients, in 16.7% of them developed relapse, in 42 (36.5 %) remission is not achieved. Of the 35 women with ACTH-NSK, remission was achieved in 30 (85.7%) individuals after AE, and 5 (14.3%) did not achieve remission.

The discussion of the results. As you know, the goals of treatment for a patient with CS are remission of hypercorticism, adequate treatment of concomitant diseases, restoration of the hypothalamic-pituitary-adrenal axis, preservation of fertility and pituitary gland function, as well as improvement of visual disturbances in cases of macroadenomas with suprasellar growth. Transsphenoidal pituitary surgery is the main treatment option in most cases, even with macroadenomas with a low probability of remission. In cases of surgical failure, another subsequent operation on the pituitary gland may be indicated in cases with a persistent tumor during post-surgical magnetic resonance imaging (MRI) and / or analysis of the pathology of adrenocorticotropic hormone-positive (ACTH +) positive pituitary adenoma in the first procedure. Medical treatment, radiation therapy, and adrenalectomy are other options when transsphenoid pituitary surgery does not help. There are several treatment options, although cabergoline and ketoconazole are most often used individually or in combination. Various therapeutic approaches are often necessary on an individual basis, both before and especially after surgery, and they must be individualized.

Conclusions. 1) The reproductive status of women with ACTH-ZSK is characterized by a significant increase in basal levels of ACTH, cortisol and prolactin against the background of hyperandrogenemia and ovarian failure compared with healthy ones ($p < 0.05$).

2) In patients with ACTH-NSCA, endogenous hypercorticism was accompanied not only by hyperprolactinemia, hyperandrogenemia ($p < 0.05$), but also by a significant decrease in estradiol and progesterone $p < 0.01$.

3) After TPA, clinical and biochemical remission was achieved in 73 (63.4%), of which 1 year after surgery, pregnancy alone occurred in 11 (7.1%). With normal menstrual cycles and levels of ACTH, cortisol and sex steroids, the planned pregnancy was unsuccessful.

4) Restoring reproductive function and pregnancy in women with CS can serve as a sensitive marker of disease remission.

Bibliography

1. Vetshev P. S., Ippolitov L. I., Vetshev S. P.- Controversial issues and negative trends in the diagnosis and surgical treatment of accidentally detected adrenal tumors // Surgery. 2015. - No. 6. -S.11-25.

2. Kalinin A. P., Maistrenko N. A., Vetshev P. S. / Surgical endocrinology // Guide for doctors. // St. Petersburg: Peter, 2014.

3. Halimova Z.Yu., Narimova GD, Kurbaniyazova G. Reproductive health of women with Cushing's syndrome // Therapeutic Journal of Uzbekistan. - Tashkent, 2014. - No. 4. - P. 194.

4. Abraham SB[1], Abel BS, Rubino D/.A direct comparison of quality of life in obese and Cushing's syndrome patients. //Eur J Endocrinol. 2013 Apr 15;168(5):787-93. doi: 10.1530/EJE-12-1078. Print 2013 May.

5. Badia X[1], Valassi E, Roset M Disease-specific quality of life evaluation and its determinants in Cushing's syndrome: what have we learnt?//Pituitary. 2014 Apr;17(2):187-95. doi: 10.1007/s11102-013-0484-2.

6. Chouros G P, Torpy D J, Gold P W.Interactions Between the Hypothalamic-Pituitary-Adrenal

Axis and the Female Reproductive System: Clinical Implications //Ann Intern Med, 129 (3), 229-40 1998 Aug 1;PMID: 9696732;DOI: 10.7326/0003-4819-129-3-199808010-00012

7.ECrespo I[1], Valassi E[1], Santos A[1], / Health-related quality of life in pituitary diseases.// Endocrinol Metab Clin North Am. 2015 Mar;44(1):161-70. doi: 10.1016/j.ecl.2014.10.013. Epub 2014 Nov 4.

8.Grossman A.B./Clinical Endocrinology//UK, 2009, 556 paes

9.Keil MF[1]. /Quality of life and other outcomes in children treated for Cushing syndrome.//J Clin Endocrinol Metab. 2013 Jul;98(7):2667-78. doi: 10.1210/jc.2013-1123. Epub 2013 May 2.

10.Khalimova Z.Yu., Grossman A.B., Powell M.P., Corbonitz M., Cudlip S.A., Gilkes K.E, Pankiv V.I., Narimova .Dj., Urmanova Yu.M.,"The frequency of reproductive disorders in women with ACTH-depend Cushing Syndrome in the Republic of Uzbekistan (RUz) , Tashkent-city and Republic of Karakalpakstan (RKK).."// 5th ENEA (European Neuroendocrine Association) Workshop Hyperprolactinemia and other endocrine causes of infertility, September 7-9, 2017, Sankt-Petersburg, Russia, Abstract Book, ID P06-14

11.Manusharova R A [Article in Russian] [Disorders of Hypothalamico-Pituitary Regulation of Adrenal and Ovarian Function in Women Suffering From Itsenko-Cushing Disease] //Vrach Delo, (2), 24-7 Feb 1989PMID: 2711656

12.Magiakou, M. A., Mastorakos, G., Webster, E. & Chrousos, G. P. The hypothalamic-pituitary-adrenal axis and the female reproductive system. Ann NY 1997, Acad Sci., 816, 42-56.

13.Nelson LM[1], Forsythe A, McLeod L, /Psychometric evaluation of the Cushing's Quality-of-Life questionnaire.//Patient. 2013;6(2):113-24. doi: 10.1007/s40271-013-0012-5.

14. Neychev V[1], Steinberg SM[2], Yang L. /Long-Term Outcome of Bilateral Laparoscopic Adrenalectomy Measured by Disease-Specific Questionnaire in a Unique Group of Patients with Cushing's Syndrome.// Ann Surg Oncol. 2015 Dec;22 Suppl 3:S699-706. doi: 10.1245/s10434-015-4605-1. Epub 2015 May 13.

15.Santos A[1], Crespo I, Aulinas A, /Quality of life in Cushing's syndrome. //Pituitary. 2015 Apr;18(2):195-200. doi: 10.1007/s11102-015-0640-y.

16.Tiemensma J[1], Depaoli S[2], Felt JM[2]. /Using subscales when scorinthe Cushing's quality of life questionnaire// Eur J Endocrinol. 2016 Jan;174(1):33-40. doi: 10.1530/EJE-15-0640. Epub 2015 Oct 2.

17.Tritos NA, Biller BM, Swearingen B. /Management of Cushing's syndrome. //Nat Rev Endocrinol. 2011;7:279-289

18. Papoian V, Biller BM, Webb SM, /Patients perception on clinical outcome and quality of life after a diagnosis of Cushing Syndrome//Endocr Pract. 2016 Jan;22(1):51-67.

19.Roset M[1], Badia X, Forsythe A, /Mapping CushingQoL scores onto SF-6D utility values in patients with Cushing'ssyndrome.//Patient. 2013;6(2):103-11. doi: 10.1007/s40271-013-0010-7.

EFFECT OF RADIATION THERAPY ON HORMONAL STATUS IN PATIENTS WITH ACROMEGALY DEPENDING ON AGE

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Aim of the study. To assess the effect of radiation therapy on hormonal status in patients with acromegaly, depending on age.

Materials and methods. The object of the study is 94 patients with somatotropic hypertension who received RT. The analysis of the peculiarities of the distribution of patients by age groups showed that the age of 83% of the examined was from 30 to 59 years. The most numerous was the age group 30-44 years old (46,8%), which included 14,9% of men and 31,9% of women. The proportion of women of reproductive age was significantly higher than that of men (37,2 and 19,2%, respectively).

Results and discussion. In all patients with newly diagnosed acromegaly, the concentration of GH and IGF-1 exceeded the permissible reference values corresponding to age. Analysis of changes in hormonal parameters under the influence of RT in dynamics revealed after RT a tendency towards normalization of hormonal metabolism in patients of all four groups. In general, in the post-radiation period, regardless of the age, taking into account their age, according to the level of GH, remission was achieved in 57,4% of patients, which was increased with increasing age ($p = 0,01$), and according to the level of IGF-1, 52% of patients ($p = 0,05$).

The greatest efficiency of RT was established at the age of 60-74 years in females, the duration of acromegaly from 6 to 10 years or more, which was confirmed by the high frequency of achieving remission (83,3%).

Key words: acromegaly, radiation therapy, growth hormone, IGF-1, age.

ВЛИЯНИЕ ЛУЧЕВОЙ ТЕРАПИИ НА ГОРМОНАЛЬНЫЙ СТАТУСА У БОЛЬНЫХ С АКРОМЕГАЛИЕЙ В ЗАВИСИМОСТИ ОТ ВОЗРАСТА

Халимова Замира Юсуповна, Иссаева Саодат Сайдуллаевна.

Цель исследования. Оценить влияние лучевой терапии на гормональный статуса у больных с акромегалией в зависимости от возраста.

Материалы и методы. Объектом исследования являются 94 больные с соматотропными АГ, получавшие ЛТ. Анализ особенностей распределения больных по возрастным группам показал, что возраст 83% обследованных был от 30 до 59 лет. Самой многочисленной оказалась возрастная группа 30-44 лет (46,8%), в которую вошли 14,9% мужчин и 31,9% женщин. Доля женщин репродуктивного возраста была значимо большей, чем мужчин (37,2 и 19,2% соответственно).

Результаты и обсуждение. У всех пациентов с впервые выявленной акромегалией концентрация СТГ и ИФР-1 превышала допустимые референсные значения, соответствующие возрасту. Анализ изменения гормональных показателей под влиянием ЛТ в динамике выявил после ЛТ тенденцию к нормализации гормонального обмена у пациентов всех четырёх групп. В целом в постлучевом периоде независимо от давности с учётом их возраста по уровню СТГ достигли ремиссии у 57,4% больных, который был увеличен с увеличением возраста ($p=0,01$), а по уровню ИФР-1 - 52% больных ($p=0,05$).

Установлена наибольшая эффективность ЛТ в возрасте 60-74 лет у лиц женского пола, продолжительностью акромегалии от 6 до 10 лет и более, которая подтверждалась высокой частотой достижения ремиссии (83,3%).

Ключевые слова: акромегалия, лучевая терапия, гормона роста, ИФР-1, возраст.

АКРОМЕГАЛИЯЛИ БЕМОРЛАРДА НУР ТЕРАПИЯНИ ЁШГА БОҒЛИҚ ХОЛДА ГОРМОНАЛ СТАТУСГА ТАЪСИРИ

Халимова Замира Юсуповна, Иссаева Саодат Сайдуллаевна.

Тадқиқот мақсади: Акромегалияли беморларда нур терапияни ёшга боғлиқ холда гормонал статусга таъсирини бахолаш.

Материал ва услублар: Текширув объекти сифатида нур терапия олган соматотроп гипофиз аденомали 94 бемор олинди. Текширув натижалари шуни кўрсатдики, текширилган беморларнинг 83%и 30 дан 59 ёшгача бўлганлар ташкил қилди. Энг кўп сонли гурух сифатида 30-44 ёшгача (46,8%) беморлар гурухи аниқланди (14,9% эркаклар ва 31,9% аёллар). Репродуктив ёшдаги аёллар эркакларга нисбатан кўп учради (37,2% ва 19,2% мос равишда).

Натижалар ва муҳокама: Янги аниқланган акромегалияли беморларнинг хаммасида ўсиш гормони ва инсулинга ўхшаш ўсиш омили-1 референс миқдори ёшга боғлиқ холда юқори бўлган. Нур терапия таъсири остида гормонал кўрсаткичарни текшириш натижаларидан аниқландики, нур терапиядан кейин 4та ёшга боғлиқ гурухларда гормонал алмашинув нормаллашган. Нур терапиядан кейинги даврда касаллик давомийлигидан қатъий назар ёшга боғлиқ холда ўсиш гормони миқдори бўйича ремиссия 57,4% (p=0,01), инсулинга ўхшаш ўсиш омили-1 миқдори эса 52%(p=0,05) беморларда бемор ёши катталашиши билан ошиб борди. Айтиш мумкинки, нур терапиянинг энг кўп смарадорлиги акромегалия давомийлиги 6-10 йил ва ундан кўп бўлган 60-74 ёшдаги аёлларда аниқланди ва бу ремиссияга эришишнинг кўплиги (83,3%) билан тасдиқланди.

Калит сўзлар: **акромегалия, нур терапия, ўсиш гормони, инсулинга ўхшаш ўсиш омили-1, ёш.**

Introduction. Currently, acromegaly treatments include surgical, drug and radiation treatments [7]. The use of the main methods of treatment (endonasal transsphenoid adenomectomy, primary and secondary drug therapy, stereotactic radiosurgery) increases the quality and duration of patients' life [9].

Despite the fact that medical and surgical therapy is effective in controlling acromegaly, RT is still offered as a valuable choice as a treatment for pituitary adenomas, to achieve remission at the hormonal level, and to control tumor mass [5, 11] in patients with acromegaly [6]. RT is performed in patients with an inoperable tumor, unacceptable hormone levels despite surgical and drug therapy, or progressive tumor growth [2, 7, 8]. Modern radiation therapy includes a complex delivery of ionizing radiation into the target tissue [1, 3, 8]. In the majority of published studies, with conventional RT, tumor growth control is achieved in 85–95% of cases, lowering GH levels by less than 5 ng / ml in almost 80% of cases 10–15 years after RT [4, 7, 10].

In a large retrospective group of 656 patients with acromegaly who received conventional RT by irradiation of the pituitary gland, patients who achieved the target GH level (<2,5 ng / ml) were 22% after 2 years, 36% after 5 years, 60% after 10 years and 74 % after 15 years [12].

Thus, RT is a highly effective method of treating patients with persistent active acromegaly after surgery and / or during conservative therapy.

Purpose of the study. To assess the effect of radiation therapy on hormonal status in patients with acromegaly, depending on age.

Materials and methods. The object of the study is 94 patients with somatotropic hypertension who received RT. All patients received traditional gamma therapy of the hypothalamic-pituitary region by a multi-field-convergent method in a total dose of 45-60 gray in 20-25 fractions every other day, only 2 patients received SRS cyberknife dose 45 gray.

The duration of the disease averaged 9,2 ±7,8 years. The follow-up period after RT was on average 7,36±8,1 years.

To achieve these goals, patients were analyzed by age and divided into groups according to the WHO classification (1982) (Table 1).

The analysis of the peculiarities of the distribution of patients by age groups showed that the age of 83% of the examined was from 30 to 59 years. The most numerous was the age group 30-44 years old (46,8%), which included 14,9% of men and 31,9% of women. The proportion of women of reproductive age was significantly higher than that of men (37,2 and 19,2%, respectively).

Table 1. Age-sex distribution of patients with acromegaly

Age	Men, n=26		Women, n=68		All, n=94	
	Абс	%	Абс	%	Абс	%
16-29	4	4,3	5	5,3	9	9,6
30-44	14	14,9	30	31,9	44	46,8
45-59	7	7,4	27	28,7	34	36,2
60-74	1	1,1	6	6,4	7	7,5
All	26	27,7	68	72,3	94	100

Attention is drawn to the progressive decline in the sample of the number of men over 61 and women over 70. Such features can be explained by the development by this age of complications of acromegaly, which are the cause of premature mortality, as well as lower population survival rate and aggressive course of acromegaly in men [12].

The peak of the manifestation of acromegaly in the general sample was at the most working age in men and women (30-44 years). This testifies to the undoubted social significance of this problem.

All patients underwent a comprehensive examination, including examination by a neuroendocrinologist, neurosurgeon, radiologist and ophthalmologist. General clinical studies were carried out; hormonal studies (study of the basal level of hormones of the pituitary gland and peripheral glands); neuroimaging studies (computed tomography and magnetic resonance imaging of the hypothalamic-pituitary region); neuro-ophthalmological studies (visual acuity, fundus and visual field).

The research materials were subjected to statistical processing using the methods of parametric and nonparametric analysis. Systematization of initial information and visualization results obtained in Microsoft office Excel 2010 tables. Data analysis was carried out using a package of applied programs. Statistical analysis was carried out using the free statistical software "MINITAB" version 14.2.1 and "IBM SPSS Statistics 23".

The median (Me), the 1st and 3rd quartiles (Q1 and Q3) were used as the parameters of the distributions of quantitative features; in the case of their normal distributions, the mean and standard deviations were used; for binary features - absolute and relative frequencies. The Mann-Whitney method was used to compare independent groups by quantitative criteria, and the Wilcoxon test for related groups. To analyze the relationship of qualitative features, a nonparametric McNemar analysis was used.

Results and discussion. The analysis of the results on the effectiveness of radiation therapy in acromegaly, depending on the age of patients in 94 patients.

The time from the moment of manifestation of the first symptoms of the disease in the form of a change in the size of the limbs, the appearance of puffiness, changes in the facial skeleton, noticed by the patient before the diagnosis was on average 3,6±2,7 years with a spread of 1 (the diagnosis was made per year, when the patient suspected him) until the age of 16.

Table 2. Dynamics of growth hormone and IGF-1 during RT, depending on age

Groups / Hormones		1st age group, n=9	2st age group, n=44	3rd age group, n=34	4st age group, n=7
GH (Mme/L)	**Before RT**	64±24,4	79,7±51,3	68,8±44,4	61,2±36,8
	After RT	22,5±20,7	11,3±14	11,3±12,2	14,3±15,6
P		0,008	0,001	0,001	0,018
IGF-1 (ng/ml)	**Before RT**	708±216,9	867,9±272	854,6±275,5	917±315
	After RT	346±166,7	233,6±121,7	232,3±108,2	315,5±172
P		0,021	0,001	0,001	0,018

Note: p is the level of statistical significance of differences in relation to before and after radiation therapy.

In all patients with newly diagnosed acromegaly, the concentration of GH and IGF-1 exceeded the permissible reference values corresponding to age. As described above, the dynamics of changes in hormones - GH and IGF-1 - were assessed before radiation therapy and after RT, depending on age.

The results of the analysis of hormonal parameters depending on age are presented in Table 2.

Analysis of changes in hormonal parameters under the influence of RT in dynamics revealed after RT a tendency towards normalization of hormonal metabolism in patients of all four groups. As the

data in Table 2 show, the highest level of growth hormone content in the pre-radiation period occurred in the age period from 30 to 44 years and amounted to 79,7±51,3 mMe/L, followed by a relatively gradual decrease with increasing age: from 45 to 59 years – 68,8±44,4 mMe/L and from 60 to 69 years old 61,2±36,8 mMe/L. After RT, this indicator was almost equally suppressed in all age groups. But at the same time, a significant decrease in GH fell on the II and III age groups and their average levels were 11,3±14 mMe/L and 11,3±12,2 mMe/L, respectively (p=0,001). In groups I and IV, the decrease in the GH level was 22,5±20,7 mMe/L and 14,3±15,6 mMe/L (p=0,008 and p=0,018), respectively.

The highest IGF-1 level before RT was found in the IV age group from 60 to 79 years old - 917±315 ng/ml and after RT IGF-1 decreased 3 times and amounted to 315,5±172 ng/ml (p = 0,018) ...

In the age group from 45 to 59 years, the average IGF-1 level was 854,6±275,5 ng/ml, after RT there was a significant decrease up to 3,7 times and was 232,3±108,2 ng/ml (p=0,001). A significant decrease in the mean level of IGF-1 was found in age group II, before RT it was 867,9±272 ng/ml and decreased to 233,6±121,7 ng/ml (p=0,001).

According to the results of the study, the level of GH before RT was increased in all patients. Decrease in the level of GH after RT in patients in age group I showed no suppression in 44,4% of patients (on average, 41,1±34,5 mMe/L, p=0,07; Fig. 1). Suppressed, but not to normal in 33,3% of patients (p=0,1). In fact, in patients of age group I, biochemical remission was achieved only in 22,2% of patients, as evidenced by the average levels of GH, which amounted to 1,2±1,14 mMe/L (p=0,12). At the age of 30 to 44 years, it was not suppressed and suppressed, but not to the norm, in 22,7% of patients, with an average level of GH of 12,8±7,8 mMe/L (p=0,03 and p=0,005, respectively) achieved remission of 54,6% (p=0,001). In age group III, after RT, GH did not suppress in 20,6% of patients (p=0,03) and was reduced, but not to the norm in 23,5% of patients (p=0,01). It should be noted that in this age group, a decrease in the level of GH to target values reached 55,9% of patients (p=0,001). At the age of 60 to 74 years, the level of GH was not suppressed in 14,3% of patients (p=0,1) and was reduced, but not to the norm, in 28,6% of patients (p=0,04), remission was achieved 57,1% (p=0,01).

