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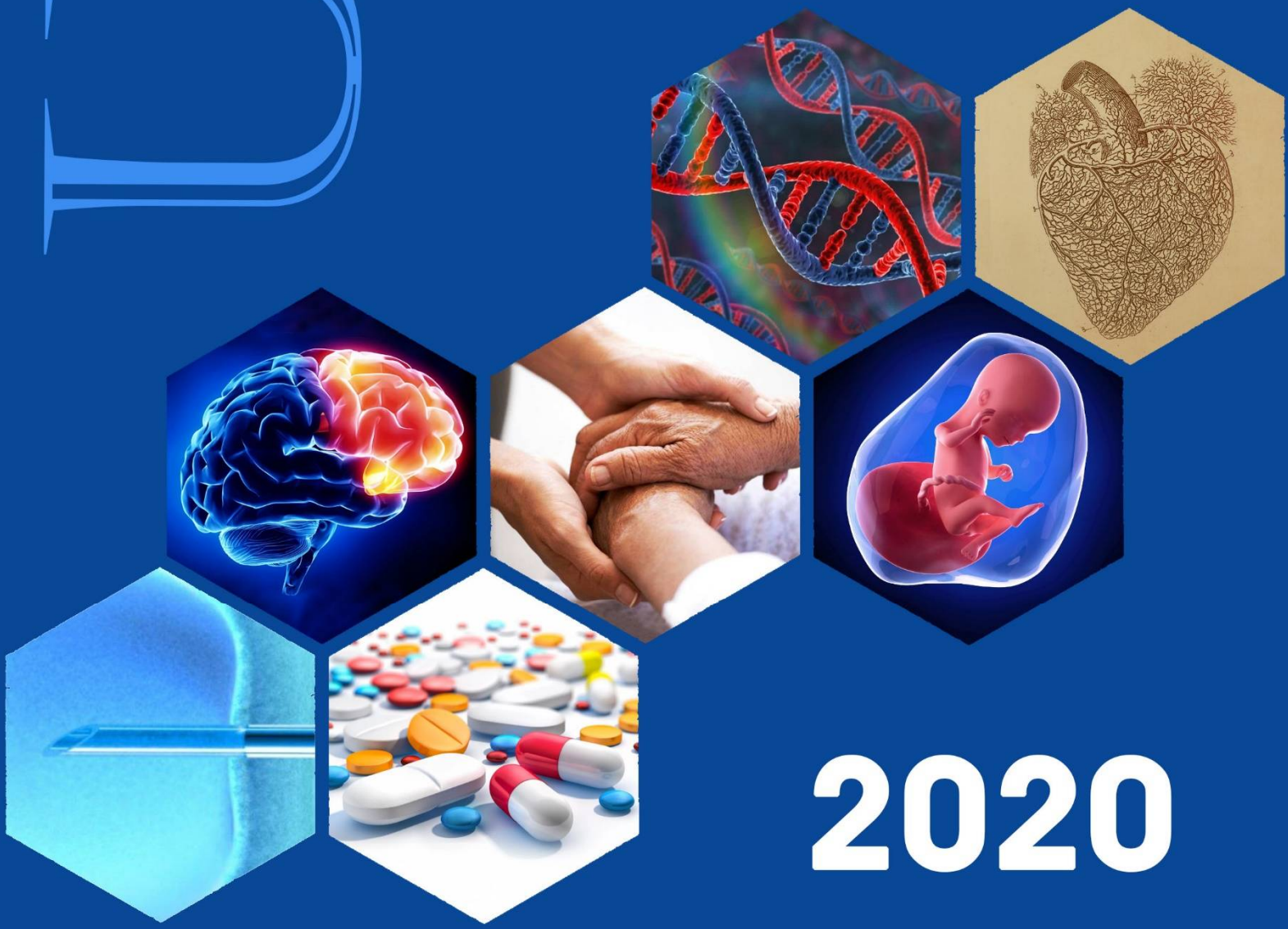

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DIAGNOSTICS OF PATIENTS WITH THROMBOEMBOLIC COMPLICATIONS OF THE VISUAL ORGAN OF RHINOSINUSOGENIC ETIOLOGY AT COVID 19

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ABSTRACT

Cavernous sinus thrombosis is one of the most severe infections of the face, orbit, ear, paranasal sinuses and oral cavity. The study aims to analyse clinical cases of carotid-cavernous sinus thrombosis in patients with complications of COVID 19. An analysis of 2 clinical cases with a diagnosis of cavernous sinus thrombosis in the presence of COVID 19 was carried out. General ophthalmic research methods (visometry, external examination, the study of pupillary reactions, ophthalmoscopy, palpation measurement of intraocular pressure), MRI, MSCT of the brain and chest, general blood test, coagulogram, biochemical blood test. These clinical examples show that cavernous sinus thrombosis develops as a complication of coronavirus infection. The cause of cavernous sinus thrombosis was inflammation of the paranasal sinuses, dry blood, diabetes mellitus. The cause of death was the development of multiple organ failure due to concomitant diseases and a decrease in patients' immune status.

Keywords: coronavirus infection, cavernous sinus thrombosis, ophthalmoscopy, paranasal sinuses.

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ДИАГНОСТИКА БОЛЬНЫХ С ТРОМБОЭМБОЛИЧЕСКИМИ ОСЛОЖНЕНИЯМИ ОРГАНА ЗРЕНИЯ РИНОСИНУСОГЕННОЙ ЭТИОЛОГИИ ПРИ COVID 19

АННОТАЦИЯ

Тромбоз кавернозного синуса - один из тяжелых осложнений инфекций области лица, орбиты, уха, околоносовых пазух и ротовой полости. Целью исследования является анализ клинических случаев тромбоза каротидно-кавернозного синуса у больных с осложнениями COVID 19. Был проведен анализ 2 клинических случаев с диагнозом тромбоз кавернозного синуса на фоне COVID 19. Были проведены общие офтальмологические методы исследования (визометрия, наружный осмотр, исследование зрачковых реакций, офтальмоскопия, пальпаторное измерение внутриглазного давления), МРТ, МСКТ головного мозга и грудной клетки, общий анализ крови, коагулограмма, биохимический анализ крови. Данные клинические примеры показывают, что тромбоз кавернозного синуса развивается как осложнение коронавирусной инфекции. Причиной тромбоза кавернозного синуса послужило воспаление придаточных пазух носа, сгушение крови, сахарный диабет. Причиной летального исхода было развитие полиорганной недостаточности, вследствие сопутствующих заболеваний и снижения иммунного статуса больных.

Ключевые слова: коронавирусная инфекция, тромбоз кавернозного синуса, офтальмоскопия, синусит околоносовых пазух.

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COVID 19 ДА КЎРУВ АЪЗОЛАРИНИНИНГ РИНОСИНУСОГЕН ЭТИОЛОГИЯЛИ ТРОМБОЭМБОЛИК АСОРАТЛАРИНИ ТАШХИСЛАШ

АННОТАЦИЯ

Каверноз синуси тромбози – юз соҳаси, орбита, қулоқ, бурун ёндош бўшлиқлари ва оғиз бўшлиғи инфекциясининг оғир асоратларидан биридир.Тадқиқотнинг мақсади COVID 19 асоратлари бор беморларда каверноз синуси тромбози клиник ҳолатларини таҳлил қилиш. COVID 19 фонидаги каверноз синус тромбози ташхисли 2 та клиник ҳолатнинг таҳлили ўтказилди. Умумий офтальмологик текширувлар (визометрия, ташқи кўрик, қорачиқнинг ёруғликка сезгирлигининг текшируви, офтальмоскопия, кўз ички босимини пальпатор текшируви), бош мия ва кўкрак қафасини МРТ ва МСКТ текшируви, умумий қон анализи, коагулограмма, қонни биохимик текшируви ўтказилди. Бу клиник ҳолатлар каверноз синусининг тромбози коронавируснинг асорати бўлиб ривожланганлини кўрсатди. Каверноз

синусининг тромбози ривожланишига бурун ёндош бўшлиқларининг яллиғланиши, қоннинг қуюқлашиши, қандли диабет сабаб бўлди. Беморларда ёндош касалликлар ва иммун холатнинг пасайиши, полиорган етишмовчилиги ўлим ҳолатига сабаб бўлди.

Калит сўзлар: коронавирус инфекцияси, каверноз синуси тромбози, офтальмоскопия, бурун ёндош бўшлиқлари синусити.

INTRODUCTION

Cavernous sinus thrombosis is one of the most severe infections of the face, orbit, ear, paranasal sinuses and oral cavity. Cavernous sinuses are formations located at the base of the skull. Their role is to drain blood from the facial veins. Cavernous sinus thrombosis most often develops as a complication of furuncles of the vestibule of the nose (50%), sphenoidal or ethmoidal sinusitis (30%) and odontogenic infections (10%). Complications of viral infections, including coronavirus infection, can develop cavernous sinus thrombosis.

Non-infectious causes of cerebral vein and venous sinus thrombosis can be localised and general. Traumatic brain injury, tumors, head and neck surgery, and implantation of a pacemaker or central venous catheter are most commonly mentioned. Common diseases that contribute to thrombosis of the cerebral veins and venous sinuses include conditions such as hemodynamic disorders (e.g., congestive heart failure, dehydration), blood disorders (polycythemia, sickle cell anemia, thrombocytopenia), and coagulopathy (with disseminated intravascular coagulation syndrome), deficiency of antithrombin, protein C and protein S), as well as thrombophilic conditions associated with pregnancy, childbirth and taking oral contraceptives, antiphospholipid syndrome, systemic vasculitis. Moreover, in 15% of cases, the cause of the development of sinus thrombosis remains unclear [5].

Complications of cavernous sinus thrombosis include meningoencephalitis, brain abscess, stroke, blindness. However, the variety of clinical manifestations, as well as the difficulties in diagnosing this pathology, often impede the establishment of the correct diagnosis.

For practicing ophthalmologists, the issues of predicting thromboembolic complications of Covid 19, the search for the most informative signs that allow determining the outcome of the disease with a high degree of reliability are becoming especially relevant. Therefore, it becomes obvious the need to search for new informative methods to study visual functions for accurate, early and differential diagnosis of thromboembolic complications of the organ of vision in Covid 19.

Purpose of the study

Analysis of clinical cases of carotid-cavernous sinus (CCS) thrombosis in patients with complications of COVID 19.

Materials and methods. An analysis of 2 clinical cases with the diagnosis of TCS against the background of COVID 19 was carried out. General ophthalmological research methods (visometry, external examination, the study of pupillary reactions, ophthalmoscopy, palpation measurement of intraocular pressure), MRI, MSCT of the brain and chest, complete blood count were carried out, coagulogram, biochemical blood test.

Results. Under our supervision there was a patient Kh.A., born in 1958, who complained of headache, dizziness, pulsating noise in the head, intensifying towards night, severe pain in the right eye, redness and swelling of the right eye, squint to the nose, double vision when looking to the left and loss of vision, drooping of the upper eyelid, difficulty in nasal breathing.

From the anamnesis of the disease - 7 days ago, he tested positive for coronavirus infection. The patient was treated in a special hospital, took anticoagulant, antibacterial and anticonvulsant therapy. Despite the treatment, the patient developed covid pneumonia and cavernous sinus thrombosis. 2-3 days ago, the patient developed pain in the right side of the head, pain behind the eyeball on the right, drooping of the upper eyelid, photophobia, decreased vision of the right eye. The patient suffers from diabetes mellitus, ischemic heart disease, hypertension, chronic hemisinusitis on the right.

Upon admission, the general condition of the patient is severe. Arterial pressure 100/80, pulse 96 beats per minute. A vision of the right eye is absent (zero), of the left eye 1.0. There is

pronounced edema of the periorbital tissue, more in the inner corner, and there is also a pulsating noise, exophthalmos, ptosis, complete ophthalmoplegia, no reposition of the eyeball, chemosis, corneal edema. On the fundus of the optic nerve disc pale, edematous, the borders are blurred, the retina is swollen, the vessels are narrowed, in the macular region there is a "cherry bone symptom". The left eye was normal.

A complete blood count showed neutrophilic leukocytosis and an increase in the erythrocyte sedimentation rate up to 23 mm/h. On the coagulogram, the activated partial thromboplastin time is 30.5 (a week ago it was 22.6), fibrinogen 11.24 (norm 2.00-4.00 g / l), PTI 75, thromboplastin time 12.2 sec. (norm 10-14 sec), international normalized ratio 1.28 (norm 0.8-1.2), thrombin time 16.0 sec (norm <30 sec).

In a biochemical blood test, blood sugar 16.26 mmol / l (norm 3.3-6.02), urea 11.8 mmol / l (norm 1.7-8.30), creatinine according to Jaffa 220.4 mmol / l (norm 61.8-123.7). Test positive for Covid 19.

MRI of the brain: MRI signs of an area of pathological intensity in the retrobulbar fatty tissue on the left (inflammatory infiltrate?). Moderate atrophy of the frontotemporal regions on both sides. Indirect signs of intracranial hypertension. Left-sided sinusitis. Parietal hyperplasia of the mucous membranes of the sphenoidal and ethmoidal sinuses.

The patient was admitted to an infectious diseases hospital, consulted by an ENT doctor. High doses of intravenous and parabulbar antibiotics, diuretics, desensitising drugs were prescribed. Performed right-sided endoscopic infundibulotomy with sanitation of the paranasal sinuses, ethmoidotomy, frontotomy, sphenotomy under intravenous anesthesia. The patient developed multiple organ failure (cardiac, pulmonary, renal), despite the ongoing therapy, the disease ended in death.

In this clinical example, the cause of cavernous sinus thrombosis was inflammation of all paranasal sinuses, blood clots, and coronavirus infection.

Second clinical case. Patient M.M. was born in 1967. On October 31, 2020, she was admitted to the intensive care unit of the Tashkent Medical Academy (TMA) in a serious condition. From the anamnesis, the patient was treated for covid pneumonia in a specialised hospital for 1 month. After complex treatment, the patient's condition improved. After being discharged from the hospital on the way home, the patient's condition deteriorated sharply. The patient was admitted to the TMA. From the anamnesis the patient suffers from diabetes mellitus.

Complaints of the patient on admission to the lack of vision in the right eye, swelling of the upper eyelid and face on the right side. Objectively: edema of the right upper eyelid, lack of movement of the eyeball in full, exophthalmos, lack of object vision, edema and cyanosis of the face on the right side. On the fundus, the optic disc is pale, edematous, the borders are indistinct, there is no physiological excavation, the arteries are narrow, the veins are dilated, and peripapillary retinal edema.

The patient underwent MRI of the brain. Conclusion: MRI signs of vascular encephalopathy, with the presence of multiple small ischemic foci, atrophy of the frontotemporal regions on both sides. Signal inhomogeneity of the right cavernous sinus (thrombosis?). Ectasia of the right facial vein. Diffuse edema of the soft tissues of the orbit and facial area on the right. MSCT examination of the brain revealed CT signs of vascular encephalopathy with atrophy of the frontotemporal regions on both sides. Pansinusitis.

The patient was consulted by an ENT doctor, ophthalmologist, neurosurgeon, maxillofacial surgeon, infectious disease specialist. Complex therapy was prescribed, despite the ongoing therapy, the outcome was fatal.

In this clinical case, due to thrombosis of the cavernous sinus, stagnation of the facial and superior orbital veins developed. The cause of cavernous sinus thrombosis was inflammation of all the paranasal sinuses, blood clots, coronavirus infection and concomitant diseases.

Conclusion. Thus, the main diagnostic criteria for cavernous sinus thrombosis are characteristic clinical symptoms (ptosis, exophthalmos, conjunctival chemosis, complete ophthalmoplegia, edema of the optic nerve head), laboratory data (neutrophilic leukocytosis,

increased erythrocyte sedimentation rate, increased blood sugar changes), MRI data of the brain (increased signal intensity from the altered sinus).

These clinical examples show that cavernous sinus thrombosis develops as a complication of coronavirus infection. The cause of cavernous sinus thrombosis was inflammation of the paranasal sinuses, dry blood, diabetes mellitus. The cause of death was the development of multiple organ failure due to concomitant diseases and a decrease in patients' immune status.

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FEATURES OF A RATIONAL DIET IN PREGNANT WOMEN SUFFERING FROM IRON DEFICIENCY ANEMIA

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ABSTRACT

According to reports of the World Health Organization, iron deficiency anaemia is found in 1.7 billion people worldwide. However, among the population of various regions of the world the number of people with latent iron deficiency, when the haemoglobin level remains within normal limits, but iron reserves in the body are already reduced - twice as much. In Uzbekistan, this indicator is 35-40% of cases. However, according to modern epidemiological and social-hygienic studies, more than 50% of anaemia cases in pregnant women are of combined nature, which predetermined the purpose and objectives of this study**.**

Keywords: anaemia, Iron deficiency, anaemia, pregnancy.

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ОСОБЕННОСТИ РАЦИОНАЛЬНОГО ПИТАНИЯ У БЕРЕМЕННЫХ СТРАДАЮЩИХ ЖЕЛЕЗОДЕФИЦИТНОЙ АНЕМИЕЙ

АННОТАЦИЯ

Согласно отчетам Всемирной организации здравоохранения, железодефицитные анемии встречаются у 1,7 млрд. населения земного шара, но при этом среди населения различных регионов мира количество людей с латентным дефицитом железа, когда уровень гемоглобина сохраняется в пределах нормальных границ, но запасы железа в организме уже снижены - в 2 раза больше. В Узбекистане данный показатель составляет 35 -40% случаев. Однако, согласно современным эпидемиологическим и социально-гигиеническим исследованиям, более 50% случаев анемии беременных имеет сочетанный характер, что и предопределило цель и задачи настоящего исследования.

Ключевые слова: анемия, железодефицитная анемия, беременность.

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TEMIR TANQISLIGI ANEMIYASIGA CHALINGAN HOMILADOR AYOLLARDA RATSIONAL OVQATLANISH XUSUSIYATLARI

ANNOTATSIYA

Jahon sog'liqni saqlash tashkilotining xabarlariga ko'ra, temir tanqisligi anemiyasi dunyo aholisining 1,7 milliardida uchraydi, ammo shu bilan birga, dunyoning turli mintaqalari aholisi orasida, yashirin temir tanqisligi bo'lgan bir qator odamlar bor, ular gemoglobin darajasi normal chegaralarda qolganda, ammo tanadagi temir do'konlari allaqachon kamaygan - 2 baravar ko'p. O'zbekistonda bu ko'rsatkich 35-40% ni tashkil qiladi. Ammo, zamonaviy epidemiologik va ijtimoiy-gigienik tadqiqotlar natijalariga ko'ra, homilador ayollarda anemiya holatlarining 50% dan ortig'i birlashtirilgan xususiyatga ega bo'lib, ushbu tadqiqotning maqsadi va vazifalarini oldindan belgilab qo'ygan.,

Kalit so'zlar: Anemia, temir tanqisligi, homiladorlik.

Reducing reproductive and perinatal losses is one of the most important areas in addressing maternal and child health. In the Republic of Uzbekistan up to the beginning of the XXI century against the high birth rate background, high rates of maternal and infant mortality were observed. This is mainly due to extragenital pathology in women of reproductive age, particularly IDA (Iron Deficiency Anemia).

Iron deficiency anaemia in pregnancy is a disease in which the iron content in serum, bone marrow and depot is reduced due to an increase in the volume of circulating blood and the need for micronutrient, a decrease in its deposit, a high rate of fetal growth [23].

In the structure of morbidity of pregnant women, IDA is found in 15-80% of pregnant women and 20-40% of births [12, 34]. According to current data, iron deficiency at the end of gestation is present in pregnant women in the hidden or obvious form [13, 15, 26, 31]. Clinically, IDA is manifested in II-III trimesters, and after childbirth the symptoms of the disease progress.

Initial iron level in the body is of great importance. Depleted iron reserves are available in 40-60% of women of reproductive age [14]. Therefore, their pregnancy occurs against the background of iron deficiency or already developed anaemia. It is known that IDA develops over a long period, and quite often the body is well adapted to it even at a moderate degree of severity [24], and pregnancy due to increased need for iron exacerbates the reserve and transport fund of iron metabolism. Some authors consider IDA to be one of the most common nutritional-dependent conditions in pregnant women. In particular, protein deficiency in the diet leads to anaemia of alimentary genesis, which further contributes to impaired protein biosynthesis in the placenta [21].

Today's main principles of iron deficiency therapy are optimising the diet and the use of various iron preparations.

Rational nutrition is one of the main conditions for a good course and outcome of pregnancy, childbirth, fetal development. By rational nutrition, in pregnant women, we mean a full set of various products according to the gestation period and the correct diet distribution during the day. The menu for a pregnant woman is made individually, considering her growth and body weight, peculiarities of the gestation course, and her work nature. The intensity of the main metabolism during pregnancy increases by 10% on average, so the energy value of food should be increased by proteins that are actively used for the formation of fetal tissues. A pregnant woman should remember that she does not eat for two but two.

Violation of the formula of balanced nutrition (lack or excess of this or that food component) leads to the violation of the enzymatic systems and metabolic processes, the development of pathological changes in the body.

Many studies have been conducted on WFA treatment in pregnant women.

The aims of iron deficiency therapy are eliminating iron deficiency and restoration of iron reserves in the body; provision of tissues playing the role of a depot with the optimal amount of iron [4].

Treatment of anaemia must be pathogenetic and follow certain principles, which consist in the correction of iron deficiency, ensuring adequate intake of trace elements, vitamins, protein, elimination of hypoxia, normalisation of hemodynamics, elimination of systemic, metabolic and organ disorders, prevention and treatment of obstetric complications, in particular fetoplacental insufficiency, hypoxia and fetal hypotrophy [19,].

Therapy with iron preparations during pregnancy should be started not from the moment of Hb reduction (as it was accepted earlier), but from the moment of the iron stock deficit detection. Therefore, to prescribe ferrotherapy, it is necessary to know the full blood picture, key indicators of iron metabolism (ferritin, iron saturation coefficient of transferrin, iron concentration in serum) [14,].

Modern iron preparations are usually divided into iron salts preparations containing Fe2+ (Sorbyfer Durules, etc.) and preparations containing complex compound Fe3+ with polymaltose (Maltofer, Ferrum Lek, Ferlatum).

To date, the discussion about the advantages and disadvantages of Fe2+ and Fe3+ continues, and patient tolerance and possible side effects are assessed [5, 26,]. Thus, Fe2+ drugs are easier to absorb than Fe3+ drugs [33]. Entering gastrointestinal tract, compounds of Fe2+ penetrate mucous cells of the intestinal mucosa, then through the mechanism of passive diffusion - into blood channel. In the blood, Fe2+ is restored in Fe3+, which binds with transferrin and ferritin to form a pool of deposited iron, and if necessary, can be used in the synthesis of Hb, myoglobin and other iron-containing compounds. During its recovery in Fe3+ in the gastrointestinal mucosa, Fe2+ salts form free radicals with damaging effect, which may lead to the development of oxidative stress and, particularly, to the development of adverse reactions by the digestive organs, which are observed in more than 20% of patients. Usually, these are dyspeptic phenomena, metallic taste in the mouth, darkened teeth and gums, nausea, vomiting, feeling of the overflow of the stomach, constipation, diarrhea [26,].

The mechanism of complications due to iron binding in the intestines of hydrogen sulfide, which is a physiological stimulus for peristalsis. When iron sulfate and hydrogen sulfide interact, insoluble iron sulfide is formed, settling on the intestinal mucosa and preventing its irritation, contributing to peristalsis, which aggravates the anaemia in pregnant women, because they already often suffer from constipation, which leads to abandonment of treatment. Due to the intestine mucosa's severe irritation, continued treatment with iron sulphate may contribute to further loss of iron through haemorrhages in the intestine (6). Darkening of teeth enamel is also associated with the interaction of iron and hydrogen sulfide, which may be contained in the oral cavity.

Thus, despite the WHO recommendations on the use of Fe2+ drugs to treat IDA as the most effective, drugs with low bioavailability based on Fe3+ are actively used due to their better tolerability [2, 26].

For IDA treatment of pregnant women, it is advisable to perform the therapy in 3 stages [1].

- Stage I - anaemia control (restoring normal Hb level);
- Stage II - saturation therapy, including restoration of iron and protein reserves in the body;
- Stage III - maintenance therapy (maintaining a normal level of all iron funds).

The daily dose for prophylaxis of anemia and mild disease treatment is 60 mg Fe2+, and for treatment of severe anaemia - 120 mg Fe2+ [20]. At present, the WHO recommends 60 mg/day of iron and 400 mg/day of folic acid in II and III trimesters of gestation before labor for WIDA prevention [2,]. In regions with IDA frequency of more than 40%, iron prophylaxis should be continued for at least 3 months after labor [19]. The dose of less than 60 mg may be ineffective, and the frequency of side effects increases with administration of more than 120 mg.

With increasing gestational age, the frequency of true iron monodeficiency decreases, and it turns into poly-deficiency microelementosis, which is observed in more than 60% of pregnant women. It should be noted that during pregnancy the mother's body is the only source of vitamins and other nutrients for the fetus [9].

Deficiency of vitamins during the pre-implantation period, and especially during pregnancy, causes significant damage to the health of the mother and child, increases the risk of perinatal

pathology, increases child mortality, and is one of the causes of prematurity, congenital ugliness, and physical and mental development disorders in children [5, 7, 10, 27].

Regular intake of multivitamins promotes a healthy child's development by meeting the mother's increased need for micronutrients [10]. At present, complex preparations are widely used, which, in addition to iron, include vitamins and trace elements (Vitrum Prenatal Forte, Pregnavit, Materna, Multi-Tabs, Elevit Pronatal, Complivit Mama, etc.). As a rule, these vitamin complexes are taken during the whole gestation period.

A decrease confirms the effectiveness of prophylaxis and early treatment of anemia in pregnant women in the frequency of complications in childbirth: premature discharge of amniotic fluid by 2.5 times, anomalies of labor activity by 2.1 times, acupuncture hemorrhage by 2.3 times, as well as a decrease in repeated reproductive losses and perinatal mortality by 3 times [21].

Based on the above, it can be concluded that WAN during pregnancy remains one of the urgent problems of obstetrics, which is explained by the significant prevalence of this pathology, its adverse effect on pregnancy, fetal and newborn condition. Given the need for long-term therapy of iron deficiency and a limited reserve of time to achieve clinical effect in pregnant women, special importance should be given to the early diagnosis of iron deficiency and timely initiation of therapeutic measures. Given the high need of pregnant women for micronutrients, it is advisable to use vitamin and mineral complexes and specialised food products, significantly reducing the frequency of pregnancy complications and improving perinatal indicators.

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CARDIALGIA IN MYOCARDIAL INFARCTION DEPENDING ON AGE AND GENDER

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ABSTRACT

In myocardial infarction, pain is localized behind the sternum, often spreading to the entire precardiac area to the sternum's left and right and even to the epigastric region. The pain occurs suddenly, quickly reaching its maximum intensity. It should be remembered that myocardial infarction pain may sometimes go away on its own if the patient has not been given appropriate medical care. The study results showed a high incidence of stabbing pain in patients with myocardial infarction in the hospital setting. In male patients with myocardial infarction, compression pain predominated, and in female patients, pressure pain predominated. Myocardial infarction patients under 60 years of age had a cutting pain predominating, while patients over 60 years of age had acute pain.

Keywords: acute myocardial infarction, sex, the character of pain, old age.

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КАРДИАЛГИЯ ПРИ ИНФАРКТЕ МИОКАРДА В ЗАВИСИМОСТИ ОТ ВОЗРАСТА И ПОЛА

АННОТАЦИЯ

При инфаркте миокарда боль локализуется за грудиной, нередко распространяясь на всю прекардиальную область слева и справа от грудины и даже на эпигастральную область. Боль возникает внезапно, быстро достигая максимальной интенсивности. Следует помнить, что боль при инфаркте миокарда иногда может пройти самостоятельно, если больному не была оказана соответствующая медицинская помощь. Результаты исследования показали, большую частоту встречаемости режущих болей у пациентов с инфарктом миокарда в

условиях стационара. Если у пациентов с инфарктом миокарда мужского пола преобладало сжимающая боль а у женщин боль давящего характера. У пациентов перенесших инфаркт миокарда до 60 лет преобладало режущая боль, а у пациентов старше 60 лет боль давящего характера.

Ключевые слова: острый инфаркт миокарда, пол, характер боли, пожилой возраст.

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ЁШИ ВА ЖИНСИГА БОҒЛИҚ ҲОЛДА МИОКАРД ИНФАРКТИДА КАРДИАЛГИЯ

АННОТАЦИЯ

Миокард инфаркти билан оғриқлар кўкрак қафасининг орқасида жойлашган бўлиб, кўпинча кўкрак қафасининг чап ва ўнг қисмидаги бутун прекордиал ва ҳатто эпигастрал атрофига тарқалади. Оғриқ тўсатдан пайдо бўлиб, тезда максимал интенсивликка етади. Шуни эсда тутиш керакки, агар беморга тегишли тиббий ёрдам кўрсатилмаган бўлса, миокард инфарктидаги оғриқ баъзан ўз-ўзидан ўтиб кетиши мумкин. Тадқиқот натижалари шуни кўрсатадики касалхонада миокард инфаркти бўлган беморларда оғриқни кескин тезлиги юқори эканлигини кўрсатди. Агар миокард инфарктига чалинган эркак беморларда сиқиш оғриғи устун бўлса, аёлларда эса босма характердаги оғриқ кучли. 60 ёшгача миокард инфаркти бўлган беморларда кескин оғриғи устунлик қилди ва 60 ёшдан ошган беморларда пресслаш оғриғи устун келди.

Калит сўзлар: ўткир миокард инфаркти, жинс, оғриқнинг табиати, қарилик.

Relevance: In myocardial infarction (MI), pain is localized behind the sternum, often spreading to the entire precardiac area to the left and right of the sternum and even to the epigastric region. In most cases, pain irradiates to the left arm, left shoulder, scapula, neck, more rarely - to interscapular space, lower jaw, both arms. The intensity and character of the pain in a MI are usually different from angina pectoris. Patients describe it as unusually strong, excruciating, "cruel" pain of squeezing, pressing, crushing or burning character, which is often accompanied by fear of death. The pain arises suddenly, rapidly reaching its maximum intensity. It is not relieved by taking isosorbide dinitrate nitroglycerin, so often narcotic analgesics (marginal or "morphine" pain) must be administered. The duration of pain in typical cases reaches 40-60 minutes (sometimes it persists for hours and days, justifying its name - status anginosus). Sometimes a "wavy" change of pain intensity is possible: after 20-30 minutes of extreme ("morphine") pains briefly subside (10-15 minutes), followed by new extreme pains. It should be remembered that MI pain can sometimes go away on its own if the patient is not provided with appropriate medical care [1].