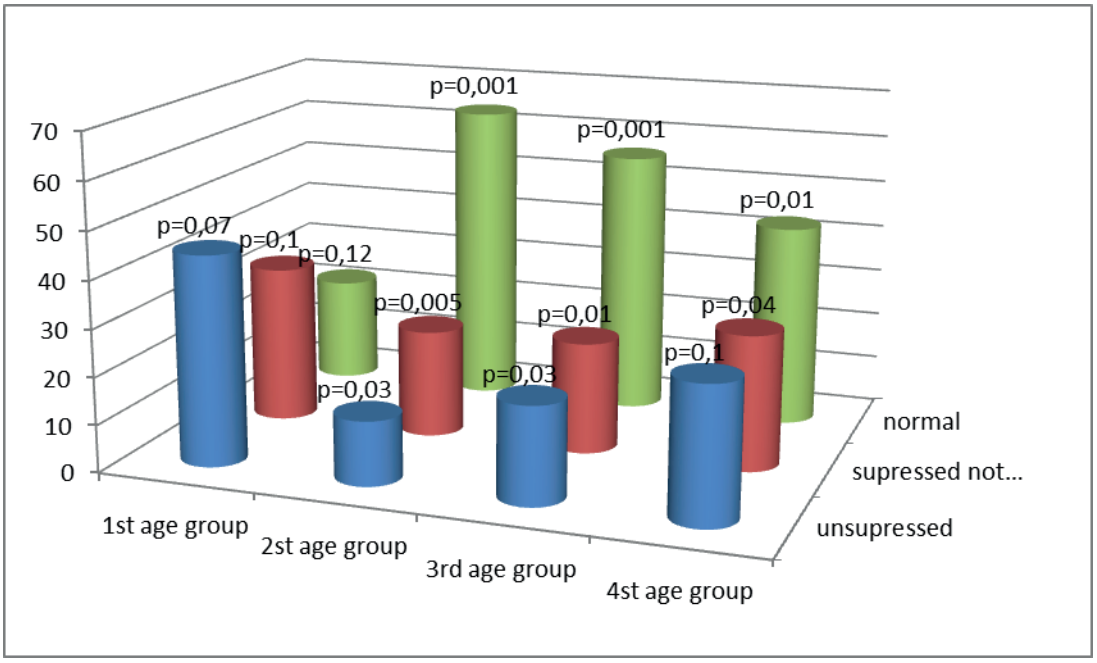

Fig. 1. Normalization of pituitary growth hormone levels during radiation therapy in different age groups

As shown by the results in the post-radiation period, the cases of achieving the target values of the level of GH increased with increasing age, 22,2%, 54,6%, 55,9% and 57,1%, respectively.

It is known that an important criterion for achieving remission in acromegaly is the normalization of the IGF-1 level to the appropriate age norm. Thus, the results of the analysis in age group I showed the absence of suppression of IGF-1 in 55,6% of patients (p=0,10) and in 44,4% there was a decrease to age norms (p=0,05). In age group II – 56,8% vs 43,2% (p=0,001); in group III – 38,2% (p=0,005) and 61,8% (p=0,001); in age group IV 28,6% and 71,4% (p=0,10 and p=0,05), respectively.

In general, in the post-radiation period, regardless of the age, taking into account their age, according to the level of GH, remission was achieved in 57,4% of patients, which was increased with increasing age (p=0,01), and according to the level of IGF-1, 52% of patients (p=0,05).

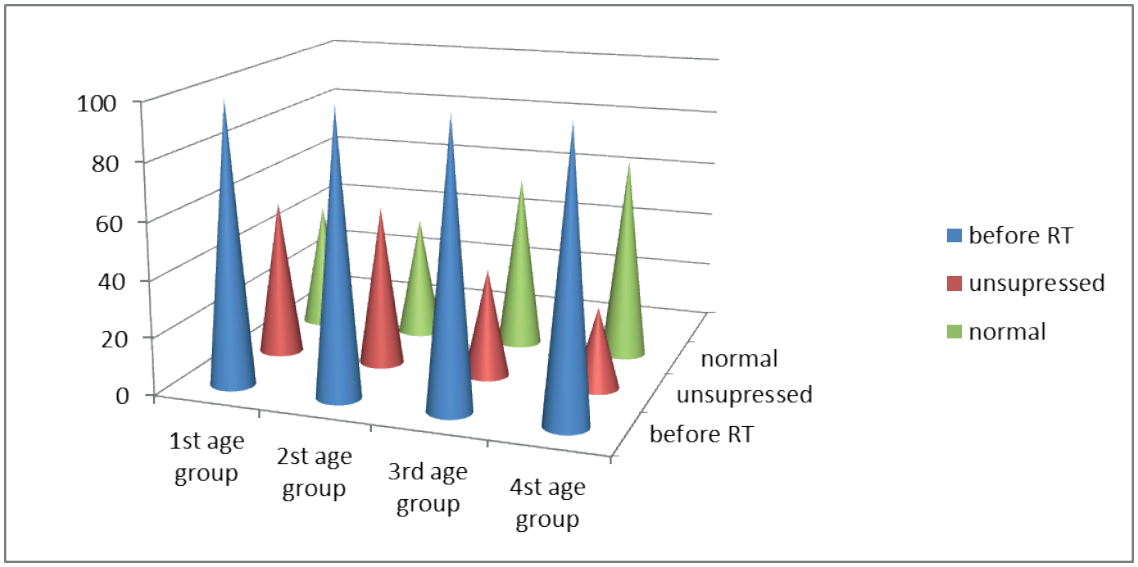

Fig. 2. Normalization of IGF-1 level against the background of RT in different age groups

At the same time, a weak negative correlation according to Pearson was revealed between the age of patients and the level of GH (r=-0,2; p=0,01) and the level of IGF-1 (r=-0,12; p=0,01; Fig. 3).

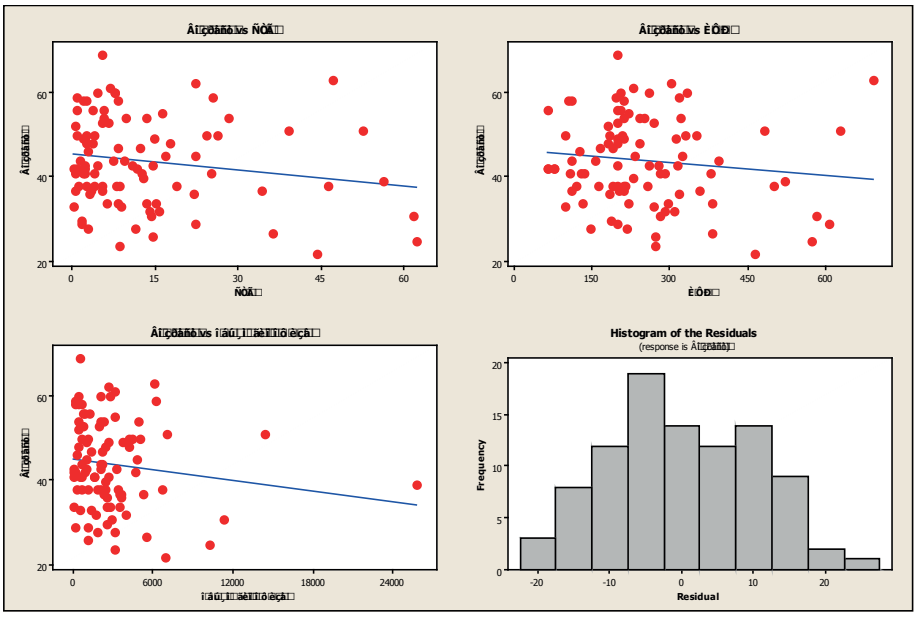

Fig. 3. Correlation analysis between: age-GH, age-IGF-1, age-pituitary gland volume

The studies, the dynamics of the hormonal status of patients before and after radiation therapy, make it possible not only to assess the effectiveness of radiation therapy in general, but also to determine the tactics of further management of patients with acromegaly.

As shown by the results of the study, the use of radiation therapy leads to a significant decrease in the level of growth hormone, IGF-1 and a decrease in the size of the growth hormone in all age periods. In the age period from 30 to 59 years, a significant improvement in the results was observed in the long term after RT (p=0,001) (Fig. 3).

Interesting data were obtained in the study of complications after radiation therapy. The results of the analysis show that the incidence of complications after radiation therapy varies in different age groups. The most common complication of acromegaly after RT was secondary hypothyroidism.

Thus, in age group I before radiation therapy, the frequency of secondary hypothyroidism was 33,3%, and after radiation therapy, their number increased to 55,6%, in group II, 13,6% and 63,6%; in group III before radiation therapy 23,5% and 76,5%; and in group IV, 42,8% and 85,7%, respectively, also the highest rate of secondary hypothyroidism developed precisely in old age. Hypogonadotropic hypogonadism at the age of 16-29 years before RT was not detected, after RT it was detected in 55,6% of patients. At the age of 30-44 years it was found in 31,8% of patients before and in 47,7% after RT. In group III, 38,2 and 52,9%. In group IV, before and after radiation therapy, the same frequency was observed – 71,4%. This is explained by the fact that the long-term effect of RT and in this age segment in persons of both sexes is involutive changes in the gonads.

The decrease in the adrenocorticotrophic function of the pituitary gland in group I before RT was 22,2%, after RT it increased to 33,3%. The highest rate was found in patients aged 45-59 years after RT (38,2%). The incidence of hyperprolactinemia after RT in all groups was increased and amounted to 22,2%, 31,8%, 41,2% and 14,3% in groups I, II, III, and IV, respectively.

Hypopituitarism is the most common late complication of radiation therapy. In group I, it was not detected before RT, after RT it was observed in 44,4% of patients. At the age of 30-44 years before RT, it was revealed in 4,6% of patients and after RT, there was an almost 12,8 one-time increase in this indicator, in the age group 45-59 years, hypopituitarism before and after RT was detected in 5.9% and 58,8 % of patients, respectively, in group III, no cases of hypopituitarism were detected, and after RT, it was detected in 71,4% of patients.

Empty sella syndrome was detected after RT in age groups I, II, III, and IV, 11,1%, 13,6%, 17,7% and 14,3%, respectively.

Partial optic neuropathy (descending atrophy of the optic nerve) before radiation therapy in age group I occurred in 44,4%, after radiation therapy their frequency increased to 55,6%. In group II, this indicator was 45,5% and 54,5%; in the III age group 47,1% and 55,9%, in the IV age group in 42,9% and 71,4% of patients, respectively. In group IV patients after RT, a decrease in visual acuity was observed; visual impairment in them was associated with multiple factors, including age-related changes, with concomitant diseases (arterial hypertension, diabetes mellitus) and the direction of growth of the pituitary adenoma (with suprasellar growth).

Conclusions. According to the analysis of data from 94 patients, 52,1% received RT in combination with drug therapy, 47,9% with surgery. At the same time, the overwhelming majority of patients were persons aged 30-59 years. The greatest efficiency of RT was established at the age of 60-74 years in females, the duration of acromegaly from 6 to 10 years or more, which was confirmed by the high frequency of achieving remission (83,3%).

References

1) Aldallal S. Acromegaly: A challenging condition to diagnose // International Journal of General Medicine. – 2018. №11. – P. 337–343.

2) Barrande L.L.E. [и др.]. Hormonal and Metabolic Effects of Radiotherapy in Acromegaly : Long-Term Results in 128 Patients Followed in a Single Center – 2015. –№ 10 (85). – P. 3779–3785

3) Bashari W.A. [и др.]. Best Practice & Research Clinical Endocrinology & Metabolism Modern imaging of pituitary adenomas Antía Fern a. – 2019. –№ 4. – P. 311-324.

4) Biermasz N.R., Roelfsema F. Long-Term Follow-Up Results of Postoperative Radiotherapy in 36 Patients with Acromegaly // The Journal of Clinical Endocrinology & Metabolism. – 2000. – Vol.85, № 7. – P. 2476–2482.

5) Epaminonda P. [и др.]. Efficacy of radiotherapy in normalizing serum IGF-I , acid-labile subunit (ALS) and IGFBP-3 levels in acromegaly // Clinical Endocrinology. – 2001. – №55,. – P. 183–189.

6) Hannon M.J., Barkan A.L., Drake W.M. The Role of Radiotherapy in Acromegaly // Neuroendocrinology. – 2016. –Vol.103, № 1. – P. 42–49.

7) Kosteljanetz M., Feldt-rasmussen U. Fractionated stereotactic radiotherapy in patients with acromegaly : An interim single– Pentre audit Fractionated stereotactic radiotherapy in patients with acromegaly : an interim single– Pentre audit // European Journal of Endocrinology. – 2015. –№ 12. –P. 685–694.

8) Losa M. [и др.]. The Role of Stereotactic Radiotherapy in Patients with Growth Hormone-Secreting Pituitary Adenoma // J Clin Endocrinol Metab. – 2015. – Vol.93, № 9. – P. 2546–2552.

9) Баркан А. Влияние предоперационной терапии аналогами соматостатина на исход

хирургического лечения СТГ-продуцирующих макроаденом гипофиза : критический анализ // Эндокринная хирургия. – 2018. –№1 (12). -С. 7–18.

10) Жулидова А.Ю. Акромегалия и коморбидные состояния. новые возможности диагностики и лечения (обзор литературы) // Российский медико-биологический вестник имени академика И.П. Павлова. – 2018. – Vol.26, №1. – P. 117-132.

11) Пронин В.С., Пронин Е.В. Международные Консенсусные Соглашения по Диагностике и Лечению Акромегалии // Журнал для непрерывного медицинского образования врачей. – 2019. –№1. – С. 49–62.

12) Халимова З. Ю., Иссаева С. С. Современные подходы лучевой терапии при соматотропиномах // Лучевая диагностика и терапия – Санкт-Петербург, 2019. - № 4. - С. 72–76.

«ПРОГНОЗИРОВАНИЯ РЕЦИДИВА АКТГ ЗАВИСИМОГО СИНДРОМА КУШИНГА У БОЛЬНЫХ В ГРУППЕ ВЫСОКОГО РИСКА»

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Транссфеноидальная аденомэктомия (ТАГ) является выбором лечения для лечения АКТГ ЗСК. Однако степень рецидива является значительным, и в настоящее время нет конкретных предикторов его прогнозирования. Хотя существует традиционный метод прогнозирования послеоперационных уровней базального кортизола, накопленные данные свидетельствуют о его недостаточности. Это требует разработки дополнительных альтернативных тестов, включая необходимость тестирования десмопрессина на каждом хирургическом центре.

Ключевые слова: ТАГ, рецидив, критерии ремиссии.

“ЮКОРИ ХАВФ ГУРУХИГА КИРУВЧИ БЕМОРЛАРДА АКТГ ГА БОГЛИК КУШИНГ СИНДРОМИНИ КАЙТАЛАНИШИНИ ТАХМИН КИЛИШ”

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Акад. Ё.Х. Туракулов номидаги Республика
Ихтисослашган илмий амалий тиббиёт маркази

Транссфеноидал аденомэктомия (ТАГ) –бу АКТГ БКС ини даволашнинг танлов давоси хисобланади. Аммо, кайталаниш сезиларли даражада ва хозирги даврда уни башорат килишнинг аник предикторлари мавжуд эмас. Операциядан кейинги базал кортизол микдори башорат килишнинг анъанавий усули булсада, тупланган далиллар уни етарли эмаслигини курсатмокда. Бу кушимча альтернатив тестларни ишлаб чикишни, шу жумладан хар бир жаррохлик марказида десмопрессинли синама куллашни талаб килади.

Калит сўзлар: Транссфеноидал аденомэктомия, кайталаниш, ремиссия критериялари

“PREDICTING RELAPSE OF ACTH –DEPENDENT CUSHING SYNDROME IN PATIENTS AT HIGH RISK”

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Transsphenoidal adenomectomy (TSS) is the treatment of choice for the treatment of ACTH DCS. However, the recurrence is significant and there are currently no specific predictors of its prediction. Although there is a traditional method of predicting postoperative basal cortisol levels, the accumulated evidence suggests that it is insufficient. It requires the development of complementary alternative tests, including the use of desmopressin in every surgical center.

Keywords: Transphenoidal adenomectomy, recurrence, remission criteria

Prevelance of the study:

ACTH dependent Cushing’s syndrome (ACTH DCS) is a severe endocrine pathology caused by chronic hypercorticism due to excessive secretion of adrenocorticotropic hormone (ACTH) by the pituitary adenoma [1, 3].

The incidence of ACTH DCS is about 1.2-2.4 new cases per 1 million people per year [5], mostly young people get involved - the average age at the time of diagnosis is about 30-40 years, more often women - the ratio of women to men is about 8: 1 [13]. As the epidemiological studies conducted in the Republic of Uzbekistan show, today the incidence of CS is 0.68 per 100 thousand population [15-22]. According to Narimova G.D. et al., the probable incidence of CS in the Republic of Uzbekistan should be 37 new cases annually [17]. From 2002 to 2017, a total of 34 deaths were recorded in patients with

CS, 31 (91.2%) of patients with ACTH-DCS and 3 (8.8%) with ACTH-IDCS cases, the causes of which were mainly cardiovascular disasters in 19 (55.9%), purulent complications of diabetes in 9 (26.5%) [23]. The severity of Cushing's syndrome is associated with a high mortality rate and a decrease in the quality of life of patients due to a high frequency of complications, such as metabolic syndrome (including arterial hypertension, visceral obesity, decreased glucose metabolism and dyslipidemia), musculoskeletal lesions, osteoporosis and bone fractures; neuropsychiatric disorders in the form of decreased cognitive function, depression, or manic states; violation of reproductive function, from menstrual irregularities to miscarriage and problems with labor, which is risky for both the mother and the fetus, sexual dysfunctions; dermatological manifestations with which the manifesto of the disease begins in the form of acne, hirsutism and seborrhea. In the absence of adequate and timely treatment and the preservation of hypercorticism, the 5-year mortality rate in patients with ACTH DCS exceeds the general population rate, reaching 50% [11].

Currently, transsphenoidal pituitary surgery (TSS) performed by an experienced neurosurgeon of the pituitary gland is the method of choice for the vast majority of patients with ACTH DCS and eliminate excess cortisol and restore normal secretion of cortisol, maintain normal pituitary function [21,23]. Up to 90% of patients with microadenomas (the tumor is less than 1 cm in diameter) and 65% of patients with microadenomas (the tumor is 1 or more cm in diameter) achieve endocrine remission by transsphenoid adenomectomy. [10]. One of the most controversial issues in assessing the degree of postoperative complication of the condition of patients with ACTH-DCS is the establishment of criteria for remission, although the definition of remission is preferred because of the possibility of relapse. Significantly less often, the authors propose the results of postoperative diagnostic tests as predictors of CD remission after TSS: tests with 1 mg dexamethasone, tests with corticotropin-releasing hormone (CRH) [2], desmopressin [12]), as well as a combined test with desmopressin and dexamethasone. The threshold values of cortisol and / or ACTH in the evaluation of sample results differ among all authors.

The use of TD in the postoperative period can detect the presence of residual neoplastic corticotrophic cells and thus indicate a possible increased risk of relapse. A desmopressin test has been proposed to monitor patients with CS. The potential benefit of the desmopressin test was first described 15 years ago in two successfully treated patients with CS. Those who were later diagnosed with relapse after the desmopressin test, based on a pathological increase in serum cortisol and ACTH, while any other biochemical anomaly, before that, showed hypercortisolism [6]. According to Bou Khalil and colleagues, 85% of patients with recurrent disease had a positive desmopressin test [4]. Of these, only six had a normal response after surgery. Recently, Ambrogio et al. [1] demonstrated that the response to desmopressin disappeared after surgery in all but 13% of patients with remission. Of 13 patients who had a relapse, 30% of patients had a positive early postoperative response to desmopressin and 40% developed a positive response with long-term follow-up. Thus, summarizing the above, it can be said that the current data confirm the supporting role of the test with the introduction of desmopressin immediately after surgery, in assessing the delayed outcome of the disease and in planning postoperative monitoring of the condition of patients with ACTH DCS. Loss of a paradoxical reaction indicates the possibility of a favorable outcome, while its preservation dictates the need for careful monitoring for the timely detection of relapse. However, an accurate assessment of the positive predictive value of the TD can be undermined by the fact that the total number of relapses in the published data is few and they can occur many years after a successful surgery. Therefore, for final conclusions in this matter, it is necessary to conduct larger studies with longer prolonging periods. Thus, TD remains one of the only valid criteria for assessing the likelihood of a tumor recurring after TSS. The introduction of this sample into clinical practice will allow, firstly, to assess the quality of the surgical removal of adenoma, secondly, to establish remission and, most importantly, to predict the recurrence of tumor growth. All of the above emphasizes the relevance of our study.

The ***aim of the study*** was to study the significance of a postoperative test with desmopressin to assess the effectiveness of TSS and outcomes compared with the postoperative level of cortisol in the group of high risk.

Material and research methods:

The object of the study was 60 patients with ACTH-dependent Cushing's syndrome (ACTH-DCS), operated on from 2000 to 2020 at the RSSPMCE of named after academician Y. Turakulov. To date, in the Republic of Uzbekistan, a desmopressin test has not been carried out at all, both in terms of diagnosis and for predicting the outcome of the disease due to the high cost of the study. To imple-

ment this test, we obtained the permission of the Ethics Committee at the Ministry of Health (No. 7 / 50-1210 of 08/08/2019), and we also received informed consent to conduct this test from all patients. Inclusion criteria were patients who underwent TSS for ACTH- DCS a transnazoseptal transsphenoid approach.

Exclusion criteria were patients with ACTH of DCS, subjected to medical, radiation, combination therapy and adrenalectomy.

The patients we studied (60 patients), depending on the level of postoperative blood cortisol, according to the Clinical Practical Recommendations of the Society of Endocrinologists (2015), were divided into 2 groups: group I consisted of patients with basal cortisol levels in the blood within ≤ 138 nmol / l, which were considered as patients who achieved remission - 18 patients, II group of blood cortisol 138-720 nmol / l, that is, 42 patients who were at high risk for reccurence. The control group consisted of 20 healthy individuals (10 men and 10 women) of the corresponding age. In total - 80 examined.

Research methods included:

1) general clinical (study of endocrine, somatic, neurological statuses);

2) instrumental (perimetric fields of vision, fundus, visual acuity, ECG, CT / MRI of the chiasmosellar region and adrenal glands; Magnetic resonance imaging of the pituitary gland with contrast

Before the surgery, all patients underwent pituitary MRI with the addition of a contrast agent with gadolinium on a Magnetom Trio A Tim 1.5 Tesla apparatus (SIEMENS, Germany). The size of the adenoma was considered its largest diameter. Under the pituitary microadenoma, education was understood to be less than 10 mm in size, and macroadenoma was 10 mm or more (Hardy J., 1969). Invasive growth was assessed by classifying the degree of invasion of the pituitary adenomas into the cavernous sinus cavity according to the Knosp Scale: for the absence of invasive growth, degrees 0-2 were taken, degrees 3-4 were considered invasive growth (Knosp E., 1993). Evaluation of MRI results was carried out by an MRI specialist, as well as an operating neurosurgeon.

3) hormonal research:

In the preoperative period: Serum cortisol was determined by radioimmunoassay (RIA) (Bekhman-Coulter, Czech Republic using Gamma-12 and Strantg 300 counters). Reference values: morning (8-9.00) - 260 - 720 nmol / l, evening (23-24.00) - less than 50 mmol / l. The study of free cortisol in daily urine was determined by the method of radioimmunoassay (RIA) (BekhmanCoulter, Czech Republic on counters Gamma-12 and Strantg 300)., Reference values - 38-208 nmol / day. The study of the level of ACTH in the plasma was determined by the method of radioimmunoassay (RIA) (BekhmanCoulter, Czech Republic on counters Gamma-12 and Strantg 300), reference values - less than 50 ng / ml (senior scientist A. Mukhamedova)

To evaluate indicators (plasma ACTH, serum cortisol) in the morning, peripheral vein blood sampling was performed on an empty stomach at 8-9.00. Blood samples were sent to the laboratory. To evaluate indicators in the evening hours (serum cortisol, ACTH plasma) blood sampling in the evening was carried out at 23-24.00, the patient was awake. The tube with ACTH was centrifuged, the plasma was frozen. Blood samples collected for determination of serum cortisol were placed in a refrigerator. The next morning, blood samples were sent to the laboratory for research.

Daily urine collection for determining free cortisol was started in the morning after the patient woke up. The patient emptied the bladder, recorded the time of urination, then all portions, starting from the second, were collected in a special container for collecting urine with a volume of 2 liters; the collection of daily urine was completed the next day 24 hours after the start - the patient collected the last portion of urine at that time in a container. The urine volume was recorded with an accuracy of 50 ml, then the urine was thoroughly mixed and about 50 ml was poured into a container for transportation to the laboratory indicating the daily volume of urine. ODST with 1 mg of dexamethasone was performed according to the following protocol: at 24.00 the patient took 2 tab of 0.5 mg dexamethasone, the next morning at 8.00 a blood was taken to determine the level of serum cortisol. A sample with 8 mg of dexamethasone (HDDT) was carried out according to the protocol: the serum cortisol level was initially determined at 8-9.00, then the patient was given orally 2 mg of dexamethasone every 6 hours for 2 days (the test was started at 8.00), on the 3rd day in the morning at 8.00 blood sampling was performed to determine serum cortisol.

In the postoperative period during the desmopressin test by enzyme-linked immunosorbent assay (ELISA) (doctor Saidova S.Kh.)

4) Histological studies of the surgical material (histopathology cabinet, histologist doctor - N.

Zhuravleva),

5) Functional test with desmopressin

The technique of the test with desmopressin.

For the test, desmopressin acetate 4 μg from Ferring Pharmaceuticals Ltd, UK was used after the conclusion and approval of the Ethics Committee of the Ministry of Health of the Republic of Uzbekistan No. 7/50-1210 (dated 08.08.2019).

The test was carried out as follows:

After an overnight 8-hour fast in the morning at 9^{00}, a permanent catheter was placed in a cubital vein, while the patient remained lying on his back for 120 minutes, that is, throughout the study period. At 9^{00}, 8 ml of blood (0min) were taken and 10 μg of desmopressin was administered as an intravenous bolus injection. Further, blood samples for measuring the level of ACTH and cortisol were obtained after 30, 60, 90 and 120 minutes. Blood pressure and heart rate were recorded throughout the study period. In order to avoid fluid overload and hyponatremia (low levels of sodium in the blood), which can be a serious side effect, fluid restriction (not more than 1.5-2 liters) for the rest of the day was recommended.

6) Statistical research methods. The data obtained were processed using computer programs Microsoft Excel and STATA. Quantitative data are represented by central trends and scatter: arithmetic mean (M) and standard deviation (SD) in the format M (SD). Comparison of two independent groups with a normal distribution was carried out using Student's t-test. In this case, and using other criteria, the null hypothesis was rejected at $p \leq 0.05$.

The results of the study:

The object of the study was the retrospective data of patients examined and treated at the RSSPMCE of the Ministry of Health of the Republic of Uzbekistan from 2000 to 2020, as well as the results of the created and conducted register of patients with CS and the data of annual monitoring of the status of patients registered in the regions of the Republic of Uzbekistan.

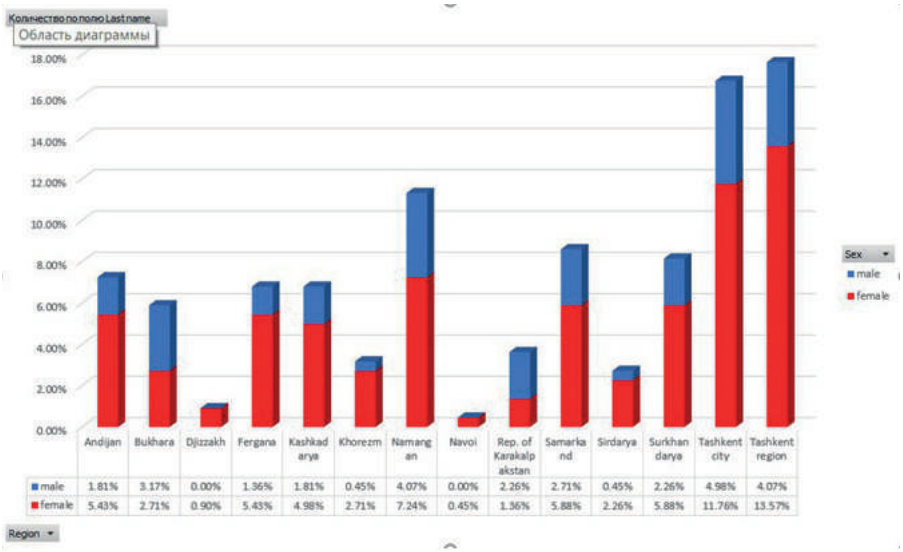

Fig. 1. Detection of patients with ACTH of DCS in regions of Uzbekistan

As can be seen from Figure 1, the ACTH DCS was more often detected in Tashkent city and Tashkent regions, and the smallest number - in the Navoi, Jizzakh and Sirdarya regions. According to the study, between 2000 and April 2020, 308 patients were registered, of whom 253 (82.1%) were patients with ACTH DCS, including 31 deaths. Of the total number of patients with ACTH DCS (222), the number of women was 157 (70.7%), and men - 65 (29.2%). Of the deceased (31), 14 were men (45.1%), 17 were women (54.8%).

Analysis of cases of ACTH DCS in the Republic of Uzbekistan showed that out of 222 patients, 108 (48.6%) were subjected to surgical intervention - TSS and 20 (9%) patients received combination therapy, in the form of TSS + adrenalectomy, radiation therapy or electrocoagulation of the adrenal vessels. Of 108 patients, 11 patients underwent repeated TSS in connection with relapse.

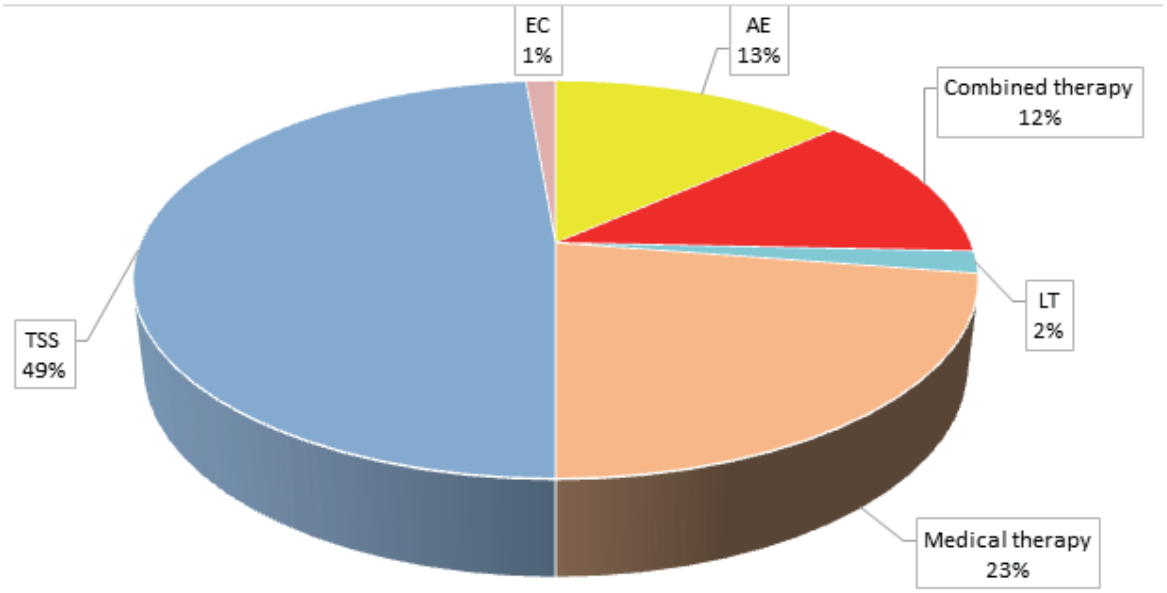

Fig2. Distribution of patients with ACTH DCS in groups according to the received therapy

Currently, of the operated TSS, 81 (75%) patients are in remission and 27 in the active phase (25%). Along with this, patients who received combination therapy (20 patients), 17 (85%) are in remission, 3 (15%) are in the active stage. The data are shown in Fig3.

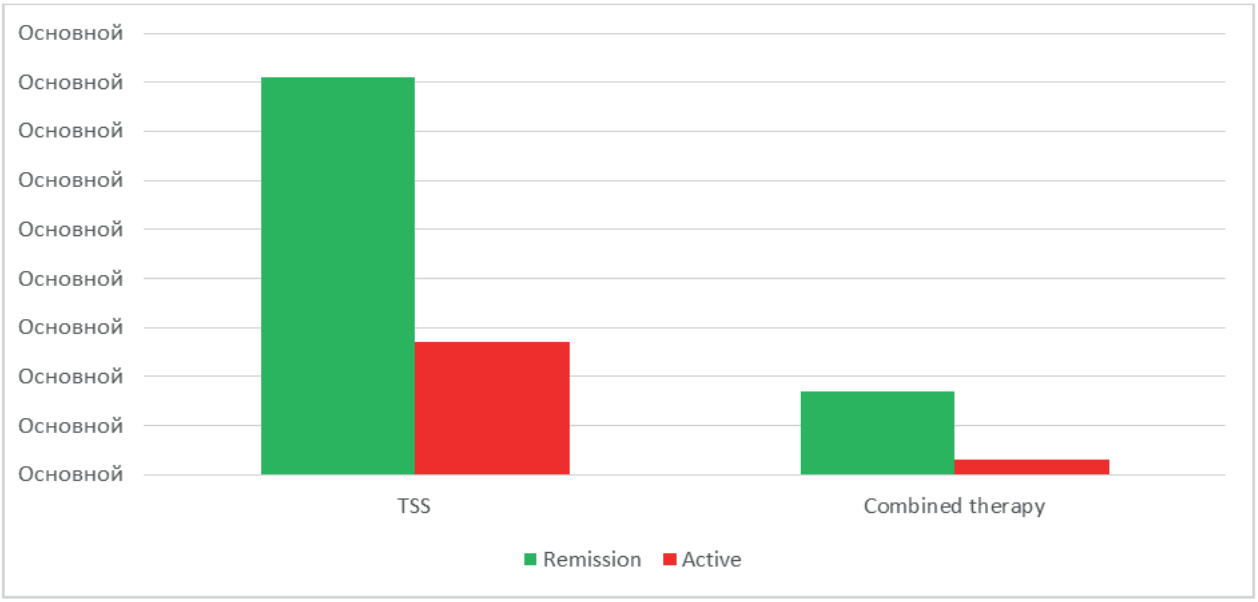

Fig3. Characterization of the condition of patients with ACTH DCS according to the register (n = 222)

60 patients with TSS were examined, of which 73.3% (44 patients) were women, 26.6% men (16 patients). The average age of women was 33.8 ± 0.39 years (from 15 to 54 years), men - 30.75 ± 0.31 (from 26 to 39) years. The duration of the disease from the moment of diagnosis was 36.4 ± 0.86 months (from 4 to 132 months).

Group II consisted of 42 patients who had blood cortisol levels after a TSS of 138 -720 nmol / L. Of these, 71.4% (30 patients) are women, 28.5% (12 patients) are men. The average age of women was 31.4 ± 0.34 (from 15 to 54 years), men –30.5±0.34 years (from 26 to 39 years).

The duration of the disease was 68.57 months (from 12 to 180 months), the duration before the manifestation was 30.43 months (from 6 to 108 months), the duration of the disease from the moment of diagnosis -39.57 ± 33.54 months (from 4 to 132 months), the age of patients at the time of diagnosis was on average

28.38 ± 7.89 years (from 15 to 49), 28.8 ± 0.4 years of women and 27.3 ± 0.6 years in men).

The duration of the preoperative period of the disease was within 5.28 months,

3 0.33 (from 1 to 60 months), the duration of the postoperative period was 34.86 ± 31.9 months (from 3 to 131 months).

Analysis of hormonal parameters in the preoperative period in group II (Table 1.) showed the following: ACTH varied from 53 to 148 ng / dl and averaged 70.32 ± 20.68 ng / dl, exceeding those of the control group in 3, 2 times ($p \leq 0.001$). A similar trend was observed in concentrations of UFC -338.04 ± 207.3 nmol / L (range from 155 to 1010 nmol / L) and in basal cortisol levels of 929.17 ± 333.2 nmol / L (range from 99.6 to 1720 nmol / L), which were significantly higher by 2.2 and 2 times, respectively, compared with the control ($p < 0.1$ and $p \leq 0.001$).

Postoperative hormone levels in the II group of patients were as follows: ACTH levels ranged from 5.2 to 177 ng / dl - and averaged 26.71 ±35.9 ng / dl,UFC - 147.6 ± 127.6 nmol / l (in the range from 23 to 540 nmol / L) and basal cortisol 450.6 ± 204.84 nmol / L (in the range from 177 to 900 nmol / L). A comparative analysis of pre and postoperative hormone levels revealed a significantly significant decrease in ACTH by 2.63 ($p \leq 0.005$), UFC by 2.28 times ($p \leq 0.001$) and basal cortisol by 2 times ($p \leq 0.001$). As the results show, the most sensitive and significant was the level of blood ACTH, then UFC and basal cortisol.

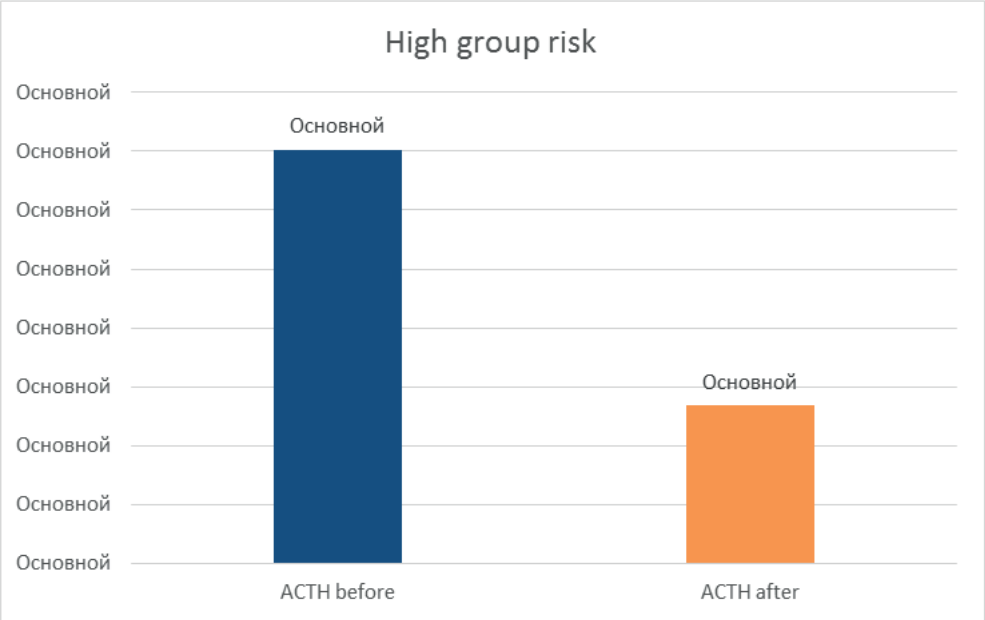

Fig 4. ACTH levels (ng / dl) before and after TSS, * - p <0.001**

Despite the fact that remission was not achieved by the levels of postoperative basal cortisol, clinical remission was observed in 8 patients of group II, disproportionate obesity, excessive hair growth, increased blood pressure, weakness in the lower extremities, menstrual irregularities and amenorrhea, change in appearance, regressed, striae on the stomach. If we analyze the data of these 8 patients separately, we obtain the following results.

Of these, 75% (6 patients) are women, 25% (2 patients) are men. The average age of patients was 31.8 ± 0.55 years. The duration of the disease from the moment of diagnosis was 52.8 ± 2.65 months (from 4 to 132 months). The age of patients at the time of diagnosis is 27.9 ± 0.48 years. The preoperative period was 8.8 ± 1.09 months, and the postoperative period was 45.09 ± 2.5 months. Preoperative levels of ACTH were 62.23 ± 0.52ng / dL, UFC 316.7 ± 9.23nmol / L and basal cortisol 802.4 ± 19.5nmol / L, i.e. only UFC and basal cortisol was much lower than other patients in this group

To achieve this goal, we conducted a thorough comparative analysis of hormonal indicators with various factors

Table 1. Clinical and hormonal characteristics of patients in the group of high risk (n = 62)

Parametres	Group patients high risk relapse (n=42)		Control (n=20)	P-value
sex	Ж=30	M=12		
age	31,4±0,34	30,5±0,34	31,85±10,72	
Disease duration	68,57±41,67			
Duration until manifestation	30,43 ±29,39			
Duration disease from manifestation(month)	39,57±33,54			
Age of patient,when diagnosis established(year)	28,38±7,89			
Duration till surgery(month)	5,28±0,33			
Duration after surgery(month)	34,86±31,9			
ACTH before (ng/dl)	70,32±20,68		21,7±10,13	P_1<0,05 P_2<0,05
ACTH after (ng/dl)	26,71±35,92			
UFC before (nmol/l)	338,04±207,3		154,2±23,38	P_1 <0,01 P_2<0,1
UFC after (nmol/l)	147,6±127,6			
Basal cortisol before (nmol/l)	929,17±333,2		466,8±134	P_1<0,01 P_2<0,05
Basal cortisol after (nmol/l)	450,6±204,84			

Note: P-reliability of differences, P_1 - II group and control, P_2 - before and after surgery

The results of desmopressin test studied groups.

Early postoperative cortisol in patients of the high risk group (n = 42) averaged 450.6 ± 204 nmol / l, ranged from 177 to 900 nmol / l. On the day of the test, the average values of basal cortisol for 0 min were 168.9 ± 131.2 nmol / L; 2.7 times lower than in the control group (from 37.1 to 500.4 nmol / L; p≤0.0001) The peak of cortisol also occurred between 30 and 60 min and amounted to 259.29 ± 190.8 nmol / L, i.e., 1.8 times lower than in the control group (from 65.2 to 791.1; p≤0.001) .Δ Cort (peak cortisol - cortisol 0) 90.38 ± 96.59 nmol / L, that is, 4.7 times higher (from 4.2 to 359.7 nmol /

L; p≤0.05), the increase in cortisol% (ΔCort-cortisol 0 * 100%) 77.06 ± 96, 67 nmol / l, that is, 18.7 times higher than in the control group. (P≤0.05).

The level of ACTH 0 was -37.26 ± 36.71ng / dl, i.e. 1.7 times higher than in the control group (from 4.6 to 162.9ng / dl (p≤0.05), the peak of ACTH between 30 and 60 min was within the range of -64.11 ± 57.09 ng / dl, i.e. 2.72 times higher than in the control group (from 10.3 to 243.7 ng / dl; p≤0,0005), Δ ACTH 26.85 ± 33.19 ng / dl, that is, 15 times higher than in the control group (from 2.1 to 140.7 ng / dl; p≤0.01), an increase in ACTH-94.41 ± 89.5, that is 11.5 times higher than in the control group (P <0.01).