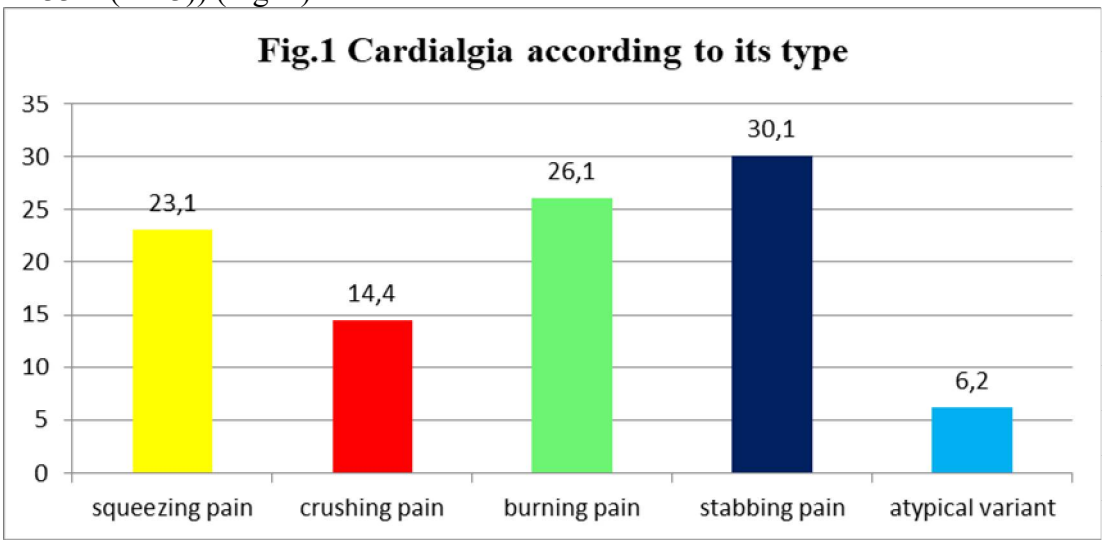
Research objective: To study the character of cardialgia in myocardial infarction depending on age and sex

Research materials and methods. The study included 631 patients undergoing inpatient treatment in Tashkent City Clinical Hospital No.7 for myocardial infarction. The follow-up period was from 2012 to 2014 (up to 6 months). The average age of patients was 63,7±11,7 years. Of these, men (n=393) 62.3% and women (n=238) 37.7%.

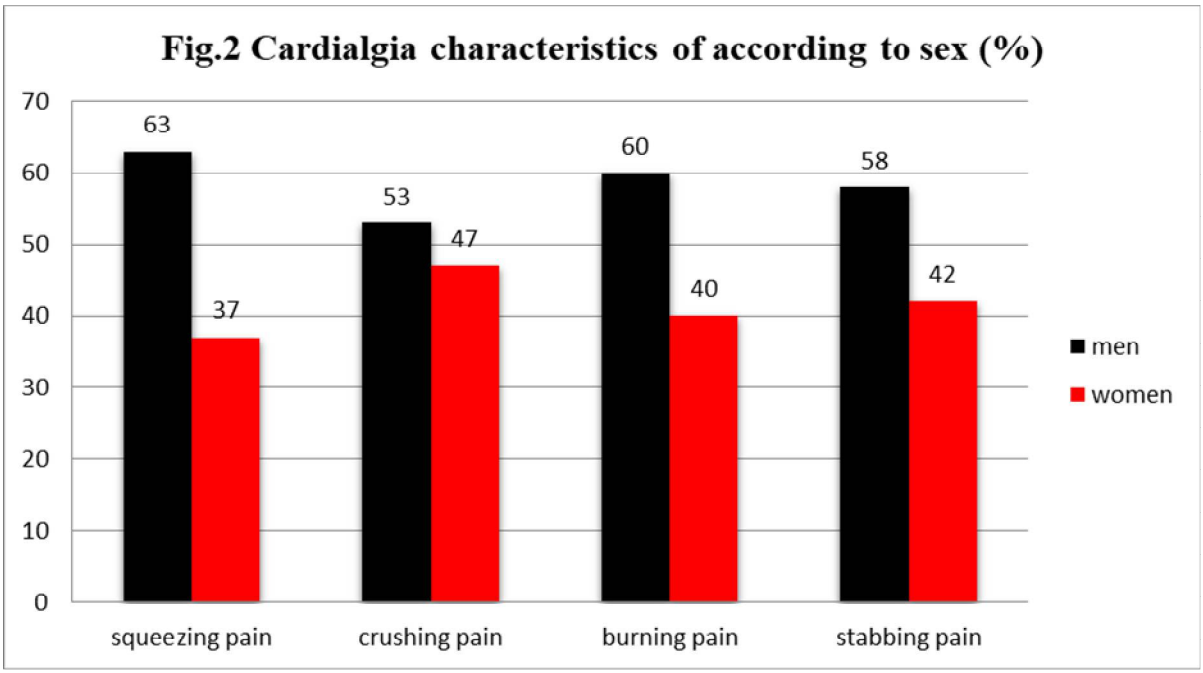
The diagnosis of MI at the inpatient stage of treatment was established according to the existing criteria of the national guidelines for the diagnosis and treatment of ST-segment elevation MI patients, 2007.

The methods of statistical analysis of the study results were performed using a package of applied statistical programs MEDIOSTAT. Standard methods of variation statistics were used: calculation of mean, standard deviation (M±m), Student's criteria ($p<0.05$).

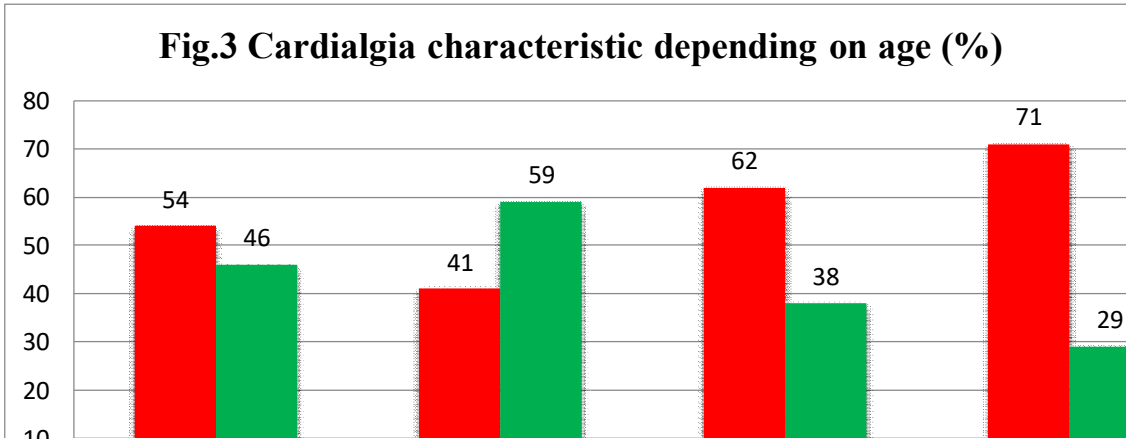
Research Results. The results showed that compressive pain was observed in 23.1% (N=146) of patients, pressing pain in 14.4% (N=91), burning pain in 26.1% (N=165) of patients, stabbing pain in 30.1% (N=190) of cases, 6.2% (N=39) of patients had atypical variants (abdominal form 31% (n=12), cerebral form 13% (n=5), irradiation of pain into shoulder and neck 23% (n=9), no pain form 33% (n=13)) (Fig. 1).



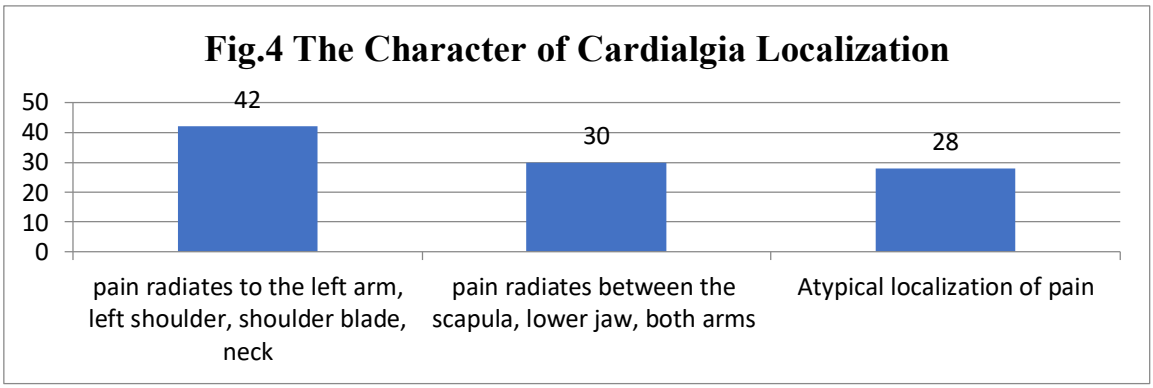
For sexual distinction, compressive pain was 17% more in men (63% (N=92)) than in women (37% (N=54)). Squeezing pain was 11.2% more in men (53% (N=48)) than in women (47% (N=43)). Burning pain 15% more in men (60% (N=99)) than in women (40% (N=66)). Cutting pain 13.8% more in men (58% (N=110)) than women (42% (N=80)). (Fig.2).



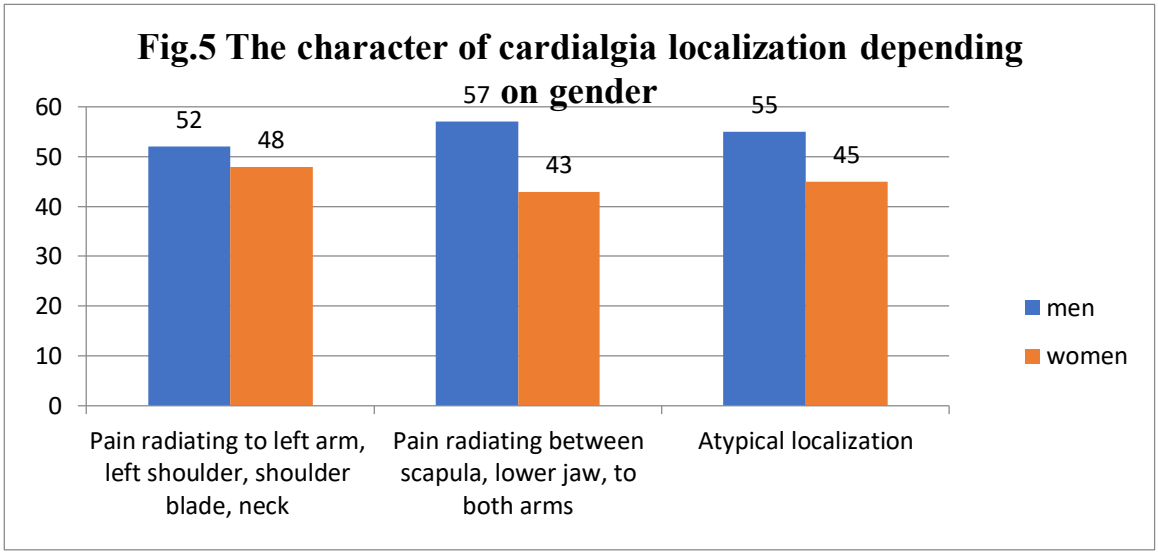
In the next stage, the nature of cardiac pain was studied according to age. Patients under 60 years of age (54% (N=79)) had 11.8% more compressive pain than patients over 60 years of age (46% (N=67)). Squeezing pain in patients over 60 years of age (59% (N=54)) was 14.6% greater than in patients under 60 years of age (41% (N=37)). Stinging pain in patients under 60 years of age (62% (N=103)) was 16.6% greater than in patients over 60 years of age (38% (N=62)). Burning pain was 24.5% more in patients under 60 years of age (71% (N=135)) than in patients over 60 years of age 29% (N=55) (Figure 3).



Studying the localization of cardialgia in 93.8% (N=592) of patients, the following was revealed: pain radiates into the left arm, left shoulder, scapula, neck 42% (N=249) of cases, interscapular space, lower jaw, both arms 30% (N=178) (Fig. 4).

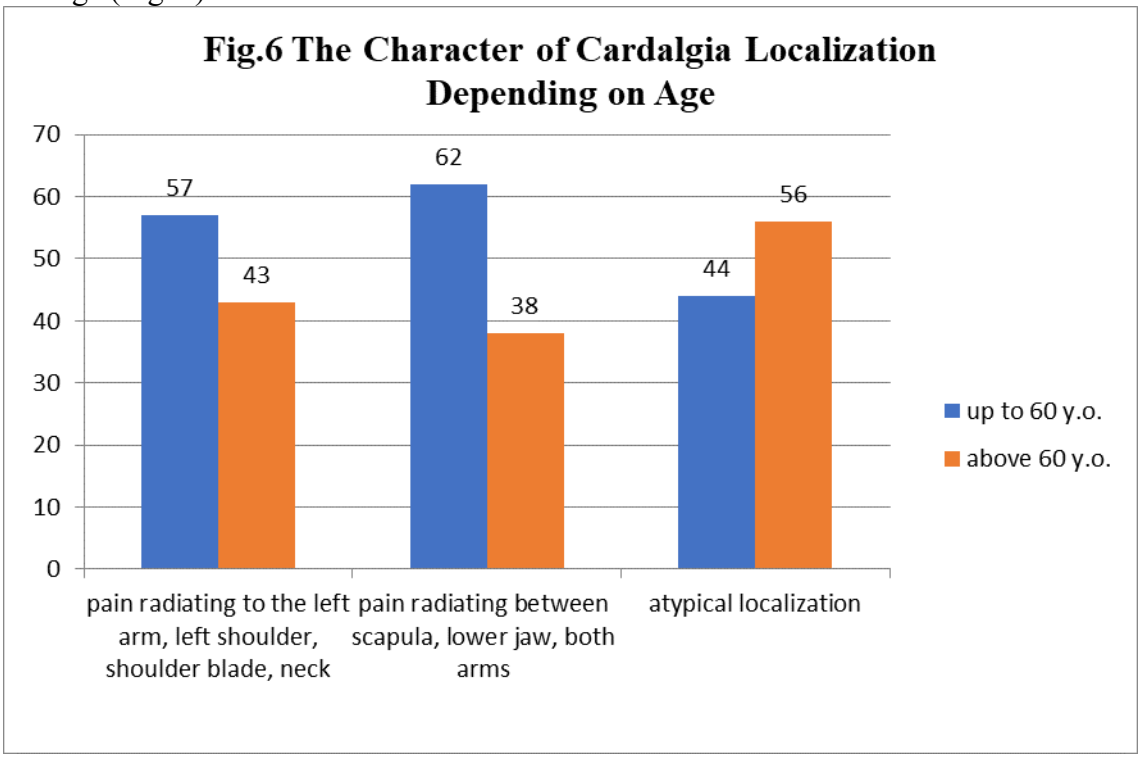


Gender differences in pain localization showed the following pain with irradiation into the left arm, left shoulder, scapula, neck in men 52% (N=130), in women 48% (N=119). Pain with irradiation to interscapular space, lower jaw, both arms in 57% (N=102) of men, 43% (N=76) of women. Atypical localization in men 55% (N=91), in women 45% (N=74) cases (Fig. 5).



Pain with irradiation into the left arm, left shoulder, scapula, the neck was observed in 57% (N=141) of patients under 60 years of age and in 43% (N=108) of patients over 60 years of age. Pain with irradiation to interscapular space, lower jaw, both arms was observed in 62% (N=111) of cases before 60 years of age, in 38% (N=67) of cases after 60 years of age. Atypical localization of

pain was observed in 44% (N=73) of cases under 60 years of age and in 56% (N=92) of cases over 60 years of age (Fig. 6).



Conclusion:

1. The results of the study showed a high incidence of stabbing pain (30% (n=190)) in patients with MI in the inpatient setting.
2. Whereas male patients with MI had a predominant compressive pain (63%(n=92)) and female patients (47%(n=43)) had a compressive pain.
3. In patients who had a MI before 60 years of age, cutting pain predominated, (71%(n=135)) and in patients over 60 years of age (59%(n=54)) pressure pain predominated.

Reference

1. Source: http://medbe.ru/materials/diagnostika-i-simptomy-ssz/boli-pri-infarkte-miokarda/ © medbe.ru

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EVALUATION OF THE EFFECTIVENESS OF FIXED PROSTHETICS ON DENTAL IMPLANTS AT DIFFERENT PERIODS OF OBSERVATION

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ABSTRACT

Today, mathematical modeling is characterized by a dynamic expansion of the subject areas of their application. A demanded area of application of mathematical modeling is the solution to choosing a rational dental treatment for a patient, taking into account the individual characteristics of the state of the dentition. The use of information technologies and the implementation of their capabilities for calculating biomechanical structures in mathematical modeling systems is a promising, relevant and popular direction in developing orthopedic dentistry.

Keywords: mathematical modeling, prosthetics, dental implants, fixed orthopedic structures.

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ОЦЕНКА ЭФФЕКТИВНОСТИ ФУНКЦИОНИРОВАНИЯ НЕСЪЕМНОГО ПРОТЕЗИРОВАНИЯ НА ДЕНТАЛЬНЫХ ИМПЛАНТАТАХ В РАЗЛИЧНЫЕ СРОКИ НАБЛЮДЕНИЯ

АННОТАЦИЯ

На сегодняшний день развитие математического моделирования характеризуется динамичным расширением предметных областей их применения. Востребованной областью приложения математического моделирования является решение задачи выбора рационального стоматологического лечения пациента с учетом индивидуальных особенностей состояния зубочелюстной системы. Применение информационных технологий и реализация их возможностей для расчета биомеханических конструкций в системах математического моделирования - перспективное, актуальное и востребованное направление развития ортопедической стоматологии.

Ключевые слова: математическое моделирование, протезирование, дентальные имплантаты, несъемные ортопедические конструкции.

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KUZATUVNING TURLI DAVRLARIDA STOMATOLOGIK IMPLANTLARDA QATTIQ PROTEZLAR FAOLIYATI SAMARADORLIGINI BAHOLASH

ANNOTATSIYA

Bugungi kunda matematik modellashtirishning rivojlanishi ularni qo'llash sohalarining dinamik kengayishi bilan ajralib turadi. Matematik modellashtirishni talab qilinadigan sohasi - bu tish holatining individual xususiyatlarini hisobga olgan holda, bemor uchun ratsional stomatologik davolanishni tanlash masalasini hal qilishdir. Matematik modellashtirish tizimlarida biomexanik tuzilmalarni hisoblash uchun axborot texnologiyalaridan foydalanish va ularning imkoniyatlarini amalga oshirish ortopedik stomatologiyani rivojlantirishning istiqbolli, dolzarb va mashhur yo'nalishi hisoblanadi.

Kalit so'zlar: matematik modellashtirish, protezlash, stomatologik implantlar, statsionar ortopedik tuzilmalar.

Introduction: To improve the quality of prosthetics with dental implants, it is necessary to develop new treatment planning programs, taking into account the existing experience and tools for modeling dentoalveolar segments' behavior, depending on the specific conditions of the patient's oral cavity. Besides, mathematical modeling can predict technical solutions' receipt, which provides for their reasonable application in the future. The effective application of mathematical modeling methods in prosthetics is due to the development of computer technologies, making it possible to obtain real results of calculating mathematical models of biological objects. The results of the analysis and study of biomechanical processes in the soft and bone tissues of the dentition, which determine the reliability of its functioning, showed their direct dependence on the values of internal stresses and deformations arising under prolonged exposure to workloads, which is of great importance for further predicting the results of orthopedic treatment. The modern level of construction and analysis of orthopedic structures requires a large number of methodological issues of dental implantology based on the accumulated practical experience and theoretical knowledge. The study of the effect of non-removable orthopedic structures shows that the magnitude and direction of functional loads in them, as in biomechanical systems with different dentoalveolar schemes, cause a significant difference in the magnitude of the forces acting on the implants, and, accordingly, on the bone and adjacent tissues.

In the works of Eroshin V.A. For the first time, the calculation of the stress-strain state (SSS), strength and rigidity of the temporary structure of a denture on a temporary dental implant "Mini" was carried out using mathematical modeling and the finite element method (FEM). A positioning system for permanent and temporary dental implants was proposed according to the scheme developed using mathematical modeling. New scientific knowledge about the strength characteristics of temporary fixed dentures based on temporary dental implants was obtained. For the first time, indications have been developed for the medical choice of the optimal design of a temporary fixed denture based on temporary implants, used for the period of osseointegration of two-stage dental implants in the process of orthopedic treatment of patients with dentition defects. As a result of the study, the effectiveness of the developed design of a temporary denture was assessed using native and stereolithographic models of the human jaw. This study will improve the efficiency of orthopedic dental treatment of patients with the use of dental implants through a scientifically grounded choice of the design of a temporary fixed denture installed on temporary implants. A temporary non-removable design of a denture has been created, supported by temporary implants and replacing the defect in the dentition, located in the projection of the installed two-stage

dental implants in such a way that they eliminate the load in this area and contribute to the effective osseointegration of the main dental implants.

The results of an experimental study of S.D. Arutyunov samples of temporary fixed dentures made it possible to establish the following. The average value of the force applied to the bridge made of Protemp material with a length of 5 units, at which its destruction occurs, is Fpr = 356 ± 39 N at p = 0.95. For bridges made of "Luxatemp" composite, the average value of the breaking load is noticeably lower: Fпр = 288 ± 29 N, although Young's moduli of these materials practically do not differ. The strongest under static loading turned out to be structures made of the material "Sinma-M" (Fpr = 414 ± 32 N), although the Young's modulus of this polymer is significantly lower. Bridges 4 pcs. in all cases, they withstood heavy loads (by about 40%). Note that the samples were loaded with concentrated forces applied to the middle of the bridge structure. When using a load distributed over 2 units, the structure could withstand 1.5-2 times higher loads. In experiments, the destruction of bridges occurred most often in the middle: a crack developed that went from bottom to top to the left or right of the middle (14th tooth) facet.

In some cases, deformation was observed in the area of the abutment teeth. Sometimes there was no brittle fracture, but under extreme loads (of the order of 300 N and more), plastic deformations proliferated, and the structure sat on the base on which the abutment teeth were attached (the gap between the lower part of the prosthesis and the base was 2–3 mm). In this case, the residual deformation (upon removal of the load) was 50–100 μm. Experiments have shown that the fatigue strength at 10 thousand cycles (chewing movements) with a probability of 80% is Fпр = 201 ± 8.6 H. For geometrically similar specimens obtained by computer milling from blocks made of the same material in laboratory conditions, the fatigue strength is 30% less and is Fpr = 172 ± 10.7 H. The long-term functioning of the prostheses was assessed on the example of a 5-unit bridge made of the Sinma-M material using traditional technology. With a cyclic load F = 201 ± 8.6 N with a probability of 80%, it must withstand 2 times less than the maximum permissible (n = 5 thousand), i.e. the safety factor of durability was introduced (k = 2). Next, a list of products of corresponding hardness, food volume, and the specific number of chewing movements N * required for grinding 1 kg of food were determined. Taking the permissible number of cycles (5 thousand) to the specific N *, the product's total mass was obtained, which can be crushed (chewed) using a temporary prosthesis without destroying it. By dividing this amount by the established daily food intake, the temporary prosthesis service (in days) was obtained for the selected diet. If this duration is insufficient, it is advisable to change the diet.

Conducted scientific research Shirokova I.Yu. for the first time, the calculation of the stress-strain state (SSS), strength and stiffness of the temporary structure of a denture on a temporary dental implant "MINI" was carried out using mathematical modeling and the finite element method (FEM). A positioning system for permanent and temporary dental implants was proposed according to the scheme developed by us using mathematical modeling. New scientific knowledge about the strength characteristics of temporary fixed dentures based on temporary dental implants has been obtained. For the first time, indications have been developed for a medical choice of the optimal design of a temporary fixed denture based on temporary implants, used for the period of osseointegration of two-stage dental implants in the process of orthopedic treatment of patients with dentition defects. For the first time, assessing the effectiveness of the developed design of a temporary denture was carried out using native and stereolithographic models of the human jaw. This study will improve the efficiency of orthopedic, dental treatment of patients using dental implants by the scientifically grounded choice of the design of a temporary fixed denture installed on temporary implants.

A temporary non-removable design of a denture has been created, supported by temporary implants and replacing the defect in the dentition, located in the projection of the installed two-stage dental implants in such a way that they eliminate the load in this area and contribute to the effective osseointegration of the main dental implants. Recommendations on the choice of construction material for the manufacture of temporary crowns and bridges are given.

In the article by V.N. Olesova. maximum stresses in the HF bone tissue under loading of the frontal or lateral parts of the prosthesis are localized around the neck of the implants, spreading to distant parts - the bottom of the nasal cavity, the walls of the maxillary sinus (see Fig. 2-4). With the load of the anterior part of the prosthesis and 6 implants 15, 12.5 and 8 mm long (diameter 3.9 mm), the stresses in the cortical bone are 6.62, 6.61, and 8.06 MPa, respectively; when the number of implants decreases to 4, the indicated stresses increase to 8.12, 9.28, and 10. The stress at the extreme implants installed with an inclination using the all-on-four technology (length 12.5 mm, diameter 3.9 mm) is 12.37 MPa. In zygomatic implants, the maximum stresses are localized along the ridge of the alveolar ridge around the implant neck and amount to 12.25 MPa, when the frontal part of the prosthesis is loaded, the zygomatic implants do not affect the magnitude of stresses in comparison with all-in-four implants. Reducing the diameter of the implants increases the stresses in the bone tissue: with an implant length of 12.5 mm and a diameter of 5, 4.3, and 3.5 mm (the number of implants is 4), the stresses in the cortical bone of the HF are 5.75, 7.20 and 10, 11 MPa. The prosthesis's lateral part loading significantly increased the stresses in the cortical bone tissue at the implants. With 6 implants and length 15; 12.5 and 8 mm, stresses from lateral loading increased, respectively, to 48.47, 49.71 and 61.00 MPa, i.e., by 86.3-86.8% in comparison with the load of the frontal region ($p < 0, 01$). In the presence of 4 implants of the indicated size, lateral loading caused stress in the cortical bone tissue equal to 51.57, 53.62 and 67.66 MPa, 82.7-85.1% more than the load of the anterior region ($p < 0, 01$). Changing the implant diameter from 3.9 to 4.3 and 5 mm reduces stress while reducing the diameter to 3.5 mm increases it.

With implants with a length of 12.5 mm, the load of the lateral part of the prosthesis on implants with a diameter of 5, 4.3 and 3 mm causes stresses in the bone, equal to 38.44, 46.38 and 54.46 MPa, respectively, which is 81 more than the stresses of the frontal part, 4-85% ($p < 0.01$). The stresses around the extreme implants installed at an angle using the all-on-four technology (151.32 MPa) are 91.8% higher than the load of the anterior part of the fixed prosthesis ($p < 0.01$). In this situation, when the lateral part of the prosthesis is loaded, the zygomatic implants reduce the stresses in the bone tissue (104.09 MPa) in comparison with the "all-in-four" technology by 30.7% ($p < 0.01$), nevertheless increasing the stresses in comparison with frontal load by 88.2% ($p < 0.01$). Relative to the average ultimate strength of the cortical bone tissue (150 MPa), the bone tissue in the extreme implants under the load of the lateral section of the fixed prosthesis "all in four" has no safety margin, and in the zygomatic implants the safety margin of the bone is 30.6% [9]. Mathematical modeling showed low stresses in the cancellous bone tissue of HF under the load of a fixed prosthesis on implants, as well as in the materials of implants and prostheses, which are far from the ultimate strength of metal and ceramic alloys, in connection with which the results of the most unfavorable variant for biomechanics are presented - the load of the lateral section of fixed HF implant prostheses. With 6 implants and their lengths 15, 12.5, and 8 mm (diameter - 3.9 mm), the stresses in the cancellous bone at HF are 5.4, 5.6 and 6.3 MPa, respectively. With a decrease in the number of implants to 4 and a length of 15, 12.5, and 8 mm, the stresses slightly increase in shorter length implants: with the above dimensions - 5, 6.1 and 6.8 MPa. The inclined installation of the extreme implants using the all-on-four technology increases the stresses at the extreme implants - 10.4 MPa. On the other hand, Zygomatic implants reduce stresses compared to those in the "all in four" option - 7.5 MPa. Reducing the implant diameter from 5 to 4.3 and 3.5 mm increases the stresses: 4.4, 4.9 and 6 MPa, respectively, for the example of a length of 12.5 m.

Thus, in the cancellous bone, the pattern of stress dependence on the size and placement of implants is repeated; the highest stresses are typical for all-on-four implants, zygomatic implants and with an implant length of 8.0 mm; Taking into account the tensile strength of the cancellous bone in these situations, the stresses approach critical. Stresses in implants and prosthetic structures during lateral loading are far from critical in titanium and ceramics. So, in implants, most of the stresses range from 37.4 to 68 MPa. More significant stresses are typical for zygomatic implants (91.8 MPa) and installed using the "all-on-four" technology (for the extreme implants, 161.5 MPa). For a prosthetic structure, typical stresses are 24–49.3 MPa. Given the large margin of safety in titanium and ceramics compared to the stresses obtained in this study, the regularities of the

dependence of stresses in implants and prostheses on the size and number of implants seem to be insignificant. Thus, according to three-dimensional mathematical modeling data, the functional load of fixed prostheses on HF implants does not cause ultimate stresses in the implants and the prosthesis; safety margin. Tensions in the bone tissue are localized around the implants' neck, spreading into the bottom of the nasal cavity and the maxillary sinuses' medial walls; stresses decrease with an increasing number, length, and diameter implants. This information should be taken into account at the planning stage of orthopedic treatment based on implants. From the point of view of practicing dentistry, it would be ideal for creating a specialized program designed to solve exactly the set problem, which determines the choice of future treatment, which would allow predicting long-term results of orthopedic treatment with the use of dental implants based on clinical and functional data. The problem of developing treatment algorithms and, on their basis, mathematical modeling of biomechanical systems and predicting the effectiveness of dental prosthetics, taking into account their general physiological and structural features of the jaw's restored segments, is urgent.

There are no less frequent works in which, using mathematical modeling methods, the design of removable dentures based on implants and biological tissues of the oral cavity is evaluated; assessment of the influence of the direction of implant placement on the strength characteristics of prostheses.

Research in this direction is of great theoretical and practical importance, aimed at developing methods for determining the magnitudes and patterns of stress redistribution towards those physiologically acceptable for tissues, since, first of all, this creates a normal working environment in the dentoalveolar system, preventing the emergence and development of pathological foci, in including restoring chewing efficiency up to 100%.

Based on the clinical and functional examination methods, such as laser Doppler flowmetry, gnathodynamometry, X-ray diagnostics, and echoosteometry, certain results were obtained to characterize the degree of osseointegration of dental implants, as well as the effect of bridges on peri-implant tissues. In this regard, mathematical modeling methods would make it possible in the short term to predict the functioning of prosthetic structures on dental implants.

Conclusions: Thus, mathematical modeling methods are aimed at long-term prediction of the functioning of bridges on dental implants. According to experts, the mathematical modeling of a long-term forecast depends on many factors. The mathematical model must include dentition's main clinical and functional parameters to improve the forecast's reliability and accuracy. In this regard, lifestyle indicators (bad habits, type of chewing, etc.) and the patient's somatic burden are also of great importance. To date, the issue of selecting the clinical and functional parameters of the patient to create an accurate mathematical model of the functioning of dentures based on dental implants remains relevant.

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MORPHOMETRIC FEATURES OF THE DENTITION IN CHILDREN WITH CHRONIC DISEASES OF THE UPPER AND MIDDLE RESPIRATORY ORGANS

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ABSTRACT

Everyone knows that the present appearance of a person plays a vital role in the formation of personality. The desire to have a beautiful smile, the correct bite is an incentive to contact an orthodontist, to correct various types of dentoalveolar anomalies (DAA). Identifying the morphofunctional community of changes in the dentofacial system (DFS) and the upper respiratory tract (URT) is an important problem in theoretical and practical dentistry, to which many scientists have attracted.

Keywords: diagnostics, the formation of organs of the bones of the dentition, frequency of occurrence.