Table 2. Results of desmopressin test of the studied groups (n = 62)

Parametres	High risk group	Control	P-value
Number (n)	42	20	-
Early postoperative cortisol (nmol / L)	450,6±204		
Early postoperative ACTH (ng / dl)	26,71±35,92		
Cortisol, at 0min, nmol / l	168,9±131,2	466,7±134,1	P <0,0001
Peak $cort_{60}$, nmol / l	259,29±190,8	485,9±139	P <0,001
ΔCort, nmol / l	90,38±96,59	19,25±5,73	P <0,05
% ΔCort, nmol / l	77,06±96,67	4,11±0,14	P <0,05
ACTH at 0 min, ng / dl	37,26±36,71	21,75±10,1	P <0,005
Peak $ACTH_{30}$, ng / dl	64,11±57,09	23,54±10,95	P <0,0005
ACTH, ng / dl	26,85±33,19	1,79±0,84	P <0,01

Note: P-reliability of differences, C-control p – high risk group and control

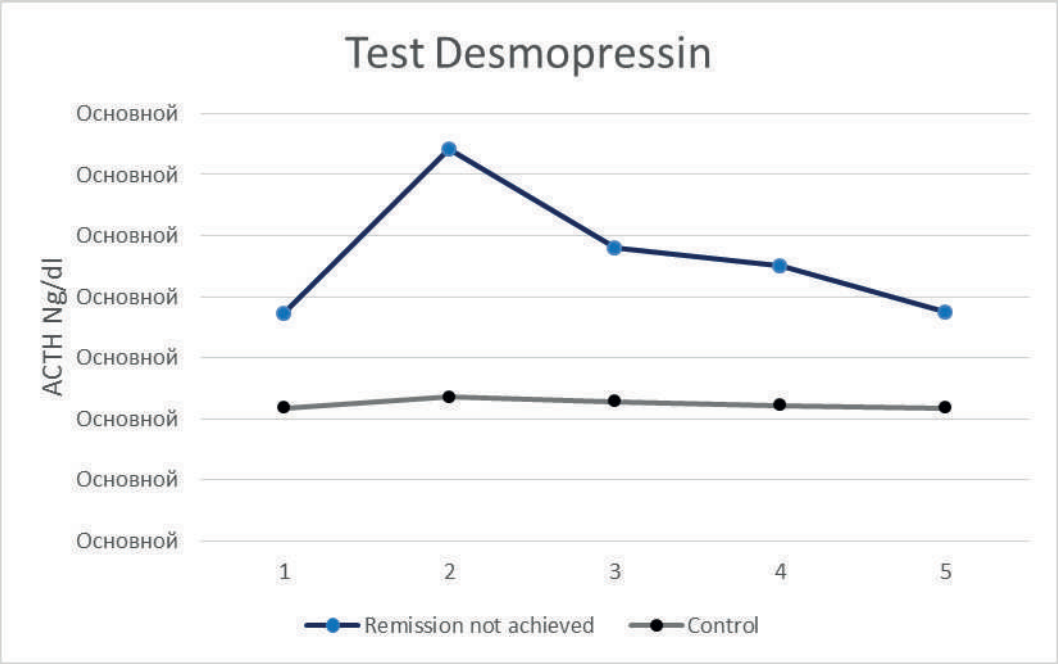

Fig. 5. The results of the dynamics of ACTH in the blood during the test desmopressin in the studied groups

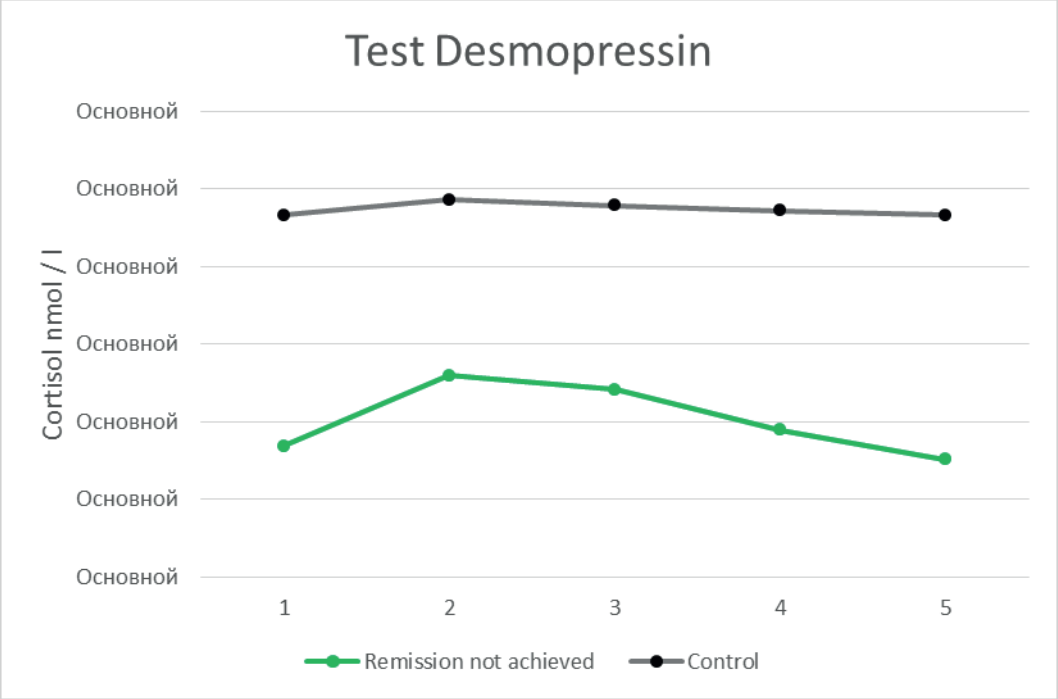

Fig.6. Results of the dynamics of cortisol in blood during the test desmopressin in the studied groups

And so, a thorough analysis of the data in the studied groups showed that TD is a sensitive tool in determining the reactivity of pituitary corticotrophic cells. Judging by the level of ACTH and cortisol during TD and carefully comparing with clinical, biochemical, hormonal indicators and risk factors, the effectiveness and radicalism of the surgical intervention can be assessed. Thus, according to the results of our studies, it is clear that TD clearly shows the line of remission and the presence of relapse, as evidenced by the significantly high reactivity of corticotrophs (possibly residual or recurring again) with a sharp overproduction of ACTH and cortisol after their stimulation in patients with doubtful outcomes of the disease or with subclinical cushingoid after TSS. Moreover, TD can help identify cases, that is, a risk group among patients with objective indicators of remission according to

the latest clinical recommendations [33 In the high risk group, 19% (8 patients out of 42) of patients had a negative reaction to desmopressin, as evidenced by an increase in cortisol levels and can serve as a negative prognostic marker of the likelihood of recurrent disease outcome.

Discussion:

Currently, the most relevant and debatable issues remain the search for reliable markers of remission ACTH-DCS after TSS. In this regard, foreign authors discuss various tests in the postoperative period - with CRH, with dexamethasone, with desmopressin to answer the question of the likelihood of relapse in each individual case and for a wide range of patients.

Romanholi D.J.et al. [12] showed that tumor identification during surgery, the presence of a tumor producing ACTH (as determined by immunohistochemistry), and the presence of a non-invasive tumor of ACTH were favorable predictors of initial remission in patients. Moreover, a younger age, a smaller tumor, and the absence of invasion of the cavernous sinus or other dural invasion were associated with prolonged remission. In addition, the minimum morning serum cortisol level <1 μg / dl after surgery had a positive predictive value of 96% for long-term remission.

According to Valassi, E. [13] et al., the frequency of remission varies depending on the location and type of tumor, the experience of a neurosurgeon, follow-up and the criteria used to determine remission. According to the literature, patients with Hook's tumor (a histological subtype of a corticotrophic tumor) may develop an aggressive clinical course, including rapid tumor growth and multiple relapses.

According to our research, in the postoperative period, there was a significant decrease in the hormonal parameters of blood and urine (ACTH, cortisol) compared with preoperative data in patients of both groups - with remission and without remission. But at the same time, in the second group, the average values of ACTH and blood cortisol after surgery were significantly higher, remaining within normal limits. It should be noted that the early postoperative level of cortisol in patients of group 1 was within 75.2 ± 8.78 nmol / L, and in group 2 much higher - 412.87 ± 55.7 nmol / L[5,7,8,9, 14,18,23]

A test with desmopressin revealed that in all blood samples after exercise in patients of group 2, the levels of ACTH and cortisol were significantly higher than in patients of group 1. Thus, this test confirmed the severity of the condition of the second group of patients in whom, according to histology, more than half the cases revealed a small cell tumor.

For accurate answers to questions, further monitoring of the quality of life of patients with ACTH-DCS in the postoperative period is necessary.

Conclusions:

1. Analysis of the desmopressin test results in patients with ACTH-DCS showed that TD is a sensitive tool in determining the reactivity of pituitary corticotrophic cells.

2. Comparison of clinical, biochemical, hormonal indicators and risk factors during TD will assess the effectiveness and radicalism of the surgical intervention. Moreover, TD clearly shows the line of remission and the presence of relapse, as evidenced by the significantly high reactivity of corticotrophs (possibly residual or recurring again) with a sharp overproduction of ACTH and cortisol after their stimulation in patients with dubious outcomes of the disease or with subclinical cushingoid after TSS.

3. The use of TD in combination with basal blood cortisol after TSS with ACTH-DCS can help identify risk groups among patients with objective remission rates according to the latest clinical recommendations. In the cohort of postoperative patients we studied, 24 patients with unreached ACTH DCS remission on the background of a TD sample in 19% of those with a blood cortisol level of more than 138 nmol / L and less than 720nmol/l had a negative reaction to desmopressin, as evidenced by an increase in cortisol levels and can serve as a negative prognostic marker of the probability of a recurrent outcome illnesses.

References:

1. Ambrosi et al. Ambrogio AG, Andrioli M, De Martin M, Cavagnini F &PecoriGiraldi F. Usefulness of desmopressin testing to predict relapse during longterm follow-up in patients in remission from Cushing's disease. EndocrineConnections 2017 6 791–799
2. Barbot M, Trementino L, Zilio M, Ceccato F, Albiger N, Daniele A, et al. Second-line tests in the differential diagnosis of ACTH-dependent Cushing's syndrome. Pituitary. (2016) 19:488–95
3. Bertagna X., Guignat L., Groussin L. et al. Cushing's disease. Best Pract Res Clin Endocrinol Metab. 2009;23:607–623.
4. Bou Khalil R, Baudry C, Guignat L, Carrasco C, Guibourdenche J, Gaillard S, Bertagna X &Bertherat J. Sequential hormonal changes in 21patientswithrecurrent Cushing's disease after successful pituitary surgery. EurJEndocrinol2011 165729-737.
5. Clayton R.N., Raskauskiene D., Reulen R.C. et al. Mortality and morbidity in Cushing's

disease over 50 years in Stoke-on-Trent, UK: audit and meta-analysis of literature. Journal of Clinical Endocrinology and Metabolism. 2011;96:632– 642.

6. Danet-Lamasou M, Asselineau J, Perez P, Vivot A, Nunes ML, Loiseau H, San-Galli F, Cherifi-Gatta B, Corcuff JB &Tabarin A. Accuracy of repeated measurements of latenight salivary cortisol to screen for early-stage recurrence of Cushing's disease following pituitary surgery. ClinEndocrinol (Oxf) 2015 82260-266. 17

7. Khalimova Z.Yu., Mirsaidova U.A. «The Sensitivity and Specificity of the Desmopressin Test in Patients with ACTH-Dependent Cushing's Syndrome Undergoing Transnasal Pituitary Adenomectomy» American Journal of Medicine and Medical Sciences 2020, 10(7): 462-465

8. Khalimova Z.Yu., Mirsaidova U.A. «Assessment of prediction of relapse of ACTH-Dependent Cushing's Syndrome in patients undergoing transsphenoidal surgery». EC Endocrinology and Metabolic Research.5.6(2020):47-59

9. Le Marc'hadour P., Muller M., Albarel F. et al. Postoperative follow-up of Cushing's disease using cortisol, desmopressin and coupled dexamethasone-desmopressin tests: a headto-head comparison. Clinical Endocrinology. 2015;83:216–222.

10. Newell-Price J., Trainer P.J., Besser G.M. et al. The diagnosis and diff erential diagnosis of Cushing's and pseudo-Cushing's states. Endocrine Reviews. 2019;19:647-672.

11. Plotz, C.M.; Knowlton, A.I.; Ragan, C. The natural history of Cushing's syndrome. Am. J. Med. 1952, 13, 597–614

12. Romanholi D.J., Machado M.C., Pereira C.C. et al. Role for postoperative cortisol response to desmopressin in predicting the risk for recurrent Cushing's disease. Clin Endocrinol (Oxf). 2008;69:117–122.24.

13. Valassi E., Biller B.M., Swearingen B. et al. Delayed remission after transsphenoidal surgery in patients with Cushing's disease. J Clin Endocrinol Metab. 2010;95(2):601-610

14. Абдухаликова Н.У, Мирсаидова У.А., Олимов С.М., Джалалов С.Ч. «ОБЗОР КЛИНИЧЕСКИХ ДОКАЗАТЕЛЬСТВ ДИАГНОСТИКИ БОЛЕЗНИ СИНДРОМА КУШИНГА С ИСПОЛЬЗОВАНИЕМ ДЕСМОПРЕССИН ТЕСТА В СРАВНЕНИИ С КОРТИЗОЛОМ» Сборник ABU ALI IBN SINO AND INNOVATION IN MODERN PHARMACEUTICS. IIIInternational Scientific and Practical Conference(2020)p275-77

15. Наримова Г.Д., Халимова З.Ю. «Ранняя диагностика синдрома Кушинга: вопросы скрининга» // Методические рекомендации. – Ташкент, 2018. - 30 С.

16. Наримова Г.Д., Халимова З.Ю. «Эндогенный синдром Кушинга: вопросы мониторинга и лечения» // Методические рекомендации. – Ташкент, 2018. - 30 С.

17. НаримоваГ.Дж., МадаминоваХ.Р.Оценка качества жизни больных с Синдромом Кушинга при консерватвином и хирургическом лечении//Международный Эндокринологический Журнал, г Киев, том 13, №2, 2017 г, стр 55 -63.

18. Халимова З.Ю., Мирсаидова У.А., «Оценка нейроэндокринной регуляции кортикотрофной функции гипофиза у больных после ТАГ» г.Ташкент. Журнал «Неврология» №2 (82), стр. 73-79

19. Халимова З.Ю., Наримова Г.Д. Особенности нарушения углеводного обмена при Синдроме Кушинга (обзор литературы) // Журнал Теоретической и Клинической медицины. – Ташкент, 2014. - №6. - С. 94 – 97.

20. Халимова З.Ю., Наримова Г.Д. Синдром Кушинга, эпидемиология и проблемные вопросы // Журнал Теоретической и Клинической медицины, Ташкент, 2013. - Специальный выпуск. – С. 94 – 97.

21. Халимова З.Ю., Наримова Г.Д. Современные аспекты хирургического лечения синдрома Кушинга по Республике Узбекистан // Сборник статей по материалам XLI-XLII Международной заочной научно-практической конференции. – Москва, 2015. - №10-11(30). – С. 62-78.

22. Халимова З.Ю., Наримова Г.Д., Алимухамедова Г.О. Особенности нарушений костного метаболизма при синдроме Кушинга // Российский Нейрохирургический Журнал имени проф. А.Л. Поленова. - Санкт-Петербург, 2014. – Специальныйвыпуск. – Том 6. – С. 392-394

23. Халимова З.Ю., Урманова Ю.М., Мирсаидова У.А. « Сравнительная характеристика до и послеоперационных гормональных значений у больных с АКТГ зависимым синдромом Кушинга в различные сроки после операции» East European Science Journal.4(56),2020.p38-44

CORRELATION OF ACROMEGALY MUSCULOSCELETAL COMPLICATIONS DEVELOPMENT WITH GENDER, AGE OF PATIENTS AND TERM OF DISEASE

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Annotation: The objective of our research was to study interrelation of acromegaly musculoskeletal complications development dependent on age, gender of patients, and the duration of the disease. The subject of the study were 110 patients with GH pituitary adenoma, who applied to the RSSPMCE within the period from 2000 to 2020 and were registered as patients with acromegaly in the RUz. Among them there were 40 (33.37%) men and 70 (63.63%) women. The mean age of the patients was 43±8.7 years old. In young age there was higher prevalence rate of osteoarthritis (49% versus 10.5%, p<0.001) and osteopenia (33.9% versus 13.2%, p<0.01). Patients with acromegaly had a high rate of musculoskeletal complications, in the structure of which a significant part is attributed to osteoporosis (60.9%) and osteoarthrosis (58.2%), with prevailing osteoarthrosis among female patients (60.5% versus 46.8%, p<0.05), and compression vertebral fractures among males (12.8% versus 5.5%, p<0.001). With the aging of patients lesions of skeletal system become more severe developing to osteoporosis, osteoarthrosis, and fractures. With the increase in the duration of the disease hypersecretion of GH caused deterioration of MSC and growth of osteoarthrosis (92.5% with duration 10-19 years, p<0.001 and 94.3% with duration 20 years and more, p<0.001) and osteoporosis (91.2% with duration 10-19 years, p< 0.001and 98.3% with duration 20 years and more, p<0.001) prevalence rate. These findings confirm the necessity of early aggressive therapy of both basic disease and initial complications in musculoskeletal system, as alterations in joints and cartilages become irreversible with aging of the patients and increase of the disease duration.

Key words: acromegaly, osteoarthrosis, osteoporosis, musculoskeletal complications.

ВЗАИМОСВЯЗЬ РАЗВИТИЯ ОПОРНО-ДВИГАТЕЛЬНЫХ ОСЛОЖНЕНИЙ АКРОМЕГАЛИИ В ЗАВИСИМОСТИ ОТ ПОЛА, ВОЗРАСТА БОЛЬНЫХ И ДАВНОСТИ ЗАБОЛЕВАНИЯ

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Аннотация: Целью нашего исследования явилось изучение взаимосвязи развития опорно-двигательных осложнений акромегалии в зависимости от пола, возраста больных и давности заболевания. Объектом исследования явились 110 больных с соматотропными аденомами гипофиза, которые обращались в РСНПМЦЭ за период с 2000 по 2020гг и вошли в регистр больных акромегалией по РУз. Из них мужчины – 40 (33,37%), женщины – 70 (63,63%). Средний возраст пациентов составил (43±8,7 лет). При этом, в молодом возрасте чаще наблюдалась остеоартриты (49% против 10,5%, p<0,001)и остеопения (33,9% против 13,2%, p<0,01). У пациентов с акромегалией наблюдается высокая частота осложнений опорно-двигательной системы, в структуре которых высокую частоту занимают остеопороз (60,9%) и остеоартроз (58,2%), с превалированием у лиц женского пола остеоартрозов (60,5% против 46,8%, p<0,05), а у мужчин – компрессионных переломов тел позвонков (12,8% против 5,5%, p<0,001). С увеличением возраста больных, усугубляется тяжесть поражений костно-суставной системы, в виде остеопороза, остеоартроза и переломов. С увеличением длительности заболевания хроническая гиперсекреция ГР приводила к усугублению ОДО и росту частоты остеоартрозов (92,5% -с длительностью 10-19 лет, p<0,001 и 94,3%- с длительностью 20 и более лет, p<0,001) и остеопороза (91,2% -с длительностью 10-19 лет, p< 0,001и 98,3%- с длительностью 20 и более лет, p<0,001). Эти данные подтверждают необходимость раннего агрессивного лечения

как основного заболевания, так и начинающихся осложнений опорно-двигательной системы, поскольку с увеличением возраста больных и длительности заболевания изменения суставов и хрящей становятся необратимыми.

Ключевые слова: акромегалия, остеоартроз, остеопороз, опорно-двигательные осложнения.

АКРОМЕГАЛИЯДА ТАЯНЧ-ҲАРАКАТЛАНИШ АСОРАТЛАРИНИНГ РИВОЖЛАНИШИДА БЕМОРЛАРНИНГ ЖИНСИ, ЁШИ ВА КАСАЛЛИКНИНГ ДАВОМИЙЛИГИ БИЛАН ЎЗАРО БОҒЛИҚЛИГИ

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Аннотация: Тадқиқот мақсади: акромегалияда таянч-ҳаракатланиш асоратларининг ривожланишида беморларнинг жинси, ёши ва касалликнинг давомийлиги билан ўзаро боғлиқлигини ўрганиш. Тадқиқотда гипофизнинг соматотроп аденомаси билан касалланган хамда РИЭИАТМарказига 2000йилдан 2020йилгача мурожаат қилган ва шу билан бирга ЎзРнинг акромегалия регистрига кирган 110та бемор қатнашди.

Улардан эркаклар – 40 (33,37%), аёллар – 70 (63,63%). Беморларнинг ўртача ёши (43±8,7 лет)ни ташкил қилди. Шунда ёшроқ беморларда кўпроқ остеоартритлар учради (49% қарши 10,5%, p<0,001) ва остеопения (33,9% қарши 13,2%, p<0,01). Акромегалия билан касалланган беморларда таянч-ҳаракатланиш тизимининг асоратлари юқори даражада учраши кузатилди, уларнинг ичида энг юқори қисмни остеопороз (60,9%) ва остеоартроз (58,2%) эгаллади, аёлларда кўпроқ остеоартроз (60,5% қарши 46,8%, p<0,05), эркакларда эса, – умуртқа танасининг компрессион синиши (12,8% қарши 5,5%, p<0,001) кузатилди. Беморларнинг ёши катталашган сари, суяк-бўғим тизимининг шикастланиши остеопороз, остеоартроз ва синишлар холатида учраши кузатилди. Касалликнинг давомийлигини ошиши билан ўсиш гормонининг сурункали гиперсекрецияси таянч-ҳаракатланиш асоратларининг оғирлашишига ва остеоартроз частотасининг ўсишига(92,5% касаллик давомийлиги 10-19 йил, p<0,001 ва 94,3% касаллик давомийлиги 20йил ва ундан юқори, p<0,001) ва остеопороз частотасининг ортишига (91,2% касаллик давомийлиги 10-19 йил, p< 0,001ва 98,3% касаллик давомийлиги 20йил ва ундан юқори, p<0,001)олиб келади. Бу маълумотлар асосий касалликни ва унинг бошланиб келаётган таянч-ҳаракатланиш тизимининг асоратларини эрта агрессив даволаш кераклигини тасдиқлади, чунки беморларнинг ёши хамда касалликнинг давомийлиги ортиши билан бўғим ва тоғайлардаги ўзгаришларнинг орқага қайтиш эҳтимоли бўлмайди.

Калит сўзлар: акромегалия, остеоартроз, остеопороз, таянч-ҳаракатланиш асоратлари.

Acromegaly is a rare chronic disease caused by hypersecretion of growth hormone and characterized by excessive tissue growth leading to significant burden of complications and associate pathologies such as cardiovascular, musculoskeletal, respiratory, endocrine, and metabolic diseases [1,5,6,8].

According to the results of various studies the prevalence of acromegaly musculoskeletal complications (MSC) varies from 60% to 75% [3,7,9]. The rate of prevalence of MSC detected among the patients with acromegaly in Uzbekistan is high with development of osteoporosis in 69.4%, arthropathy in 59%, and osteopenia in 36.6% of the cases [11]. At the same time any joints can be involved and the complications vary from osteoarthritis to arthralgia and fractures [3,13], resulting in early invalidation of the patients. Invalidity, as a result of acromegaly, is often underestimated and it can affect many aspects of everyday life [2,10]. Nowadays the reason of such a high prevalence rate of acromegaly complications is late diagnostics, inadequate therapy, and absence of patients' dedication to the therapy in the cases of inappropriate therapeutic strategy choice with consequent incomplete fulfillment of the recommendations. All these reasons lead to long-term chronic effect of

hypersomatotropinemia causing irreversible alterations in skeletal system with aging [4,12].

It is known that growth hormone (GH) has age and gender differences, but, nevertheless, there are various studies of the correlation between the musculoskeletal complications with these parameters [7,8,9].

On the basis of all the aforesaid, ***the objective*** of our research was to study correlation between acromegaly musculoskeletal complications development and gender, age of the patients, and duration of the disease.

Materials and methods.

The subject of the study were 110 patients with somatotropic pituitary adenoma, who applied to the RSSPMCE within the period from 2000 to 2020 and were registered as patients with acromegaly in the RUz. Among them there were 40 (33.37%) men and 70 (63.63%) women. Mean age of the patients was 43±8.7 years old. According to the age the patients were distributed to three groups: I group under 30, II group 30-44 years old, and the III group of patients of 45 years old and elder.

Acromegaly diagnosis was established on the basis of clinical manifestations of the disease and confirmed by high serum GH, IGF-1, which were above the age-specific normal values. For the definition of pituitary hormones and peripheral glands we used radio immune and enzyme immunoassays. The study included common clinical, biochemical tests, neurological status tests; inner organs and thyroid US. Besides that, we studied various parameters of vision such as field of vision, eye bottom, and acuity of vision. For the detection of MSC we performed chest and spine x-ray with bone densitometry. Pituitary adenoma was diagnosed on the basis of MRI of hypothalamus-pituitary area.

Results and discussion.

Among the musculoskeletal disorders we isolated the most prevalent ones according to the results of our study and literature data. The structure of acromegaly MSC in the studied patients was the following (Figure 1):

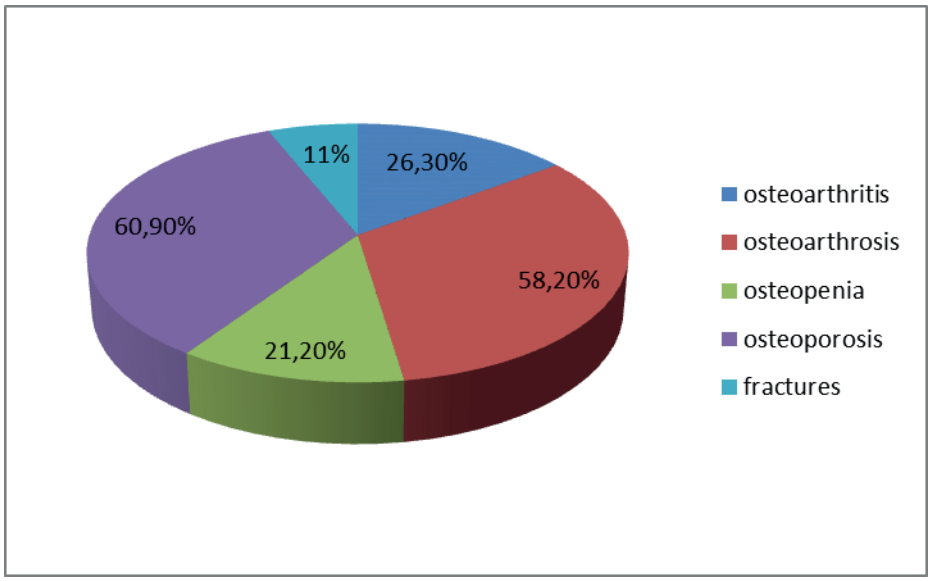

Figure 1. The structure of acromegaly MSC.

Figure 1 shows that the most prevalent manifestations of musculoskeletal complications in the patients in our study were osteoporosis (60.9%) and osteoarthrosis (58.2%).

According to the set problems we studied the correlation between the MSC development and patients' age, where age gradation was established in compliance with WHO recommendations (2016) (Figure 2).

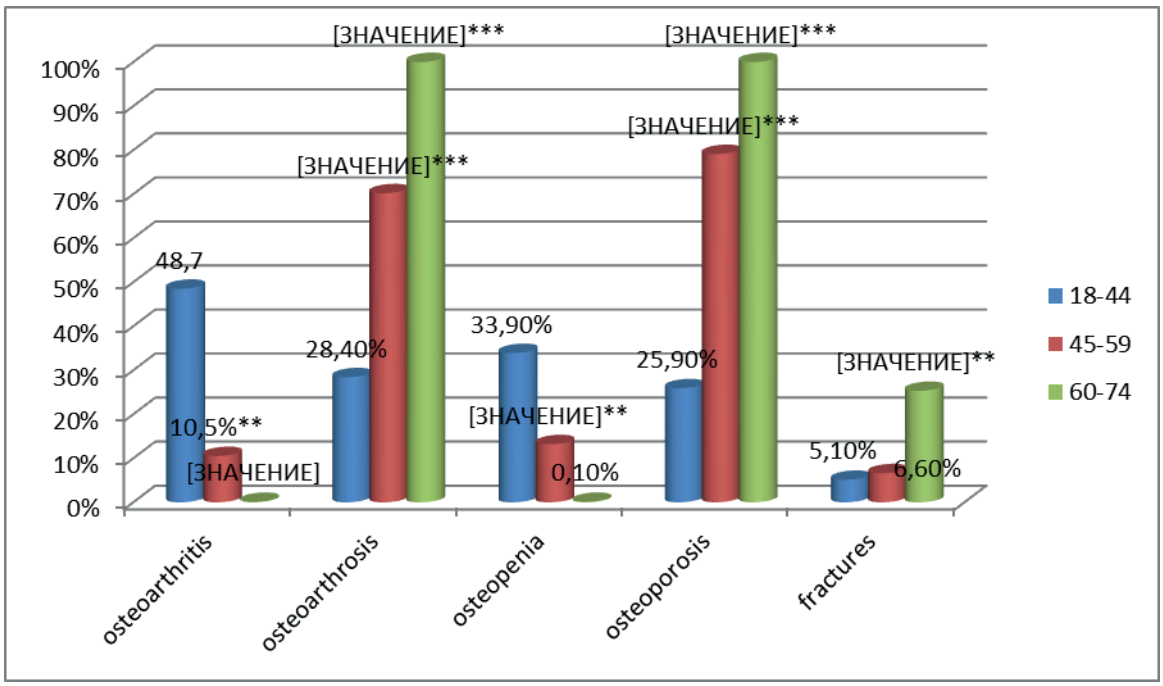

Figure 2. Acromegaly MSC structure in various age groups.
Note: *- p< 0.05, ** - p< 0.01, *** p< 0.001

According to the results the structure of acromegaly MSC changed dependently on the age. In the young age there was a greater prevalence of osteoarthritis (49% versus 10.5%, p<0.001) and osteopenia (33.9% versus 13.2%, p<0.01). Patients' aging resulted in deterioration of bone-articulate system lesions due to the rise of prevalence rate of osteoporosis (100% in the age of 60-74 years old versus 79.1% in 45-59 years old, p<0.001 and 25.9% in 18-44 years old. p<0.001), osteoarthrosis (100% in the age of 60-74 years old versus 70.2% in 45-59, p<0.001 and 28.4% in 18-44. p<0.001), and fractures (25.3% in the age of 60-74 years old versus 6.6% in 45-59, p<0.001, and 5.1% in 18-44 years old). Later we asked a question: are there gender differences in the development of acromegaly MSC? (Figure 3.)

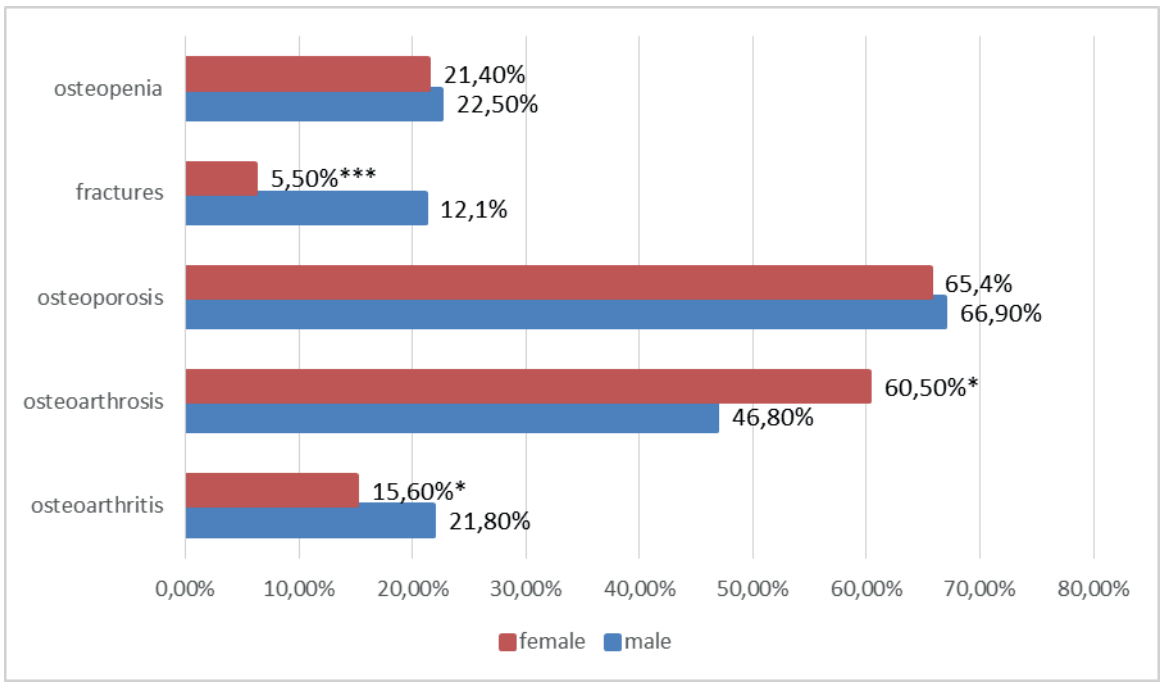

Figure 3. Gender peculiarities of acromegaly MSC structure. Note: *- p< 0.05, ** - p< 0.01, *** p< 0.001

According to the obtained results osteoporosis was prevalent among both male and female patients (66.9% in men, 65.4% in women). There were gender differences in acromegaly MSC structure among the studied patients. While female patients more often had osteoarthrosis (60.5% versus 46.8%, p<0.05), male patients more often suffered fractures (12.8% versus 5.5%, p<0.001).

After that we studied peculiarities of acromegaly MSC development dependent on the term of the disease (Figure 4).

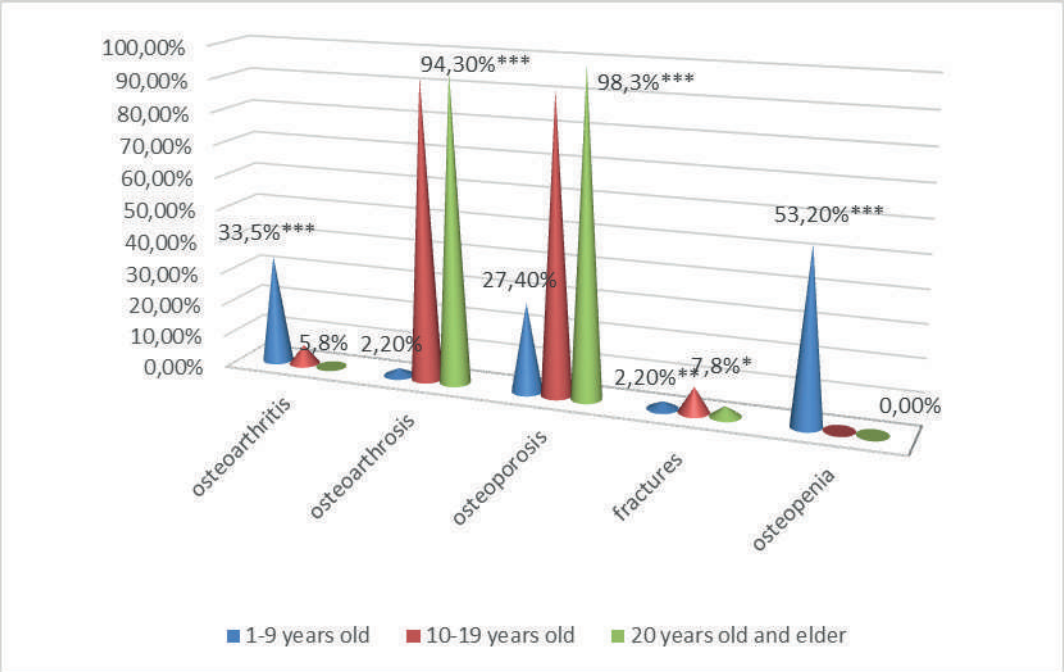

Figure 4. MCS structure in patients with acromegaly dependent on the term of disease.
Note: *- p< 0.05, ** - p< 0.01, *** p< 0.001.

According to the results of our study patients with acromegaly lasting up to 10 years the prevailing MSC was osteoarthritis (34.7%) and osteopenia (51%). With the increase of the term of GH hypersecretion the severity of skeletal system lesion increased resulting in the rise of prevalence rate of osteoarthrosis (92.5% with duration 10-19 years, p<0.001 and 94.3% with duration 20 and more years, p<0.001) and osteoporosis (91.2% with duration 10-19 years, p< 0.001 and 98.3% with duration 20 and more years, p<0.001).

Conclusion

Thus, patients with acromegaly have high prevalence rate of musculoskeletal complications, in the structure of which the most prevalent was osteoporosis (60.9%) and osteoarthrosis (58.2%), with osteoarthrosis more often observed in female patients (60.5% versus 46.8%, p<0.05) and compression vertebral fractures in male patients (12.8% versus 5.5%, p<0.001). Patients' aging resulted in deterioration of bone-articulate system lesions due to the rise of prevalence rate of osteoporosis (98.3% in the age of 60-74 years old versus 92.5% in 45-59 years old, p<0.001 and 25.9% in 18-44 years old. p<0.001), osteoarthrosis (100% in the age of 60-74 years old versus 70.2% in 45-59, p<0.001 and 28.4% in 18-44. p<0.001), and fractures (25.3% in the age of 60-74 years old versus 6.6% in 45-59, p<0.001, and 5.1% in 18-44 years old). With the increase of the term of GH hypersecretion the severity of skeletal system lesion increased resulting in the rise of prevalence rate of osteoarthrosis (92.5% with duration 10-19 years, p<0.001 and 94.3% with duration 20 and more years, p<0.001) and osteoporosis (91.2% with duration 10-19 years, p< 0.001 and 98.3% with duration 20 and more years, p<0.001). These findings confirm the necessity of early aggressive therapy of both basic disease and initial complications in musculoskeletal system, as alterations in joints and cartilages become irreversible with aging of the patients and increase of the disease duration.

References

1. Ana M. Ramos-Leví and Mónica Marazuela*Bringing Cardiovascular Comorbidities in Acromegaly to an Update. How Should We Diagnose and Manage Them? Front Endocrinol

(Lausanne). 2019; 10: 120. Published online 2019 Mar 7. doi: 10.3389/fendo.2019.00120
2. Biermasz NR, Pereira AM, Smit JW, Romijn JA, Roelfsema F. Morbidity after long-term remission for acromegaly: persisting joint-related complaints cause reduced quality of life. J Clin Endocrinol Metab. 2005;90(5):2731–2739.
3. Bonadonna S, Mazziotti G, Nuzzo M, Bianchi A, Fusco A, De Marinis L, Giustina A. Increased prevalence of radiological spinal deformities in active acromegaly: a cross-sectional study in postmenopausal women. J Bone Miner Res. 2005;20(10):1837–1844.
4. Colao A, Cannavo S, Marzullo P, Pivonello R, Squadrito S, Vallone G, Almoto B, Bichisao E, Trimarchi F, Lombardi G. Twelve months of treatment with octreotide-LAR reduces joint thickness in acromegaly. Eur J Endocrinol. 2003;148(1):31–38.
5. Giustina A, Chanson P, Kleinberg D, Bronstein MD, Clemmons DR, Klibanski A, et al. Expert consensus document: a consensus on the medical treatment of acromegaly. Nat Rev Endocrinol. (2014) 10:243–8. 10.1038/nrendo.2014.21 [PubMed] [CrossRef] [Google Scholar]
6. Holdaway IM, Rajasoorya RC, Gamble GD. Factors influencing mortality in acromegaly. J Clin Endocrinol Metab. (2004) 89:667–74.
7. Killinger Z, Payer J, Lazurova I, Imrich R, Homerova Z, Kuzma M, Rovensky J. Arthropathy in acromegaly. Rheum Dis Clin North Am. 2010;36(4):713–720
8. Melmed S. Medical progress: acromegaly. N Engl J Med. (2006) 355:2558–73.
9. Melmed S., Casanueva F. F, Klibanski A., . Bronstein M. D, Chanson P., Lamberts S. W., . Strasburger C. J, . Wass J. A. H, and Giustina A. A consensus on the diagnosis and treatment of acromegaly complications Pituitary. 2013; 16(3): 294–302.
10. Miller A, Doll H, David J, Wass J. Impact of musculoskeletal disease on quality of life in long-standing acromegaly. Eur J Endocrinol. 2008;158(5):587–593. doi: 10.1530/EJE-07-0838. [PubMed] [Cross Ref]
11. Safarova Sh., Khalimova Z., Kholikova A., Ibragimova S., Mannapova U., Mirtuhtaeva M., Mirsaidova U. Clinical-Epidemiological Peculiarities of the Acromegalic Osseous-Articular Complications in the Republic of Uzbekistan, / American Journal of Medicine and Medical Sciences ,10(5): 284-289doi:10.5923/j.ajmms. 20201005.02.
12. Wassenaar MJ, Biermasz NR, Bijsterbosch J, Pereira AM, Meulenbelt I, Smit JW, Roelfsema F, Kroon HM, Romijn JA, Kloppenburg M. Arthropathy in long-term cured acromegaly is characterised by osteophytes without joint space narrowing: a comparison with generalised osteoarthritis. Ann Rheum Dis. 2011;70(2):320–325.
13. Wassenaar MJ, Biermasz NR, Hamdy NA, Zillikens MC, van Meurs JB, Rivadeneira F, Hofman A, Uitterlinden AG, Stokkel MP, Roelfsema F, Kloppenburg M, Kroon HM, Romijn JA, Pereira AM. High prevalence of vertebral fractures despite normal bone mineral density in patients with long-term controlled acromegaly. Eur J Endocrinol. 2011;164(4):475–483.