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МОРФОМЕТРИЧЕСКИЕ ОСОБЕННОСТИ СТОМАТОЛОГИИ У ДЕТЕЙ С ХРОНИЧЕСКИМИ ЗАБОЛЕВАНИЯМИ ВЕРХНИХ И СРЕДНИХ ОРГАНОВ ДЫХАНИЯ

АННОТАЦИЯ

Всем известно, что настоящее время внешний облик человека играет важную роль в становлении личности. Желание обладать красивой улыбкой, правильным прикусом является стимулом для обращения к врачу-ортодонту, с целью исправления различных видов зубочелюстных аномалий (ЗЧА). Выявление морфофункциональной общности изменений зубочелюстной системы (ЗЧС)и верхних дыхательных путей (ВДП) является важной проблемой теоретической и практической стоматологии, к которой сегодня привлечено внимание многих ученыхм.

Ключевые слова: диагностика, формирования органов костей зубочелюстной системы, частота встречаемости.

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YUQORI VA O'RTA NAFAS OLISH A'ZOLARINING SURUNKALI KASALLIKLARI BILAN KASALLANGAN BOLALARDA TISH-JAG' SISTEMASINING MORFOMETRIK XUSUSIYATLARI

ANNOTATSIYA

Hammaga ma'lumi, hozirgi davrda shaxsning shakllanishida insonning qiyofasi muhim rol o'ynaydi. Turli xil tish-jag' anomaliyalarini (TJA) tuzatish maqsadida, chiroyli tabassumga, tog'ri tishlarga ega bo'lish istagi shifokor-ortodontga murojaat qilish uchun sabab hisoblanadi. Tish-jag' tizimi (TJZ) va yuqori nafas yo'llarining (YNY) morfofunksional umumiyligini ochib berish nazariy va amaliy stomatologiyada muhim muammo bo'lib va hozirgi kunda ko'plab olimlarning diqqatini jalb qilmoqda.

Kalit so'zlar: diagnostika, tish jag' a'zolari shakllanishi, analiz tahlili.

Relevance: In recent years, a significant amount of work has appeared in studying the relationship between the size of the head and somatotypes and proportions of the human body. [1, 3, 5, 8, 11]. However, as the author [9] points out, anthropometric studies of recent years have shown that the physical status of modern man has undergone certain changes compared to that presented in the works of the mid-20th century and one of the main reasons is that the works devoted to physical development, more attention is paid to the somatotype and much less to the head.

Everyone knows that the present appearance of a person plays an important role in the formation of personality. The desire to have a beautiful smile, the correct bite is an incentive to contact an orthodontist, to correct various types of dentoalveolar anomalies (DAA).

The growth and development of the human body from the embryo stage to its adult state is a very complex phenomenon that undergoes many changes under the neuro-humoral mechanisms controlling the differentiation, development and maturation of organs and systems. Various causes can influence the growth parameters of different parts of the human body, both physical [4, 5], mental [6], information loads [11], and pathological [2, 6, 4, 7]. According to the author [10], in children and adolescents, female gains in the general growth of the body appear at 7, 12-13 years old, growth gains in the upper part of the face - 11 and 14 years old, lower third - in 11 and 15; the sagittal diameter of the head also increases evenly.

This study aims to determine the morphometric features in children with chronic pathologies of the upper and middle respiratory system.

Research material and methods: To study and evaluate the morphometric parameters of the head, face, DFS, bone and tooth age in children with ChRSP, we took 480 children of both sexes aged 6 to 18 years (I group) living in the city of Bukhara; of which 250 boys (52.1%) and 230 girls (47.9%); to compare the obtained morphometric parameters, a group of practically healthy (group II) was taken, the number of 300 children of both sexes aged 6 to 18 years; 185 boys (61.6%) and 115 girls (38.33%); the examined children were distributed by the age category of the examined (table №1).

Table 1

According to the age group of the children surveyed, n = 780

Age	Boys		Girls		Total
	Healthy children	Children with ChRSP	Healthy children	Children with ChRSP	

6-9	50	75	35	71	231
10-13	65	80	35	79	259
14-18	70	95	45	80	290
Total	185	250	115	230	780

The study of morphometric data on the physical development of all examined children who applied to a specialist and were partially registered in the dispensary of the regional children's and adult multidisciplinary hospitals, and the departments of Orthopedic Dentistry and Orthodontics, Otorhinolaryngology and Pediatrics of the Bukhara State Medical Institute

The results and their discussion. The primary parameters of physical development include standing, body weight and chest circumference in a pause: As can be seen, the results of the study in healthy children showed that the growth in 6-10 year old male children ranged from 114.7 sm up to 134.1 sm, averaging 124.4 ± 0.48 sm. When measured, body weight ranged from 15.8 kg to 31.6 kg, on average, it was equal to 24.6 ± 0.33 kg. The chest circumference ranged from 55.4 to 72.9 sm, on average - 62.7 ± 0.38 sm. In 6-10 year old children, the female span ranged from 120.0 sm to 135.4 sm, averaging 128, 8 ± 0.92 sm; body weight from 18.1 kg to 35.2 kg, averaging 25.8 ± 0.22 kg; chest circumference ranged from 57.4 to 73.9 sm, on average - 61.0 ± 0.56 sm.

As a result of studies, it was found that the growth in 10-13 year old male children ranged from 134.7 sm to 155.2 sm, averaging 143.9 ± 0.26 sm. Body weight ranged from 17.8 kg to 50, 4 kg, on average it was equal to 37.0 ± 0.98 kg. The chest circumference is in the range from 60.4 to 77.1 sm, on average - 68.2 ± 0.31 sm. For girls 10-13 years old, the growth ranged from 134.4 sm to 159.6 sm, averaging 145.4 ± 0.53 sm; body weight ranged from 25.2 kg to 52.4 kg, on average it was 34.2 ± 0.97 kg; the chest circumference is in the range from 60.6 to 78.5 sm, on average - 69.5 ± 0.36 sm.

Studies have shown that growth in 14-18 year old male children ranged from 148.5 sm to 178.8 sm, averaging 165.1 ± 0.33 sm. Body weight ranged from 49.3 kg to 69.4 kg, on average, was equal to 61.2 ± 0.77 kg. When measuring the chest circumference is in the range from 66.8 to 95.5 sm, on average - 81.0 ± 0.46 sm. The growth in girls aged 14-18 years old ranged from 150.4 sm to 182.4 sm, averaging 166.1 ± 0.23 sm; body weight ranged from 50.3 kg to 71.4 kg, averaging 62.8 ± 0.37 kg; the chest circumference is in the range from 68.8 to 105.5 sm, on average - 93.0 ± 0.26 sm.

The study results in patients with ChRSP showed that growth in 6-10 year old male children ranged from 108.5 sm to 133.2 sm, averaging 122.2 ± 0.28 sm. When measured, body weight ranged from 14, 0 kg to 30.6 kg, on average, it was equal to 22.6 ± 0.13 kg. The chest circumference was from 50.4 to 70.9 sm, an average of 60.2 ± 0.34 sm. Height in 6-10 year old female children ranged from 111.0 sm to 136.1 sm, an average of 125, 7 ± 0.72 sm; body weight ranges from 18.1 kg to 38.1 kg, averaging 24.2 ± 0.42 kg; the chest circumference ranged from 53.3 to 69.9 sm, an average of 57.3 ± 0.47 sm.

As a result, it shows that the growth in 10-13 year old male children ranged from 130.4 sm to 153.2 sm, averaging 141.8 ± 0.16 sm. Body weight ranged from 17.1 kg to 48.4 kg, on average, was 36.0 ± 0.48 kg. The chest circumference ranges from 55.4 to 74.1 sm, an average of 64.5 ± 0.21 sm. At the same age, girls' growth ranged from 131.2 sm to 157.4 sm, averaging 143 5 ± 0.63 sm; body weight ranged from 23.2 kg to 52.8 kg, an average of 33.2 ± 0.47 kg; the chest circumference is in the range from 58.4 to 75.3 sm, on average - 66.9 ± 0.86 sm.

Table 2.

Morphometric parameters of a healthier person than children and children with ChRSP according to their "principle of the golden ratio."

Age and sex / Param.person (sm)		6-9 age		10-13 age		14-18 age	
		Boys	**Girls**	**Boys**	**Girls**	**Boys**	**Girls**
Physio. face height	**Healthy**	17,1±0,10	17,3±0,12*	17,2±0,10	17,5±0,12*	18,8±0,40	19,2±0,02*
	ChRSP	16,6±0,07	17±0,05*	16,5±0,08	17,0±0,05*	17,2±0,02	17,4±0,05*

MHF	**Healthy**	11,5±0,10	11,2±0,12	11,7±0,13	11,3±0,12	11,9±0,22	11,8±0,01
	ChRSP	11,1±0,06	11,2±0,04*	11,0±0,07	11,5±0,04*	11,6±0,22	11,6±0,20*
Height in / part of the face	**Healthy**	5,8±0,05	5,8±0,05	5,8±0,05	5,8±0,05	5,9±0,08	5,9±0,08
	ChRSP	5,6±0,03	5,7±0,02	5,7±0,03	5,7±0,02	5,9±0,07	5,9±0,08
Height of media / parts of the face	**Healthy**	5,7±0,05	5,9±0,05*	5,8±0,05	5,9±0,05*	5,9±0,08	6,0±0,08*
	ChRSP	5,5±0,03	5,8±0,02*	5,6±0,03	5,8±0,02*	5,8±0,08	5,9±0,01*
Height n / a part of the face	**Healthy**	5,7±0,05	5,9±0,05*	5,8±0,05	5,9±0,05*	6,0±0,05	6,0±0,05*
	ChRSP	5,7±0,03	5,6±0,02	5,7±0,03	5,6±0,02	5,8±0,08	5,8±0,07
Fibonacci number	**Healthy**	1:1,611	1:1,60	1:1,619	1:1,60	1:1,680	1:1,70
	ChRSP	1:1,585	1:1,630	1:1,601	1:1,630	1:1,620	1:1,640

Note: * - confidence indicator (P <0.05) compared with the previous age.

Thus, the study showed that MHF and PhHF in children with ChRSP are smaller than in healthy children. The growth rate of the face's morphometric parameters in healthy children is almost the same at regular intervals, and in children with ChRSP, they change spasmodically. In healthy male children, the growth rate is lower than with male children suffering from ChRSP. It has been established that the ratio of the upper, middle and lower parts of the face in girls of all groups is closer to the "principle of the golden ratio" compared to boys. In children with ChRSP, especially in boys, the face ratio does not correspond to the Fibonacci number.

Morphometric parameters of the head and DFS of children of both sexes of 6-9, 10-13 and 14-18 age groups, healthy children and children ChRSP: he results obtained on the head and DFS of healthy children show that in a 6–9-year-old group of male children, the HG ranged from 48.5 to 60.1 sm, on average - 51.8 ± 0.24 sm, LHD from 13.5 to 16,9 sm, on average - 15.0 ± 0.42 sm, THS varied from 11.5 to 14.0 sm, on average - 12.8 ± 0.56 sm, TFS was from 9.6 to 13.8 sm, on average - 11.4 ± 0.18 sm, VDH ranged from 10.8 to 14.1 cm, on average - 11.8 ± 0.1 cm.

Head and DFS indices in a 6–9 year old group of male children, patients with ChRSP the HG fluctuated from 45.5 to 52.6 sm, on average –48.8 ± 0.22 sm, LDH from 12.5 to 16.9 sm, on average - 14.8 ± 0.14 sm, THS ranged from 11.5 to 14.0 sm, on average - 12.0 ± 0.16 sm, TFS was from 9.4 to 12.8 sm, on average - 11.2 ± 0.06 sm, VHS ranged from 10.2 to 13.1 sm, on average - 12.0 ± 0.04 sm.

The trend of a gradual increase in the head and face's size continued in the health of male children 10-13 years old. The data showed that the exhaust gas ranged from 50.0 to 58.4 sm, which averaged 54.9 ± 0.14 sm; LDH ranged from 16.8 to 19.6 sm, an average of 17.8 ± 0.03 sm; THS ranged from 12.1 to 18.8 sm, on average it was 15.5 ± 0.19 sm; TFS was in the range of 10.6-16.6 sm, an average of 13.6 ± 0.10 sm and VHS ranged from 12.6 to 16.5 sm, which averaged 15.1 ± 0.10 sm.

Conclusions.

1. Body weight in healthy children aged 6-9 years increases faster than body length; in males from 6-9 years, growth increases by 1.57 times, in females 1.64 times; and body weight is 2.71 times in boys in women is 2.79 times. The dimensions of the chest's circumference in a pause of 10-13 years in healthy males increase by 1.44 times, and in females -1.45 times.

2. It was revealed that MHF and PhHF in children with ChRSP are less than in healthy children. The growth rate of the face's anthropometric parameters in healthy children is almost the same at regular intervals of time, and in children with ChRSP, they change spasmodically.

3. It was revealed that the ratio of the upper, middle and lower parts of the face in girls of all groups is closer to the "principle of the golden ratio", compared with boys. In children with ChRSP, especially in boys, the ratio of the parts of the face does not correspond to the Fibanacci number:

An analysis of bone age in children with ChRSP showed that their bone age is later than in healthy children; from 6 months (6-9 years) to 2.5-3 years (at 10-13 years).

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TYPE 2 DIABETES DEPENDING ON THE PRESENCE OF COMPLICATIONS FROM THE KIDNEYS AND PERIODONTAL DISEASE BEFORE AND AFTER PROSTHETICS WITH REMOVABLE PLATE DENTAL PROSTHESES

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ABSTRACT

CKD is not a highly specialized, "nephrological" problem, but a General medical one. Patients with CKD are at risk of developing diseases of the oral cavity. Data from the specialized literature indicate that a low level of dental health contributes to systemic complications in nephrological patients. Unfortunately, in practice, an isolated course of these pathologies is quite rare, as a rule, they proceed in combination, mutually burdening each other. There are many approaches to treating these diseases of the oral cavity, but there is still no consensus on the most appropriate treatment tactics, the results of which would suit both the doctor and the patient. It is often difficult to predict the success of treatment, and the definition of the quality of life, which has recently become widespread in medicine, can help the dentist. The quality of life is an integral characteristic of the patient's physical, psychological, emotional and social functioning, based on his subjective perception. To date, it has been proven that the parameters of the patient's quality of life have an independent prognostic value and are more accurate factors of the patient's condition during treatment than the general somatic status.

Keywords: periodontal diseases, after prosthetics, removable dental plates, orthopedic prostheses.

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ЗАБОЛЕВАНИЕМ СД 2 ТИПА В ЗАВИСИМОСТИ ОТ НАЛИЧИЯ ОСЛОЖНЕНИЙ СО СТОРОНЫ ПОЧЕК И ЗАБОЛЕВАНИЯ ПАРОДОНТА ДО И ПОСЛЕ ПРОВЕДЕНИЯ ПРОТЕЗИРОВАНИЯ СЪЕМНЫМИ ПЛАСТИНОЧНЫМИ ЗУБНЫМИ ОРТОПЕДИЧЕСКИМИ ПРОТЕЗАМИ

АННОТАЦИЯ

ХБП - не узкоспециальная, «нефрологическая», а общемедицинская проблема. Пациенты с ХБП относятся к группе риска развития заболеваний полости рта. Данные специальной литературы свидетельствуют о том, что низкий уровень стоматологического здоровья способствует прогрессированию системных осложнений у нефрологических больных. К сожалению, на практике изолированное течение этих патологий встречается довольно редко, как правило, они протекают в сочетании, взаимно отягощая друг друга. Существует множество подходов к лечению этих заболеваний полости рта, но до сих пор нет единого мнения о наиболее подходящей тактике лечения, результаты которой устраивали бы как врача, так и пациента. Часто бывает трудно предсказать успех лечения, и определение качества жизни, которое в последнее время получило широкое распространение в медицине, может помочь стоматологу. Качество жизни - это интегральная характеристика физического, психологического, эмоционального и социального функционирования пациента, основанная на его субъективном восприятии. На сегодняшний день доказано, что параметры качества жизни больного имеют самостоятельное прогностическое значение и являются более точными факторами состояния больного в процессе лечения, чем общий соматический статус.

Ключевые слова: заболевания пародонта, после проведения протезирования, съемными пластиночными зубными, ортопедическими протезами.

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2 ТУРДАГИ КАНДЛИ ДИАБЕТНИНГ СУРУНКАЛИ БУЙРАК ХАСТАЛИГИ БИЛАН АСОРАТЛАНГАН БЕМОРЛАРДА ОЛИБ КУЙИЛАДИГАН ПЛАСТИНКАЛИ ТИШ ПРОТЕЗЛАРИ БИЛАН ПРОТЕЗЛАШДАН ОЛДИНГИ ВА КЕЙИНГИ ПАРАДОНТ ТУКИМАСИНИНГ ХОЛАТИ

АННОТАЦИЯ

СБК тор ихтисослашган, "нефрологик" эмас, балки умумий тиббий муаммодир. СБК бўлган беморлар огиз бўшлиғи шиллиқ қавати касалликлари учун ҳам хавф туғдиради. Ушбу махсус адабиётлар шуни кўрсатадики, огиз бўшлиғи шиллиқ қавати ва тиш қаторлари қисман нуқсонлари ҳам нефрологик беморларда тизимли асоратларнинг ривожланишига ёрдам беради. Афсуски, амалда бу патологияларнинг изоляция қилинган оқими жуда кам учрайди, одатда, улар бир-бирига ўзаро таъсир қилиб, биргаликда ҳаракат қилишади. Ушбу оғиз касалликларини даволаш учун кўплаб ёндашувлар мавжуд, аммо натижалар шифокор ва беморга мос келадиган энг қулай даволаш усуллари ҳақида ҳеч қандай келишув мавжуд эмас. Кўпинча даволанишнинг муваффақиятини тахмин қилиш қийин ва яқинда тиббиётда кенг тарқалган ҳаёт сифатини аниқлаш тиш шифокорига ёрдам бериши мумкин. Ҳаёт сифати-беморнинг субъектив идрокига асосланган жисмоний, психологик, ҳиссий ва ижтимоий фаолиятининг ажралмас характеристикаси. Бугунги кунга келиб, беморнинг ҳаёт сифати параметрлари мустақил прогностик аҳамиятга эга ва беморнинг даволаниш жараёнида умумий соматик мақомга қараганда аниқроқ омиллар эканлиги исботланган.

Калит сўзлар: Парадонт касалликлари, протездан кейинги ҳолат, ортопедик протезлар, қисман пластинкали протезлар.

Relevance. Therefore, before kidney transplantation, they need to exclude existing risk factors - foci of odontogenic infection. Simultaneously, the lack of debridement of the oral cavity after

surgery can lead to graft rejection and, in general, adversely affect the prognosis of kidney disease treatment. Therefore, dental rehabilitation is of great practical importance for patients with CKD.

Purpose of the study. Comprehensive assessment of patients' dental status with diabetes mellitus depends on renal dysfunction and the development of dental rehabilitation measures to improve their quality of life.

The most common pathologies of the dentoalveolar system in type 2 diabetes mellitus include defects in the dentition and periodontal disease, which are not only the cause of deterioration in the quality of life and a decrease in the working capacity of patients but also the cause of several somatic diseases and their unfavorable course. Both dentition defects and periodontal diseases are difficult to treat, leading to a significant decrease in the dentoalveolar system's functionality. They are characterized by a long period of rehabilitation. Unfortunately, in practice, an isolated course of these pathologies is quite rare, as a rule, they proceed in combination, mutually burdening each other. There are many approaches to the treatment of these diseases of the oral cavity, but there is still no consensus on the most appropriate treatment tactics, the results of which would suit both the doctor and the patient. It is often difficult to predict the success of treatment, and the definition of the quality of life, which has recently become widespread in medicine, can help the dentist. The quality of life is an integral characteristic of the patient's physical, psychological, emotional and social functioning, based on his subjective perception. To date, it has been proven that the parameters of the patient's quality of life have an independent prognostic value and are more accurate factors of the patient's condition during treatment than the general somatic status.

In this work, we studied the method of replacing dentition defects with removable plate dental prostheses in case of concomitant periodontal diseases in patients with type 2 diabetes, depending on the presence of kidney disease, assessed their results both in terms of improving the dental status and in terms of improving the quality of patients life.

60 patients with diabetes mellitus and dentition defects were examined. The examination was carried out twice: before the treatment and after it. All patients were divided into 2 groups: 30 patients with type 2 diabetes complicated by CKD, 30 patients with only type 2 diabetes; Patients in the group with type 2 diabetes and complicated CKD were divided into 2 groups depending on the use of the drug "LOROBEN" in the treatment. All patients also received the drug dipyridamole at an average therapeutic dose of 50 mg 3 times a day for 20 days.

The quality of life of patients was determined using the OhIP-14 questionnaire, which includes 14 questions that allow assessing the impact of the oral cavity on the quality of life, according to the following criteria: daily life, chewing food, ability to communicate. There were 5 answer options, which range from "very often" to "never" and are rated from 5 to 1 point, respectively. Patient quality of life was assessed prior to treatment. Also, a questionnaire was conducted using the OhIP-14 questionnaire after treatment.

During a survey conducted before treatment, patients of the first and second groups complained of pain and burning sensation in the tongue and oral mucosa, a change in taste, an unpleasant odor from the oral cavity, the presence of defects in the dentition and the associated difficulties in communication and eating. When examining the oral cavity in all patients, in addition to defects in the dentition, inflammation, swelling of the gingival papillae, hyperemia of the gums, and severe bleeding were noted.

The analysis of the questionnaires and questionnaires filled out by patients before treatment showed that according to all quality of life criteria, except for the ability to communicate, the quality of life of patients with type 2 diabetes complicated by CKD with periodontal diseases treated by the traditional method was significantly worse than that of patients. , who were treated with the antiseptic drug "LOROBEN" (Table 1).

The dependence of the patients' life quality on the method of therapy before the replacement of dentition defects

Patient groups	Criterion

	everyday life	chewing food	ability to communicate
Patients undergoing traditional treatment	13.4± 1,8*	7,3± 1,5*	9.7±1 ,8*
Patients with LOROBEN therapy	14,3± 1,5*	8,6± 1,3*	8,4±1 ,1*

Thus, this study showed that oral diseases such as defects in the dentition and periodontal disease, in the presence of general somatic disease of type 2 diabetes with complicated CKD, significantly reduce patients' quality of life, affecting both the ability to eat and communicate and overall well-being people, and should be considered not only as a medical problem but also as a social problem. Therefore, great attention should be paid to their elimination and prevention of their occurrence**.** At the same time, it can be seen from our study that different methods of treatment have a different effect on the quality of life of patients: although prosthetics with removable plate dentures and traditional treatment significantly improves the quality of life of patients, it is inferior to dental, orthopedic treatment with the use of the antiseptic drug LOROBEN, at which the quality of life criteria are close to those of practically healthy people. Therefore, when choosing a treatment method, it is necessary not only to proceed from the clinical picture in the oral cavity but also to take into account many other indicators, which in the future can significantly affect the success of the treatment.

Conclusion.

Orthopedic treatment of partial and complete dentoalveolar defects with removable lamellar dentures using the LOROBEN antiseptic preparation is the most effective way to replace dentition defects with concomitant periodontal pathology and aggravated general somatic disease, type 2 diabetes mellitus and chronic kidney disease, allowing patients not to lead a full life inconvenience associated with eating and communicating with people.

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ASSESSMENT OF CHANGES IN THE QUALITY OF LIFE OF PATIENTS WITH TYPE 2 DIABETES IN LAMELLAR DENTAL ORTHOPEDIC PROSTHESES

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ABSTRACT

The most common pathologies of the dental system in diseases of type 2 diabetes mellitus include defects in the dentition and periodontal diseases, which are not only the cause of deterioration in the quality of life and reduced working capacity of patients but also the cause of several somatic diseases and their unfavourable course. Both dental defects and periodontal diseases are difficult to treat, leading to a significant decrease in the dental system's functional capabilities, and they are characterized by a long period of rehabilitation. There are many approaches to treating these diseases of the oral cavity, but there is still no consensus on the most appropriate treatment tactics, the results of which would suit both the doctor and the patient. It is often difficult to predict the success of treatment, and the definition of the quality of life, which has recently become widespread in medicine, can help the dentist. Quality of life is an integral characteristic of the patient's physical, psychological, emotional and social functioning, based on his subjective perception.

Keywords: pathologies of the dentoalveolar system, diseases of diabetes mellitus, somatic diseases.

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ОЦЕНКА ИЗМЕНЕНИЯ КАЧЕСТВА ЖИЗНИ ПАЦИЕНТОВ С ЗАБОЛЕВАНИЕМ СД 2 ТИПА В ПЛАСТИНОЧНЫМИ ЗУБНЫМИ ОРТОПЕДИЧЕСКИМИ ПРОТЕЗАМИ

АННОТАЦИЯ

К наиболее частым патологиям зубочелюстной системы при заболеваниях сахарным диабетом 2 типа относятся дефекты зубных рядов и болезни пародонта, которые являются не только причиной ухудшения качества жизни и снижения трудоспособности пациентов, но и причиной ряда соматических заболеваний и их неблагоприятного течения. Как дефекты зубных рядов, так и заболевания пародонта трудно поддаются лечению, ведут к значительному снижению функциональных возможностей зубочелюстной системы, для них характерен длительный период реабилитации. Существует множество подходов к лечению этих заболеваний полости рта, но до сих пор нет единого мнения о наиболее подходящей

тактике лечения, результаты которой устраивали бы как врача, так и пациента. Часто бывает трудно предсказать успех лечения, и определение качества жизни, которое в последнее время получило широкое распространение в медицине, может помочь стоматологу. Качество жизни-это интегральная характеристика физического, психологического, эмоционального и социального функционирования пациента, основанная на его субъективном восприятии.

Ключевые слова: патологиям зубочелюстной системы, заболеваниях сахарным диабетом, соматических заболеваний.

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2 ТУРДАГИ КАНДЛИ ДИАБЕТ БИЛАН КАСАЛЛАНГАН БЕМОРЛАРДА ОЛИБ КУЙИЛАДИГАН ПЛАСТИНКАЛИ ТИШ ПРОТЕЗЛАРИДАН КЕЙИН ХАЁТ СИФАТИНИ БАХОЛАШ

ANNOTATSIYA

Tish- jag’ tizimning 2-toifa diabet mellitusida eng ko'p uchraydigan patologiyalariga tish va periodontal kasallikdagi nuqsonlar kiradi, bu nafaqat hayot sifatining yomonlashuvi va bemorlarning mehnat qobiliyatining pasayishi, balki bir qator somatik kasalliklar va ularning noqulay yo'nalishi sababidir. Tish tish nuqsonlarini ham, periodontal kasalliklarni ham davolash qiyin, bu dentoalveolyar tizimning funksionalligini sezilarli darajada pasayishiga olib keladi, ular uzoq vaqt reabilitatsiya davri bilan ajralib turadi. Ushbu og'iz kasalliklarini davolash uchun ko'plab yondashuvlar mavjud, ammo natijalar shifokor va bemorga mos keladigan eng qulay davolash usullari haqida hech qanday kelishuv mavjud emas. Ko'pincha davolanishning muvaffaqiyatini taxmin qilish qiyin va yaqinda tibbiyotda keng tarqalgan hayot sifatini aniqlash tish shifokoriga yordam berishi mumkin. Hayot sifati-bemorning sub'ektiv idrokiga asoslangan jismoniy, psixologik, hissiy va ijtimoiy faoliyatining ajralmas xarakteristikasi.

Kalit so'zlar: tish patologiyasi, qandli diabet, somatik kasalliklar.

Relevance. Unfortunately, in practice, an isolated course of these pathologies is quite rare, as a rule, they proceed in combination, mutually burdening each other. There are many approaches to treating these diseases of the oral cavity, but there is still no consensus on the most appropriate treatment tactics, the results of which would suit both the doctor and the patient. It is often difficult to predict the success of treatment, and the definition of the quality of life, which has recently become widespread in medicine, can help the dentist. Quality of life is an integral characteristic of the patient's physical, psychological, emotional and social functioning, based on his subjective perception.

The research aim. To date, it has been proven that the parameters of the patient's quality of life have an independent predictive value and are more accurate factors of the patient's condition during treatment than the general somatic status.

Research materials and methods. In this work, we studied the method of replacing dentition defects with removable plate dental prostheses in case of concomitant periodontal diseases in patients with type 2 diabetes, depending on the presence of kidney disease, assessed their results both in terms of improving the dental status and in terms of improving the quality of life. Patients. 60 patients with diabetes mellitus and dentition defects were examined. The examination was carried out twice: before the treatment and after it. All patients were divided into 2 groups: 30 patients with type 2 diabetes complicated by CKD, 30 patients with only type 2 diabetes; Patients in the group with type 2 diabetes and complicated CKD were divided into 2 groups depending on the use of the drug "LOROBEN" in the treatment. All patients also received the drug dipyridamole at an average therapeutic dose of 50 mg 3 times a day for 20 days.

The quality of life of patients was determined using the OhIP-14 questionnaire, which includes 14 questions that allow assessing the impact of the oral cavity on the quality of life, according to the

following criteria: daily life, chewing food, ability to communicate. There were 5 answer options, which range from "very often" to "never" and are rated from 5 to 1 points, respectively. Patient quality of life was assessed prior to treatment. Also, a questionnaire was conducted using the OhIP-14 questionnaire after treatment.

During a survey conducted before treatment, patients of the first and second groups complained of pain and burning sensation in the tongue and oral mucosa, a change in taste, an unpleasant odor from the oral cavity, the presence of defects in the dentition and the associated difficulties in communication and eating. When examining the oral cavity in all patients, in addition to defects in the dentition, inflammation, swelling of the gingival papillae, hyperemia of the gums, and severe bleeding were noted.

The analysis of the questionnaires and questionnaires filled out by patients before treatment showed that according to all quality of life criteria, except for the ability to communicate, the quality of life of patients with type 2 diabetes complicated by CKD with periodontal diseases treated by the traditional method was significantly worse than that of patients. , who were treated with the antiseptic drug "LOROBEN" (Table 1).

Dependence of patients' quality of life on the method of therapy before replacement of dental defects

Patient groups	Criteria		
	daily life	Chewing	ability to communicate
Patients receiving treatment with traditional methods	14.5±1,9*	7,4±1,6*	9.8±1,9*
Patients with LOROBEN therapy	15,4±1,6*	8,7±1,4*	8,5±1,2*

After the treatment, most of the patients had no complaints. When examining the oral cavity, there was a decrease in hyperemia and swelling of the gums, decreased bleeding, and the absence of pathological gingival pockets.

The analysis of OhIP-14 questionnaires showed a significant improvement in patients' quality of life with type 2 diabetes after orthopedic treatment (Tables 2, 3).