ВОЗМОЖНОСТИ РАННЕЙ ДИАГНОСТИКИ ДИСФУНКЦИИ МИОКАРДА У ПАЦИЕНТОВ С СИНДРОМОМ ТИРЕОТОКСИКОЗА

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РЕЗЮМЕ: Основная функция гормонов щитовидной железы заключается в поддержании баланса сердечной функции наряду с регуляцией обмена веществ. Любые изменения в уровне гормонов щитовидной железы будут оказывать влияние на нормальное функционирование сердца. Первоначальное повышение уровня гормонов приведет к увеличению сократительной способности левого желудочка, что далее приведет к повышению сердечного выброса, в то время как хроническое воздействие тиреотоксикоза приведет к снижению насосной функции сердца, к увеличению риска аритмий, снижению общей функции левого желудочка, фиброзу и, в конечном итоге, приведет к сердечной недостаточности. Дисфункция сердца является одной из основных причин смерти в случаях гипертиреоза, что в основном обусловлено значительными изменениями гемодинамики, обусловленными нарушением мышечной функции сердца. Ранняя диагностика изменений в структуре миокарда и его ранних функциональных биомаркерах является краеугольным камнем для улучшения качества жизни, продолжительности жизни и общего состояния здоровья пациента. В данной статье описаны современные возможности и попытки ранней диагностики сердечной дисфункции, развившейся в результате синдрома тиреотоксикоза.

Ключевые слова: синдром тиреотоксикоза, гипертиреоз, сердечная дисфункция, аритмии, фибрилляция предсердий, сердечная недостаточность, натриуретический пептид, BNP, NT-pro-BNP, speckle tracking эхокардиография.

ТИРЕОТОКСИКОЗ СИНДРОМИ БИЛАН БЕМОРЛАРДА МИОКАРД ДИСФУНКЦИЯСИ ХОЛАТИНИ ЭРТА ТАШҲИСОТИ ИМКОНИЯТЛАРИ

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РЕЗЮМЕ

Қалқонсимон без гормонларини асосий вазифаси юрак фаолиятини ва моддалар алмашинуви мувозанатини сақлашдадир. Гормонларни қонда миқдорини ўзгариши юракни нормал ишлашига катта таъсир кўрсатади. Бошланғич даврда гипертиреоз холати чап қоринчани қисқариш қобилиятини оширади, бу юрак отиш фракциясини кўпайишига олиб келади. Шу билан бирга сурункали гипертиреоз юракни қон хайдаш хусусиятини пасайтиради, аритмиялар ривожланишига олиб келади, фиброзга ва, натижада, юрак етишмовчилигига олиб келади. Юрак дисфункцияси гипертиреоз холатларида ўлимни асосий сабабларидан бири хисобланади ва у гемодинамикани сезиларли бузилишлари натижасида ривожланади. Миокард структурасида ўзгаришларни эрта ташҳисоти ва буни эрта функционал биомаркёрларини аниқлаш беморларни хаёт сифатини кўтаришда, давомийлигини узайтиришда ва умуман саломатлигини яхшилашда катта аҳамиятга эга. Ушбу маоқолада тиреотоксикоз синдроми натижасида ривожланган юрак дисфункциясини ташҳислашда хозирги кундаги имкониятлар ва харакатлар кўрсатилган.

Калит сўзлар: тиреотоксикоз синдроми, гипертиреоз, юрак дисфункцияси, аритмия, хилпилловчи аритмия, юрак етишмовчилиги, натриуретик пептид, BNP, NT-pro-BNP, speckle tracking эхокардиографияси.

POSSIBILITIES OF MYOCARDIUM DYSFUNCTION'S EARLY DIAGNOSTICS IN THYROTOXICOSIS

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The main function of thyroid hormones (TH) is to maintain a balance in cardiac function along with the regulation of metabolism. Any alterations in the thyroid hormone levels will further affect the normal functioning of the cardiac muscles. Initial raise in the hormones will result in increased contractility of the left ventricle (LV) resulting in the raise of cardiac output, whereas chronicity of the disease will cause reduction in normal behaviour of cardiac function, thereby causing increased risk of arrhythmias, reduction in global function of LV, fibrosis and ultimately will result in heart failure (HF). Cardiac dysfunction is one of the main causes of death in hyperthyroid cases, which is mainly due to remarkable changes in the haemodynamics resulting from abnormal muscle function of heart and diaphragm. Early diagnosis of changes in myocardium structure and its early functional biomarkers is the cornerstone to improve patient's life's quality, longevity and their health generally. There are described the current opportunities and attempts to early diagnosis of cardiac dysfunction developed as a result of thyrotoxicosis syndrome.

Introduction

Thyrotoxicosis syndrome is known for its ability to have a negative effect on the patient's cardiovascular system, causing at least a significant deterioration in the quality of life, including disability and death, against the background of inadequate therapy. To date, attempts are being made to create a set of measures for the early identification of a special risk group, among which the effect of excess production of TH has a more pronounced effect than in the rest of the cohort of patients, leading to the early development of complications such as atrial fibrillation (AF), gradually developing into a permanent form and HF that reduces the ability to work, and sometimes the ability to self-service. However, these attempts, possibly due to the small number of study groups, inconsistent results, or the isolation of the components of early diagnosis - either the biochemical side or the functional - for one reason or another, did not reach the stage when it could be confidently, in order to prevent irreversible complications of the syndrome thyrotoxicosis, use certain methods to identify patients at risk.

Thyrotoxicosis syndrome is a polyetiological pathology, which, first of all, develops due to Graves' disease, and less often, due to toxic adenoma and multinodular toxic goiter. The incidence of cardiovascular complications of thyrotoxicosis syndrome varies due to the difference in the criteria presented for research. For example, the incidence of thyrotoxic cardiomyopathy was 12-68% of all cases of hyperthyroidism; left ventricular diastolic dysfunction was 47%; dilated cardiomyopathy 1%, and only 1/3 of them were reversible; pulmonary hypertension - in 29.6% of patients with subclinical hyperthyroidism and 39.6% of patients with overt hyperthyroidism [7]. Despite the obvious influence of the duration of the underlying disease on the development of complications, both in the literature and in practice, there are cases with a short history of the disease and severe complications, and vice versa - cases of a long history of thyrotoxicosis and the absence of clinically significant cardiovascular traces of thyrotoxicosis. This speaks of the influence of various factors and not only the severity or duration of the main disease. The literature review presents us with the following assumptions: older age, previous ischemic heart disease, disorders of the valvular apparatus of the heart for various reasons, hypertension, severity or presence of endocrine ophthalmopathy, large size of the thyroid gland, higher levels of free thyroxine (fT4), total triiodothyronine (T3) and antibodies to the thyroid

stimulating hormone receptor (TSHr-AB) [7]. Conditions with previous cardiovascular pathology or the manifestation of a permanent form or clinically pronounced paroxysmal form of AF or HF does not raise doubts about the early radical therapy of thyrotoxicosis syndrome by radioactive ablation of the thyroid gland and senselessness and the danger of conservative therapy, which requires another 12-18 months from the patient. In contrast to this situation, asymptomatic patients, in the early stages of cardiac dysfunction without complaints of impaired pumping function of the heart or rhythm disturbances, with sinus rhythm without pathological changes on a single electrocardiogram, remain under the attention of specialists. Only with the progression of HF or in situations where the arrhythmia is clinically manifested or becomes permanent for registration on a single recording of an electrocardiogram - only in these situations does the endocrinologist decide to conduct radical therapy. At the same time, according to the results of numerous studies, the prognosis of decompensated HF is worse than that of cancer patients. Up to 70% of men and 63% of women die in the first 6 years after the first symptoms of HF [24]. For the early diagnosis of HF of a wide etiology, attempts are made to identify biochemical markers, as well as the latest techniques of echocardiographic examination. The most justified numerous studies with great prospects for application in routine practice today are the determination of NP and the speckle tracking echocardiography (STE) method. However, narrowing the focus on thyrotoxicosis syndrome, points for discussion arise when these methods are applied in this pathology.

The biochemical assessment of cardiac dysfunction considered the use of various markers of damage - troponin, creatine kinase, natriuretic peptides (NP), and others. It should be noted that the values of the first two increase with myocardial necrosis, which is rarely observed in thyrotoxicosis syndrome [3]. Physiologically, the level of NP increases with stretching and pressure overload of the left ventricular tissue. These processes are observed in the development of HF, however, it should also be taken into account that the level of NP is increased in the following conditions: 1) acute and chronic renal failure; 2) arterial hypertension; 3) diseases accompanied by pulmonary hypertension; 4) older age; 5) female sex; 6) liver cirrhosis; 7) hyperthyroidism; 8) sepsis) 9) chemotherapy [11]. It would be logical to assume that the use of NP as a marker of cardiac dysfunction in thyrotoxicosis syndrome would lead to an increase in false-positive results and overdiagnosis of cardiac dysfunction. However, a review of the literature of the studies carried out presents conflicting results.

There are a lot of publications message that the largest increasing NP (brain natriuretic peptide and its precursor – N-terminal-pro-BNP) observed in overt hyperthyroidism, less in subclinical one and least in hypothyroidism [5; 17, 21] The other study show that treatment new-onset hyperthyroidism lead to decresing brain natriuretic peptide (BNP) up to reference values and BNP interpretation in hyperthyroidism can lead to misdiagnosis of HF [6]. There is also case report about patient with acute decompensated HF on base of overt hyperthyroidism, where initial BNP value - 800,6 pg/ml with congestion in both circulation circles, tachysistolic form AF and thyrotoxicosis - in 2 weeks of treatment with antithyroid drugs, beta-blockers, diuretics and anticoagulants with congestion resolution, left ventricular ejection fraction increasing from 26% to 48% and conversion of AF to normosystolic form, but thyrotoxicosis remaining - value of BNP continue to be high - 940,2 pg/ml [8]. Namely, the cardiac function improving not to reflect on BNP level, presumably because of hyperthyroid status continuation.

However, when we analyze literature we met publications that showed detection BNP/NT-pro-BNP useful for cardiac dysfunction diagnostics. So, in 2005 the investigation carried out by Chinese scientists on 67 patients with hyperthyroidism and 32 healthy volunteers showe that BNP was higher in hyperthyroid patients and that largest amount was found in patients with clinical and echocardiographic signs ventricular dysfunction [22].

In 2009, the other group of Chinese scientists research 58 children with hyperthyroidism, 28 from them had diagnosis thyrotoxic heart, 30 children was selected as control group. This research showed that sensitivity and specificity of BNP using was 92,86% and 90,00%, respectively [11]. In favor of NP revealing as objective monitoring of cardiac dysfunction in hyperthyroidism said indian researchers [14]. Summarizing the above mentioned studies, we can say that conflicting data from various studies require further study of the use of NP as a predictor of cardiac dysfunction.

In the echocardiographic assessment practice of cardiac pathology, methods of quantitative assessment of heart function have recently begun to be used, in particular, such a method as STE. The technique involves the assessment of deformation (changes in the size of the myocardium), twisting and untwisting of the myocardium segmentally and globally, which reflects myocardial contractility

and, which is especially important, provides a quantitative assessment of these parameters. The previous technique of tissue echocardiography did not make it possible to evaluate depending on the angle in the scan, i.e. the assessment of the movement of myocardial fibers was carried out only in the longitudinal plane. The STE technique makes it possible to assess the movement of the myocardium in three planes (longitudinal, circular and radial) [1].

For a clearer understanding of the method's essence, it should be noted that the LV myocardium consists of two layers: subendocardial, which envelops the LV in a clockwise helical manner, and subepicardial, which envelops the LV in a helical counterclockwise direction. If we look from the apex of the heart, it rotates counterclockwise during systole, and the base of the heart - clockwise. When the apex and base of the LV rotate in opposite directions, the myocardium thickens and shortens in the longitudinal direction - roughly speaking, contraction can be compared to "squeezing a rag." Thus, when ultrasound is conducted into the myocardial tissue, they are scattered and reflected in the form of speckles (spots) in the gray scale of a two-dimensional image. It is the movement of these speckles during twisting-systole and untwisting-diastole that is evaluated by the STE technique. Further, the software of the technique allows you to translate this movement into a graphic image and, on the basis of this, calculate the numerical values of the myocardial contractility.

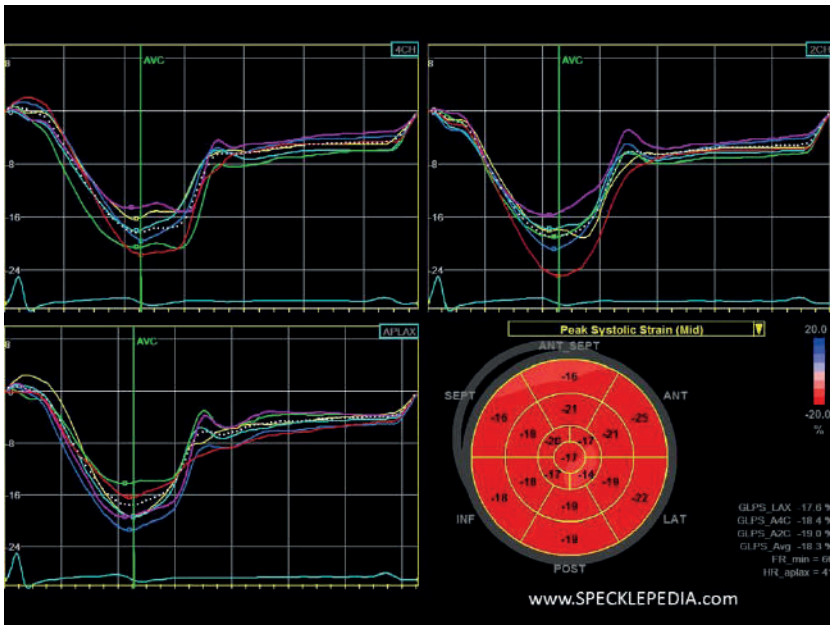

Fig. 1. *Speckle tracking echocardiography. Indicators in a healthy person. Indicators of global longitudinal strain (GLS) in different segments of the myocardial section vary from -16 to -22, which corresponds to normal values [25].*

Until now, there are difficulties with the generally accepted standards for strain indices and strain rate according to STE [12]. In the HUNT study, which included 1266 healthy individuals, the mean values of longitudinal strain and strain rate, respectively, were: -17.4% in women and -15.9% in men [4]. Due to the fact that, the peculiarities of specialized software from different manufacturers leading to the evaluation parameters are not interchangeable, the recommendations provide a range of average values [9]. As an approximate guideline, The Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging recommendations indicate the value of the global longitudinal deformation -20%, the absolute values above which indicate the norm [9]. It was found that women are characterized by higher absolute values of myocardial deformation and with age, global deformation decreases [1, 4]

A large number of positive results of STE use served as the basis for the publication of separate recommendations on these echocardiographic techniques: " Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics " (ASE / EAE, 2011) and "Definitions for a common standard for 2D speckle tracking echocardiography" (EACVI /ASE , 2015) [12, 22]. It should be noted that the technique has demonstrated the reproducibility and availability for clinical use of tissue Doppler sonography and echocardiographic assessment of myocardial deformation and

was noted in the European guidelines for the diagnosis and treatment of HF (ESC, 2016) [19].

The use of STE has been described in various pathologies cases. There is evidence of the positive use of STE in risk stratification of patients with CHF [14], in assessing the function of the right ventricle and left atrium, with left ventricular hypertrophy, with ischemic heart disease, with HF, with diseases of the pericardium and restrictive cardiomyopathy, with valvular pathology, in assessing the effect of cardiotoxicity in the treatment of oncopathology. In the latter case, echocardiographic assessment of myocardial function - LV ejection fraction is used to diagnose the cardiotoxic effect of anticancer therapy [18]. According to the literature, a decrease in myocardial deformation is a more informative indicator than LV ejection fraction for early detection of asymptomatic systolic dysfunction caused by pharmacological influence in the treatment of oncopathology. [11, 17].

Taking into account such a wide scope of application of the STE method, and also its prospects, it is necessary to study its possibilities in case of thyrotoxicosis syndrome to improve the cardiovascular prognosis of patients. At the same time, further studies are needed, including multicenter studies to study the diagnostic accuracy and reproducibility of STE indicators in this pathology. In addition, the STE software of various manufacturers of echocardiographic equipment needs to be standardized. Nevertheless, STE assessment of myocardial deformation and LV twisting can be very useful in a number of clinical situations as an accessory tool for quantitative characterization of myocardial and cardiac function in general. There is evidence that such a generally accepted characteristic of myocardial function as ejection fraction in in some cases may be insufficiently informative and not correlate with the severity of the clinical condition, especially in the initial stages of HF [9, 19]. It is not by chance that an independent term has been proposed to denote cardiac pathology in such patients - “HF with a preserved ejection fraction”. The use of modern echocardiographic techniques expands the diagnostic capabilities in terms of assessing the systolic and diastolic functions in this category of cardiac patients with a number of pathological conditions, and it is quite possible, in thyrotoxicosis syndrome too.

The scope of application of STE in the literature for thyrotoxicosis syndrome is not wide enough - there are only a few articles with using this method in describing mechanical changes of the LV structure in thyrotoxicosis syndrome. A study by Greek scientists Aroditis K. and his team [2], published in 2016, investigated this problem in 44 patients with newly diagnosed Graves’ disease compared with a control group of 43 healthy volunteers, where they observed the effect of excess TH on the heart and changes, occurring within 6 months of therapy. It should be noted that, according to the authors, this study is the first to use the latest technique for assessing heart function by STE echocardiography in Graves’ disease.

Cardiac function was assessed using traditional echocardiography and STE. Initially, in the group of patients with manifest thyrotoxicosis, the indicators of contractile function were significantly higher, including the end-diastolic dimension of the LV (LV EDD)uu, the size of the atria, the thickness of the posterior wall of the myocardium, and the impairment of the relaxation function of the left ventricular myocardium was reliably presented. STE parameters such as longitudinal, transverse and radial myocardial deformities and strain rate during relaxation were comparable in both groups. After 6 months of thyrostatic therapy with euthyroidism achievement in the group of patients the indicators of LV size during diastole, LV mass, volume and diameter of the left atrium decreased significantly. The ejection fraction did not undergo significant changes. On the other hand, there was an improvement in diastolic function. On STE echocardiography, indicators of longitudinal and radial myocardial deformation did not show significant changes at baseline, in comparison with the control group, as well as after 6 months and the achievement of euthyroidism. However, in the final period of the study, the radial deformation of the myocardium in patients with HF was significantly higher than in the control group, and after therapy, compared with the initial value, it did not show a significant change. The fact that there was no dynamics in the indicators of longitudinal and radial deformation indicates the absence of a significant change of systolic function after therapy. The study provides a strong correlation between the level of free T4 and the thickness of the interventricular septum, as well as a significant correlation with the TAPSE indicator (the amplitude of mixing the level of the tricuspid valve in systole, which characterizes the contractility of the right ventricle).

Another study by Indian scientists published in 2018 included 50 patients with Graves’ disease and thyroiditis (1:1) [15]. Probably, the inclusion of patients with thyroiditis was not entirely correct, due to the fact that irreversible cardiovascular complications are rarely observed because of the short duration and low severity of thyrotoxicosis in thyroiditis. Also, in contrast to the previous work, the

selection was carried out regardless of the duration of thyrotoxicosis and there was no control group. Traditional echocardiography and STE echocardiography were used. As in the previous work, there was an increase in the sizes of the myocardium (end-systolic and end-diastolic LV dimensions), as well as LV volume (end-systolic and end-diastolic LV volumes), an increase in pumping function (ejection fraction, shortening fraction). Among 50 patients, left ventricular systolic dysfunction was observed in 4%, while diastolic dysfunction was detected in 12%. Among patients with diastolic dysfunction, 4% had normal ejection fraction and the values of global longitudinal deformity were threshold, which, according to the authors, is given as an early sign of systolic dysfunction by the authors.

These two works presented the characteristic changes that occur in the structure of the heart when exposed to excessive amounts of thyroid hormones, describing the early signs by the most sensitive methods. Obviously, in the first work in the group of patients, there was no need for radical therapy of thyrotoxicosis, the patients had a short duration of thyrotoxicosis and diseases that independently cause structural damage to the heart were excluded. In the second study, there were patients with a longer duration of the underlying disease, however, the diversity of selection, the lack of control after the therapy did not make it possible to identify a group with irreversible structural changes in the myocardium. Determination of the cardiovascular prognosis in a patient with thyrotoxicosis should presumably combine the analysis of a whole set of data, including risk factors - gender, age, existing cardiovascular diseases, duration of thyrotoxicosis, the degree of aggression of thyrotoxicosis (the level of thyroid hormones, the level of autoantibodies to the TSH receptor), condition cardiovascular system - biochemical and functional. Such an approach would allow patients at risk not to waste time for 12-18 months of conservative therapy, as suggested by the current approach of the European and American Thyroid Association (ETA, 2018; ATA, 2016), while all studies show that as increasing the duration of thyrotoxicosis and the patient's age, the cardiovascular prognosis also worsens.

Conclusion

There is a great prospect for the application of methods for detecting NP and STE in combination with clinical, biochemical and functional data of patients with thyrotoxicosis syndrome to determine their further cardiovascular prognosis, which requires large-scale multicenter studies in this direction. It is necessary to assess the likelihood of obtaining false-positive results when detecting NP against the background of thyrotoxicosis, as well as to determine the role of STE. Such a step would make a great contribution to the development of a system for personalized prediction of the development of cardiovascular complications of thyrotoxicosis syndrome against the background of conservative treatment and radioiodine therapy, with the aim of early detection in patients of changes in the cardiovascular system, respectively, in improving the quality of life, reducing disability and mortality rates in this patient categories

References

1. Abduch M.C., Alencar A.M., Mathias W.Jr, Vieira M.L. Cardiac mechanics evaluated by speckle tracking echocardiography // Arq Bras Cardiol. – 2014. Vol.102 (4). - 403-412.