Quality of life indicators before and after traditional treatment and replacement of dental defects with removable prostheses

Patient groups	Criteria		
	daily life	Chewing	ability to communicate
Before treatment	14.5±1,9*	7,5±1,7*	9.9±1,6*
After treatment	9,8±1,3*	5,6±1,4*	6,8±1,3*

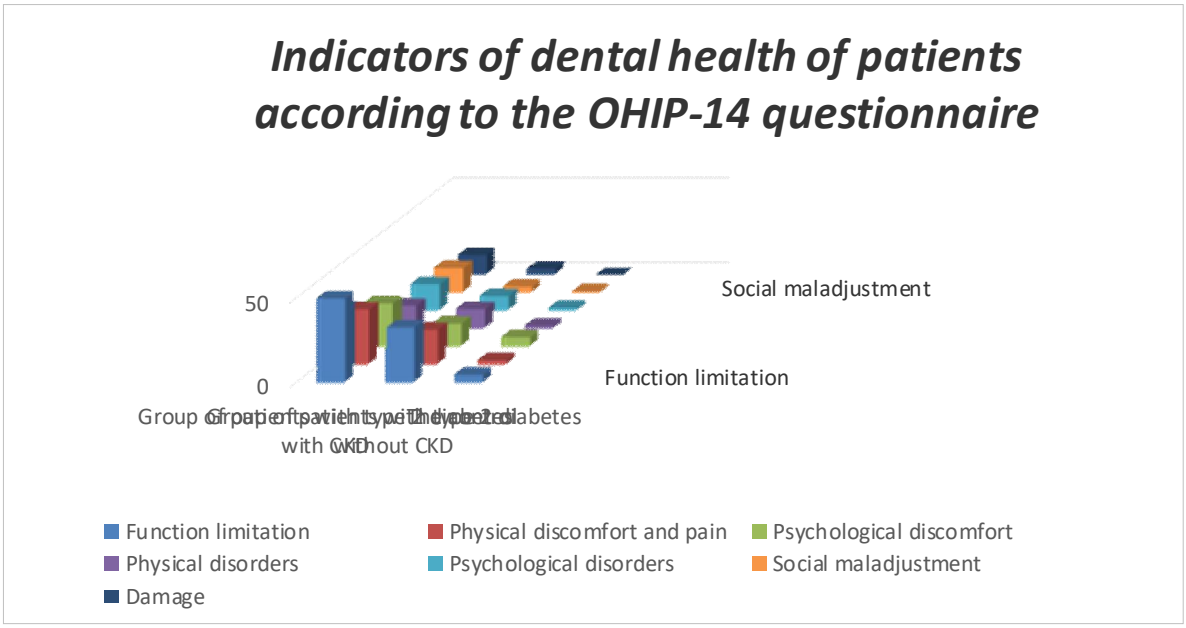
Quality of life indicators before and after treatment with LOROBEN and replacement of dental defects with removable prostheses

Patient groups	Criteria		
	daily life	Chewing	ability to communicate

Before treatment	14,5 ±1,7 *	8,9 ±1, 7*	9,9 ±1, 4*
After treatment	6,8± 0,5*	4,5 ±0, 4*	4,7 ±0, 6*

It should also be noted that patients with type 2 diabetes mellitus complicated by CKD, in whom dentition defects were replaced with removable otopedic constructions, who used LOROBEN before treatment, note significantly better indicators in all quality of life criteria than patients with type 2 diabetes mellitus complicated CKD receiving traditional treatment (Table 4).

Dependence of patients' quality of life on the method of therapy after replacement of dental defects



Patient groups	Criteria		
	daily life	Chewing	ability to communicate
Patients undergoing traditional treatment	9,9± 1,4*	5,7± 1,9*	6,7± 1,3*
Patients with LOROBEN therapy	6,7± 0,5*	4,3± 0,5*	4,6± 0,2*

Chart 3. Indicators of dental health of patients according to the OHIP-14 questionnaire

The results obtained and their discussion. The study of the results of determining the quality of life using the OHIP-14 index revealed the integral value of this index in healthy individuals. There was a significant decrease in the life quality by almost two times in the presence of type 2 diabetes, complicated by CKD, and this relationship is directly related to the severity of the clinical picture of the disease. The quality of life, assessed by the questionnaire, in dental patients before treatment was worse than in healthy people (Diag. 3). Thus, in patients before treatment, physical functioning was 60% less than in healthy people. In patients, respectively: physical discomfort and pain were 50% less, and psychological disorder was 42.3% more. The total changes in physical health accounted for 35.6% of physical health in healthy people.

The use of the LOROBEN antiseptic, which has a bactericidal effect on causative agents of infectious diseases of the oral cavity, opportunistic microorganisms and fungi, and its use in the pre-prosthetic rehabilitation period in patients with type 2 diabetes complicated by CKD had a positive effect on the adaptation of patients to the prosthesis. Therefore the quality of life of patients significantly improved. Thus, after orthopedic treatment of partial and complete loss of teeth in

dental patients with type 2 diabetes and complicated CKD, compared with the data before treatment, the indicators of functional limitation decreased by 50.3%, physical discomfort and pain decreased by 69%, the indicator of Psychological discomfort decreased by 28, 5%, physical disorders decreased by 33.6%, psychological disorders decreased by 51.3%, social maladjustment decreased by 56.0%, damage decreased by 59.4%. Thus, mental health improved by 50.7%, which increased the total results of physical health by 43.3% and psychological health by 51%.

Thus, this study showed that oral diseases such as defects in the dentition and periodontal disease, in the presence of general somatic disease of type 2 diabetes with complicated CKD, significantly reduce patients' quality of life, affecting both the ability to eat and communicate and overall well-being people, and should be considered not only as a medical problem but also as a social problem. Therefore, great attention should be paid to their elimination and prevention of their occurrence. At the same time, it can be seen from our study that different methods of treatment have a different effect on the quality of life of patients: even though prosthetics with removable plate dentures and traditional treatment significantly improves the quality of life of patients, it is inferior to dental orthopedic treatment with the use of the antiseptic drug LOROBEN, at which the quality of life criteria are close to those of practically healthy people. Therefore, when choosing a treatment method, it is necessary not only to proceed from the clinical picture in the oral cavity, but also to take into account many other indicators, which in the future can significantly affect the success of the treatment.

Orthopedic treatment of partial and complete dentoalveolar defects with removable lamellar dentures using the LOROBEN antiseptic preparation is the most effective way to replace dentition defects with concomitant periodontal pathology and aggravated general somatic disease, type 2 diabetes mellitus and chronic kidney disease, allowing patients not to lead a full life inconvenience associated with eating and communicating with people.

Conclusions.

The use of the quality of life questionnaire in patients of the examined groups with type 2 diabetes mellitus with complicated and uncomplicated CKD at this stage made it possible to optimize the choice of the therapy method and control the treatment process, which contributed to an increase in the effectiveness of treatment of patients with type 2 diabetes mellitus complicated and not malignant CKD with removable plate dentures.

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INFLUENCE OF MYCOPLASMA AND CYTOMEGALOVIRUS INFECTION ON THE FREQUENCY OF EXACERBATION OF BRONCHIAL ASTHMA IN CHILDREN

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ABSTRACT

The article presents the results of analyses, the spread of mycoplasma and cytomegalovirus infection among children with bronchial asthma. To achieve control of the severity of bronchial asthma and improve the disease's detection, it is of great interest to identify the role of intracellular infections capable of long-term spread and, consequently, to the constant maintenance and intensification of allergic inflammation. These infections primarily include mycoplasma, chlamydial, cytomegalovirus infections. We examined 106 children (74 boys and 32 girls) aged from 3 to 18 years. In the period of exacerbation of bronchial asthma in children with cytomegalovirus and mycoplasma, there were signs of impaired bronchial patency, mainly in the middle and peripheral sections, and in the central sections of the respiratory tract. Besides, there is a decrease in immune parameters in patients with cytomegalovirus and mycoplasma, which is the cause of the infection. In the period of clinical remission, they retain signs of bronchial obstruction, which indicates a readiness for the development of an asthmatic attack.

Keywords: bronchial asthma; mycoplasma infection; cytomegalovirus infection; children; acute respiratory infections; allergens; trigger factors.

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ВЛИЯНИЕ МИКОПЛАЗМЕННОЙ И ЦИТОМЕГАЛОВИРУСНОЙ ИНФЕКЦИИ НА ЧАСТОТУ ОБОСТРЕНИЕ БРОНХИАЛЬНОЙ АСТМЫ У ДЕТЕЙ

АННОТАЦИЯ

В статье представлен результаты анализов, распространение микоплазменной и цитомегаловирусной инфекции среди детей, страдающих от бронхиальной астмы. В целях достижения контроля выраженности симптомов бронхиальной астмы и улучшения выявление заболевания, большой интерес представляет собой выявление роли внутриклеточных инфекций, способных к длительному распространению и, следовательно, к постоянному поддержанию и усилению аллергического воспаления. К таким инфекциям в первую очередь можно отнести микоплазменную, хламидийную, цитомегаловирусную инфекции. Нами было обследовано 106детей (74 мальчика и 32 девочек) в возрасте от 3 до 18 лет, в периоде обострения бронхиальной астмы у детей с наличием цитомегаловирус и микоплазма отмечались признаки нарушения бронхиальной проходимости преимущественно как в средних и периферических отделах, так и в центральных, отделах дыхательных путей. Кроме этого отмечается снижения иммунных показателей у больных, которые имеют цитомегаловирус и микоплазма, который является причиной развития инфекции. В периоде клинической ремиссии у них сохраняется признаки обструкции бронхов, что указывает на готовность к развитию астматического приступа.

Ключевые слова: бронхиальная астма; микоплазменная инфекция; цитомегаловирусная инфекция; дети; острые респираторные инфекции; аллергены; триггерные факторы.

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МИКОПЛАЗМА ВА ЦИТОМЕГАЛОВИРУС ИНФЕКЦИЯЛАРИНИНГ БОЛАЛАРДА БРОНХИАЛ АСТМА ХУРУЖЛАРИ СОНИГА ТАЪСИРИ

АННОТАЦИЯ

Мақолада таҳлил натижалари, бронхиал астма билан касалланган болалар орасида микоплазма ва цитомегаловирус инфекциялари учраш сони келтирилган. Бронхиал астма симптомларини назорат қилишга эришиш ва касалликни аниқлашни яхшилаш мақсадида, аллергик яллиғланиш жараёнларини доимий равишда чақириб, кучайтириб борадиган, узоқ вақт давомида тарқалиш хусусиятига эга, хужайра ичи инфекцияларининг ролини аниқлаш катта қизиқиш уйғотади. Бундай инфекцияларга биринчи навбатда микоплазма, хламидия, цитомегаловирус каби инфекцияларни мисол қилиб келтириш мумкин. 3 ёшдан 18 ёшгача бўлган, 106 нафар болаларни (улардан 74 та ўғил ва 32 қиз болалар) ўргандик.

Цитомегаловирус ва микоплазма инфекцияси аниқланган болаларда бронхиал астма касаллиги хуружи даврида, нафас йўлларининг ўрта ва периферик қисмлари билан бир қаторда марказий қисмларида ҳам бронхларда ўтқазишнинг бузилиш белгилари аниқланди. Бундан ташқари, цитомегаловирус ва микоплазма инфекцияси бор болаларда иммунитет кўрсаткичларининг пасайиши кузатилди, бу эса инфекция ривожланишига сабаб бўлади. Клиник ремиссия вақтида ушбу болаларда бронхиал обструкция белгилари сақланиб қолиши, астматик хуружлар ривожланишига тайёрлигини кўрсатади.

Калит сўзлар: бронхиал астма; микоплаза инфекцияси; цитомегаловирус инфекцияси; болалар; ўткир респиратор инфекциялар; аллергенлар; триггер факторлар.

Relevance. One of the most significant and widespread diseases among children and adults is bronchial asthma, one of the pressing health problems [1,2,3].

Bronchial asthma refers to a hereditary allergic disease. Environmental factors have a strong influence on their formation and clinical course. As a result, the period of remission will be shortened. [1,2,4,5,6,7,8]

It is known that bronchial asthma pathogenesis is based on bronchial hyperreactivity, a chronic inflammatory process of the respiratory tract. Under the influence of triggering, allergenic factors and infectious agents, bronchial asthma is exacerbated. According to modern hypotheses, the connection between an infectious agent and bronchial asthma exacerbations is not denied. Viruses and other infectious agents are non-atopic factors that aggravate the risk of developing the disease and the frequency of exacerbations when exposed to them. It has been proven that in 80% of cases in children, exacerbations of bronchial asthma are caused by viral infections of the respiratory tract, and in adults this figure is 50%. [3,4,5,6].

In the literature, it is noted that 27-30% of children with bronchial asthma are carriers of latent latent infection (Chlamidiapneumoneae, mycoplasmapneumoneae, herpes viruses, cytomegalovirus, adenovirus, respiratory syncytial virus). Latent infections persist in the upper respiratory tract's lymphoid tissue, thereby affecting bronchial asthma's clinical course [3,4,5,6,9,10,11,12].

According to the literature, it has been established that recurrent respiratory diseases with reversible bronchial obstruction in children are early diagnostic criteria for mild bronchial asthma [12,13,14,15].

Thus, to achieve control of the severity of bronchial asthma symptoms and improve the detection of the disease, it is of great interest to identify the role of intracellular infections that are capable of long-term spread and, consequently, to constant maintenance and intensification of allergic inflammation. These infections primarily include mycoplasma, chlamydial, cytomegalovirus infections.

In connection with the above, the study aims to study the effect of mycoplasma and cytomegalovirus infection on the frequency of exacerbation of bronchial asthma in children.

Materials and methods of research: We examined 106 children (74 boys and 32 girls) aged 3 to 18 years who were undergoing routine examination and treatment with a diagnosis of Bronchial asthma in the periods 2018-2020 based on the children's allergological department at the Tashkent medical academy. All patients underwent clinical and laboratory examination. The assessment of the bronchial asthma clinical course in the examined patients was carried out according to the Republic of Uzbekistan protocol.

The laboratory study of sick children included the enzyme immunoassay determined the determination of fragments of deoxyribonucleic acid of cetomigalovirus, mycoplasma in sputum by the polymerase chain reaction method, in addition, the content of immunoglobulins IgA, IgM, IgG.

The assessment of the function of external respiration was determined by a computer spirograph (Neurosoft 2000-2010). Respiratory monitoring was also carried out: a study of the circadian rhythm of bronchial patency based on the peak expiratory flow rate's determination using an individual peak flow meter and subsequent mathematical processing.

We divided all examined children into 3 groups, depending on the clinical and laboratory data. Macrotes of 22 healthy children of the same age were examined as a control group.

1 - the group consisted of 61 children with bronchial asthma (CMV and MP were not found in their macros)

2 - the group consisted of 24 children with bronchial asthma (CMV was found in their macroses)

3 - the group consisted of 21 children with bronchial asthma (CMV and MP were found in their macroses).

Research results and their discussion. The impact of external factors on the exacerbation of bronchial asthma is significant. Table 1 shows that in patients of the first group, the average frequency of attacks is 2.1 ± 0.05. In patients of this group, we did not find the presence of CMV and MP in the body; in them, the main influencing factor was the effect of the allergen. They had colds, changes in air temperature provoking allergies. In patients of groups 2 and 3, the frequency of exacerbation of bronchial asthma differs sharply from the indicators of group 1. Since these groups of patients have provoked CMV and MP, the disease is exacerbated more often than in patients who do not have this factor. In patients of the 1st group, the frequency of relapses was observed when the exposure to the allergen was on average 2.4 ± 0.05 (P≤0.05), in patients of the 2nd group this indicator was more frequent than in patients of the 1st group. It amounted to 3.1 ± 0.06 P≤0.04), and in patients of group 3, the frequency of relapses was even more often than indicators of groups 1 and 2, which amounted to 4.2 ± 1.04 (P≥0.05), in other words, 2 times more often than in patients of group 1. Besides, it can be noted that the blossoming of flowers and the presence of food allergens also increase the exacerbation. If on average the frequency of relapses per year in patients of groups 1 and 2 was 2.1 ± 0.05 and 2.6 ± 0.04, respectively, then the average rate of recurrence of group 3 was 3.9 ± 1.1. of patients, the results of sputum analysis showed a large number of granulocytes, eosinophils, macrophages, and leukocytes. Also, CMV was found in patients of the second group, and infection in patients of the third group of MP.

Table №1.

The frequency of relapses in patients with bronchial asthma, depending on the cause

№ group	Allergen	Food howling allergen	Cold	Temperature change	Blooming flowers	The average frequency of attacks
1st	2,4± 0,05	1,9±0,07	1,9±0,06	2,2 ±0,04	2,3±0,05	2,1±0,05
2nd	3,1±0,06	2,8±0,07	2,2±0,08	2,4±1,05	2.6±1,06	2,6±0,04*
3rd	4,2±1,04	3,9±1,4	3,6±0,4	3,9±1,05	4,1±2,04	3,9±1,1**

Note: * - differences relative to the data of the first group (P≤0.04)

** - differences relative to the data of the second group (P≥0.05)

Evaluation of external respiration results in patients with bronchial asthma during an exacerbation is given in the table. 2. The results showed that in the children of the control group, no changes were found in the indicators of forced vital capacity (FVC), forced expiratory volume in the first second (FEV) and peak expiratory flow rate (PSV).

Table 2 shows that in children of the first group, the FVC indicators in the period of exacerbation of the disease showed a decrease compared to control indicators (77.26 ± 5.04 and 104.20 ± 0.84, respectively, p <0.001), and during the period of remission, the recovery of FVC was noted, but still they were lower than those of the control group. Besides, during the exacerbation period, the FEV (67.08 ± 4.35) and PSV (60.44 ± 4.71) indicators in this group were also lower than those in the control group, although during the remission period these indicators were increased, they did not reach control indicators.

In patients of the second group, the FVC indices during the exacerbation period were lower than those in the sick children of the first group, 75.68 ± 7.43 and 77.26 ± 5.04, respectively; during the period of remission, these indicators improved, but they were lower than those of the first group (p <0.001). The FEV and PSV indicators also tended to decrease during the exacerbation of the

disease, and during the period of clinical remission, these indicators improved, all the same, these indicators were lower than in sick children of the first group during their remission.

In patients of the third group, the indices of LPV, FEV and PSV during the exacerbation were lower than those of the first and second groups, and during the period of clinical remission, the FVC indicator reached the level of the first and second groups (p <0.001), and during the period of remission they were lower than those of the first and the second group (p <0.001).

Table №2.

The state of external respiration in sick children with bronchial asthma.

Sign	Control	1-group children with BA		2-group BA with CMV infections		3-group BA with MP infections	
		Exacerbation period	Remissionperiod	Exacerba-tion period	Remission period	Exacerba-tion period	Remissionperiod
FVC	104,20±0,84	77,26±5,04	98,03±4,36	75,68±7,43	95,75±6,95	72,86±5,86	96,68±4,36
FEV_1	104,10±0,77	67,08±4,35	98,01±4,43	72,89±5,97	87,94±4,80	70,36±6,70	85,48±4,61**
PSV	105,30±1,07	60,44±4,71	84,64±4,61*	68,15±5,81	80,37±3,50 *	67,08±4,35	79,68±6,918**

Note: * - differences with control data (P≤0.01)

** - differences relative to the data of the first and second groups (P≤0.01)

Table 3 shows the indices of humoral immunity in patients with bronchial asthma of all groups during the period of attacks. Table 3 shows that the level of immunoglobulin IgM in the control group was 1.07 ± 0.04 g / l, and in patients of the first group, this indicator was at the level of the control 1.12 ± 0.03 g / l and was also noted within the control group of indicators of immunoglobulins IgG and IgA (P <0.05).

The indices of the humoral immunity of sick children of the second group of both immunoglobulin IgM and immunoglobulin IgG were lower than the indicator of the control, while the indicator of the level of immunoglobulin IgA was at the level of the control 1.32 ± 0.05 g / l.

In patients of the third group, the IgM (0.87 ± 0.03 g / l), IgG (9.0 ± 0.25 g / l) indicators were lower than the levels of the control and first groups (P <0.05). The state of immunoglobulin A remained almost unchanged, remained at the level of the control group.

Table №3.

Indicators of humoral immunity in patients with bronchial asthma during attacks

Indicators		Control group n=22	1 – group n=61	2 - group n=24	3- group n= 21
IgM	g/l	1,07±0,04	1,12±0,03	0,91±0,03*	0,87±0,03**
IgG	g/l	10,6±0,37	11,3±0,32	9,7±0,19*	9,0±0,25**
IgA	g/l	1,70±0,07	1,63±0,05	1,32±0,05*	1,33±0,05*

Note: * - differences with the data of the control group (P <0.05);

** - differences relative to data from groups 1 and 2 (P <0.05)

Conclusion. Thus, the study results show that the provoking factors of exacerbation of bronchial asthma are the presence of an allergen, a food factor, changes in the temperature factor, and colds. The addition of a secondary infection of CMV and MP exacerbates the process; if they are present, the frequency of attacks increases 2-3 times than a seasonal allergic disease. During the exacerbation of bronchial asthma in children with CMV and MP, there were signs of impaired bronchial patency, mainly in the middle and peripheral regions, and in the central, respiratory tract sections. Also, there is a decrease in immune parameters in patients with CMV and MP, which is the cause of the infection. In the period of clinical remission, they retain signs of bronchial obstruction, which indicates a readiness for the development of an asthmatic attack.

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ЎЗБЕК ТИББИЁТ ЖУРНАЛИ
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THE PREVALENCE OF CHRONIC KIDNEY DISEASE IN CHILDREN AND ADOLESCENTS WITH TYPE 1 DIABETES MELLITUS IN THE REPUBLIC OF UZBEKISTAN

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ABSTRACT

Epidemiological data were studied based on the developed protocols filled into 594 children and adolescents of type 1 diabetes composed at dispensary registration in endocrinological dispensaries of Republic of Karakalpakistan, Khorezm, Surkhandarya, Andijan, Namangan, Fergana regions and in the city of Tashkent. Studied: HbA1c and MAU were determined by the biochemical analyzer DCA Vantage (Activ Sistem Simens) Germany, GFR was calculated using the Schwarz formula. A clinical and epidemiological study on the population of children and adolescents with type 1 diabetes for the first time allowed us to establish the actual prevalence of CKD: in children, 19.4% and in adolescents, 35.5%. Among children and adolescents with type 1 diabetes with CKD, most were in stage I and II of CKD.

Keywords: CKD, children, adolescents, diabetes, mellitus.

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ЭПИДЕМИОЛОГИЯ ХРОНИЧЕСКОЙ БОЛЕЗНИ ПОЧЕК У ДЕТЕЙ И ПОДРОСТКОВ С САХАРНЫМ ДИАБЕТОМ 1 ТИПА В РЕСПУБЛИКЕ УЗБЕКИСТАН

АННОТАЦИЯ

Эпидемиологические данные изучались на основании разработанных протоколов, заполненных 594 детям и подросткам СД 1 типа состоящие на диспансерном учете в эндокринологических диспансерах РКК, Хорезмской, Сурхандарьинской, Андижанской, Наманганской, Ферганской областях и в городе Ташкенте. Изучались: HbA1c и МАУ

определялись биохимическим анализатором DCA Vantage (Activ Sistem Simens) Германия, СКФ рассчитывалась по формуле Шварца. Клинико-эпидемиологическое исследование на популяции детей и подростtков СД 1 типа впервые позволило установить фактическую распространенность ХБП: у детей 19,4% и у подростков 35,5%. Среди детей и подростков с СД 1 типа с наличием ХБП большинство находились на I и II стадии ХБП.

Ключевые слова: ХБП, дети, подростки, сахарный диабет.

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ЎЗБЕКИСТОН РЕСПУБЛИКАСИДА 1 ТУР ҚАНДЛИ ДИАБЕТ БОЛАЛАР ВА ЎСМИРЛАРДА СУРУНКАЛИ БУЙРАК КАСАЛЛИГИНИ ТАРҚАЛГАНЛИГИ

АННОТАЦИЯ

Эпидемиологик маълумотлар ишлаб чиқилган протоколлар асосида РКК, Хоразм, Сурхондарё, Андижон, Наманган, Фарғона вилоятлари ва Тошкент шаҳрида эндокринологик диспансерларда рўйхатдан ўтган 1 тур диабет касаллиги бўлган 594 болалар ва ўспиринлар томонидан тўлдирилди. Ўрганилди: НвА1с ва МАУ DCA Vantage (Activ Sistem Simens) биокимёвий анализатори томонидан аниқланди, КФТ Шварц формуласи ёрдамида ҳисоблаб чиқилди. Биринчи турдаги қандли диабетга чалинган болалар ва ўспиринлар популяциясида ўтказилган клиник ва эпидемиологик тадқиқотлар биринчи марта СБКнинг ҳақиқий тарқалишини аниқлашга имкон берди: болаларда 19,4% ва ўспиринларда 35,5%. СБК борлиги билан 1тур қандли диабетга чалинган болалар ва ўспиринлар орасида кўпчилик I ва II босқичда эди.

Калит сўзлар: СБК, болалар, ўспиринлар, қандли диабет.

RELEVANCE: Chronic kidney disease (CKD) is one of the most significant medical and socio-economic problems of our time. The social significance of CKD consists of the continuing growth of its prevalence, early disability of patients. The high cost of RRT and, in this connection, insufficient availability in most regions of the world, where 80% of humanity lives, makes CKD one of the problems of practical nephrology and practical public health as a whole [1,2,3,8].

The results of Uzbekistan's epidemiological studies have shown that DN.'s problem is no less acute for our country. According to the National Registry of children and adolescents with DM. of type 1 in Uzbekistan, the cause of death in children in 50% and 70% of cases is chronic renal insufficiency (CKI) with an average life expectancy of children since the onset of disease of 5.2 years, and in adolescents 6.4 years due to chronic hyperglycemia and late diagnostics of early stages of DM. [Alikhanova N.M., 2001, Alimova N.U. 2017].

According to the data of diabetes registry conducted in 2010, DN (at the stage of proteinuria) had been diagnosed in 30582 (27.53%) DM patients throughout the Republic, with 4243 (33.82%) type 1 DM patients. According to screening data from 2012 in Uzbekistan of children, adolescents and adults with DM. type 1, the prevalence of DN. in stage 4 severe proteinuria has decreased compared to 1998, but remains high and is 5.28%, 11.1% and 25.9%, respectively, therefore the problem of prognosis, early diagnosis and prevention of DN. progression is extremely urgent for the domestic pediatric nephrology and diabetology.

Due to the increasing number of patients with renal failure developed as a result of various nosological forms, the National Kidney Foundation of the USA, with the participation of a large group of experts (committee K/DOQI- Kidney Disease Outcomes Quality Initiative) in 2002 proposed to combine kidney diseases in the term "chronic kidney disease" (CKD) [4,7,10,11]. The

CKD concept was introduced into the practice of endocrine service of the Republic of Uzbekistan in 2015 by the resolution of the Republican Scientific and Practical Conference of Endocrinologists.

The supersensory concept of CKD is especially relevant for patients with DM. In this regard, there was a need to study the prevalence and quality of treatment of different stages of DN. according to the new classification, taking into account GFR and stages of CKD in children and adolescents with type 1 DM. in Uzbekistan. Simultaneously, clinical and epidemiological features and risk factors in children and adolescents with type 1 DM. that predispose to the development of nephropathy are poorly studied.

RESEARCH OBJECTIVE: To study the prevalence of chronic kidney disease in children and adolescents with type 1 diabetes mellitus in Uzbekistan.

MATERIALS AND METHODS: To conduct an epidemiological study there were examined children and adolescents with type 1 diabetes registered in endocrinological dispensaries of the Republic of Karakalpakistan, Khorezm, Surkhandarya, Andijan, Namangan, Fergana regions and in Tashkent city, 594 persons in total (Table 1).

Table 1

Distribution of children and adolescents with DM type 1 by region

Region	Sex	Children, n=335	Teenagers, n=259
Surkhandarya, n=21	b, n/%	5/62,5	8/61,5
	g, n/%	3/37,5	5/38,5
Namangan, n=41	b, n/%	11/39,3	13/61,5
	g, n/%	17/60,7	5/38,5
Fergana, n=102	b, n/%	26/40,6	18/47,4
	g, n/%	38/59,4	20/52,6
Khorezm, n=122	b, n/%	29/36,7	22/51,2
	g, n/%	50/63,3	21/48,8
Andijan, n=78	b, n/%	20/43,5	16/50,0
	g, n/%	26/56,5	16/50,0
Republic of Karakalpakistan, n=110	b, n/%	34/45,9	17/47,2
	g, n/%	40/54,1	19/52,8
Tashkent city, n=120	b, n/%	14/38,9	39/46,4
	g, n/%	22/61,1	45/53,6
Total, n=594	b, n/%	139/41,5	128/ 49,4
	g, n/%	196/58,5	131/ 50,6

The distribution of children and adolescents with type 1 DM according to age and sex was 56.4% (n=335) for children and 43.6% (n=259) for adolescents. Of the total number of patients examined, males accounted for 44.9% (n=267) and females for 55.1% (n=327).

RESEARCH METHODS. Epidemiological data were studied based on the developed protocols filled in by children and teenagers with type 1 DM. on the dispensary records in the mentioned regions.

Inclusion criteria for the study were: type 1 DM, age greater than 1 year and less than 18 years, absence/presence of proteinuria.

Exclusion criteria were: ketoacidosis, ketosis.

Anthropometric method to assess physical development, BMI, clinical and biochemical methods (determination of glycemia, determination of HbA1c and microalbuminuria by biochemical analyzer DCA Vantage (Activ Sistem Simens) Germany, glomerular filtration rate (GFR) was calculated by Schwartz formula: GFR = Height (cm) × ratio/creatinine (μmol/L) (ml/min/1.73 m2) [5].

RESULTS AND DISCUSSION: The study examined the distribution of children and adolescents with type 1 DM. according to anthropometric parameters (Table 2). The study of gender differences in children and adolescents with type 1 DM. revealed a predominance of females among children 41.5/58.5% (n=139/196) and adolescents 49.4/50.6% (n=128/131). In recent years, studies have begun to take into account the sex of the patient as an important criterion in the development of renal pathology, and new approaches to the treatment of CKD depending on this attribute are being developed [8].

Table 2.

Distribution of children and adolescents with type 1 DM depending on anthropometric data by region

Region		Children, n=335			Teenagers, n=259		
		Sex	Height	Weight	Sex	Height	Weight
Surkhandarya, n=21	b, n/%	5/62,5	144,4±20,2	34,8±8,8	8/61,5	158,9±13,4	45,1±7,5
	g, n/%	3/37,5	122,7±18,6	26,0±8,2	5/38,5	144,8±10,3	35,2±8,5
Namangan, n=41	b, n/%	11/39,3	150,5±13,7	43,2±18,2	13/61,5	136,1±18,5	30,3±8,0
	g, n/%	17/60,7	143,6±18,7	40,8±15,8	5/38,5	140,4±28,6	26,1±11,9
Fergana, n=102	b, n/%	26/40,6	148,8±17,3	38,7±11,1	18/47,4	143,7±25,3	43,7±16,1
	g, n/%	38/59,4	140,0±20,6	34,6±12,0	20/52,6	145,6±11,9	38,4±8,0
Khorezm, n=122	b, n/%	29/36,7	141,4±30,2	40,6±16,7	22/51,2	144,2±26,1	39,7±15,3
	g, n/%	50/63,3	139,8±18,4	37,0±12,2	21/48,8	142,4±18,1	39,2±11,3
Andijan, n=78	b, n/%	20/43,5	133,2±17,7	30,7±11,2	16/50,0	162,9±9,7	53,3±9,6
	g, n/%	26/56,5	134,3±15,4	30,9±10,6	16/50,0	160,4±16,1	48,8±7,6
Republic of Karakalpakistan, n=110	b, n/%	34/45,9	147,3±20,1	40,2±17,3	17/47,2	154,8±18,0	45,3±11,5
	g, n/%	40/54,1	146,0±16,8	42,5±15,0	19/52,8	148,8±21,1	43,9±14,8
Tashkent city, n=120	b, n/%	14/38,9	132,0±20,6	30,2±14,8	39/46,4	164,3±13,4	50,7±11,8
	g, n/%	22/61,1	133,5±18,4	30,6±10,5	45/53,6	155,3±7,3	46,9±8,3
Total, n=594	b, n/%	139/41,5	142,8±22,5	37,6±15,4	128/ 49,4	154,4±20,7	45,8±13,6
	g, n/%	196/58,5	139±36,3	36,3±13,3	131/ 50,6	150,4±15,8	43,0±11,2

One of our research objectives was to assess the true prevalence of CKD by stage in children and adolescents with type 1 DM based on screening studies based on serum creatinine and GFR calculations. The prevalence of CKD was assessed for the first time in children and adolescents with type 1 DM. in the Uzbek population using screening data.

Data on the distribution of children with type 1 DM by CKD stages, depending on the region, are shown in Table 3.

Table 3.

Frequency of children with type 1 DM by CKD stage by region

Region	CKD (-) c NAU, n=270		CKD stage								
			I, n=25		II, n=22		III, n=14		IV, n=4		V, n=0
	n	%	n	%	n	%	n	%	n	%	-
Surkhandarya, n=8	7	87,5	-	-	1	12,5	-	-	-	-	-
Namangan, n=28	24	85,7	2	7,1	1	3,6	1	3,6	-	-	-
Fergana, n=64	63	98,4	-	-	-	-	1	1,6	-	-	-
Khorezm, n=79	62	78,5	5	6,3	7	8,9	4	5,1	1	1,3	-
Andijan, n=46	31	67,4	4	8,7	6	13,0	5	10,9	-	-	-

Republic of Karakalpakistan, n=74	63	85,1	6	8,1	5	6,8	-	0,0	-	-	-
Tashkent city, n=36	20	55,6	8	22,2	2	5,6	3	8,3	3	8,3	-
Total, n=335	270	80,6	25	7,5	22	6,6	14	4,2	4	1,2	-

The majority of children with type 1 DM 80.6% (OR 17.3; 95% CI 11.8-25.3; p<0.00001) in the research regions were without the presence of CKD, 7.5% were in stage I CKD; 6.6% in stage II CKD; 4.2% in stage III and 1.2% in stage IV CKD.

Among children with CKD (n=65), the majority were mostly in stages I and II of CKD (47-72.3% - OR 6.8; 95% CI 3.2-14.7; p<0.00001). In the Republic of Karakalpakistan and Surkhandarya region, there were no stage III and IV CBP cases among the examined children with type 1 DM. 1 child in Khorezm region and 3 children in Tashkent city had been detected CKD Stage IV.

Thus, most children with type 1 diabetes in the surveyed regions were at stages I and II of CKD.

Most adolescents with type 1 DM 64.5% (OR 3.3; 95% CI 2.3-4.72; p<0.00001) in the surveyed regions were without CKD, 17.0% were in stage I CKD; 8.1% in stage II CKD; 4.6% in stage III and 5.8% in stage IV CKD. No stage V CKD was detected among the examined adolescents with type 1 DM (Table 4).

Table 4.

Frequency of adolescents with type 1 DM by CKD stage by region

Region	CKD (-) с НАУ, n= 167		стадии CKD								
			I, n=44		II, n=21		III, n=12		IV, n=15		V, n=0
	n	%	n	%	n	%	n	%	n	%	
Surkhandarya, n=13	9	69,2	2	15,4	2	15,4	-	0,0	-	0,0	-
Namangan, n=36	12	92,3	-	0,0	-	0,0	1	7,7	-	0,0	-
Fergana, n=13	38	100,0	-	0,0	-	0,0	-	0,0	-	0,0	-
Khorezm, n=38	29	67,4	8	18,6	4	9,3	2	4,7	-	0,0	-
Andijan, n=43	20	62,5	6	18,8	6	18,8	-	0,0	-	0,0	-
Republic of Karakalpakistan, n=32	27	75,0	6	16,7	3	8,3	-	0,0	-	0,0	-
Tashkent city, n=84	32	38,1	22	26,2	6	7,1	9	10,7	15	17,9	-
Total, n=259	167	64,5	44	17,0	21	8,1	12	4,6	15	5,8	-

In the Republic of Karakalpakistan and Surkhandarya, Fergana and Andijan provinces, there was no stage III and IV CKD cases among the surveyed adolescents with type 1 diabetes. Stage IV CKD was detected in 15 adolescents in Tashkent city, which can be explained by a relatively good diagnosis and treatment rate.

Thus, most investigated adolescents with type 1 DM. in the regions were in stages I and II of CKD.

CONCLUSIONS:

1. Clinical and epidemiological study on the population of children and adolescents with type 1 DM. in Uzbekistan allowed establishing, for the first time, the actual prevalence of CKD: in children 19.4% and adolescents 35.5%. Among children and adolescents with type 1 diabetes with CKD, the majority were in stages I and II of CKD.

(2) The study of gender differences in children and adolescents with type 1 diabetes revealed a predominance of females among children 41.5/58.5% and adolescents 49.4/50.6%, which plays an important role in the formation of risk groups for further research.

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ЎЗБЕК ТИББИЁТ ЖУРНАЛИ
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STATISTICAL ANALYSIS OF THE PREVALENCE OF DIABETES AND OBESITY IN THE REPUBLIC OF UZBEKISTAN FOR 5 YEARS

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ABSTRACT

Endocrine pathology occupies one of the top places in the structure of general morbidity and indicates a high level of persistent disability, disability, and Republic population mortality. Statistical analysis data showed a high incidence of obesity and diabetes mellitus, in particular type 2 diabetes. The diabetes mellitus prevalence data Analysis in terms of the number of people applying to medical institutions revealed an increase in the indicator in the regions and the whole country. The widespread occurrence of endocrine pathology requires appropriate organisational and treatment-and-prophylactic measures that will ensure the adequacy and availability of qualified assistance to the population, a high medical and technical level and the maximum approach to specialised patients endocrinological care. To solve the accumulated problems, PP №4295 of April 19, 2019 “On approval of the National Program to improve endocrinological care for the Republic of Uzbekistan population for 2019-2021” was approved. The authors recommend timely fulfilment of the tasks set by PP 4295.

Keywords: prevalence, morbidity, obesity, type 2 diabetes mellitus.

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СТАТИСТИЧЕСКИЙ АНАЛИЗ РАСПРОСТРАНЕННОСТИ САХАРНОГО ДИАБЕТА И ОЖИРЕНИЯ В РЕСПУБЛИКЕ УЗБЕКИСТАН ЗА 5 ЛЕТ

АННОТАЦИЯ

Эндокринная патология занимает одно из ведущих мест в структуре общей заболеваемости и указывает на высокий уровень стойкой утраты трудоспособности, инвалидности и смертности населения Республики. Данные статистического анализа показали высокий уровень заболеваемости ожирения и сахарного диабета, в частности сахарного диабета 2 типа. Анализ данных о распространенности сахарного диабета по обращаемости населения в лечебно-профилактические учреждения выявил рост показателя как по регионам, так в целом по всей Республике. Широкое распространение эндокринной патологии требует проведения соответствующих организационных и лечебно-профилактических мероприятий, которые позволят обеспечить адекватность и доступность квалифицированной помощи населению, высокий медико-технический уровень и максимальное приближение к пациентам специализированной эндокринологической помощи. Для решения накопившихся проблем было утверждено ПП №4295 от 19 апреля 2019 г «Об утверждении Национальной программы по совершенствованию эндокринологической помощи населению Республики Узбекистан на 2019-2021гг.». Авторы рекомендуют своевременно исполнять задачи, поставленные ПП 4295.

Ключевые слова: распространенность, заболеваемость, ожирение, сахарный диабет типа 2.

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O'ZBEKISTON RESPUBLIKASIDA 5 YILDAGI QANDLI DIABET VA SEMIZLIK TARQALISHI

ANNOTATSIYA

Endokrin patologiya umumiy kasallanish tarkibida yetakchi o'rinlardan birini egallaydi va respublika axolisining doimiy nogironlikning va o'limning yuqori darajasini ko'rsatadi. Statistik taxlil ma'lumotlariga ko'ra, semizlik va qandli diabet, ayniqsa qandli diabet 2 turi kasalligi darajasi yuqori bo'lgan. Qandli diabetning tarqalishi to'g'risidagi ma'lumotlarni tibbiyot muassasalariga murojaat qilganlar soni bo'yicha taxlil qilish natijasida, barcha xududlarda va jami Respublikada xam ko'rsatkichning oshishi aniqladi. Endokrin patologiyaning keng tarqalishi axoliga malakali yordamning yetarliligi va mavjudligini, yuqori tibbiy va texnik darajani va bemorlarga ixtisoslashtirilgan endokrinologik yordamni maksimal darajada yaqinlashtirishni ta'minlaydigan tegishli tashkiliy va davolash-profilaktika choralarini talab qiladi.Yuqorida etilgan muammolarni xal qilish maqsadida 2019 yil 19 aprelda "2019-2021yillarda O'zbekiston Respublikasi axolisiga endokrinologik yordamni takomillashtirish Milliy Dasturni tasdiqlash to'g'risida"gi 4295 sonli Prezident Qarori qabul qilindi. Mualliflar 4295 sonli PQ tomonidan belgilangan vazifalarni o'z vaqtida bajarishini tavsiya etadilar.

Kalit so'zlari: tarqalish, semizlik, 2-tur qandli diabet.

Introduction. Endocrine pathology occupies one of the top places in the structure of general morbidity and indicates a high level of persistent disability, disability and mortality of the Republic population. Of particular importance is the significant prevalence of diabetes mellitus and its medical and social significance for all contingents of the population, which requires appropriate organisational and treatment-and-prophylactic measures. Numerous large-scale studies have proven that diabetes mellitus (DM) is one of the main causes of mortality in the population, one of the causes of which is obesity (2,4,6,8,11,14,17).

Type 2 diabetes mellitus (type 2 diabetes) is a multifactorial disease. The etiological factors in the development of diabetes mellitus 2 are non-corrected factors: genetic, demographic and corrected factors: overnutrition, obesity, hypodynamia, stress (1,3,10,12,13,15,19).

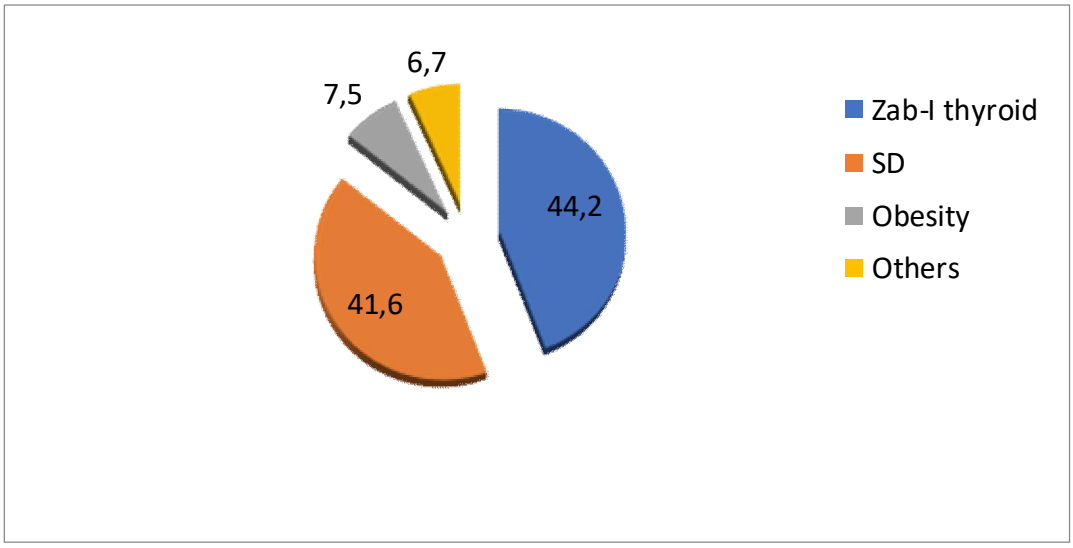
Among the external risk factors for the development of type 2 diabetes, obesity is the most significant. According to the results of the project "Improving the health care system" ("Health 3") in Uzbekistan, half of the population is overweight (BMI> 25 kg / m2), and one fifth is obese (BMI> 30g / m2) (9).

This work will analyse the incidence and prevalence of these pathologies in the Republic population over five years.

Materials and methods. To analyse the prevalence of endocrine diseases, in particular, diabetes mellitus and obesity among the population of our Republic, we have processed the annual statistical reports of the Ministry of Health of the Republic of Uzbekistan (Form No. 13), from 2015 to 2019, which provide information on the data on treatment institutions for patients with endocrine pathology, in particular with diabetes mellitus and obesity. Statistical analysis was performed using the Med Stat software.

Results and discussion. When studying the prevalence in the structure of endocrine pathology of the Republic of Uzbekistan as of 01.01. -the main share is accounted for by diseases of the thyroid gland (44.2%) and diabetes mellitus (41.6%), the next more common disease is obesity (7.5%), and the share of other endocrine diseases such as diseases of the hypothalamic-pituitary system, diseases of the adrenal glands and the reproductive system accounted for a total of 6.7%. (fig. 1).

Figure: 1. The structure of endocrine diseases in the Republic (2019)



When studying the prevalence of major endocrine diseases over the past 5 years, it showed that the main role in the formation of endocrine pathology and its growth belongs to diabetes mellitus, type 2 diabetes mellitus obesity (Table 1).

Table 1

The number of endocrine patients registered in the dispensary for 5 years

№	Nosology	2015		2019		Growth in%	
		abs	100 thousand us	abs	100 thousand us	abs	100 thousand us
1.	Total, endocrine-logical problems	496 176	1585,3	618 010	1858,4	20,0	14,7
2.	Total thyroid loss	262841	821,8	273305	839,8	3,8	2,14
3.	Diabetes mellitus, total	170 536	544,9	257 457	774,2	33,8	29,6
4.	Diabetes 2 types	151 853	485,2	239 565	720,4	36,6	32,6
5.	Obesity	26451	72,7	46 353	139,4	42,3	54,9

During the study period, there was a significant increase in the number of obese (1.9 times) and diabetes (1.4 times). The rate of increase in obesity is greater than in diabetes and thyroid diseases.

Comparative analysis of the prevalence of diabetes mellitus in all regions revealed an increase in the disease (Table 2).

Table 2

Comparative increase in the prevalence of diabetes mellitus by region over 5 years

№	Regions	2015		2019		Growth in%	
		abs	100 thousand us	abs	100 thousand us	abs	100 thousand us
1.	Republic of Karakalpakstan	7794	438,6	11985	641,0	35,0	31,6
2.	Andijan region	13106	454,6	21525	701,9	39,1	35,2
3.	Bukhara region	12587	699,2	17836	941,3	29,4	25,7
4.	Jizzakh region	8157	645,8	11558	854,6	29,4	24,4
5.	Kashkadarya region	6750	225,6	10516	327,3	35,8	31,3
6.	Navoi region	4695	510,0	6838	698,1	31,3	26,9
7.	Namangan region	12248	474,9	17758	645,1	31,0	26,4
8.	Samarkand region	18577	523,4	28389	747,3	34,6	30,0

9.	Syrdarya region	5264	671,6	8620	426,2	38,9	35,3
10	Surkhandarya region	6222	260,9	10953	1038,7	43,2	38,8
11	Fergana region	18750	539,6	28910	964,6	35,1	31,3
12	Tashkent region	19280	694,5	27958	784,9	31,0	28,0
13	Khorezm region	11022	636,6	21059	1147,2	47,7	44,5
14	c. Tashkent	26084	1094,9	33552	1336,7	22,3	18,1
	The Republic of Uzbekistan	**170536**	**544,9**	**257457**	**774,2**	**33,8**	**29,6**

An increase in the prevalence of diabetes mellitus is observed in all regions, but a significant increase in the number of patients with diabetes mellitus compared with the republican indicator is noted in Khorezm, Surkhandarya, Syrdarya and Andijan regions. The growth rate of patients with diabetes mellitus in these regions was 44.5%, 38.8%, 35.3%, and 35.2%.

In quantitative terms, type 2 diabetes is 85% –90% of the total number of patients suffering from this disease. As a rule, it develops in people over 40 years of age. Finally, over 80% of these patients are overweight or obese. In this regard, the prevalence of type 2 diabetes was studied. The growth rate in the Republic was 32.6%. On average, the number of patients with type 2 diabetes in the Republic has increased 1.6 times over 5 years. The growth rate, depending on the regions, was higher than the republican indicators in patients with Khorezm (48.5%), Kashkadarya (40.6%), Bukhara (39.6%), Syrdarya (39.4%) and Samarkand regions (35.7 %). An increase below the republican indicators was observed among patients in the Jizzakh region (27.8%) and Tashkent (21.4%).

The prevalence of obese patients over five years was also studied, depending on the regions. Comparative analysis of the prevalence of obese patients in all regions revealed an increase in the disease, except for patients in the Syrdarya region (Table 3).

Table 3

Comparative growth in the prevalence of obesity by region over 5 years

№	Regions	2015		2019		Growth in%	
		abs	100 thousand us	abs	abs	100 thousand us	100 thousand us
1.	Republic of Karakalpakstan	916	51,5	2406	130,6	61,9	79,1
2.	Andijan region	907	31,5	1876	62,2	51,6	30,7
3.	Bukhara region	2001	111,1	2282	122,0	12,3	10,9
4.	Jizzakh region	1355	107,3	2861	215,9	52,6	**108,7**
5.	Kashkadarya region	182	6,1	731	23,2	75,1	17,1
6.	Navoi region	940	102,1	1266	132,1	25,8	30,0
7.	Namangan region	112	4,3	481	17,8	76,7	13,5
8.	Samarkand region	1722	48,5	9536	256,3	81,9	**207,8**
9.	Syrdarya region	4587	585,2	2698	330,1	-70,3	-255,1
10	Surkhandarya region	449	18,8	580	23,1	22,6	4,2
11	Fergana region	2082	59,9	5373	148,4	61,3	88,5
12	Tashkent region	2671	96,5	3671	128,63	27,2	32,1
13	Khorezm region	1498	86,5	3372	186,8	55,6	**100,3**
14	c.Tashkent	7029	295,1	9228	374,4	23,8	79,3
	The Republic of Uzbekistan	**26451**	**84,5**	**46353**	**139,4**	**42,9**	**54,9**

The largest increase in the number of obese patients was observed in Samarkand (5.5 times) and Kashkadarya (4.3 times) regions. During the study period, the number of obese patients increased by 2-2.5 times among patients with RKK, Fergana, Khorezm, Jizzakh and Andijan regions. In other regions, the number of obese patients also increased (from 1.15 to 1.75 times).

Timely identification of SD and forecasting the situation is of great importance. The incidence of newly diagnosed diabetes mellitus during the study period increased by 1.7 times (Table 4).

Table 4

Indicators of primary incidence of diabetes mellitus in the Republic of Uzbekistan (per 100 thousand population)

№	Regions	Years		growth in 5 years	The growth rate over 5 years (in %)
		2015	2019		
1.	Republic of Karakalpakstan	57,6	96,0	38,4	40,04
2.	Andijan region	63,8	110,5	46,7	42,3
3.	Bukhara region	111,2	125,7	14,5	11,5
4.	Jizzakh region	21,0	81,9	60,9	74,4
5.	Kashkadarya region	29,8	46,0	16,2	35,2
6.	Navoi region	61,0	109,1	48,1	44,1
7.	Namangan region	46,1	92,8	46,8	50,4
8.	Samarkand region	100,3	123,6	23,3	18,9
9.	Syrdarya region	81,5	314,0	232,5	74,1
10	Surkhandarya region	39,4	74,0	34,6	46,8
11	Fergana region	78,5	127,3	48,8	38,3
12	Tashkent region	72,6	133,9	61,3	45,8
13	Khorezm region	84,0	167,5	83,5	49,8
14	c.Tashkent	125,3	113,3	-12,0	-10,6
15	**The Republic of Uzbekistan**	**70,5**	**112,8**	**42,4**	**37,5**

The highest rate of newly diagnosed diabetic patients was observed among the population of Jizzakh (4.2 times) and Syrdarya (4.1 times). The high rate of detectability is explained by the fact that in these regions screening was carried out for the early detection of diabetes mellitus, in particular type 2 diabetes, among the population over 40 years old. Also, a high rate of detection was observed among the population of Namangan (2.2 times), Khorezm (2.1 times), Surkhandarya (2 times) and Fergana (2 times) regions.

A similar upward trend is observed in primary obesity rates in most regions of the Republic, except for Tashkent, Surkhandarya, Navoi and Jizzakh regions, as well as in Tashkent (Table 5).

Whereas the level of obese patients increased by more than 1.5-2.2 times in Jizzakh, Khorezm, Samarkand, Fergana regions, as well as in RKK and Tashkent city. When comparing the prevalence of type 2 diabetes and obesity, it can be concluded that both the frequency of type 2 diabetes and obesity tended to increase in the Khorezm and Samarkand regions.

Table 5

Primary obesity incidence rates in the Republic of Uzbekistan (per 100 thousand population)

№	Regions	Years		Growth in 5 years	The growth rate over 5 years (in %)
		2015	2019		
1.	Republic of Karakalpakstan	18,1	55,8	37,7	67,6
2.	Andijan region	20,3	23,6	3,4	14,3
3.	Bukhara region	17,5	49,7	32,2	64,8
4.	Jizzakh region	54,1	49,5	-4,6	-9,3
5.	Kashkadarya region	4,4	9,4	4,9	52,6
6.	Navoi region	53,7	47,5	-6,2	-13,0
7.	Namangan region	1,9	10,5	8,5	81,5
8.	Samarkand region	33,4	101,7	68,4	67,2
9.	Syrdarya region	24,0	70,6	46,6	66,0
10	Surkhandarya region	7,7	4,9	-2,7	-55,3

11	Fergana region	63,1	37,3	-25,8	-69,2
12	Tashkent region	46,7	47,3	0,6	1,4
13	Khorezm region	37,7	64,5	26,8	41,6
14	c.Tashkent	76,8	73,9	-3,0	-4,0
15	**The Republic of Uzbekistan**	**31,9**	**44,7**	**12,8**	**28,6**

Our study results showed an increase in the overall incidence of diabetes mellitus in the Republic (from 70.5 in 2015 to 112.8 in 2019 per 100 thousand population) and obesity (from 31.9 in 2015 to 44, 7 in 2019 per 100 thousand population). The growth rate over 5 years was 37.5% and 28.6%, respectively. The most pronounced positive trend is observed in Jizzakh, Syrdarya and Namangan regions; the growth rate was 74.4%, 74.1%, and 50.4%. The increase in the number of newly diagnosed patients in Jizzakh and Syrdarya regions can be explained by screening tests for type 2 diabetes in people over 40 years old.

Compared to other regions of the Republic, a low growth rate is noted in the Samarkand (18.9%) and Bukhara (11.5%) regions. The absence of an increase in morbidity during the study period is typical for Tashkent city (-10.2%).

Conclusion. Statistical analysis data showed a high prevalence of obesity and diabetes mellitus, in particular type 2 diabetes. Obesity is one of the leading risk factors for diabetes, cardiovascular diseases, and oncopathology (1,5,7,13,16,18,20). In this regard, the prevalence of obesity was also studied, which also showed an increase in the number of patients in all regions, except for the Syrdarya region.

Trends in the prevalence of endocrine diseases, particularly type 2 diabetes and obesity in the Republic of Uzbekistan, confirm the high relevance of endocrine pathology (8.20).

So, the data analysis on the prevalence of diabetes mellitus in terms of the population turnover to medical institutions revealed an increase in the indicator both in the regions and in the whole country as a whole. The trends we identified are similar to world data and confirm the high relevance of diabetes mellitus in the modern world (1,3,21,22,27). The widespread occurrence of endocrine pathology requires appropriate organisational and treatment-and-prophylactic measures to ensure the adequacy and availability of qualified assistance to the population, a high medical and technical level and the maximum approximation of specialised endocrinological care to patients.

It is expedient to determine the most priority program activities, including prevention of diabetes mellitus and its complications, as well as medical and social assistance to diabetes mellitus. To solve the accumulated problems, the Ministry of Health, together with the Academician YO.Kh. Turakulov, a draft resolution was prepared “On approval of the National program for improving endocrinological assistance to the Republic of Uzbekistan population for 2019-2021”, which was approved on April 19, 2019, No. 4295.

PP 4295 includes all social, medical and organisational issues, proposals for providing quality care for patients with endocrine diseases, including diabetes mellitus. The main goals of the Program are to improve medical and social care for patients with diabetes mellitus by improving legislation regulating the actions of health authorities, local authorities, state and non-governmental organisations to provide sufficient funding to address the problems of diabetes mellitus, as well as improve the health status of patients with diabetes mellitus, quality of life, reducing the number of complications, increasing the average life expectancy by improving the quality and volume of diabetes prevention, improving the quality of medical care for patients with diabetes.

In fulfillment of the tasks set by PP 4295, the following activities are carried out; screening of diabetes mellitus among people over 40 years old, an on-line register of patients with diabetes mellitus has been created, aimed at reducing the frequency of chronic complications, modern methods of diagnosing endocrinological patients are being introduced in regional EIAs by the

uninterrupted provision of reagents for the determination of glycated hemoglobin and thyroid hormones.

Also, in each EOS there are schools of self-control of patients with diabetes mellitus, where patients with diabetes mellitus, as well as their relatives (constant updating of knowledge in the field of prevention, treatment, self-control of diabetes mellitus, behavioral skills, healthy lifestyle).

Work is underway to provide all sick children, adolescents, pregnant women with the necessary insulin preparations (analog insulins) and devices for insulin administration (insulin pens, insulin pumps) and self-control means.

The provision of medical care in the field of endocrinology has a special place in the health care system since endocrine diseases in most cases have a chronic course and lead to high-cost treatment, severe complications that contribute to high disability and mortality.

The widespread application of the experience and achievements of leading foreign countries in endocrinology allows us to provide specialised care for patients with diabetes mellitus at the world level using medical technologies of the latest generation.

Conclusions.

1. Data of statistical analysis showed a high prevalence of obesity and diabetes mellitus, particularly type 2 diabetes mellitus.

2. The analysis revealed an increase in morbidity rates, especially pronounced with type 2 diabetes

3. Effective conduct of the diabetes register will allow for clinical and epidemiological monitoring of diabetes throughout the Republic.

4. Timely fulfillment of the tasks set by the PP 4295 “On approval of the National Program for the improvement of endocrinological care for the population of the Republic of Uzbekistan for 2019-2021.”

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UZBEK MEDICAL JOURNAL

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Dr. med. science on behalf of the members
of the National Council of Experts
Republican Specialized Scientific
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RESOLUTION OF THE NATIONAL COUNCIL OF EXPERTS "PLACE OF INSULIN DEGLUDEK IN PEDIATRIC PRACTICE IN RUZ"

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РЕЗОЛЮЦИЯ НАЦИОНАЛЬНОГО СОВЕТА ЭКСПЕРТОВ «МЕСТО ИНСУЛИНА ДЕГЛУДЕК В ПЕДИАТРИЧЕСКОЙ ПРАКТИКЕ В РУЗ»

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MILLIY EKSPERTLAR KENGASHINING QARORI “INSULIN DEGLUDEKNING RUZDA PEDIATRIKA AMALIYYATIDA O’RNI”

On October 9, 2020, the Council of Experts-Endocrinologists of the Republic of Uzbekistan (RUz) was held in Tashkent, dedicated to insulin therapy issues in children and adolescents with type 1 diabetes and the use of ultra-long-term insulin of a new generation degludek (IDeg).

The Council was chaired by Dr. F.A.Khaidarova, deputy director for therapeutic work of the PSSPEMC, the chief physician of the PSSPEMC, the chief endocrinologist of the Ministry of Health of the Republic of Uzbekistan.

The Council was attended by: G.N. Rakhimova, MD, DSc, Professor, Head of the Department of Endocrinology, TashIUV; N.U. Alimova, candidate of medical sciences, chief

pediatrician-endocrinologist of the Ministry of Health of the Republic of Uzbekistan, junior researcher Scientific Department of Pediatric Endocrinology, Ministry of Health of the Republic of Uzbekistan; A.V. Alieva, Ph.D., Deputy Chief Physician of the Clinic of the RSNPMTSE MH RUz; Sh.Sh. Azimova, Ph.D., Head of the Department of Pediatric Endocrinology, RSNPMTSE, Ministry of Health of the Republic of Uzbekistan; PC. Sultanova, doctor of the Department of Pediatric Endocrinology, RSNPMTSE, Ministry of Health of the Republic of Uzbekistan; E.F. Pavlova, pediatric endocrinologist, Tashkent City Endocrinological Dispensary, Ministry of Health of the Republic of Uzbekistan; B.K. Teshaev, Chief Physician, Kashkadarya Regional Endocrinological Dispensary; OH. Mavlyanov, Chief Physician, Jizzakh Regional Endocrinological Dispensary; G. Sh. Negmatova, Chief Physician, Samarkand Regional Endocrinological Dispensary; N.N. Bakhrieva, pediatric endocrinologist, Samarkand Regional Endocrinological Dispensary; F.S. Khamedova, pediatric endocrinologist, Bukhara Regional Endocrinological Dispensary.

A.V. Kiyaev, Doctor of Medicine, Professor of Hospital Pediatrics Department, Ural State Medical University, Ministry of Health of Russia; Head of Regional Center of Pediatric Endocrinology, Regional Children's Clinical Hospital, Ekaterinburg; Chief freelance pediatric endocrinologist, Ministry of Health of Russia in the Ural Federal District was invited as well. Chief freelance pediatric endocrinologist of the Ministry of Health of Sverdlovsk region.

The Council’s initiator was Novo Nordisk, on behalf of which N.Ye greeted the members of the Council. Kovalenko, CEO and vice president of the company in the CIS countries, Mongolia and Georgia, noting that Novo Nordisk is a global pharmaceutical company with a 95-year history of innovation and leadership in treating diabetes mellitus (DM) and other diseases. Almost every second patient uses Novo Nordisk drugs to treat diabetes every day, and this is more than 30 million patients in 170 countries. The company has consistently made a comprehensive effort to defeat diabetes - discovering, developing and manufacturing better biopharmaceutical drugs, and making them available to patients around the world, ensuring their correct use in medical practice and improving the quality of patient care. (1)

The company has representative offices in 170 countries of the world. The company has been operating in Uzbekistan for over 25 years, providing patients and doctors with the opportunity to use the most effective drugs, improving patients’ quality and life expectancy with serious illnesses.

The company pays great attention to innovative products, developing a line of drugs to treat diabetes. Thus, the 2nd phase of research on a new, highly effective insulin with a frequency of 1 time/week administration has been completed. In addition to DM, the company’s drugs occupy leading positions in treating growth disorders, obesity, and hemophilia. NOT. Kovalenko drew the attention of the Expert Council members because the innovative ultra-long-acting insulin IDEG was registered in Uzbekistan in 2017. However, the possibility of using this drug appeared only now. The world has accumulated a great deal of experience in using IDeg, the high efficiency and safety of which has been proven in clinical randomized trials and data from real clinical practice. The particular benefits of IDeg are observed in children and adolescents with type 1 diabetes. The introduction of this drug into real clinical practice improves the quality of life and prognosis of patients.

Opening the Council of Experts, Dr. med. F. Khaidarova noted that significant changes had taken place in the field of diabetes treatment in Uzbekistan recently. So in 2019, the first National Recommendations for the treatment of type 2 diabetes were issued. A pilot project was carried out and the most cost-effective and informative methods of screening for type 2 diabetes were identified, which are used to detect type 2 diabetes in the Republic of Uzbekistan. Also Ph.D. F. Khaidarova noted that all children and adolescents with type 1 diabetes are provided with insulin analogues at the expense of the state. A training program for doctors accompanied the transfer of children to insulin analogues with Novo Nordisk’s support. The first results of treatment after transfer are encouraging by a decrease in hypoglycemia, an improvement in glycemic control, and an improvement in children and adolescents’ well-being.