2. Aroditis K., Pikilidou M., Vourvouri E., Hadjistavri L., Zebekakis P., Yovos J., Efthimiadis G., Karvounis H. Changes in cardiac function and structure in newly diagnosed Graves' disease. A conventional and 2D-speckle tracking echocardiography study // Int J Cardiovasc Imaging. – 2016. – Vol.33(2). -187-195.

3. Bae, Eun & Lim, Sang & Jeong, Myung & Kim, Weon & Kim, Jung-Tae & Park, Ok & Kang, Ho-Cheol & Ahn, Young & Cho, Jeong & Park, Jong & Chung, Min & Kang, Jung. A Case of Acute Myocardial Infarction Associated with Hyperthyroidism // Korean Circulation Journal. – 2004. - Vol. 34. – 209.

4. Dalen H., Thornstensen A., Aase S.A., et al. Segmental and global longitudinal strain and strain rate based on echocardiography of 1266 helathy individuals: the HUNT study in Norway // Eur J Echocardiogr. – 2010. – Vol.11(2). -176-183.

5. Ertugrul D.T., Gursoy A., Sahin M., Unal A.D., Pamuk B., Berberoglu Z., Ayturk S., Tutuncu N.B., Demirag N.G. Evaluation of brain natriuretic peptide levels in hyperthyroidism and hypothyroidism // Journal of National Medical Association. - 2008. -Vol. 100(4). - 401-405.

6. Ertugrul D.T., Yavuz B., Ata N., Yalcin A.A. Decreasing Brain Natriuretic Peptide Levels after Treatment for Hyperthyroidism // Endocrine Journal. - 2009. - Vol. 56(9). - 1043-1048.

7. Khodjaeva S.Kh., Ubaydullaeva N.B., Nasirkhodjaev Ya.B. Thyrotoxic cardiomyopathy. Risk

factors analysis in patients with thyrotoxicosis and atrial fibrillation. – Herald TMA. Special edition to conference “Diabetes mellitus of XXI century. Global issues. Local solution”. – 2019. – 62.

8. Kishida C., Naito R., Kasuya H., Kaneko T. et al. A Case of Heart Failure with Hyperthyroidism Demonstrating Discrepancy between the Clinical Course and B-type Natriuretic Peptide Levels // Internal Medicine. - 2018. - Vol. 57(12). - 1747-1749.

9. Lang R.M., Badano L.P., Mor-Avi V., et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging // Eur Heart J Cardiovasc Imaging. – 2015. – Vol. 16 (3). - 233-270.

10. Lin X.M., Wen F.Q., Chen T., Ding L., Chang X.Y., Zhang W. Value of Serum Brain Natriuretic Peptide in the Diagnosis of Hyperthyroid Heart Disease in Children // Chinesse Journal of Contemporarry pediatrics. – Vol. 11(8). – 631-634.

11. Mangla A. Brain-Type Natriuretic Peptide (BNP) // MedScape materials. – 2019. - https://emedicine.medscape.com/article/2087425-overview#a2

12. Mondillo S., Galderisi M., Mele D., et al.; Echocardiography Study Group Of The Italian Society Of Cardiology (Rome, Italy). Speckle-tracking echocardiography: a new technique for assessing myocardial function // J Ultrasound Med. – 2011. – Vol. 30(1). - 71-83.

13. Mor-Avi V., Lang R.M., Badano L.P., et al. Current and evolving echocardiographic techniques for the quantitative evaluation of cardiac mechanics: ASE/EAE consensus statement on methodology and indications endorsed by the Japanese Society of Echocardiography // Eur J Echocardiogr. – 2011. – Vol. 12(3). - 167-205.

14. Muthukumar S., Sadacharan D., Ravikumar K., Mohanapriya G., Hussain Z., Suresh R.V. A Prospective Study on Cardiovascular Dysfunction in Patients with Hyperthyroidism and Its Reversal After Surgical Cure // World Journal of Surgery. - 2016. -Vol. 40(3). - 622-628.

15. Nahum J., Bensaid A., Dussault C., et al. Impact of longitudinal myocardial deformation on the prognosis of chronic heart failure patients // Circ Cardiovasc Imaging. – 2010. – Vol. 3(3). - 249-256.

16. Namitha K., Narasimha D. Pai2, J. Kannan, Thangasheela A., Francis N. P. Monteiro. Study of left ventricular function by speckle tracking echocardiography and conventional echocardiography in patients with hyperthyroidism // J. Evolution Med. Dent. Sci. – 2018. – Vol. 7 (32). - 3629-3634.

17. Ozmen B., Ozmen D., Parildar Z., Mutaf I., Bayindir O. Serum N-terminalpro-B-type natriuretic peptide (NT-pro-BNP) levels in hyperthyroidism and hypothyroidism // Endocrine Research. - 2007. - Vol. 32(1-2). - 1-8.

18. Pizzino F., Vizzari G., Qamar R., et al. Multimodality imaging in cardiooncology // J Oncol. – 2015. – Vol. 26. – 39-50.

19. Plana J.C., Galderisi M., Barac A., et al. Expert consensus for multimodality imaging evaluation of adult patients during and after cancer therapy: a report from the American Society of Echocardiography and the European Association of Cardiovascular Imaging // Eur Heart J Cardiovasc Imaging. – 2014. – Vol. 15(10). - 1063-1093.

20. Ponikowski P., Voors A.A., Anker S.D., et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) Developed with the special contribution of the Heart Failure Association (HFA) of the ESC // Eur Heart J. – 2016. – Vol. 37(27). - 2129-2200.

21. Schultz M., Faber J., Kistorp C., Jarlov A., Pedersen F., Wiinberg N., Hildebrandt P. N-terminal-pro-B-type natriuretic peptide (NT-pro-BNP) in different thyroid function states // Clin Endocrinol (Oxf). - 2004. - Vol. 60(1). - 54-59.

22. Silvet H., Young-Xu Y., Walleigh D., Ravid S. Brain natriuretic peptide is elevated in outpatients with atrial fibrillation // American Journal of Cardiology. - 2003. - Vol. 92. - 1124-1127.

23. Voigt J.U., Pedrizzetti G., Lysyansky P., et al. Definitions for a common standard for 2D speckle tracking echocardiography: consensus document of the EACVI/ASE/Industry Task Force to standardize deformation imaging // Eur Heart J Cardiovasc Imaging. – 2015. – Vol. 16(1). - 1-11

24. Либов И.А. Современный взгляд на патогенез сердечной недостаточности и основы ее лечения // Лечащий врач. – 2001. – № 8. – С. 45-49

Links

25. https://specklepedia.com/normal-case-1/

QUESTIONS OF EPIDEMIOLOGY, ETIOPATHOGENESIS, TREATMENT AND PROGNOSIS OF HEART FAILURE IN PATIENTS WITH DIABETES MELLITUS.

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The combination of diabetes mellitus and chronic heart failure (DM and CHF) is a dangerous cocktail that is an important risk factor and the main comorbid condition that accompanies the risk. DM is one of the most significant causes of chronic heart failure (CHF). This article discusses the issues of epidemiology, pathophysiology, basic principles of treatment strategy and prognosis of CHF outcomes in patients with DM2.

Keywords: diabetes mellitus, chronic heart failure, Cardiovascular diseases, sugar-reducing drugs.

ВОПРОСЫ ЭПИДЕМИОЛОГИИ, ЭТИОПАТОГЕНЕЗА, ЛЕЧЕНИЯ И ПРОГНОЗА СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ.

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Сочетание сахарного диабета и хронической сердечной недостаточности- (СД и ХСН)-опасный коктейль, который является важным фактором риска и основным коморбидным состоянием, сопутствующим риску. СД является одной из значимых причин развития хронической сердечной недостаточности (ХСН). В данной статье обсуждаются вопросы эпидемиологии, патофизиологии, основные принципы лечебной стратегии и прогноза исходов ХСН у больных СД2.

Ключевые слова: сахарный диабет, хроническая сердечная недостаточность, сердечно-сосудистые заболевания, сахароснижающие препараты.

QANDLI DIABET BILAN OG'RIGAN BEMORLARDA YURAK ETISHMOVCHILIGINI EPIDEMIOLOGIYASI, ETIOPATOGENEZI, DAVOLASH VA PROGNOZLASH MASALALARI.

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Qandli diabet va surunkali yurak etishmovchiligining birga kechishi xavfli kokteyl bo'lib, u muhim xavf omili va xavf bilan bog'liq asosiy komorbid holatdir. Qandli diabet surunkali yurak etishmovchiligining muhim sabablaridan biridir. Ushbu maqolada Qandli diabet bilan og'rigan bemorlarda surunkali yurak etyshmochiligini epidemiologiyasi, patofiziologiyasi, davolash strategiyasi asosiy printsiplari va surunkali yurak etishmovchiligining prognoz qilish masalalari muhokama qilinadi.

Kalit so'zlar: qandli diabet, surunkali yurak etishmovchiligi, yurak-qon tomir kasalliklari, gipoglikemik dorilar.

Diabetes mellitus (DM) is one of the most pressing problems of modern medicine, the prevalence of which is growing every year and the rate of growth of DM today has taken the scale of a worldwide epidemic. Over the past 10 years, the incidence rate has increased by 2 times, and according to the IDF in 2015 reached 415 million people, in 2017 425 million and according to the latest data in 2019, 463 million people in the world aged 20-79 years suffer from diabetes, and according to forecasts by 2030, their number will increase to 700 million. the majority of patients with DM are those at the age of the greatest work activity [1,2].

DM causes the development of serious micro-and microvascular complications: nephropathy, retinopathy, neuropathy, diabetic foot syndrome, myocardial infarction(MI), chronic heart failure (CHF), stroke, leading to high disability and mortality of patients [3,4].

According to Alimov A. In and co. as of 01.01.2019, there are 230,610 patients with diabetes registered in Uzbekistan: 18,349 patients with type 1 diabetes and 212,261 patients with type 2 diabetes. The prevalence of type 2 diabetes is 7.9% among people over 35 years of age and has increased 1.6 times over the past 14 years (4). According to conducted screening in rural regions of Uzbekistan for identification of diabetes and IGT among 6189 individuals revealed a high prevalence of type 2 diabetes in high risk patients (13.3%), compared with the data of the national register of 5-6%, indicating the importance of screening for active detection of people with diabetes, IGT and IFG in order to begin treatment and prevent the development of severe complications. The prevailing risk factors for diabetes among the rural population over 40 years of age in Uzbekistan were: AH-78.6%; obesity (BMI >30) - 43.3%, HD - 42%, hereditary predisposition-35.2%. (Ibragimova N. sh., et al., 2018) [5,6].

Diagnosis of these conditions is not difficult and is available at all levels of the health organization, however, in Uzbekistan, as in many other countries of the world, there is still a discrepancy between the data on registration for diabetes and the results of epidemiological studies (Akbarov Z. S. et al., 2016; Ismailov S. I., et al.,2012) [7].

Type 2 diabetes is one of the established risk factors for the development of cardiovascular diseases, which has been proven in the results of numerous studies. The high incidence of CVD in type 2 diabetes is due not only to the presence of risk factors such as hyperglycemia, hypertension, and dyslipidemia, but also to the existence of a number of factors that accelerate the development and progression of vascular complications in diabetes. These include hereditary predisposition to antipathies, bad habits, congenital or acquired disorders of lipid metabolism, blood clotting systems [3,4,9,10].

The risk of developing coronary heart disease (CHD) in patients with type 2 diabetes is 2-4 times higher, and the risk of developing myocardial infarction (MI) is 6-10 times higher than in the General population. The clear relationship between type 2 diabetes and CVD is a well-known fact, confirmed by the results of numerous population studies. The main causes of high mortality in patients with diabetes are cardiovascular diseases. In the progression and development of CVD in patients with type 2 diabetes, the leading role belongs to risk factors (FR). Based on the results of numerous international epidemiological prospective studies, various scales have been proposed for calculating the total cardiovascular risk [4,9,10].

Epidemiology, etiopathogenesis of chronic heart failure in diabetic patients

The combination of diabetes mellitus and chronic heart failure (DM and CHF) is a dangerous cocktail that is an important risk factor and the main comorbid condition that accompanies the risk. DM is one of the most significant causes of chronic heart failure (CHF). Foreign epidemiological studies show that about 12% of patients with type 2 diabetes have signs of CHF, and 15-26% of people with CHF suffer from type 2 diabetes. The problem of combining CHF and DM2 has become so urgent that despite the existence and regular updating of separate Recommendations for both CHF and DM2, in 2019 special Recommendations for the combination of CHF and DM2 were published, proposed by experts from the American Heart Association and Heart Failure Society of America [3,4].

Chronic heart failure (CHF) as the final stage of all CVD takes a leading position in the structure of total mortality and permanent disability, including in people of working age. Currently, in all developed countries in the structure of the main causes of chronic heart failure (CHF) in addition to arterial hypertension (AH) and CHD, the share of type 2 diabetes mellitus (DM2) is increasing, which reaches 27% in the Pan-European sample [9.10].

At the same time, metabolic disorders, in particular hyperglycemia, as a risk factor for death, ranks third, second only to hypertension and Smoking, and obesity is among the top five risk factors for death.

Most cardiovascular diseases (CVD) are associated with
disorders of carbohydrate and lipid metabolism, which eventually lead to
joins inflammation in adipose tissue, the development of resistance to
insulin and obesity, endothelial dysfunction, atherosclerotic
vascular remodeling, myocardial hypertrophy, increased stiffness, and left ventricular diastolic dysfunction.

The prevalence of CHF in patients with DM-2 aged <65 years, both men and women, is higher

than in the General population — 4 and 8 times, respectively [13, 14]. Diastolic dysfunction, diagnosed in 50-75% of patients with DM-2 without concomitant cardiovascular pathology, is considered by researchers as a manifestation of diabetic cardiomyopathy [4,16,17]. CHF with a reduced ejection fraction in patients with DM is accompanied by a significantly higher probability of death and hospitalization compared to patients without DM [4.18]. Patients with DM-2 and CHF have the worst long-term prognosis. In patients with diabetes, there is an increased risk of heart failure progression (CHF) — HR 1.17; 95% CI 1.04-1.32 and hospitalizations for CHF — HR 1.19; 95% CI 1.04-1.36, patients with diabetes and CHF also differ in longer periods of inpatient treatment [4.19]. The basis for the development of CHF in DM are macrogiopathy of the coronary arteries, structural remodeling of the myocardium, myocardiodystrophy and neuropathy. Large-scale studies of BEST, RESOLVD, and MERIT-HF have confirmed that patients with type 2 diabetes have a higher rate of hospitalization and duration of hospital stay than those without carbohydrate metabolism disorders [20,21].

In the last decade, such as the imbalance of circulating hormones, inflammatory cytokines and adipocytes are considered as molecular factors involved in the aggravation of structural and functional changes of the heart and blood vessels in patients with CVD, combined with metabolic disorders.

In CHF, the presence of concomitant DM2 is associated with higher overall and cardiovascular mortality, as well as a higher frequency of nonfatal complications that are the causes of repeated hospitalizations). The important role of DM2 as a comorbidity complicating the course of CHF dictates the need to clarify the pathophysiological mechanisms by which concomitant DM2 can worsen the prognosis of CHF, which is necessary to improve the effectiveness of treatment of this category of patients [4, 20].

In the Framingham study, the relative risk of developing CHF in patients with type 2 diabetes aged 45-74 years was 2 times higher in men and 6 times higher in women compared to patients without diabetes [15]. The high incidence of CHF in patients with type 2 diabetes was also demonstrated in the well-known epidemiological study NHANESI (The National Health and Nutrition Examination Survey) [22].

As the etiopathogenesis of this combined pathology, it should be noted that the etiological relationship of CHF and DM is mutually directed. So, a long course of DM can lead to the development of myocardial dysfunction and CHF, the cause of development can be endothelial dysfunction, dyslipidemia, disorders of the clotting system, hyperglycemia, which affects the function and morphology of the myocardium. On the other hand, CHF can lead to the development of type 2 diabetes, as a result of hyper perfusion of organs and hyper activation of neurohumoral systems, pathogenic shifts develop that contribute to an increase in the concentration of glucose in the blood. These include reducing the consumption of glucose by muscle tissue, increased gluconeogenesis in the liver, kontrinsulfarin effects of catecholamine. The second mechanism for the development of CHF in patients with type 2 diabetes can be the direct effect of prolonged hyperglycemia on the heart muscles and its damage. Myocardial damage on the background of hyperglycemia is mediated by microangiopathy, impaired calcium transport and fatty acid metabolism. An example of a glucose-toxic effect on the myocardium can be considered the development of diabetic cardiomyopathy, which can be considered as a combination of violations of the properties of the myocardium, electrophysiological processes and hyper cate cholanemia [4,20,23].

The prevalence of CHF in patients with type 2 diabetes at the age of <65 years, both in men and women, is higher than in the General population by 4 and 8 times, respectively. Diastolic dysfunction, diagnosed in 50-75% of patients with type 2 diabetes without accompanying cardiovascular pathology, is considered as a manifestation of diabetic cardiomyopathy (Ostroumova). CHF with a reduced ejection fraction in patients with type 2 diabetes is associated with a significantly higher probability of death and hospitalization compared to patients without diabetes. Patients with type 2 diabetes and CHF have the worst long-term prognosis [4,20,23].

Choice of hypoglycemic drugs in people with DM2 at risk of developing CHF and those who already have CHF

The degree of influence of intensive hypoglycemic therapy on the risk of macro vascular complications in DM remains debatable [4.24]. Thus, in the UKPDS (United Kingdom Prospective Diabetes Study) [25] in the intensive care group, there was a 16% reduction in the risk of cardiovascular conditions: fatal or non-fatal MI and sudden cardiac death, but it was not statistically significant (p=0.052). Other major RCTS were also devoted to studying the effect of intensive antidiabetic therapy on the risk of macro vascular complications in comparison with standard therapy: ACCORD (Action to

Control Cardiovascular Risk in Diabetes) [26], ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) [27] and VADT (Veterans Affairs Diabetes Trial) [28].

In General, a meta-analysis of four major RCTS: UKPDS, ACCORD, ADVANCE, and VADT revealed a moderate and statistically insignificant reduction in the risk of major macro vascular conditions, including those associated with CHF, between groups with more intensive glycemic control (average HbA1C values of 6.4-7.0%) and its less intensive control (HbA1C levels 7,3-8,4%) [4, 26,27,28].

Biguanides (Metformin) is currently considered as the preferred initial hypoglycemic drug in individuals with DM2 in

absence of contraindications. It has the same position in persons with DM2 in combination with CHF. Before 2006 it was considered contraindicated in CHF because of fears the development of such rare complications such as lactic acidosis. Now it is shown that in such patients, its use is associated with a favorable effect on the prognosis. Thus, in a meta-analysis of 9 cohort studies, which included almost 34 thousand patients, it was demonstrated that the use of Metformin in individuals with CHF and DM2 was accompanied by a distinct decrease in overall mortality (by 20%) and the frequency of decompensation of CHF [12,29]. The UKPDS RCT sub analysis provides data on a possible reduction in the risk of myocardial infarction when Metformin is prescribed [30]. Experts recommend the use of Metformin as a basic hypoglycemic agent in people with DM2 who are at risk of developing CHF, as well as in patients with pre-existing CHF. It should be canceled in cases of severe decompensation of CH [31].

Sulfonylureas in the treatment of patients with DM2 with CHF are currently considered less preferable in comparison with a number of other classes of hypoglycemic drugs. At the same time, in several serious RCTS (UKPDS, BARI-2D, ADVANCE) [12,32], there was no clear evidence of an increase in cardiovascular risk (SSR) when using this group of drugs. The evidence can also be a large RCT of CAROLINA (Cardiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes). The results of the CAROLINA ® study were presented at the 79th scientific conference of the American Diabetes Association, which showed that the study reached the primary endpoint (Major Adverse Cardiac Event-MACE)-the onset of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke (three major cardiovascular events (3P-MACE)). These were recorded in 11.8% (356) in the linagliptin group and 12.0% (362) in the glimepiride group [33]. The General safety profile of linagliptin corresponded to the previously defined one, no new data was established. For the secondary endpoint and hospitalization cases due to unstable angina, linagliptin did not differ from glimepiride. 4P-MACE-13.2% when using linagliptin, 13, 3% – glimepiride is required.

In some patients with DM2 and CHF, the use of insulin therapy is required to achieve compensation of carbohydrate metabolism, but their use is associated with an increase in body weight, the risk of hypoglycemia, which requires caution and careful laboratory control. Although data from several RCTS (ORIGIN, UKPDS, BARI-2D) [34] did not show a worsening of the cardiovascular prognosis against the background of the use of insulin drugs, however, other reports show the possibility of increasing cardiovascular mortality in people with DM2 and CHF who received insulin, in comparison with other hypoglycemic drugs.

Drugs of the thiazolidinedione group are not recommended for use in persons with DM2 with CHF [35,36]. Drugs in this group may increase the risk of developing clinical manifestations of CHF in those with DM2 WHO have not previously had these manifestations. This position is supported by data from RCTS Proactive and RECORD, as well as meta-analysis data, where the use of both representatives of thiazolidinedione's was associated with an increased risk of CHF decompensation, in comparison with placebo [12,35,36].