A National Online Diabetes Registry is under development. A pilot project for online registration of children and adolescents with type 1 diabetes is completed and is at the data processing stage.

The Chairperson of the Council stressed that introducing new drugs into clinical practice is an integral process of improving medical care. Determining innovative IDeg in real pediatric practice is an important task for its further implementation and application. The purpose of this Council is to determine the clinical profile of children and adolescents with type 1 diabetes, in whom IDeg will have the greatest advantages, with the subsequent development of measures for the implementation of IDeg in real clinical practice with the support of the state.

Further prof. G.N. Rakhimova, dwelling on the main problems in insulin therapy for type 1 diabetes in adolescent children.

Prof. G.N. Rakhimova noted that due to the widespread use of insulin analogs in children worldwide, glycemic control goals have significantly “tightened”: the recommended glycated hemoglobin (HbA1c) is less than 7%. According to the latest recommendations of the International Society for the Study of Diabetes in Children and Adolescents (ISPAD) from 2018, goals should be individually defined, as close to normal as possible, without severe hypoglycemia and frequent mild to moderate hypoglycemia, given excessive stress/burden. diseases on a child with diabetes and their families. (2) At the same time, it is extremely important not only to reach the target level but also to be in the target glycemic range (TIR) from 3.9 to 10 mmol / L for at least 60% -70% of the time. (3) A 10% increase in time off-target results in a dramatic increase in the risk of developing diabetic retinopathy and nephropathy by 64% and 40%, respectively. (4)

The most important difficulties in the management of type 1 diabetes in children and adolescents, according to Professor G.N. Rakhimova, are the following:

1. High glucose variability due to increased insulin sensitivity and changing daily routine;
2. Children and adolescents are in a state of active growth, which changes the need for insulin;
3. Associated high risk of hypoglycemia and hyperglycemia with ketoacidosis;
4. Children and parents find injections and self-control cumbersome and often interfere with the insulin administration, leading to poor glycemic control.

Speaking about hypoglycemia, the speaker noted that hypoglycemia is the most common acute complication in treating type 1 diabetes in children and adolescents. The risk of recurrent and severe hypoglycemia is a factor limiting optimal glycemic control.

The consequences of hypoglycemia in children under the age of 5-6 are abnormalities in the brain’s structure and functioning, a decrease in cognitive functions and memory processes. (5) Severe prolonged hypoglycemia, especially when asymptomatic during sleep, can lead to “dead in bed” syndrome.

Hypoglycemia has an extremely negative effect on both the patients themselves and their parents’ quality of life, causing fear, anxiety, and depression. The desire to avoid hypoglycemia reduces treatment adherence, worsens control. (6)

The most common cause of hypo- and hyperglycemia is high 24-hour and day-to-day blood glucose variability. (3)

On the stability of glycemia, according to prof. G.N. Rakhimova, such factors as attention to injection technique (injection sites, depth) have a positive effect; flexible selection of insulin doses; more frequent self-monitoring with correction of treatment; the use of ultra-long-acting insulin analogues with proven low variability of action, to which IDeg belongs.

Particular attention was paid to the problem of diabetic ketoacidosis (DKA), which develops in about 10% of children, more often in children under 6 years of age and during puberty from 13 to 18 years. (7) DKA is the cause of death in 70% of patients with type 1 diabetes for up to ten years. The main cause of death is the progression of intracranial hypertension and cerebral edema. In 10-25% of patients, persistent cognitive disorders persist in decreased memory and intelligence, impaired attention and pronounced microstructural damage to the brain. (8)

Treatment of DKA and its consequences imposes an additional financial burden on both the state and the family. (nine)

Thus, the goals of treating children and adolescents with type 1 diabetes are presented as achieving close to normal indicators of carbohydrate metabolism, preventing the development of DKA and severe hypoglycemia, achieving a good quality of life in patients with type 1 diabetes and their parents, ensuring normal growth in children, full physical and mental development.

All this is possible only with patient education, the use of modern control methods and the use of modern insulins with improved qualities.

Then the floor was given to Ph.D. N.U Alimova shared her statistical data, noting that currently, 3263 children and adolescents with type 1 diabetes are registered at the dispensary. About 90% of children receive long-acting and ultra-short-acting insulin analogues with 100% payment by the state. At the same time, the average age of a child with DM1 registered, according to the data of the pilot project of the National Register, obtained in October this year, is 11.9 years, the average duration of DM is about 4 years, the average HbA1c is 8.3%.

The average incidence of hypoglycemia was 8.7%, and DKA 10.5%. The estimated cost of treatment of one case of DKA in the intensive care unit's conditions and subsequent treatment in the department for 10 days, which amounted to 7 million sums, was also presented. Thus, the estimated amount of treatment for all DKA cases per year is 2 394 million sums.

Speaking about IDeg, N.U. Alimova noted the unique mechanism of prolongation of action due to the formation of multi-hexameric structures in the subcutaneous tissue, followed by their uniform dissociation into monomers, which, being absorbed into the bloodstream, reach organs and tissues, and have a hypoglycemic effect (10). This mechanism determines the duration of action for more than 42 hours, the flat profile of the action in the equilibrium state and the variability of the antihyperglycemic effect is 4 times lower than that of insulin glargine (IGlar). (11.12)

The half-life of IDeg is 25 hours, which is 2 times the half-life of other basal insulin analogues. Moreover, the duration of action of IDeg does not depend on the dose, as well as the age of the patients. (13) Introducing the BEGIN Young study evaluating the efficacy and safety of IDeg versus insulin detemir (IDet) in children 1 to 18 years of age, N.U. Alimova noted that with equal glycemic control and a comparably low number of hypoglycemia in patients treated with IDeg, the frequency of DKA was 41% lower. In addition, the daily insulin dose in the IDeg group was 30% lower. (14)

Noting that IDeg has been registered since 1 year (15), the speaker singled out groups of patients in whom IDeg would have the most pronounced clinical advantages. Children with frequent hypoglycemia are prone to DKA, children and adolescents uncompensated on other insulins.

The first clinical experience was shared with experts by Ph.D. Sh.Sh. Azimov, noting the possibility of introducing IDegs at intervals of 8 to 40 hours. The safety and efficacy of the flexible mode of administration of IDeg were proven in the BEGIN Flex study for type 1 diabetes patients. With equal glycemic control, the risk of nocturnal hypoglycemia on IDEG administered at intervals of 8 to 40 hours was 40% lower compared to IGlar administered at the same time daily. (16) Although such a regimen has not been studied in children, given the comparable pharmacodynamic and pharmacokinetics of IDeg in children and adults (13), the drug can be used in children if clinically justified. (16)

Sh.Sh. Azimova presented her clinical case of a 13-year-old female patient who has type 1 diabetes for 1.5 years, who are actively involved in sports and, despite strict self-control and calculation of XE, high glycemic variability and frequent unpredictable hypoglycemia against the background of decompensated diabetes, confirmed by continuous daily monitoring. Transfer from IGlar at a dose of 24 U / day to IDeg 22 U / day. led to stabilization of the level of glycemia, hypoglycemia stopped. Repeated continuous 24-hour glucose monitoring was planned. High satisfaction with the treatment with IDEG was noted both by the patient herself and by her mother.

Further, the chairman of the Council F.A. Khaidarova, gave the floor to prof. A.V. Kiyayev, who has extensive experience in using IDeg in children in the Ural Federal District, where he is the chief freelance specialist - a pediatric endocrinologist. Prof. A.V. Kiyaev presented data from a joint

study with prof. J. Hirsch on the use of IDeg in real clinical practice. The study included 27 children with type 1 diabetes under the age of 10 years (average age - 6.7 years), meeting the following criteria: no compensation for the disease (cf. HbA1c 8.3%); labile course of diabetes: pronounced variability of glycemia, difficulty in selecting the dose of basal insulin; tendency to nocturnal and asymptomatic hypoglycemia during ongoing therapy. At the same time, patients (parents) exercised regular self-monitoring.

During the year against the background of IDeg treatment, HbA1c decreased from 8.3% to 7.7%. Episodes of hypoglycemia (absolute total frequency per patient) decreased from 59 to 37, episodes of nocturnal hypoglycemia (absolute total frequency per patient) from 31 to 14, severe hypoglycemia was not detected. The average weft dose of basal insulin decreased from 0.4 U / kg / day to 0.27 U / kg / day. on ID. (17)

A dose reduction was also shown when analyzing the case histories of 48 adolescents with type 1 diabetes, transferred to IDeg from insulin glargine and IDet in a hospital setting. The dose decreased from 0.48 U / kg / day to 0.32 U / kg / day.

Further prof. A.V. Kiyaev shared the titration schemes for IDEG, noting the ease of titration when transferring from other basal insulins with a dose reduction of 10-20% and reaching a stable state in 3-4 days.

During the discussion in groups, the moderators were Ph.D. A.V. Alieva, Ph.D. WELL. Alimova and Ph.D. Sh.Sh. Azimov, answers were found to several questions necessary to understand the place of IDeg in the treatment of children and adolescents with type 1 diabetes.

So the experts named the main benefits of insulin degludec in children and adolescents with type 1 diabetes:

- Improved glycemic control,
- A decrease in the number of hypoglycemia, including nocturnal
- Reduction of ketoacidosis
- Low variability of action
- Reducing the daily dose
- Possibility of flexible dosing
- Shelf life is 8 weeks, which is especially important when prescribing small doses (15)
- Improving the quality of life
- Use from 1 year

Clinical situations in children and adolescents with type 1 diabetes were listed, in which insulin degludec is most indicated:

- The labile flow of SD
- Children under 10 years old
- Adolescents during puberty
- Children with frequent hypoglycemia
- Frequent DCA, despite adherence to self-monitoring recommendations
- Athletes with type 1 diabetes
- Children with concomitant diseases (glomerulonephritis, bronchial asthma, etc.)

The question was raised about the existing difficulties in managing children and adolescents with type 1 diabetes. The most acute issue is the education of children and adolescents, as well as self-monitoring of glycemia using glucometers or continuous monitoring devices. The need to supplement the National Recommendations on the management of children and adolescents with type 1 diabetes in the Republic of Uzbekistan was noted.

In conclusion, the members of the National Expert Council adopted a resolution:

1. Insulin degludec is a new generation of ultra-long-acting insulin with proven clinical benefits in the form of reduced hypoglycemia, reduced risk of DKA, dose reduction, improved quality of life, flexible administration.
2. The use of IDEG in some patients will have clinical and pharmacoeconomic advantages.

These patients include children and adolescents with a labile course of diabetes, frequent hypoglycemia, a tendency to DKA, as well as children and adolescents with severe comorbidities, athletes.

Providing these groups of patients with IDeg at the expense of public funds will improve these patients' quality of life and prevent fatal complications.

To improve the quality of medical care for children and adolescents with type 1 diabetes in the Republic of Uzbekistan, it is necessary:

1. Make appropriate amendments to the National guidelines for the treatment of type 1 diabetes in children and adolescents.
2. Improve the provision of self-control facilities for children and adolescents with type 1 diabetes at the state's expense.
3. Expand training programs, organization of "SD schools" for children and adolescents.

Conflict of Interest Information:

The article was prepared based on the speeches of independent experts presented within the National Expert Council framework, which took place on October 09, 2020. The council was held with the support of Novo Nordisk.

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CLINICAL AND THYROID ASPECTS IN CHILDREN AND ADOLESCENTS WITH HYPERTHYROUS IN CONDITIONS OF IODINE DEFICIENCY

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ABSTRACT

In the last decade, there has been an increase in the incidence of juvenile hyperthyroidism and its prevalence among children is 0.02%, which makes it extremely difficult to conduct extensive cohort clinical studies among children with hyperthyroidism. We have studied the clinical and thyroid aspects in children and adolescents with hyperthyroidism in iodine deficiency conditions. It was revealed that in conditions of iodine deficiency, hyperthyroidism develops more often in adolescence, girls get sick more often than boys and the gender ratio averages 1: 2. Thyrotoxicosis is more severe in children than in adolescents; children are more likely to fear and aggressiveness. However, 100% of adolescents had emotional lability and increased anxiety. Intellectual changes were also more typical for adolescents, who noted a decrease in memory (85.7%), concentration (95.7%), school performance (87%) and impaired attention (100%). Delay in physical development was revealed in 24.2% of children. Weight deficit was found in 42.4% of children. At the same time, 13% of adolescents were diagnosed with overweight/obesity of the 1st degree. Diffuse goiter was diagnosed in 69.7% of children, nodular goiter - in 15.2%, multinodular goiter - in 15.2%. Further research on hyperthyroidism in this age group is needed.

Keywords: hyperthyroidism, thyrotoxicosis, Graves' disease, nodular / multinodular toxic goiter, children, adolescents, anatomical and physiological features, metabolism.

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КЛИНИЧЕСКИЕ И ТИРЕОИДНЫЕ АСПЕКТЫ У ДЕТЕЙ И ПОДРОСТКОВ С ГИПЕРТИРЕОЗОМ В УСЛОВИЯХ ЙОДДЕФИЦИТА

АННОТАЦИЯ

В последнее десятилетие отмечается рост заболеваемости ювенильным гипертиреозом и его распространенность среди детей составляет 0,02%, что делает крайне затруднительным проведение крупных когортных клинических исследований среди детей с гипертиреозом. Нами проведено изучение клинико-тиреоидных аспектов у детей и подростков с гипертиреозом в условиях йоддефицита. Выявлено, что в условиях йоддефицита гипертиреоз чаще развивается в подростковом возрасте, девочки болеют чаще, чем мальчики и гендерное

соотношение в среднем составляет 1:2. Тиреотоксикоз тяжелее протекает у детей, чем у подростков, у детей чаще отмечались чувство страха и агрессивность. Однако 100% подростков имели эмоциональная лабильность и повышенная тревожность. Интеллектуальные изменения также оказались более характерными для подростков, которые отмечали снижение памяти (85,7%), концентрации (95,7%), успеваемости в школе (87%) и нарушения внимания (100%). У 24,2% детей выявлена задержка физического развития. У 42,4% детей выявлен дефицит веса. В тоже время у 13% подростков диагностированы избыточная масса тела/ожирение 1 степени. Диффузный зоб диагностирован у 69,7% детей, узловой зоб - у 15,2%, многоузловой зоб - у 15,2%. Необходимо дальнейшее исследование гипертиреоза в данной возрастной группе.

Ключевые слова: гипертиреоз, тиреотоксикоз, болезнь Грейвса, узловой/многоузловой токсический зоб, дети, подростки, анатомо-физиологические особенности, метаболизм.

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YOD ETISHMOVCHILIGI SHAROITIDA GIPERTIREOZLI BOLALAR VA O'SMIRLARDA KLINIK VA TIREOID ASPEKTLARI

ANNOTATSIYA

So'nggi o'n yilda balog'at yoshiga etmagan bolalarning gipertireoz bilan kasallanish darajasi oshdi va uning bolalar orasida tarqalishi 0,02% ni tashkil qiladi, bu esa gipertireozga chalingan bolalar o'rtasida katta kohort klinik tadqiqotlar o'tkazishni juda qiyinlashtiradi. Yod etishmovchiligi sharoitida gipertireozli bolalar va o'smirlarda klinik va tireoid aspektlarni o'rganib chiqdik. Yod tanqisligi sharoitida gipertireoz o'smirlar davrida tez-tez rivojlanib borishi, qizlar o'g'il bolalarga qaraganda tez-tez kasal bo'lib turishi va jinslar nisbati o'rtacha 1: 2 ekanligi aniqlandi. Tireotoksikoz bolalarda o'smirlarga qaraganda og'irroq bo'ladi; bolalarda qo'rquv va tajovuzkorlik hissi ko'proq uchraydi. Biroq, 100% o'smirlarda emotsional o'zgaruvchiligi va tashvishligi kuchaygan. Intellektual o'zgarishlar, shuningdek, xotira (85,7%), kontsentratsiya (95,7%), maktabda o'qish (87%) kamayganligini va e'tiborning buzilishi (100%) o'smirlarda ko'proq xos bo'lgan. Jismoniy rivojlanishning kechikishi bolalarning 24,2 %da aniqlandi. Og'irlik tanqisligi bolalarning 42,4 %da aniqlandi. Shu bilan birga, o'smirlarning 13 foizida ortiqcha vazn / 1-darajali semirish tashxisi qo'yilgan. Diffuz bo'qoq bolalarning 69,7 %da, tugunli bo'qoq - 15,2 %da, ko'p tugunli bo'qoq - 15,2 %da aniqlangan. Ushbu yosh guruhidagi hipertireoz bo'yicha qo'shimcha tadqiqotlar o'tkazish kerak.

Kalit so'zlar: gipertireoz, tireotoksikoz, Greyvs kasalligi, tugunli / ko'p tugunli bo'qoq, bolalar, o'smirlar, anatomik va fiziologik xususiyatlar, metabolizm.

Relevance. Thyrotoxicosis is a clinical condition that results from increased metabolism due to excess thyroid hormone. The term thyrotoxicosis is not synonymous with hyperthyroidism. Hyperthyroidism is an excess of thyroid hormones due to their increased production and secretion [6]. Most hyperthyroidism cases in children are associated with Graves' disease (HD), which accounts for 10-15% of all childhood thyroid diseases [5]. Besides, recently there have been reports indicating an increase in juvenile hyperthyroidism incidence over the past decades [3]. Pediatric patients account for less than 5% of the total number of patients with Graves' disease, and the prevalence in children is 0.02% [4]. Therefore, there are very few extensive cohorts clinical studies and scientific data on hyperthyroidism in the pediatric population. Accordingly, it is inappropriate to apply adult standards to children.

The purpose of our study was to determine the clinical and thyroid features of hyperthyroidism in children and adolescents living in the Republic of Uzbekistan in conditions of iodine deficiency.

Materials and methods.

From 2014-2019, we examined 33 children and adolescents with hyperthyroidism in the active phase at the age of 2-18 years. The control group consisted of 23 children and adolescents, without endocrine pathology of the same age.

The diagnosis of pathology of the thyroid gland (TG) and other systems was established based on anamnesis data, clinical manifestations, biochemical and hormonal laboratory studies, ultrasound of the thyroid gland, fine-needle aspiration biopsy of the thyroid gland according to indications), which were carried out at the RSPMCE named after Academician Y. Kh. Turakulov. Anthropometric studies included determining height, weight, body mass index (BMI) using centile tables (WHO, 2005). Blood samples were taken from the subjects in the morning after a 12-hour overnight fast. TSH levels (norm 0.28-4.0 mIU / l), over T4 (norm 1.1-1.8 ng/dl) and free T3 (norm 2.5-4.3 ng/dl), were determined using a closed-type immunochemical analyzer Cobas e 411 Hitachi from Hoffman Le Roche (Switzerland) and its reagents.

Thyroid ultrasound scans were performed using Affiniti 50 Philips Healthcare J, Philips HD 7XE, Esaote Mylab 40 (Holland) linear high-frequency 7.5 MHz transducers. Scanning protocol in all cases included both transverse and longitudinal imaging of the thyroid gland in real-time.

Statistical processing of the results was performed using Microsoft Excel computer program. Significance of differences was established at $p<0.05$.

Results and discussion.

Of the 33 patients (21 girls and 12 boys), 29 (87.9%) were referred to the Turakulov Republican Scientific and Practical Center for Medical Treatment by paediatricians and general practitioners, and 4 (12.1%) went directly to the clinic. The age and sex of the examined children and adolescents are presented in Table 1. At the time of registration of the disease, 18 (54.5%) patients with childhood hyperthyroidism lived in the city, 15 (45.5%) lived in rural areas.

Table 1

Age and gender 33 children and adolescents with hyperthyroidism.

Age, years	Gender		Total
	man	woman	
<11	5 [50%]	5 [50%]*	10 (30,3%)**
11–14	5 [33.3%]	10 [66,7%]	15 (45,5%)
15–19	2 [25%]	6 [75%]	8 (24,2%)
Все	12 (34.3%)	21 (63.6%)	33 (100)

* numbers in [] brackets represent the percentage of patients of each gender,

** the numbers in () brackets represent the percentage of patients in each age group.

Analysis of the data of 305 patients with hyperthyroidism in the child population, obtained in a 35-year research work by Iranian scientists Azizi, F. et al. Showed that hyperthyroidism develops more often in adolescence, girls get sick more often than boys and the gender ratio on average is 1: 4 [2]. In our study, at the moment, the ratio is 1: 2, children accounted for 30.3%, adolescents 69.7%.

Anamnesis vitae showed that 11 (33.3%) children studied by us were born before 37 weeks, of which 9.1% were born deeply prematurely. Moreover, 1 (3%) child with hyperthyroidism was born post-term. 27.3% (9) children were born small, a large fetus was registered in 15.2% (6) cases. At the same time, anamnesis familiaris (Table 2) in the majority of children and adolescents with hyperthyroidism was burdened with various diseases, including autoimmune diseases of the thyroid gland (94%).

Table 2

Complicated family history of juvenile hyperthyroidism

Nosology	**Number**	**%**
Graves' disease	6	18,2
Autoimmune thyroiditis	25	75,8
Diffuse goiter	6	18,2
Systemic autoimmune diseases	7	21,2
Vitiligo	1	3,0
Type 2 diabetes mellitus	2	6,1
Obesity	12	36,4
PCY	1	3,3
Anemia	17	51,5

Most often, children and adolescents with hyperthyroidism in childhood had viral diseases, including seasonal respiratory infections, as well as childhood infectious diseases 2 months to 4 years before the onset of hyperthyroidism (Table 3). Of these, in 24.2% (8) children, the disease's onset was noted 3-6 months after the transferred viral infections (ARI, viral hepatitis A, rubella, chickenpox).

Table 3

Past diseases in children and adolescents with hyperthyroidism

Nosology	**Number**	**%**
ORI	30	90,9
Bronchopneumonia	7	21,2
Tonsillitis	12	39,4
Rubella	6	18,2
Epidemic parotitis	2	6,1
Chickenpox	19	57,6
Viral hepatitis A	14	42,4
Viral hepatitis B	1	3,0
OKI	13	39,4

On examination, 26 (78.8%) patients had a diffuse enlargement of the thyroid gland by palpation. The mean duration of hyperthyroidism was 2.2 ± 0.3 years (range, 1 month to 8 years). The diagnosis was clinically evaluated and laboratory-confirmed, including serum concentrations of free thyroxine (wT4)> 1.8 ng/dl, free triiodothyronine (wT3)> 4.3 ng/dl, and thyroid-stimulating hormone (TSH) <0.28 mU / l. A detailed history and anthropometric data were documented for each patient, and a physical examination was performed. The clinical picture of hyperthyroidism in children and adolescents is presented in Table 4.

Table 4:

Clinical characteristics of 33 patients with juvenile hyperthyroidism.

Symptoms	Children, %	Teenagers, %	Symptoms	Children, %	Teenagers, %
Finger tremor	100	100	Increased fatigue	100	100
Tremor of the tongue	80	47,8	Irritability	100	100
Whole body tremor	20	13	Feeling of fear	100	91,3
Sweating	90	95,7	Hyperactivity	50	30,4
Sleep disturbance	100	87	Muscle weakness	20	17,4

Poor academic performance	70	87	Myasthenia gravis	0	4,3
Heat intolerance	60	65,2	Decreased concentration	80	95,7
Increased appetite	70	60,9	Impaired attention	90	100
Weight loss	90	91,3	Decreased memory	80	95,7
Thirst	70	56,5	Emotional lability	90	100
Frequent bowel movements diarrhea	80	65,2	Increased anxiety	80	100
Stomach ache	60	34,8	Aggressiveness	80	21,7
Enhanced intestinal peristalsis	60	78,3	Fussiness	20	30,4

The phenomena of thyrotoxicosis were more severe in children than in adolescents. They more often had tremors of the fingers of outstretched arms, tongue and whole body, sleep disturbances, increased appetite, thirst, and gastro-enteric disturbances. Weight loss was recorded in both groups, but only in the adolescent group, 13% were diagnosed with overweight/obesity grade 1.

Psycho-emotional changes are a common symptom among children and adolescents with hyperthyroidism [1, 7]. Increased fatigue and irritability were noted in all children and adolescents. The feeling of fear was more typical for the younger age group. However, emotional lability, fussiness, increased anxiety and aggressiveness were more often observed in adolescents. Intellectual changes also became more typical for adolescents, who noted decreased memory, concentration and attention deficit, and low academic performance. Nocturnal enuresis (18.2%) and encephalopathy (69.7%) were typical for both groups.

The data obtained by us in children and adolescents with hyperthyroidism living in the region with iodine deficiency differ somewhat from the data of the study by Minamitani K. et al. (2017), conducted among children and adolescents with hyperthyroidism living in Japan, i.e. those who did not have an iodine deficiency state, where the main clinical symptoms are goiter (68.4%), increased sweating (53.4%), fatigue (50.4%), anxiety (47.4%) and tremor of the fingers (45.1%). Exophthalmos (38.3%), weight loss (36.1%) and tachycardia (33.8%) were also common. Weight loss and tremors of the fingers were less common in children [6].

An assessment of children and adolescents' physical development showed that in the group with hyperthyroidism, the average height values were 152.5 ± 2.4 cm, which corresponded to the area of "average" values (42.9 ± 5.2 centiles). At the same time, normal growth indicators were found in 60.6% (20) children, 9.1% (3) children had a height above 95 age centiles, 24.2% (8) children were found to be undersized with a delay in physical development (PBS). The average weight indices in the group with hyperthyroidism were 43.2 ± 1.8 kg (45.7 ± 4.8 centiles). During the height of hyperthyroidism, weight loss was noted on average by 4.7 ± 0.5 kg. The BMI in the group with hyperthyroidism averaged 18.0 ± 0.5 kg / m2, while 42.4% (14) children were underweight. At the same time, in the control group, the average values of height were 158.2 ± 1.9 cm ($p < 0.05$), weight 49.8 ± 1.5 kg ($p < 0.05$), children with PBS and weight deficit were revealed was not, 1 boy (5.3%) was overweight.

According to the thyroid gland ultrasound results in the group of children and adolescents with hyperthyroidism, diffuse goiter was diagnosed in 69.7% (23), nodular goiter in 15.2% (5), multinodular goiter was also diagnosed in 15.2% (5). The picture of autoimmune changes in thyroid tissue was detected in 87.9% (29) of the hyperthyroidism subjects. In the control group, no pathology was revealed in the structure of the thyroid gland; diffuse goiter of the 1st degree was diagnosed in 17.4% (4) children and adolescents. The average volume of the thyroid gland in

patients with hyperthyroidism was significantly greater and amounted to 25.2 ± 3.7 mm3, in the control group - 8.1 ± 0.2 mm3 (p <0.001).

All patients with nodular and multinodular goiter underwent fine-needle aspiration biopsy, 2 children (1 boy, 1 girl) were diagnosed with papillary thyroid carcinoma, 1 girl - follicular thyroid carcinoma. These children underwent total thyroidectomy, followed by radioiodine therapy with I131. All patients who underwent thyroidectomy receive hormone replacement therapy with levothyroxine drugs registered in the Republic of Uzbekistan.

Conclusions:

1. In conditions of iodine deficiency, hyperthyroidism develops more often in adolescence, and girls get sick more often than boys and the gender ratio averages 1:2.
2. In the majority of children and adolescents with hyperthyroidism, in 94% of cases, family history is burdened by various diseases of the thyroid gland.
3. 3-6 months before the onset of hyperthyroidism, 24.2% of children suffered from viral infections (ARI, viral hepatitis A, rubella, chickenpox).
4. Thyrotoxicosis is more severe in children than in adolescents; children more often feel fear and aggressiveness. However, 100% of adolescents had emotional lability and increased anxiety. Intellectual changes were also more typical for adolescents, who noted a decrease in memory (85.7%), concentration (95.7%), school performance (87%) and impaired attention (100%).
5. 9.1% of children had a height above the 95th age centile, 24.2% of children had a delay in physical development. During the height of hyperthyroidism, weight loss was noted on average by 4.7 ± 0.5 kg. Weight deficit was revealed in 42.4% of children. At the same time, 13% of adolescents were diagnosed with overweight/obesity grade 1.
6. Among the pediatric group patients with hyperthyroidism, diffuse goiter was diagnosed in 69.7%, nodular goiter - in 15.2%, multinodular goiter - in 15.2%. The picture of the thyroid gland's autoimmune changed tissue was revealed in 87.9% of the hyperthyroidism subjects.

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RADIOIODOTHERAPY OF PAPILLARY THYROID CANCER. REVIEW

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ABSTRACT

In recent decades, there has been an increase in thyroid cancer incidence in most countries of the world, with papillary cancer being the most common form of thyroid oncopathology. The question of using radioiodine therapy for papillary thyroid cancer is decided depending on the degree of postoperative risk of recurrence of the disease. Radioactive iodine is recommended in intermediate or high risk of recurrence of thyroid cancer after radical thyroidectomy, which reduces the likelihood of disease progression and increases survival. The purpose of radioiodine therapy is to ablate the thyroid tissue remaining after thyroidectomy and metastases that accumulate radioactive iodine. The drug's recommended activity for radioablation is 30 mCi in the intermediate-risk group and from 30 to 150 mCi with a high risk of relapse, while the total doses and frequency of courses vary widely. Acute side effects of radioiodine therapy, the likelihood of which increases with a dose of radioiodine more than 100 mCi, include allergic reactions to iodine, post-radiation mumps and sialoadenitis, gastritis, cystitis, pulmonitis (with metastases to the lungs), bone marrow depression, transient amenorrhea and hypospermia. The listed violations are transient and last from several days to several months.

Keywords: thyroid gland, papillary cancer, radioiodine therapy, post-radiation complications

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РАДИОЙОДТЕРАПИЯ ПАПИЛЛЯРНОГО РАКА ЩИТОВИДНОЙ ЖЕЛЕЗЫ. ОБЗОР

АННОТАЦИЯ

Последние десятилетия наблюдается увеличение заболеваемости раком щитовидной железы в большинстве стран мира, при этом наиболее распространенной формой тиреоидной онкопатологии является папиллярный рак. Вопрос о применении радиойодтерапии при папиллярном раке щитовидной железы решается в зависимости степени послеоперационного риска рецидива заболевания. Радиоактивный йод рекомендуется в случае промежуточного или высокого риска рецидива рака щитовидной железы после радикальной тиреоидэктомии, что уменьшает вероятность прогрессирования заболевания и увеличивает выживаемость. Целью радиойодтерапии является аблация оставшейся после тиреоидэктомии ткани щитовидной железы и метастазов, накапливающих радиоактивный йод. Рекомендуемая активность препарата для проведения радиоаблации составляет 30 мКи в группе промежуточного риска и от 30 до 150 мКи при высоком риске рецидива, при этом суммарные дозы и кратность курсов широко варьируют. К острым побочным эффектам радиойодтерапии, вероятность которых повышается при дозе радиойода более 100 мКи, относятся аллергические реакции на йод, постлучевые паротит и сиалоаденит, гастрит, цистит, пульмонит (при метастазах в легкие), костномозговая депрессия, транзиторные аменорея и гипоспермия. Перечисленные нарушения носят преходящий характер и длятся от нескольких дней до нескольких месяцев.

Ключевые слова: щитовидная железа, папиллярный рак, радиойодтерапия, постлучевые осложнения

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QALQONSIMON BEZI PAPPILYAR SARATONINIDA RADIOYODTERAPIYA XOSIYATLARI

ANNOTATSIYA

So'nggi o'n yilliklarda dunyoning aksariyat mamlakatlarida qalqonsimon bez saratoni bilan kasallanish ko'paymoqda, papiller saratoni tiroid onkopatologiyasining eng keng tarqalgan shakli hisoblanadi. Papiller tiroid saratoni uchun radioiodine terapiyasini qo'llash masalasi operatsiyadan keyingi kasallik qaytalanish xavfi darajasiga qarab hal qilinadi. Radikal tiroidektomiyadan so'ng qalqonsimon bez saratonining takrorlanish xavfi yuqori yoki yuqori bo'lgan hollarda radioaktiv yod tavsiya etiladi, bu kasallikning rivojlanish ehtimolini pasaytiradi va hayotni oshiradi. Radioiodid terapiyasining maqsadi tiroidektomiyadan keyin qolgan qalqonsimon bez to'qimasini va radioaktiv yod to'playdigan metastazlarni yumshatishdir. Preparatning radioablyatsiya uchun tavsiya etilgan faolligi oraliq xavf guruhida 30 mCi ni tashkil qiladi va relaps xavfi yuqori bo'lgan taqdirda 30 dan 150 mCi gacha, kurslarning umumiy dozalari va chastotasi juda farq qiladi. 100 mCi dan oshadigan radioiodine dozasi bilan ortib boradigan radioiodine terapiyasining o'tkir yon ta'siriga yod, nurlanishdan keyingi parotit va sialoadenit, gastrit, sistit, pulmonit (o'pka metastazlari bilan), suyak iligi depressiyasi, vaqtinchalik amenore va gipospermiya kabi allergik reaktsiyalar kiradi. Ro'yxatda keltirilgan qoidabuzarliklar vaqtinchalik va bir necha kundan bir necha oygacha davom etadi.

Kalit so'zlar: qalqonsimon bez, papiller saraton, radioiodiodoterapiya, nurlanishdan keyingi asoratlar.

In recent decades, there has been an increase in the incidence of thyroid gland cancer (TG) in most countries. In Russia, over 10 years, this indicator in the Russian Federation has almost doubled and is 6.1 per 100,000 population, about 8,000 primary cases are registered annually. Simultaneously, malignant neoplasms of the thyroid gland are rarely the cause of death, since 90% of cases are highly differentiated cancer (papillary, follicular) with a good clinical prognosis, and the most common form of adenocarcinoma is papillary cancer (about 80%). A high degree of differentiation of thyroid adenocarcinomas determines the ability of cells to produce thyroglobulin (TG), a specific protein of thyroid tissue, and to concentrate iodine TG molecule ensures the formation of thyroid hormones. This is the basis for the use of determination of the level of TG in the blood to control the effectiveness of treatment - the identification of residual tissue and the use of radioiodine for diagnostic and therapeutic purposes.

Principles of treatment of patients with papillary cancer The extent of surgical intervention depends on the disease's degree of risk. So, hemithyroidectomy is considered an adequate operation for tumors up to 4 cm in diameter without extrathyroid invasion, determined clinically or by ultrasound (ultrasound), and / or metastatic lymph nodes, a hereditary factor, and a history of head and neck irradiation. In cases where the tumor size is more than 4 cm or there is a pronounced extrathyroid invasion, regional or separated metastases, thyroidectomy is performed with the maximum removal of tumor tissue. If metastases to the central zone's lymph nodes (anterior lymph nodes) are detected at the preoperative stage or intraoperatively, central lymphadenectomy (CLAE) is recommended. The widespread form of the disease (tumor more than 4 cm in diameter, limited by the thyroid gland, or any size that extends beyond the organ) and preoperatively verified metastases to the lymph nodes of the neck's lateral tissue are an indication for prophylactic CLAE. The question of the use of radioiodine therapy (RIT) for papillary thyroid cancer is decided depending on the degree of postoperative risk of recurrence of the disease, the stratification of which is based on the recommendations of the American Thyroid Association in 2009, modified in 2015 [2, 7, 8, 12].

The following cases are considered to be at low risk of recurrent papillary cancer *:

- macroscopically, all tumor tissue is removed, locoregional and distant metastases, extrathyroid and vascular invasion is absent, the first whole body scintigraphy (WBS) with 131I does not reveal metastatic foci, the histological variant is non-aggressive;
- metastases to regional lymph nodes are absent (cN0, c - clinical classification) or no more than 5 lymph nodes are affected (pN1, p - pathological classification), the size of metastases does not exceed 0.2 cm in the largest dimension (micrometastases);
- papillary microcarcinoma is intrathyroid (unifocal or multifocal), in these cases, BRAFV600E ** mutations are considered not prognostically significant.

The intermediate risk group includes:

• intrathyroid papillary cancer less than 4 cm in diameter in the presence of the BRAFV600E mutation;
• affection of more than 5 lymph nodes (cN1 or pN1), metastases are up to 3 cm in size in the largest dimension (macrometastases);
• microscopic extrathyroid invasion;
• papillary cancer with vascular invasion;
• multifocal papillary microcarcinoma with microscopic extrathyroid invasion and BRAFV600E mutation;
• the presence of metastatic foci on the neck, accumulating radioactive iodine according to the first SVT with 1 31I. The following options are considered to be at high risk of recurrent papillary cancer:
• residual tumor;
• tumor in combination with the TERT * ± BRAF mutation;
• damage to lymph nodes pN1 with any metastatic node more than 3 cm in the largest dimension;
• macroscopic extrathyroid invasion;
• proven distant metastases;
• high concentration of triglycerides, typical for distant metastases.

Radioactive iodine is used in the intermediate or high risk of recurrence of thyroid cancer after radical thyroidectomy, which reduces the likelihood of disease progression and increases survival. RIT is not indicated at low risk, since it does not affect patients' mortality in this group. RIT aims to ablate the thyroidectomy tissue of the thyroid gland and metastases that accumulate radioactive iodine. The first course of RIT is performed 3–6 weeks after thyroidectomy. In those cases when organ-preserving thyroid surgery was initially performed, assignment of the patient to the group of an intermediate or high risk of recurrence is an indication for performing thyroidectomy in a radical volume. The effectiveness of radioiodine ablation depends on the activity of absorption of 131I by thyrocytes, which in turn is determined by the level of thyroid-stimulating hormone (TSH). It is recommended to perform RIT before prescribing levothyroxine, and a low iodine diet should be followed for 3-4 weeks prior to RIT. For those patients who receive levothyroxine, this drug is discontinued 4 weeks before RIT; an alternative is the administration of recombinant human TSH (rhTSH), which allows the patient to be examined treated with radioiodine without canceling levothyroxine sodium. The target is a TSH level of more than 30 mU / L. However, the optimal concentration of this hormone has not been determined. To assess the radiopharmaceutical accumulation, SVT with 131I is performed at a dose of 2–5 (to determine the residual tissue after thyroidectomy) to 10 mCi (to detect distant metastases). RIT is performed in case of high uptake of the drug by the tumor, using 30 mCi in the intermediate-risk group and from 30 to 150 mCi in the high-risk group. Distant metastases to the lungs are amenable to treatment with radioiodine, however, with an increase in the size of metastatic foci, the effectiveness of RIT decreases. Monitoring the patient in dynamics is aimed at early detection of recurrence or disease progression (metastasis). Thyroid status (TSH, free fractions of thyroxine and triiodothyronine) is analyzed 2-3 months after the primary treatment to assess replacement therapy's adequacy with sodium levothyroxine. After 6-12 months, to confirm remission, an examination, ultrasound, computed tomography (CT) according to indications, SVT, a blood test for TG against the

background of stimulation (withdrawal of levothyroxine 4 weeks before analysis or administration of rhTTG) and antibodies to thyroglobulin (AT-TG). Postoperative patient management involves dynamic risk stratification, according to which four main groups are distinguished depending on the results of treatment.

I. Biochemical remission:
- Ultrasound, SVT, CT do not reveal pathological foci;
- unstimulated TG - less than 0.2 ng / ml;
- stimulated TG - less than 1.0 ng/ml.

In this group of patients, the probability of recurrence is 1–4%.

II. Biochemical relapse:
- Ultrasound, SVT, CT do not reveal pathological foci;
- unstimulated TG - more than 1.0 ng/ml;
- stimulated TG - more than 10 ng/ml; Anti-TG antibodies (AT-TG).

In about 30% of patients in this group, biochemical parameters spontaneously decrease, in 20 - remission after additional RIT is observed, in 20% - structural relapse. In this regard, maintaining a stable concentration of TG or its decrease allows in most cases to be limited to observation. With an increase in TG or an AT-TG bend, an active examination and additional RIT are recommended. Mortality from thyroid cancer does not exceed 1%.

III. Uncertain tumor status: - ultrasound, SVT, CT do not reveal pathological foci or the results are non-specific;
- unstimulated TG - from 0.2 to 1.0 ng / ml;
- stimulated TG - from 1.0 to 10.0 ng / ml;
- AT-TG titer is stable or decreases.

The probability of structural relapse in this group is slightly lower than in the previous one - 15–20% (nonspecific changes may be stable or disappear). In most cases, observation (imaging, TG) and biopsy are performed for suspicious changes. Mortality from thyroid cancer does not exceed 1%.

IV. Structural relapse:
- structural or functional signs of a tumor at any level of TG or AT-TG.

In about 50-60% of patients in this group, the tumor persists despite additional treatment. Mortality from thyroid cancer with regional metastases is 11%, with distant - 50%.

The degree of the disease risk determines the choice of the thyroid hormone therapy regimen: - replacement therapy aimed at correcting hypothyroidism, the target TSH level is 0.5–2.0 mU / l; - suppressive therapy, suppressing TSH-dependent growth of residual tumor cells, TSH less than 0.1 mU / l, free thyroxine - does not exceed the upper limit of the norm; - mild suppression, TSH in the range of 0.1–0.5 mU / l. Suppressive therapy is carried out in the high-risk and structural relapse group (except for patients with atrial fibrillation for whom mild suppression is recommended), as well as in the group of intermediate risk, biochemical relapse and undetermined tumor status (except in cases of tachycardia and menopause, when mild suppression is recommended, as well as people over 60 years old, patients with atrial fibrillation and osteoporosis, for whom replacement therapy is recommended).

Determination of TG has considered the most sensitive method of dynamic observation since this indicator is a specific marker of thyrocytes and cells of highly differentiated thyroid cancer (papillary and follicular). For this study, methods with a sensitivity of at least 0.2 ng/ml are used. It should be borne in mind that AT-TG presence in the blood can cause a false-negative result of a TG study.

At the same time, TG can be detected within several months after the initial treatment; therefore, it is not advisable to determine it earlier than three months after the last treatment stage. Postoperative study of TG and AT-TG during therapy with levothyroxine is recommended every 6-12 months. In the high-risk group, the intervals may be shorter, and in biochemical remission, more - from 12 to 24 months. Redetermination of stimulated triglycerides is carried out in high-risk groups, structural and biochemical relapse, and status uncertainty, while in low risk and

biochemical remission, retesting of triglycerides is not recommended. The TSH level is assessed at least once every 12 months. An ultrasound of the neck is indicated after 6-12 months, depending on the risk group and the TG study results.

In case of detection of suspicious lymph nodes according to ultrasound data with a maximum size of more than 0.8–1.0 cm, a targeted fine-needle biopsy is recommended with the determination of TG in the lavage from the needle. With a smaller lymph node size, dynamic observation is possible. CT scan is justified in case of questionable ultrasound results concerning the prevalence of the disease, suspicion of the proliferation of the neck organs, as well as to detect metastases to the lungs and lymph nodes of the mediastinum in the high-risk group with an increased TG level (usually more than 10 ng/ml) or AT bend -TG, regardless of SVT data. CT or MRI of the abdominal cavity, MRI of the brain and skeleton are recommended for high-risk patients with increased TG concentration (usually more than 10 ng/ml) in the presence of signs of metastatic lesions of these organs, as well as in the absence of metastases to the lungs, lymph nodes of the neck and mediastinum [2].

Most relapses are detected in the first three years of diagnosis, while local relapses and regional metastases do not worsen the prognosis. In rare cases, a relapse may develop after 20 years. According to AR Shaha, the survival rate for highly differentiated thyroid cancer in the low-risk group is 99%, medium-87%, high-57% [5, 6, 11, 14, 15].

Conclusion of radioiodine therapy

For treatment and diagnostics, radioactive 131I with a half-life of 8.05 days is used. The penetration capacity of β-particles, which make up 90% of the radiation, does not exceed 2.2 mm, which avoids damage to the surrounding tissues. The drug's recommended activity for carrying out radioablation is, as noted above, in the intermediate risk group - 30 mCi, in the high-risk group - from 30 to 150 mCi, while the total doses and frequency of courses vary widely. Acute side effects of radioiodine therapy, the likelihood of which increases with a dose of radioiodine more than 100 mCi, include allergic reactions to iodine, post-radiation mumps and sialoadenitis, gastritis, cystitis, pulmonitis (with metastases to the lungs), bone marrow depression, transient amenorrhea and hypospermia. The listed violations are transient and last from several days to several months. Long-term consequences of radioiodine use are cancers of other localizations, the risk of which increases with doses of the drug above 600–700 mCi [4].

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ANALYSIS OF MORTALITY IN 2 TYPES OF DIABETES MELLITUS IN THE REPUBLIC OF UZBEKISTAN

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ABSTRACT

There has been an increase in morbidity and mortality from type 2 diabetes mellitus (DM2) in recent years. The causes of death of patients with diabetes mellitus 2 are cardiovascular diseases, chronic renal failure and oncological diseases. The total number of men who died was higher than that of women, regardless of region. The most significant increase in the number of patients who died was observed in Republic of Karakalpakstan, in Khorezm, in Kashkadarya, Samarkand, in Fergana Surkhandarya regions.

Keywords: 2 types of diabetes mellitus, mortality, causes, risk factors.

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АНАЛИЗ СМЕРТНОСТИ ПРИ САХАРНОМ ДИАБЕТЕ 2 ТИПА ПО РЕСПУБЛИКЕ УЗБЕКИСТАН

АННОТАЦИЯ

В последние годы отмечается рост заболеваемости и смертности от сахарного диабета 2 типа (СД2). Причинами смерти больных СД 2 являются сердечно-сосудистые заболевания, ХПН и онкологические заболевания. Общее число умерших мужчин было больше, чем женщин, независимо от регионов. Наибольший рост умерших больных наблюдался в РКК, в

Хорезмской, в Кашкадарьинской, Самаркандской, в Ферганской и в Сурхандарьинской областях.

Ключевые слова: 2 вида сахарного диабета, смертность, причины, факторы риска.

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ЎЗБЕКИСТОН РЕСПУБЛИКАСИДА ҚАНДЛИ ДИАБЕТНИНГ 2 ТУРИДАГИ ЎЛИМНИ ТАХЛИЛ ҚИЛИШ

АННОТАЦИЯ

Сўнгги йилларда қандли диабет 2 тури касаллиги ва ўлим даражаси ошди. Қандли диабет билан касалланган беморларнинг ўлимига юрак қон томир касалликлари, сурункали буйрак етишмовчилиги ва онкологик касалликлар сабаб бўлади. Ўлган эркакларнинг умумий сони, худудлардан қатъй назар, аёлларга қараганда кўпроқ эди. Вафот этган беморлар сонининг энг катта ўсиши Қорақалпоғистон Республикасида, Хоразм, Қашқадарё, Самарқанд, Фарғона ва Сурхандарё вилоятларида кузатилди.

Калит сўзлар: қандли диабетнинг 2 тури, ўлим, сабаблари, хавф омиллари.

Over the past 20 years, the patients' number with diabetes has increased almost 3 times, from 130 million in 1990 to 425 million patients with diabetes, 8.8% of the world's population (1,2,8,10). According to the UN and WHO, 1 patient dies from diabetes every 7 seconds globally, 12 people fall ill every 10 seconds; about 4.6 million patients die annually. More than 50% of diabetes mellitus develops the disease in the active working age - 40-59. Considering the spread of diabetes, experts from the World Diabetes Federation predict that the number of patients with diabetes by 2030 will increase 1.5 times and reach 552 million people, mainly due to patients with type 2 diabetes (1,7,8,9,10). Of the 56.9 million deaths worldwide in 2016, more than half (54%) were due to the following 10 causes. Coronary heart disease and stroke claim the most lives - in 2016, a total of 15.2 million. Over the past 15 years, these diseases have remained the leading causes of death worldwide (1,3,8). In 2016, 3.0 million people died from chronic obstructive pulmonary disease, and 1.7 million people died from lung cancer (along with cancer of the trachea and bronchi). Diabetes claimed 1.6 million lives in 2016 versus less than 1 million in 2000 (1.3.8).

An increase in mortality accompanies the increase in the incidence of type 2 diabetes. As you know, the main cause of death in the general population is cardiovascular (48%) and oncological (21%) diseases; In the overall structure of mortality among non-communicable diseases, diabetes is 3.5%, ranking 6th (2, 3). Some authors believe that diabetes is already taking 5th place, arguing that 8–9% of the population die from diabetes (4, 6.7). By 2030, diabetes will be the 7th leading cause of death worldwide (1,7,11). And this assumption is entirely justified, since it is known that in half of the patients with cardiovascular diseases (CVD), in particular with coronary heart disease, there is a violation of carbohydrate metabolism (7), and in case of a lethal outcome they are referred to the group of patients who died from CVD. However, the cause of the change in coronary vessels could be due to the presence of diabetes. In some countries and several regions of the Russian Federation, in the structure of mortality in 2004, diabetes ranked third after cardiovascular and oncological diseases (8, 9). Without data on diabetes mortality, it is impossible to assess the epidemiological situation for diabetes and socioeconomic significance. Comparative analysis of death rates from diabetes in developed countries shows that the highest rates are observed in the USA, Italy, Israel, the lowest mortality rates are noted in France, Greece, and Japan.

Practically in all studies concerning the study of mortality in patients with type 1 and type 2 diabetes, it was noted that patients live 5-10 years less and die 1.5-2.5 times more often than their peers without diabetes (9, 10.11). Mortality among men is higher than among women; after 80 years, mortality rates level out (1.9). All this testifies to the relevance of studying the mortality causes, risk factors and prevention possibilities.

Research methods and materials. Mortality data were analyzed based on the annual reports of 14 endocrinological dispensaries of the Republic of Uzbekistan for 2013 and 2019, based on the statistical reporting form CER 13.

Results and its discussion: The total number of patients with diabetes was: in 2013 -143 620, in 2019-257 457 patients, of which with 2 types of diabetes 127 343 and 239 565, respectively.

In 2013, only 4 641 deaths of patients with diabetes were registered, 21.7 / 100 thousand of the population of them:

• DM 2 types 3930 patients, which amounted to 19.4 per 100 thousand population (84.7%);

In 2019, only 7210 deaths of patients with diabetes were registered, 23.3 / 100 thousand of the population of them:

• Diabetes mellitus 2 types of 6838 patients, which amounted to 20.6 per 100 thousand population (83.2%) (94.8%);

During the studied period, the indicator ranged from 21.7 to 23.3 per 100 thousand of the population.

In a comparative analysis of mortality rates, depending on the regions, it was found that during the study period the number of patients who died in general increased by 1.5 times, and patients with type 2 diabetes by 1.7 times. The largest increase in the number of patients who died was observed in the RKK (4.3 times in patients with type 1 diabetes and 4.1 times in patients with type 2 diabetes), in Khorezm (4.1 times in patients with type 1 diabetes and 4.7 times in patients with Type 2 diabetes), in Kashkadarya (2.01 and 2.7 times, respectively), Samarkand (1.7 and 2.6 times, respectively), in Fergana (2.1 and 2.2 times, respectively) and Surkhandarya (in 2.1 and 2.2 times, respectively) (Table 1). According to the International Diabetes Federation (7) and some authors, mortality is higher in men; and, apparently for biological reasons, the older the age, the higher the mortality rate. Simultaneously, there are isolated studies that indicate the predominance of women among the deceased patients with type 2 diabetes (1,7,10), or the gender difference is not revealed. In this regard, mortality rates were studied depending on patients' sex with diabetes mellitus (Table 2).

Over the entire observation period in the population of patients with diabetes, the total number of deaths in men was higher than in women, regardless of regions. In 2013, the mortality rate among women with diabetes was 39.7%, among men - 60.3%; in 2019 - 43.5% and 56.5%, respectively. When analyzing mortality rates for the study period, the number of sick women who died increased 1.7 times, while the number of men who died increased 1,4 times.

In most countries of Europe, America, Australia, and CIS countries, CVD is the main cause of death of patients with type 2 diabetes, which may be due to lifestyle, dietary habits, and genetic factors. In the structure of the causes of death of patients with type 2 diabetes, one can also distinguish oncological diseases, infections, kidney diseases.

According to the State Statistical Office of the Republic of Uzbekistan in 2018, more than 60% of mortality falls on diseases of the circulatory system (5) (table 3)

Table 3

Distribution of deaths by major causes of death (with the total number of deaths,%)

Cause of death	%
Neoplasms	9,7%
diseases of the circulatory system	**60,3%**
respiratory diseases	4,0%

diseases of the digestive system	5,6%
Infectious and parasitic diseases	1,5%
Accidents, poisoning and injury	6,5%
Other diseases	12,4%

Due to the mortality structure among patients with diabetes mellitus in the Republic was also considered.

As an analysis result for 2013-2019, the following structure of mortality was revealed among people in whom diabetes and its complications were the direct cause of death and are presented in Table 4.

Table 4

The structure of mortality in patients with diabetes mellitus

№	Causes of death	2013 (in%)	2019 (in%)	Growth (in%)
1.	**Cardiovascular diseases**	**3502**	**5602**	**37,5**
	Of them:			
	Chronic heart failure	1959	3302	40,7
	Myocardial infarction	711	952	25,3
	insult	832	1348	38,3
2.	**Gangrene of the lower extremities**	**163**	**131**	**-24,4**
3.	**Chronic renal failure**	**679**	**1041**	**34,8**
4.	**Diabetic coma**	**21**	**23**	**8,7**
5.	**oncological diseases**	**192**	**294**	**34,7**
6.	**Others**	**84**	**119**	**29,4**

The analysis results showed that in Uzbekistan, the main cause of death is CVD (acute myocardial infarction, heart failure, and stroke), which is 75.4% in 2013 and 77.7% in 2019 the total mortality in general. In second place by causes of death is a chronic renal failure (14.6% and 14.4%, respectively) and in third place is cancer (4.1% and 4.0%, respectively) and other diseases (1.8% and 1.7 % respectively). Other diseases include tuberculosis, accidents, cirrhosis of the liver, and other diseases.

During the study period, the number of deceased patients with type 2 diabetes from CVD, chronic renal failure and oncological diseases increased by 1.5 times. In contrast, the number of patients who died from gangrene of the lower extremities decreased (0.8 times).

Thus, the main cause of death and, accordingly, CVD's main risk factor in patients with diabetes mellitus, which ultimately makes a significant contribution to the overall structure of CVD and complications in the adult population.

Conclusions:

1. During the study period, the number of deceased patients increased by 1.5 times, and patients with type 2 diabetes by 1.7 times.
2. Over the entire observation period in the population of patients with diabetes, the total number of deaths in men was higher than in women, regardless of the regions
3. The analysis results showed that in Uzbekistan, the main cause of death is CVD (acute myocardial infarction, heart failure and stroke), which is 75.4% in 2013 and 77.7% in 2019 total mortality in general.
4. During the study period, the number of deceased patients with type 2 diabetes from CVD, chronic renal failure and oncological diseases increased by 1.5 times. While the number of patients who died from gangrene of the lower extremities decreased (0.8 times).

Table 1.

Comparative analysis of diabetes mortality rates for 2013 and 2019.

Name of regions	abs				Growth	
	2013		2019		abs in%	
	Total	SD type 2	Total	SD type 2	Total	SD type 2
The Republic of Uzbekistan	**4641**	**3920**	**7210**	**6838**	**35,6**	**42,7**
Republic of Karakalpakstan	50	50	214	205	76,6	75,6
Andijan	620	500	529	509	-17,2	1,8
Bukhara	315	244	475	436	33,7	44,0
Jizzakh	201	197	316	312	36,4	36,9
Kashkadarya	188	130	378	356	50,3	63,5
Navoi	93	84	169	161	45,0	47,8
Namangan	344	273	597	530	42,4	48,5
Samarkand	501	326	876	850	42,8	61,6
Surkhandarya	154	142	319	303	51,7	53,1
Syrdarya	357	305	224	211	-59,4	-44,5
Tashkent	395	345	674	632	41,4	45,4
Fergana	524	472	1089	1036	51,9	54,4
Khorezm	94	76	390	359	75,9	78,8
c.Tashkent	805	776	960	938	16,1	17,3

Table 2

DM mortality rates depending on the sex of patients and the region for 2013-2019.

Name of regions	2013				2019				Growth in% abs			
	women		men		women		men		women		men	
	Total	SD type 2	Total	SD type 2	Total	SD type 2	Total	SD type 2	Total	SD type 2	Total	SD type 2
The Republic of Uzbekistan	**1844**	**1526**	**2797**	**2394**	**3134**	**2892**	**4076**	**3946**	**31,4**	**39,3**	**41,2**	**47,2**
Republic of Karakalpakstan	18	18	32	32	98	94	116	112	72,4	71,4	81,6	80,9
Andijan	301	225	319	275	317	289	324	312	1,5	11,9	5,0	22,1
Bukhara	111	86	204	158	210	185	265	257	23,0	38,5	47,1	53,5
Jizzakh	85	82	116	115	151	139	195	184	40,5	37,5	43,7	41,0
Kashkadarya	80	53	108	77	178	157	241	233	55,2	67,0	66,8	77,3
Navoi	33	30	60	54	93	79	137	122	56,2	55,7	64,5	62,0
Namangan	140	105	204	168	255	237	324	314	37,0	46,5	45,1	55,7
Samarkand	177	114	324	212	303	281	478	469	32,2	54,8	63,0	75,7
Surkhandarya	54	49	100	93	103	86	166	159	39,8	41,5	47,6	43,0
Syrdarya	161	138	196	167	144	126	232	222	-15,5	-24,8	11,8	9,5
Tashkent	139	120	256	225	221	197	346	333	26,0	32,4	37,1	39,1
Fergana	184	165	340	307	311	277	561	556	39,4	44,8	40,8	40,4
Khorezm	33	24	61	52	103	84	187	174	67,4	70,1	68,0	71,4
c.Tashkent	328	317	477	459	409	397	504	499	5,4	8,0	19,8	20,2

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EPIGENETIC ASPECTS OF THE DEVELOPMENT OF INACTIVE PITUITARY ADENOMAS

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ABSTRACT

This article provides an overview of 17 literary sources of recent years, devoted to the pathogenesis, epigenetic factors in the development of inactive pituitary adenomas. The prevalence of pituitary adenomas is about 15% among all intracranial neoplasias and on average reaches 15–20 cases per million population per year, while the frequency of clinically manifested pituitary tumors varies from 2–2.5 to 9 cases per 10,000 population. According to autopsy studies, the incidence of Inactive pituitary adenomas (IPA) is approximately 25%. IPAs are mainly found in persons aged 20-50 years, with a predominance in females.

Keywords: inactive pituitary adenomas, epigenetic aspects, genes, methylation, microRNA.

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ЭПИГЕНЕТИЧЕСКИЕ АСПЕКТЫ РАЗВИТИЯ НЕАКТИВНЫХ АДЕНОМ ГИПОФИЗА

АННОТАЦИЯ

В данной статье приведен обзор 17 литературных источников последних лет, посвящённых патогенезу, эпигенетическим факторам развития неактивных аденом гипофиза. Распространенность аденом гипофиза составляет около 15% среди всех интракраниальных неоплазий и в среднем достигает 15–20 случаев на 1 млн населения в год, при этом частота клинически проявляющихся опухолей гипофиза варьирует от 2–2,5 до 9 случаев на 10 000 населения. По данным аутопсийных исследований встречаемость «немых» аденом гипофиза (НАГ) составляет приблизительно 25%. НАГ в основном обнаруживаются у лиц в возрасте 20—50 лет, с преобладанием у лиц женского пола.

Ключевые слова: неактивные аденомы гипофиза, эпигенетические аспекты, гены, метилирование, микроРНК.

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ГИПОФИЗ НОФАОЛ АДЕНОМАЛАРИ РИВОЖЛАНИШИНИНГ ЭПИГЕНЕТИК ТАМОЙИЛЛАРИ

АННОТАЦИЯ

Ушбу мақолада гипофиз нофаол аденомалари ривожланишининг патогенези, эпигенетик омилларига бағишланган охирги йилларда чоп этилган 17 илмий адабиётларнинг таҳлили келтирилган. Гипофизнинг тарқалиши барча интракраниал неоплазиялар орасида 15% ни ташкил этади ва йилига 1 миллион аҳолига ўртача 15-20 ҳолатга етади, бунда гипофизнинг клиник намоён бўладиган ўсмалари частотаси 10 000 аҳолига 2-2,5 дан 9 ҳолатгача ўзгаради. Отопси тадқиқотларига кўра, фаол бўлмаган гипофиз аденомаси (ФБГА) касаллиги тахминан 25% ни ташкил қилади. ФБГА асосан 20-50 ёшдаги одамларда учрайди, аёллари устунлик қилади.

Калит сўзлар: фаол бўлмаган гипофизнинг аденомлари, эпигенетик жиҳатлар, гендер, метилизация, микроРНК

The prevalence of pituitary adenomas is about 15% among all intracranial neoplasias and on average reaches 15–20 cases per million population per year, while the frequency of clinically manifested pituitary tumors varies from 2–2.5 to 9 cases per 10,000 population. According to autopsy studies, the incidence of “silent” pituitary adenomas (NAP) is approximately 25%. IPAs are mainly found in persons aged 20-50 years, predominant in females [4].

Diseases of the pituitary gland and HPAS in the Republic of Uzbekistan among all endocrinopathies takes the third place (9.4%) after diseases of the thyroid gland and diabetes mellitus;

The 10-year analysis of the statistical reports of the EOS on the pathologies of the pituitary gland showed that the number of disabled people suffering from the pathology of the hypothalamic-pituitary system increased (respectively from 3.6% to 5.7%, i.e. by 1.7 times), which is only established after they reach large sizes and develop severe complications [4].

IPA proceeds without visible clinical manifestations, impaired secretion of pituitary hormones, and the manifestation of the disease, as a rule, occur in the late stages, when the “mass” effects of tumor tissue come to the fore. The tendency to suprasellar growth of IPA determines a high frequency of hormonal (more than 30%), visual (50-60%), neurological (more than 80%); reproductive disorders (over 60%) [3]. Due to the compression of the surrounding healthy tissue of the tumour’s pituitary gland, a clinical picture of partial or total hypopituitarism is formed (hormone replacement therapy is required in 30-60% of cases). IPA recurrences’ high frequency mechanisms after surgical treatment have not been disclosed, which account for more than 40% of cases [3].

The pathogenesis of pituitary tumors is one of the urgent problems of neuroendocrinology. To date, the most widespread is the multistage model of pituitary tumorigenesis, according to which the initiation of the development of a pituitary tumor occurs as a result of chromosomal mutations. The foregoing testifies to the need to research both the pathogenesis of IPA and a comprehensive study of their morphological and functional characteristics, clinical manifestations of the disease, the functional state of the pituitary gland, the development of a clinical and morphological functional classification of IPA, new approaches in diagnosis, treatment and rehabilitation [15].