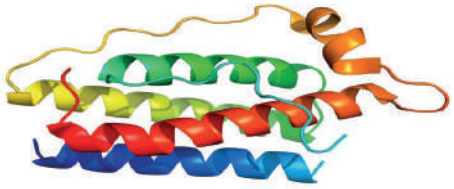
As for the use of glucagon-like peptide-1 receptor agonists in DM with CHF, several RCTS (LEADER, ELIXA, EXCEL, SUSTAIN-6) [37] have demonstrated that argpp-1 can reduce SSR in the General population of patients with DM2. With DM2 in combination with CHF, they are quite safe, although they do not have direct favorable effects on the prognosis (they do not reduce the risk of CHF decompensation). In individuals who have recently undergone CHF decompensation, their use requires caution (RCT FIGHT) [12,38].

Dipeptidyl peptidase-4 (idpp-4, dipeptidyl peptidase-4 (DPP-4) inhibitors) These oral medications are usually considered for DM2 as 2nd-line medications, in addition to Metformin. According to the

RCT (SAVOR TIMI-53, EXAMINE, TECOS, VIVIDD) [39], the use of idpp-4 is not associated with any adverse effect on the cardiovascular prognosis. In individuals with high SSR, saxagliptin increases the risk of CHF decompensation. Given the limited and contradictory data available, experts are currently cautious about the possibility of using idpp-4 in individuals with established CHF, as well as in those who have a high risk of its development [12,39,41].

A multicenter, randomized, double-blind, placebo-controlled study, SAVOR—TIMI 53 (Saxagliptin Assessment of Vascular Outcomes Recorded in Patients with Diabetes Mellitus-Thrombolysis in Myocardial Infarction 53) [4,41], focused on the effect of the DPP-4 inhibitor saxagliptin on cardiovascular outcomes, involved ~16,500 patients with DM-2 aged ≥40 years with a history of CVD (n=12929) and/or multiple FRS of their development (n=3533). The level of HbA1c at the screening visit was 6.5-12.0%, history of MI 38.0% and 37.6%, CHF 12.8% and 12.8%, coronary artery revascularization 43.1% and 43.3%, and was comparable in the saxagliptin and placebo groups. At the end of the follow-up period (an average of 2.1 years), both positive and negative effects of saxagliptin on cardiovascular events were noted — HR 1.00; 95% CI 0.89-1.12 (p=0.99), but a statistically significant increase in the frequency of hospitalization due to CHF progression in the saxagliptin group compared to the placebo group-3.5% vs 2.8%; OR 1.27; 95% CI 1.07-1.51 (p=0.007) [4.41].

The next group of drugs that is used in the treatment of DM and CHF is inglt-2, which is the first and so far the only class of sugar-lowering drugs for which there is strong evidence of a favorable effect on the cardiovascular prognosis, especially in patients with DM2 and CHF with low LV FV. Against the background of their use in patients with DM2 AND CHF with low LV FV in the RCT series (CANVAS, CVD-REAL), there was a decrease in total (49%) and cardiovascular mortality, a decrease in the frequency of CHF decompensation by 33-39%, which undoubtedly makes them the hypoglycemic drugs of choice in such individuals [12,42,43]. In addition, inglt-2 can be used as a component of a preventive strategy in people with DM2 AND a high risk of developing CHF (including post-infarction patients).



The prognosis of chronic heart failure in patients with diabetes mellitus

It is known that DM2, as comorbidity, leads among other diseases that burden the clinical course of all CVD without exception, mainly due to the early development of cardiovascular complications that worsen the prognosis. For a long time, it was believed that compensation of carbohydrate metabolism in patients with DM2 is a key factor in the prevention of cardiovascular complications, however, meta-analysis data showed that even intensive control of glycaemia does not reduce the risk of developing cardiovascular complications (Parry M., 2015; Wang Y., 2015; Newman J. D., 2017).

On the other hand, heart failure leads to a significant increase in the death rate of diabetic patients. For example, in the DIABHYCAR study, the annual mortality rate of diabetics who developed heart failure was 12 times higher than in patients with diabetes without heart failure (36.4 and 3.2 %) [20,21]. In a large American cohort study that included 151,738 diabetic patients over 65 years of age, the 5-year survival rate for patients with heart failure was 12.5%, compared to 80% for diabetics without heart failure [45]. In another BEST study, the presence of DM was independently correlated with an increase in cardiovascular mortality in patients with ischemic cardiomyopathy [20,44].

DM2 has a significant adverse effect on the prognosis in individuals with various variants of CHF. According to large meta-analyses, it is considered a significant independent risk factor for death in CHF with a low LV ejection fraction (LVF). Among people with CHF at low

LVF and DM2 risk of decompensation of heart failure (CHF) is approximately 2 times higher than in patients with CHF without diabetes. Individuals with a combination of these two conditions also show a higher rate of repeated hospital admissions for CHF, and a lower quality of life. SD2

it also negatively affects the course of CHF with preserved LVF, increasing the risk of decompensation and mortality. In randomized controlled trials (RCTS) CHARM I and I-PRESERVE [46,47], it is shown that these adverse effects of DM2 in this variant of CHF may be even more pronounced than in individuals with CHF with low LVF.

CONCLUSIONS

Thus, type 2 diabetes is an important risk factor for chronic heart failure, independent of coronary heart disease, hypertension, and other factors. Diabetes patients have a high incidence and mortality rate from heart failure. It is known that the close Association of heart failure and diabetes is due to the greater frequency and severity of its risk factors in diabetes mellitus, accelerated development of atherosclerosis and specific diabetic myocardial damage associated primarily with metabolic and neurohumoral disorders. However, the mechanisms of cardiac dysfunction directly related to diabetes require further study.

Literature:

1. 1. IDF Diabetes Atlas, 8th edition. Brussels: International Diabetes Federation; 2017. Available from: https://www.idf.org/e- library / epidemiology research / diabetes atlas /
2. 2. IDF Diabetes Atlas, 9th edition. Brussels: International Diabetes Federation; 2019.Available from: https://www.idf.org/e- library / epidemiologyresearch / diabetesatlas /
3. 3. Dedov II, Shestakova MV, Vikulova OK. Epidemiology of diabetes in the Russian Federation: clinical and statistical analysis according to the Federal register of diabetes. Diabetes Mellitus. 2017; 1 (20): 13-41. (In Russ.) Grandfathers AI, Shestakova MV, Vikulova OK. Epidemiology of diabetes mellitus in the Russian Federation: clinical and statistical analysis according to the Federal Register of Diabetes. Diabetes. 2017; 1 (20): 13-41.
4. 4. Ostroumova O. D.1,2, Goloborodova I. B.1, Fomina V. M. Cardiovascular risks in patients with type 2 diabetes. Cardiovascular Therapy and Prevention, 2018; 17 (4): 81-94.
5. 5. Clinical recommendations for the treatment of type 2 diabetes. A guide for doctors // Alimov A.V. et al., Tashkent. - 2019. -- S. 5
6. 6. Materials of the XVII Summit of the Heads of the East European Diabetes Associations "Unity for Good". Tashkent April 19-21, 2019
7. 7. Alikhanova N.M., Akbarov Z.S., Ismailov S.I. Epidemiological aspects of diabetes in the city of Tashkent based on register data. International Endocrinology Journal. No. 2 (74) .2016. 111-114s.
8. 8. Kobalava Zh.D., Medovshchikov VV, Yeshniyazov NB, Khasanova E.R. The modern paradigm of pathophysiology, prevention and treatment of heart failure in type 2 diabetes
9. 9. Shestakova MV, Dedov II. Diabetes mellitus in the Russian Federation: Arguments and facts. Ter arkh. 2016; 88 (10): 4-8. (In Russ.) Shestakova M.V., Dedov I.I. Diabetes mellitus in the Russian Federation: arguments and facts. Therapeutic Archive. 2016; 88 (10): 4-8. doi: 10.17116 / terarkh201688104-8.
10. 10. Russell ND, Cooper ME. 50 years forward: mechanisms of hyperglycemia-driven diabetic complications. Diabetologia. 2015; 58 (8): 1708-14. doi: 10.1007 / s00125-015-3600-1.
11. 11. Gregg EW, Li Y, Wang J, et al. Changes in diabetes-related complications in the United States, 1990-2010. N Engl J Med. 2014; 370 (16): 1514-23. doi: 10.1056 / NEJMoa1310799.
12. 12. Bagriy A.E., Suprun E.V., Mikhaylichenko E.S., Golodnikov I.A. Chronic heart failure and type 2 diabetes mellitus: state of the problem.
13. 13. Sarwar N, Gao P, Seshasai SR, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010; 375: 2215-22. doi: 10.1016 / S0140-6736 (10) 60484-9.
14. 14. Kannel WB, McGee DL. Diabetes and cardiovascular disease: the Framingham study. JAMA. 1979; 241: 2035-8.
15. 15. Kannel WB, McGee DL. Diabetes and cardiovascular disease. The Framingham study. JAMA. 1979; 241 (19): 2035-8. doi: 10.1001 / jama.1979.03290450033020.
16. 16. Boyer JK, Thanigaraj S, Schechtman KB, Perrez JE. Prevalence of Ventricular Diastolic Dysfunction in Asymptomatic, Normotensive Patients with Diabetes Mellitus. The American Journal of Cardiology. 2004; 93: 870-5. doi: 10.1016 / j. amjcard.2003.12.026.
17. 17. Bell DS. Diabetic cardiomyopathy: a unique entity or a complication of coronary artery disease? Diabetes Care. 1995; 18: 708-14.
18. 18. Sarma S, Mentz RJ, Kwasny MJ, et al. Association between diabetes mellitus and post-discharge outcomes in patients hospitalized with heart failure: findings from the EVEREST trial. European Journal of Heart Fail. 2013; 15: 194-202.
19. 19. Greenberg BH, Abraham WT, Albert NM, et al. Influence of diabetes on characteristics and outcomes in patients hospitalized with heart failure: a report from the Organized Program to Ini-

tiate Lifesaving Treatment in Hospitalized Patients with Heart Failure (OPTIMIZE-HF). American Heart Journal. 2007; 154: 271-8. doi: 10.1016 / j.ahj.2007.05.00.001.

20. 20. Mardanov B.U., Korneeva M.N., Akhmedova E.B. heart failure and diabetes mellitus: separate issues of etiopathogenesis, prognosis and treatment. Rational pharmacotherapy in cardiology. 2016.No.12. (6) .743-748.

21. 21. Vaur L, Gueret P, Lievre M, et al. Development of congestive heart failure in type 2 diabetic patients with microalbuminuria or proteinuria: observations from the DIABHYCAR (type 2 DIABetes, Hypertension, Cardiovascular Events and Ramipril) study. Diabetes Care. 2003; 26: 855-860. doi: 10.2337 / diacare.26.3.855.

22. He J, Ogden LG, Bazzano LA, et al. Risk factors for congestive heart failure in US men and women: NHANESIepidemiologic follow-up study. Arch Intern Med. 2001; 161: 996-1002. doi: 10.1001 / archinte. 161.7.996.

23. 23. Iribarren C, Karter AJ, Go AS. et al. Glycemic Control and Heart Failure Among Adult Patients with Diabetes. Circulation. 2001; 103: 2668-73. doi: 10.1161 / 01.CIR.103.22.2668.

24. 24. Turnbull FM, Abraira C, Anderson RJ, et al. Intensive glucose control andmacrovascular outcomes in type 2 diabetes. Diabetologia. 2009; 52: 2288-98. doi: 10.1007 / s00125-009-1470-0.

25. 25. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucosecontrol with sulphonylureas or insulin compared with conventional treatment and riskof complications in patients with type 2 diabetes (UKPDS 33). Lancet. 1998; 352: 837-53. doi: 10.1016 / S0140-6736 (98) 07019-6.

26. 26. Gotto AM, Bailey K, Gohdes D, et al. The Action to Control Cardiovascular Risk in Diabetes Study Group (2008) Effects of intensive glucose lowering in type 2 diabetes. The N Engl J Med. 2008; 358: 2545-59. doi: 10.1056 / NEJMoa0802743.

27. 27. Chalmers J, MacMahon S, Patel A, et al. The ADVANCE Collaborative Group (2008) Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. The N Engl J Med. 2008; 358: 2560-72. doi: 10.1056 / NEJMoa0802987.

28. 28. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. The N Engl J Med. 2009; 360: 129-39. doi: 10.1056 / NEJMoa0808431.

29. 29. Eurich DT, Weir DL, Majumdar SR, et al. Comparative safety and effectiveness of metformin in patients with diabetes mellitus and heart failure: systematic review of observational studies involving 34,000 patients. Circulation: Heart Failure. 2013; 6 (3): 395-402. doi: 10.1161 / CIRCHEARTFAILURE.112.000162.

30. 30. Fujita Y, Inagaki N. Metformin: new preparations and no glycemic benefits. Current diabetes reports. 2017; 17 (1): 5. doi: 10.1007 / s11892-017-0829-8.

31. 31. Sanchez-Rangel E, Inzucchi SE. Metformin: clinical use in type 2 diabetes. Diabetologia. 2017; 60 (9): 1586-93. doi: 10.1007 / s00125-017-4336-x.

32. 32. Zoungas S, Arima H, Gerstein HC et al. Effects of intensive glucose control on microvascular outcomes in patients with type 2 diabetes: a meta-analysis of individual participant data from randomized controlled trials. The lancet Diabetes & endocrinology. 2017; 5 (6): 431-7.doi: 10.1016 / S2213-8587 (17) 30104-3.

33. 33. The cardiovascular safety profile of the drug Trazhenta® was confirmed with prolonged use. Effective pharmacotherapy. 2019. Volume 15. No. 31. Endocrinology. www.boehringer-ingelheim.ru

34. 34. Li J, Tong Y, Zhang Y, et al. Effects on all-cause mortality and cardiovascular outcomes in patients with type 2 diabetes by comparing insulin with oral hypoglycemic agent therapy: a meta-analysis of randomized controlled trials. Clinical therapeutics. 2016; 38 (2): 372-86.e6. doi: 10.1016 / j.clinthera.2015.12.006.

35. 35. Seferović PM, Petrie MC, Filippatos GS, et al. Type 2 diabetes mellitus and heart failure: a position statement from the Heart Failure Association of the European Society of Cardiology. European journal of heart failure. 2018; 20 (5): 853-72. doi: 10.1002 / ejhf.1170.

36. 36. Pich C, Michalik L. The Janus face of rosiglitazone. Oncotarget. 2018; 9 (102) 37614-5. doi: 10.18632 / oncotarget.26532.

37. 37. Jia X, Alam M, Ye Y, et al. GLP-1 receptor agonists and cardiovascular disease: a meta-analysis of recent cardiac outcome trials. Cardiovascular drugs and therapy. 2018; 32 (1): 65-72. doi: 10.1007 / s10557-018-6773-2.

38. 38. Scheen AJ. GLP-1 receptor agonists and heart failure in diabetes. Diabetes & metabolism.

2017; 43 (Suppl. 1): 2S13-2S19. doi: 10.1016 / S1262-3636 (17) 30068-X.

39. 39. Schernthaner G, Cahn A, Raz I. Is the use of DPP-4 inhibitors associated with an increased risk for heart failure? Lessons from EXAMINE, SAVOR-TIMI 53, and TECOS. Diabetic care. 2016; 39 (Suppl.2): S210-S218. doi: 10.2337 / dcS15-3009.

40. 40. Scirica BM, Braunwald E, Raz I, et al. Heart Failure, Saxagliptin, and Diabetes

41. 41. Mellitus: Observations from the SAVOR-TIMI 53 Randomized Trial. Circulation.

42. 42. Zelniker TA, Wiviott SD, Raz I, et al. SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials. The lancet. 2019; 393 (10166): 31-9. doi: 10.1016 / S0140-6736 (18) 32590-X.

43. 43. Kosiborod M, Cavender MA, Fu AZ, et al. Lower risk of heart failure and death in patients initiated on sodium-glucose cotransporter-2 inhibitors versus other glucose-lowering drugs: the CVD-REAL study (comparative effectiveness of cardiovascular outcomes in new users of sodium-glucose cotransporter-2 inhibitors). Circulation. 2017; 136 (3): 249-59. doi: CIRCULATIONAHA.117.029190.

44. Domanski M, Krause-Steinrauf H, Deedwania P, et al. The effect of diabetes on outcomes of patients with advanced heart failure in the BEST trial. J Am Coll Cardiol. 2003; 42: 914-22. doi: 10.1016 / S0735-1097 (03) 00856-8.

45. Volkova EA, Malygina O.F. Diabetes mellitus and cardiovascular disease. Actual approach to lifestyle modification and treatment of patients with type 2 diabetes. Consilium Medicum. 2019 21 (1): 74-80.

46. Kristensen SL, Mogensen MU, Jhund PS, et al. Clinical and echocardiographic characteristics and cardiovascular outcomes according to diabetes status in patients with heart failure and preserved ejection fraction: a report from the I-Preserve Trial (Irbesartan in Heart Failure With Preserved Ejection Fraction). Circulation. 2017; 135 (8): 724-35. doi: 10.1161 / CIRCULATIONAHA.116.024593.

47. Damman K, Solomon SD, Pfeffer MA, et al. Worsening renal function and outcome in heart failure patients with reduced and preserved ejection fraction and the impact of angiotensin receptor blocker treatment: data from the CHARM study program. European journal of heart failure. 2016; 18 (12): 1508-17. doi: 10.1002 / ejhf.609.

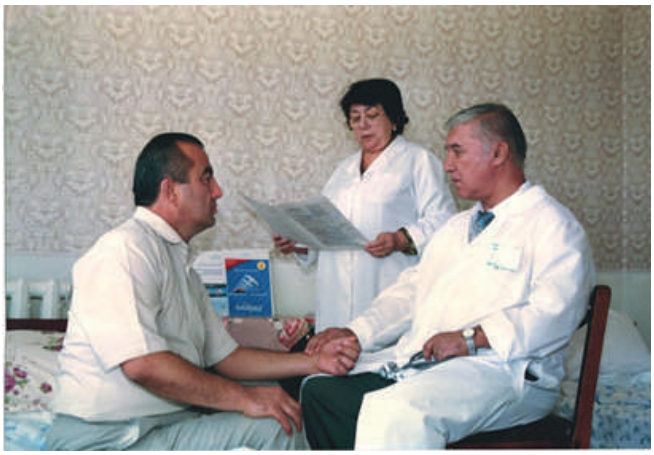
Акбаров Зоирходжа Собирович (1945-2020г.). Выдающийся деятель медицинской науки, основоположник диабетологической школы в Узбекистане, доктор медицинских наук, профессор Акбаров Зоирходжа Собирович.

Акбаров Зоирходжа Собирович родился в семье интеллигентов 15 сентября 1945 года в городе Ташкент. После окончания школы поступил в Ташкентский медицинский институт по направлению лечебное дело. Его очень интересовала наука, поэтому профессиональную деятельность он начал в Институте химии растительных веществ Академии наук Республики Узбекистан и в 1974 году защитил кандидатскую диссертацию.

В 1978 году Акбаров Зоирходжа Собирович начал работать в научно-исследовательском центре эндокринологии, в 1983 году он возглавил вновь образованную им научную лабораторию диабетологии. В 1987 году Акбаров Зоирходжа Собирович получил звание старшего научного сотрудника по специальности эндокринология. В 1998 году защитил докторскую диссертацию, в 2000 году получил звание профессора. В 1997-2009 годах работал в качестве заместителя директора по научной работе, в 1996-2001 годах занимал должность главного эндокринолога Министерства здравоохранения Республики Узбекистан.

Акбаров Зоирходжа Собирович стал инициатором первых исследований в области сахарного диабета в Узбекистане, в том числе осложнений сахарного диабета, под его руководством впервые в Узбекистане был создан регистр сахарного диабета, одним из первых в мире он провёл клинические испытания по помповой терапии, он также стал основоположником генетических исследований в области сахарного диабета и его осложнений у лиц узбекской национальности. Его усилиями в Узбекистане были организованы первые школы по самоконтролю у больных сахарным диабетом.

Акбаров Зоирходжа Собирович является автором 6-и авторских свидетельств, 5-и монографий, 2-х учебников, 15-и методических пособий и более 400 научных статей и тезисов. Им подготовлены 2 доктора наук и 13 кандидатов наук в области эндокринологии. Ученый высокой эрудиции, принципиальный, талантливый, в своей деятельности З.С.Акбаров постоянно совершенствовал свою профессиональную деятельность.



Патенты

1. «Способ диагностики сахарного диабета». Патент № IDP 04749, 2001г.
2. «Учет и мониторинг сведений о больных сахарным диабетом». (Свидетельство о регистрации №BGU 00188 от 06.05.2009г.).
3. «Мониторинг больных с сахарным диабетом 1 и 2 типа в Республике Узбекистан» (Свидетельство о регистрации №BGU 20140001 от 26.08.2014г.).
4. «Калькулятор риска инфаркта миокарда у больных СД 2 типа узбекской популяции» (Свидетельство о регистрации №DGU 02845 от 13.11.2014.
5. «Программа для расчёта хлебных единиц при сахарном диабете 1 типа» (Свидетельство о регистрации №DGU 20170130 от 14.03.2017г.).
6. Акрамова Г.Г, Акбаров З.С., Юсупова М.Д., Тахирова Ф.А., Норматова Н.М. «Калькулятор риска пролиферативной диабетической ретинопатии при СД2 узбекской популяции». (Свидетельство о регистрации №DGU 20170362 от 05.06.2017г.).

Он ушёл из жизни 11 октября 2020 года прожив жизнь добросовестного и честного человека, уважаемого гражданина своей страны.

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O‘RTA OSIYO ENDOKRINOLOGIK

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