Although mutations of somatic genes are rarely found in sporadic IPA, recent studies confirm epigenetic modification as a potential cause of oncogenesis and tumor progression, leading to important diagnostic and therapeutic applications. In biology, in particular, in genetics, it is the study of patterns of epigenetic inheritance - changes in expression genes or cell phenotype caused by mechanisms that do not affect the DNA sequence [5].

Epigenetic changes are preserved in a number of mitotic divisions of somatic cells, and can also be transmitted to future generations. Examples of epigenetic changes are DNA methylation and histone deacetylation [12].

The epigenome is a set of molecular markers that regulate genes' activity, but do not change the primary structure of DNA. For the first time, the term "epigenetics" was used in 1942 by the English biologist Konrad Waddington.

5 main epigenetic mechanisms can lead to a change in gene expression: 1) DNA methylation, 2) histone modification, 3) gene imprinting, 4) epigenome authors, 5) transcriptional regulators.

One example of epigenetic changes in eukaryotes is the process of cell differentiation. During morphogenesis, pluripotent stem cells form various pluripotent embryonic cell lines, giving rise to fully differentiated cells. In other words, one fertilized egg - a zygote - gives rise to multiple types of cells: neurons, muscle cells, epithelium, vascular endothelium, etc. In this case, in a series of sequential cell divisions, some genes are activated and, at the same time, others are inhibited by epigenetic mechanisms.

A second example can be demonstrated with vole mice. In autumn, before the cold snap, they are born with a longer and thicker coat than in spring, although the intrauterine development of "spring" and "autumn" mice occurs against a background of almost identical conditions (temperature, day length, humidity, etc.). Studies have shown that a signal that triggers epigenetic changes leading to increased coat length is a change in the gradient of melatonin concentration in the blood (it decreases in spring and increases in autumn). Thus, epigenetic adaptive changes (an increase in coat length) are induced even before the onset of cold weather, which is beneficial for the body.

Current data confirm epigenetic changes in at least 24 genes of pituitary adenomas, which have been divided into 5 groups depending on the function and epigenetic changes:

1) 16 tumor suppressor genes acting through DNA methylation;
2) 2 oncogenes are overexpressed by acetylation and hypomethylation of histones;
3) 3 imprinted genes with selective allelic action;
4) 1 author of an epigenome inducing abnormal activity on a genome scale;
5) 2 regulators of transcription, indirectly modifying the genome.

Of these, 5 genes (CDKN2A, GADD45y, FGFR2, caspase-8, and PTAG) demonstrated a particular susceptibility to epigenetic modification with abnormal DNA methylation > 50% of AG samples. Several genes have shown correlations between epigenetic modification and clinically relevant parameters, including invasiveness (CDKN2A; DAPK; Rb1), gender (MAGE-A3), tumor size (GNAS1), and histopathological subtype (CDKN2A; MEG3; p27; RASSF1A; Rb1) [10 ,13].

In recent studies, reports have appeared on the fundamental role of microRNA in developing pituitary tumors. The earlier opinion that microRNAs are involved in the development of pituitary adenomas is indirectly confirmed by the observation that deletions of those regions of chromosome 13 in which miR-15a and miR-16 are localized are often found in pituitary adenoma cells [9,16].

By measuring the activity of 217 genes encoding microRNAs, certain specific combinations of gene activity characteristic of a particular form of cancer were identified. Cancer types can be classified based on microRNAs. This allows doctors to determine from which tissue the tumor has developed and choose the appropriate course of treatment based on the tissue type information. It has been established that microRNAs determine, for example, whether chronic lymphocytic leukemia develops slowly or acquires an aggressive form [14].

Another application of microRNAs in the diagnosis and treatment of cancer may be in their use for prognosis. Thus, in the form of lung cancer NSCLC [en], a low concentration of miR-324a

may serve as an indicator of poor survival, and a high concentration of miR-185 or a low concentration of miR-133b indicates the presence of metastases and, therefore, poor survival in the colon and rectal cancer [11.12].

Extracellular miRNAs remain more stable in blood plasma and are overexpressed in cancer and measured in the laboratory. In classic Hodgkin's lymphoma, plasma miR-21, miR-494, and miR-1973 are reliable markers indicating the disease's presence [14,17].

A study on miRNAs in tissues of inactive adenomas showed that a specific subset of miRNAs might be associated with a decreased level of transforming growth factor beta (TGFβ) and altered expression of some molecular components of the TGF signaling pathway (Smad3, Smad6, Smad9, MEG and DLK1) [17].

In the subgroup of hormone-inactive adenomas, microRNA expression profiling successfully differentiates microadenomas and macroadenomas [8]. MicroRNAs are actively released by tumor cells and can serve as non-invasive markers for tumor diagnosis. Circulating miRNAs can be associated with miRNAs' tissue expression, which confirms the hypothesis that the spectrum of circulating miRNAs associated with neoplasia may reflect the state of specific tumors [9]. The ability of miRNAs to regulate many genes makes them suitable for innovative therapeutic strategies [10]

A special role in the development of tumors is played by dysregulation of microRNA, which violates methylation.

Methylation is adding one carbon atom and three hydrogen atoms (the so-called methyl group - CH3) to another molecule. Removal of a methyl group is called demethylation. DNA methylation is a modification of a DNA molecule without changing its nucleotide sequence, i.e. it is an epigenetic mechanism associated with gene repression. Violations in DNA methylation lead to various pathological processes in the body, including can play a role in oncogenesis. Studies have found high levels of methylation in invasive and large pituitary tumors (17). Overexpression of DNA methyltransferase has been found in pituitary tumors, especially in macroadenomas. Differences in methylation at CpG sites in promoter regions can distinguish several types of tumors from normal pituitary tissue. Histone modifications have been associated with increased p53 expression and longer progression-free survival of pituitary tumors; sirtuins are expressed at higher levels of GH expression compared to non-functional adenomas and correlate inversely with the size of somatotrophs. Upregulation in citrullinating enzymes may be an early pathogenic marker of prolactin.

Numerous genes associated with cell growth and signaling show altered methylation status for pituitary tumors, including cell cycle regulators (17)

Given the absence of recurrent oncogenic mutations and copy number changes in many pituitary tumors, epigenetic mechanisms represent an interesting biological pathway for further study. Further elucidation of the mechanisms underlying gene dysregulation is necessary before the development of viable therapeutic strategies. Some compounds that inhibit epigenetic modifications, FDA cleared, although it remains to be determined whether compounds that globally affect DNA methylation and histone modifications can provide specificity and efficacy in targeting genetic pathways unregulated in pituitary tumors. More targeted strategies for modulating epigenetic modifications, although currently still at an early stage of development, may be promising for treating pituitary tumors (10).

So, a complex classification of epigenetic, genetic and histopathological signs of pituitary adenomas can increase the prognostic value in relation to their use in clinical practice.

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GROWTH DIFFERENTIATION FACTOR 15 (GDF15): AS AN EARLY PROGNOSTIC AND DIAGNOSTIC BIOMARKER IN METABOLIC DISEASES

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ABSTRACT

Metabolic diseases are a group of diseases associated with metabolic disorders reaching epidemic proportions in the population. The main cause of metabolic disorders is a poor lifestyle, unbalanced diet, low physical activity, stress. All this increases the risk of cardiovascular disease, type 2 diabetes and some other diseases. Growth factor differentiation 15 (GDF15) is an early prognostic and diagnostic biomarker for metabolic diseases. GDF-15 was first named macrophage inhibitory cytokine-1 or MIC-1. GDF-15 belongs to the transforming growth factor-beta (TGFβ) superfamily, which is expressed in low concentrations in most organs and is activated due to organ damage: liver, kidney, heart and lungs. The main functions of GDF-15 in the regulation of inflammatory pathways and involvement in the regulation of apoptosis, cell repair and growth are biological processes observed in cardiovascular and neoplastic diseases. These functions of GDF-15 have not been fully elucidated, but GDF-15 is a strong prognostic protein for patients with metabolic diseases such as heart disease, diabetes, obesity and cancer.

Keywords: cardiovascular disease, cardiovascular risk, diabetes, adipokines, biomarkers, growth differentiation factor-15, inflammation, cytokine.

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ФАКТОР ДИФФЕРЕНЦИАЦИИ РОСТА 15 (GDF15): КАК РАННИЙ ПРОГНОСТИЧЕСКИЙ И ДИАГНОСТИЧЕСКИЙ БИОМАРКЕР ПРИ МЕТАБОЛИЧЕСКИХ ЗАБОЛЕВАНИЯХ

АННОТАЦИЯ

Метаболические заболевания –это группа заболеваний, связанных с нарушениями обмена веществ, который достигает масштабов эпидемии среди населения. Основная причина нарушения обмена веществ являются неправильный образ жизни,

несбалансированное питания, низкая физическая активность, стрессы. Все это повышает риск развития сердечно - сосудистой патологии, сахарного диабета 2-го типа и ряда других заболеваний. Фактор роста дифференцировки 15 (GDF15) является ранний прогностический и диагностический биомаркер при метаболических заболеваниях. Впервые GDF-15 был назван как цитокин-1, ингибирующий макрофаги, или MIC-1. 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. Эти функции GDF-15 не полностью выяснена, но было показано, что GDF-15 является сильным прогностическим белком для пациентов с метаболическими заболеваниями, такими как болезни сердца, сахарный диабет, ожирение и рак.

Ключевые слова: сердечно-сосудистые заболевания, сердечно-сосудистый риск, сахарный диабет, адипокины, биомаркеры, фактор дифференцировки роста-15, воспаление, цитокин.

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ЎСИШНИНГ ФАРҚЛАШ ОМИЛИ 15 (GDF-15): МЕТАБОЛИК КАСАЛЛИКЛАРДА ЭРТА ТАШХИСЛАШНИНГ ПРОГНОСТИК ВА ДИАГНОСТИК БИОМАРКЕРИ

АННОТАЦИЯ

Метаболик касалликлар бу – моддалар алмашинуви билан боғлиқ бўлган, ахоли ўртасида эпидемик қамровга эга бўлиб бораётган кассалликлар гурухидир. Метаболик касалликларнинг асосий сабаби нотўғри турмуш тарзи, жисмоний фаолликнинг камлиги, стрессдир. Буларнинг барчаси юрак қон томир патологиясини, иккинчи турдаги қандли диабет ва бошқа бир қатор касалликлар ривожланиш хавфини оширади. Ўсишни фарқлаш омили-15 (GDF15) метаболик касалликларда эрта ташхислашнинг прогностик ва диагностик биомаркери хисобланади. Илк бор GDF-15 цитокин-1 ингибирловчи макрофаг йоки МИЦ-1 деб номланган. GDF-15 ўзгарувчан ўсиш омили бетта (TGFβ) супероиласига мансуб бўлиб, аксарият аьзоларда паст концентрацияда намоён бўлади ва айрим аьзолар жумладан ўпка, юрак, жигар ва буйраклар шикастланиши туфайли фаоллашади. GDF-15 нинг асосий функциялари бу яллиғланиш йўлларини бошқаришда ва апоптоз, хужайраларни тиклаш ва хужайралар ўсишни бошқаришда иштирок этади, бу юрак қон томир ва неопластик касаликларда кузатидадиган биологик жараёнлардир. Юқорида келтирилган функцияларининг барчаси тўлиқлигича ўрганилмаган, аммо GDF-15 нинг юрак хасталиклари, семириш, диабет ва саратон каби меаболик касалликларга чалинган беморлар учун кучли прогностик оқсил эканлиги кўрсатилди.

Калит сўзлар: Юрак қон томир касалликлари, юрак қон томир хавфи, қандли диабет, адипокинлар, биомаркерлар, яллиғланиш, ўсишни фарқлаш омили 15, цитокин.

Introduction.

GDF-15 is a growth factor whose expression increases with age. Biological age is associated with several markers, such as oxidative stress, protein glycation, inflammation, and hormonal changes. Many of these stresses induce GDF-15 expression. GDF-15 levels are also affected by environmental factors regardless of genetic background. Studies have shown that GDF-15 levels are

a new and powerful predictor of all-cause mortality in the general population. Higher GDF-15 levels are associated with increased cardiovascular and non-cardiovascular mortality; it plays a key role in developing and progressing cardiovascular diseases, such as heart failure, coronary artery disease, diabetes, cancer and cognitive impairment (Figure 1) [1]. Increased expression of GDF-15 is a hallmark of many cancers, including breast, colorectal, pancreatic, and prostate. Many epithelial tumor cell lines secrete high levels of GDF-15. High GDF-15 expression in the tumor is also associated with elevated serum GDF-15 levels, suggesting the use of serum GDF-15 measurement for diagnosis and treatment of cancer (Crownteen U.T.,2005).

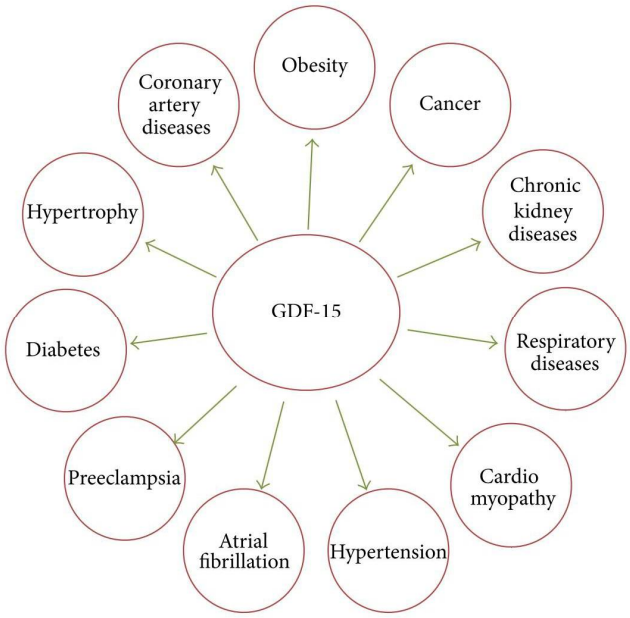

Figure 1 - GDF-15 role in various diseases. GDF-15 plays an important role in regulating metabolism, cardiovascular system, obesity, cancer and chronic diseases.

GDF-15 expression and release

GDF-15 is highly expressed in the placenta and prostate but is also expressed in the heart, pancreas, liver, kidney and colon [2]. It is a stress-induced cytokine that is also secreted by macrophages, vascular smooth muscle cells, cardiomyocytes, adipocytes and endothelial cells after tissue damage, anoxia and proinflammatory cytokine responses. GDF-15 plays a role as an endocrine factor if it is present in the bloodstream [3]. GDF-15 is highly expressed in response to various cytokines and growth factors such as interleukin-1 (IL-1), TNF, angiotensin II and TGF-β. GDF-15 expression is strongly induced in cardiomyocytes after ischemia/reperfusion [4].

GDF-15 is generated in the form of a propeptide. The N-end is cleaved off and released as a disulfide-linked dimeric active form of the protein [9]. The direct molecular biological target of GDF-15 is the p53 protein, which is induced by oxidative stress and has an anti-apoptotic effect on target cells. This effect is closely related to transcription factor 3 activating survival protein (ATF3), which is negatively regulated by p53 protein expression. Thus, GDF15 inhibits the N-terminal c-Jun kinase, the Bcl-2-related death promoter, and the epidermal growth factor receptor, and also activates various intracellular signaling pathways such as Smad, endothelial nitric oxide synthase (eNO), phosphoinositide-3-kinase. and serine/threonine kinase. The result end of this relationship is the suppression of both tumor necrosis factor alpha and IL-6 synthesis. Adipocytokines in obese individuals may contribute to p53 activation in adipose tissue and lead to insulin resistance and DM2. It is still unclear whether the proapoptotic ability of GDF-15 depends on tissue type. In general, GDF15 can act as a protective, anti-apoptotic, and sometimes pro-apoptotic factor, while promoting tissue growth, maturation, and differentiation of various cells (Figure 1).

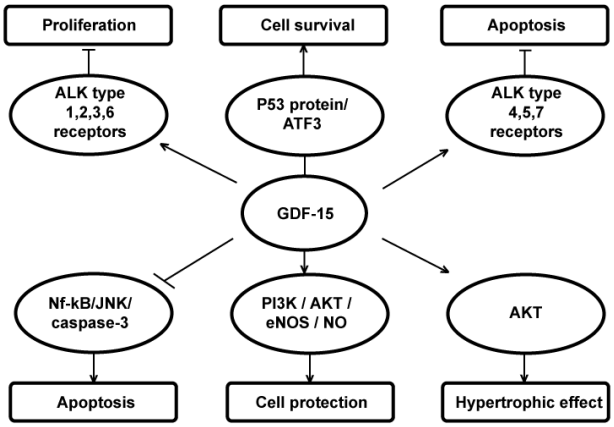

Figure 2: The figure shows that GDF-15 can regulate the inflammatory response, cell growth, and differentiation in several ways related to the progression and prognosis of cardiovascular disease.
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Obesity is a risk factor for diabetes and cardiovascular disease. Excess body weight is associated with increased health problems and causes increased cardiovascular morbidity and

mortality. GDF-15, released from macrophages, liver and white adipose tissue, can act as a metabolic regulator. GDF-15 acts as an adipokine, similar to adiponectin and leptin, so it is also called a cardiokin (Crownteen U.T.,2005). Adipokines generally regulate lipid and glucose metabolism, increase insulin sensitivity, regulate food intake and body weight, and protect against chronic inflammation in adipose tissue [5].

The diagnostic and prognostic value of increased serum growth differentiation factor-15 is discussed as a putative stress-sensitive anti-inflammatory cytokine elevated in patients with established cardiovascular disease, stroke, DM2, chronic kidney disease, infections, liver cirrhosis, malignancies, respiratory and renal failure. GDF-15 may be an independent marker of cardiovascular dysfunction and cardiovascular disease in the elderly.

In the DM2 population, serum GDF-15 levels have been positively associated with body mass index, body fat, fasting glucose levels, glycated hemoglobin, insulin resistance index, waist-to-height ratio, age, blood pressure, triglycerides, creatinine, glucose, CRP, diabetic nephropathy, and anemia [6,7].

GDF-15 is a prognostic biomarker of cardiovascular mortality in the general population and patients with asymptomatic atherosclerosis [8]. Elevated GDF-15 predicts survival in patients with idiopathic pulmonary arterial hypertension, heart failure, myocardial infarction, stable CHD, and patients with aortic stenosis [9].

GDF15 can also be associated with the development of cardiac pathology in DM2 patients. In individuals before DM2, GDF-15 concentration was not independently associated with the onset of DM2 during the follow-up period [10]. In contrast, elevated GDF-15 levels have demonstrated a prognostic value for cardiovascular complications, all of which cause cardiovascular mortality and mortality in diabetics with established cardiovascular disease, nephropathy, hypertension, and rheumatic disease (Crownteen U.T.,2005).

Conclusion

GDF-15 may be a prognostic and diagnostic marker of cardiovascular and diabetic disease. The role of elevated GDF-15 as a prognostic marker in diabetics has been widely discussed. GDF-15 is a predictor of subsequent insulin resistance and impaired glucose control in obese individuals. Predicting elevated GDF-15 levels in individuals with DM2 without cardiovascular disease or other comorbidities that may increase cardiovascular risk is not well established. Prospects for the use of GDF-15 in routine clinical practice are likely to affect their ability to predict CVD outcomes and mortality.

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ENDOSCOPIC ENDONASAL TRANSSPHENOIDAL APPROACH FOR PITUITARY ADENOMAS: A PROSPECTIVE STUDY

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ABSTRACT

The surgical approach for hypophysectomy has undergone a sweeping revolution in the past three decades. With the advent of endoscopes, better instrumentation, better illumination and viewing cameras, endoscopic endonasal trans-sphenoidal approach to sella has now largely become the norm. This study aims to present our experience, analysing the surgical outcomes of this approach in patients with pituitary adenoma, pertaining to the entirety of tumor removal, alleviation of symptoms and rate of complications and this prospective study conducted at our Center from 2011 to 2020. There was no incidence of any vascular complications or focal neurological deficit in our study. The pure endoscopic approach is a safe, efficacious, and minimally invasive technique for removing pituitary adenomas. The results have been encouraging in our prospective study. However, the importance of learning curve in endoscopic skull base surgery and use of a multidisciplinary collaboration cannot be overemphasized.

Keywords: pituitary adenoma, endoscopic endonasal surgery, endoscopic transsphenoidal approach, endoscopic hypophysectomy.

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ЭНДОСКОПИЧЕСКИЙ ЭНДОНАЗАЛЬНЫЙ ТРАНССФЕНОИДАЛЬНЫЙ ДОСТУП К АДЕНОМАМ ГИПОФИЗА: ПРОСПЕКТИВНОЕ ИССЛЕДОВАНИЕ

АННОТАЦИЯ

Хирургический подход к аденомэктомии гипофиза претерпел радикальную революцию за последние три десятилетия. С появлением эндоскопов, лучшего инструментария, лучшего освещения и обзорных камер, эндоскопический эндоназальный транссфеноидальный доступ к турецкому седлу теперь в значительной степени стал нормой.

Цель данного исследования - представить наш опыт, проанализировать хирургические результаты этого подхода у пациентов с аденомой гипофиза, касающиеся полного удаления опухоли, облегчения симптомов и частоты осложнений. Это проспективное исследование проводилось в нашем специализированном медицинском центре с января 2011 года по июнь 2020 года. В нашем исследовании не было случаев сосудистых осложнений, очагового неврологического дефицита. Чистый эндоскопический доступ - это безопасный, эффективный и малоинвазивный метод удаления аденом гипофиза. Результаты нашего проспективного исследования обнадеживают. Тем не менее, важность обучения в эндоскопической хирургии основания черепа и использования мультидисциплинарного сотрудничества невозможно переоценить.

Ключевые слова: аденома гипофиза, эндоскопический эндоназальный подход, эндоскопическое удаление аденом гипофиза

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ГИПОФИЗ АДЕНОМАЛАРИГА ЭНДОСКОПИК ЭНДОНАЗАЛ ТРАНССФЕНОИДАЛ ЖАРРОХЛИК УСУЛИ: ПРОСПЕКТИВ ИЗЛАНИШ

АННОТАЦИЯ

Гипофиз аденомектомиясига жарроҳлик усули сўнгги ўттиз йил ичида тубдан инқилобни бошдан кечирди. Эндоскопларнинг пайдо бўлиши, яхши асбобсозлик, ёруғлик ва камераларни кўриш билан эндоскопик эндоназал трансфеноидал турк эгарига кириш энди одатий ҳолга айланди. Ушбу тадқиқотнинг мақсади ўз тажрибамизни тақдим этиш, гипофиз аденомаси бўлган беморларда ушбу ёндашувнинг жарроҳлик натижаларини ўсмани тўлиқ олиб ташлаш, симптомларни юмшатиш ва асоратланиш даражаси бўйича таҳлил қилишдир. Ушбу истиқболли тадқиқот бизнинг ихтисослашган тиббиёт Марказимизда 2011 йилдан 2020 йил июнгача ўтказилган. Бизнинг тадқиқотимизда қон томир асоратлари, фокал неврологик дефитсит ҳолатлари бўлмаган. Аниқ эндоскопик усул гипофиз аденомаларини олиб ташлаш учун хавфсиз, самарали ва минимал инвазив усул ҳисобланади. Бизнинг истиқболли тадқиқотлар натижалари бизни қувонтиради. Шу билан бирга, бош суягининг эндоскопик жарроҳлиги ва мултидисиплинар кооперациядан фойдаланиш бўйича машғулотларнинг аҳамиятини инобатга олиш мумкин эмас.

Калит сўзлар: гипофиз аденомаси, эндоскопик эндоназал усул, эндоскопик гипофиз аденомэктомияси

Horsley first described the removal of a pituitary tumor by open craniotomy in the late nineteenth century. Since then, the surgical approach to pituitary adenomectomy has undergone a radical revolution. In 1907, Schloffer et al were the first to report the transsphenoidal approach for a sellar tumor using a lateral rhinotomy. In 1909, Cushing et al. pioneered the sublabial transseptal transsphenoidal approach. In the 1960s, Hardy introduced an operating microscope for transphenoidal surgery, which offered intraoperative magnification and stereoscopic imaging. Traditional transseptal / translabial access has long been considered standard [1].

With the advent of endoscopes and improved instrumentation, Jankowski in 1992 proposed a fully endoscopic approach to pituitary adenomectomy [2]. The main obstacle to the transition from microscopic to endoscopic technique was the lack of bimanual dissection. Stamm et al. promoted a binostrile approach to the Turkish saddle, allowing "four hands" to work in one surgical field [3].

Endoscopic transsphenoidal access to the Turkish saddle has become the norm in many ways. The direct endoscopic endonasal approach is minimally invasive, offering an angular view

and a broader panorama of the skull base's important anatomical structures while eliminating the need for craniotomy and brain retraction.

Several authors have compared the results of endoscopic and microscopic methods. De Klotz et al [4], in their meta-analysis, documented higher rates of total tumor resection (79% vs 65%), lower rates of liquorrhea (5% vs7%), septal perforation (0% vs5%), and postoperative epistaxis (1% vs4%) with endoscopic endonasal approach versus sublabial approach.

Rotenberg et al. [5] concluded that the two approaches had similar results regarding large tumor resection and resolution of hormonal abnormalities, but the endoscopic approach was associated with fewer complications, shorter hospital stays, and duration of surgery.

Goudakos et al [6] reported similar rates of resection of large lesions and liquorrhea between the two methods, but with a lower incidence of postoperative diabetes insipidus and shorter hospital stays endoscopic approach study group. Other systematic reviews also confirm the safety and short-term effectiveness of endoscopic pituitary surgery [7].

However, Ammirati et al. [8] in their meta-analysis concluded that endoscopic excision of pituitary adenoma in the short term does not seem to provide any advantages over microscopic technique, and the incidence of vascular complications was higher with endoscopic surgery than with microscopic surgery.

Previously considered contraindications to transsphenoidal surgery, such as spreading the lesion anterior to the tubercle and over the sphenoid bone plane, behind the clivus into the posterior fossa, a dumbbell tumor with an extensive suprasellar component is now eliminated using an extended endoscopic approach [9, 10]. The limitation of 2D viewing with an endoscope is overcome with 3D cameras.

The purpose of this study is to present our experience and analyze the surgical results of endoscopic endonasal transsphenoidal pituitary adenomectomy in patients with pituitary gland lesions.

Materials and methods.

This prospective study was carried out in the Department of Neurosurgery of the Republican Specialized Scientific and Practical Medical Center of Endocrinology named after academician Y.Kh. Turakulov from January 2011 to September 2020.

Patient selection

Patients were selected from among those who attended the Center's consultative polyclinic during the specified study period. The study included patients diagnosed with a pituitary tumor who require surgical treatment. Patients were included in the study after obtaining informed written consent in their native language.

Patient assessment

The patient's demographic profile was collected as well as a detailed medical history. Patient complaints suggested:

• Mass effects of education (headache, vomiting, visual impairment, limitation of eyeball movements)

• Endocrinological abnormalities (menstrual irregularities, infertility, galactorrhea, coarsening of facial features, enlarged limbs, hirsutism, gynecomastia, significant weight gain/loss)

Possible additional concomitant complaints from the nose, ears or throat have been noted. A general and systemic examination was carried out, including an ophthalmological assessment.

Research

• Routine examinations (complete blood count, blood sugar, kidney and liver function tests, coagulation profile, chest x-ray, electrocardiogram)

• Hormone profile: serum prolactin, growth hormone, IGF-1, adrenocorticotropic hormone, cortisol, thyroid-stimulating hormone, free thyroxine, follicle-stimulating hormone, luteinizing hormone levels)

• Radiological imaging: MRI of the brain with an increase in gadolinium and conventional computed tomography of the paranasal sinuses.

• Ophthalmologic examination: all patients underwent visual acuity, eye movement, perimetry to assess the visual field, and fundoscopy.

Indications for surgery

a. Macroadenoma of the pituitary gland (tumor size> 1 cm in largest dimension) causing compression symptoms and/or
b. A functional tumor of the pituitary gland, leading to hormonal imbalances that are not controlled by drug treatment.

Surgical data

All patients were operated on under general anesthesia. The stages of the operation were as follows (Fig. 1).

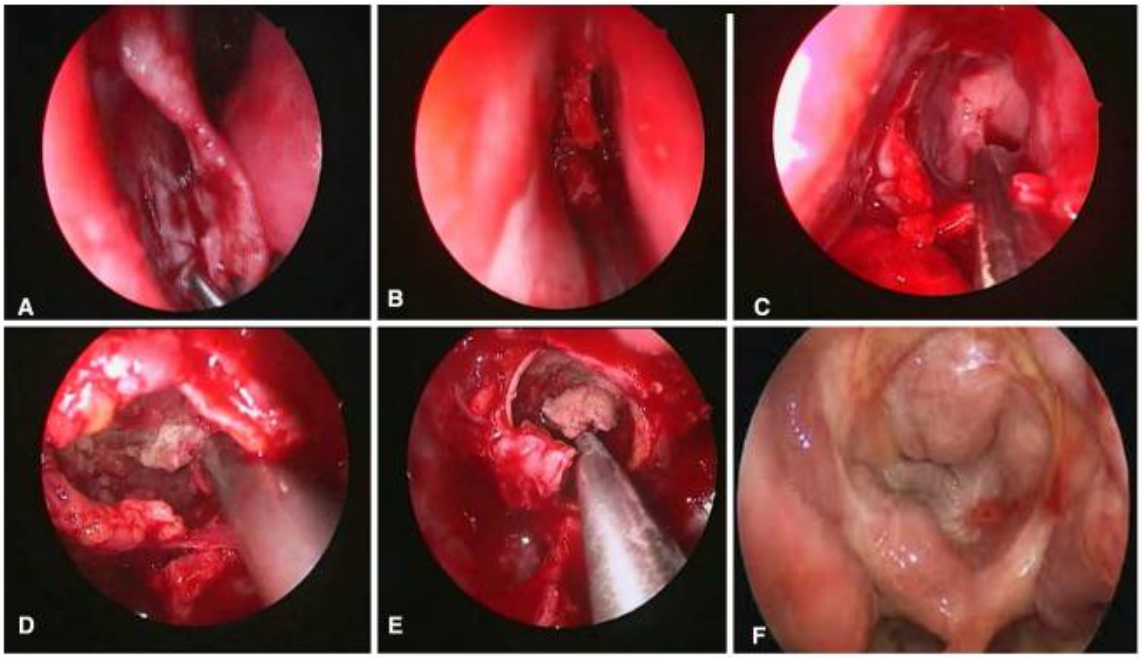

Figure: 1. Step-by-step intraoperative images of transsphenoidal adenomectomy. **A.** Treatment of the naso-septal flap. **B.** Posterior septectomy. **C.** Wide sphenoidotomy. **D, E**. Removal of the tumor**. F.** Plastic repair of a sellar defect.

Nasal stage of the operation

Access creation: Patients with a significant deviation of the nasal septum will undergo endoscopic septoplasty. Turbines that obstruct the operative field or the passage of instruments are eliminated in different ways - coagulation or partial turbinectomy. Hadad-Bassagasteguy Flap Lift: The nasal flap, at the base, is lifted and placed in the nasopharynx for later use. A posterior septectomy is performed to obtain a binostrile approach while preserving the mucous membrane on one side. The sphenoid bone's mouth is found 12-15 mm above the posterior choana's upper edge and expands downward. The anterior and lower walls of the sphenoid sinuses between the two orifices of the sphenoid bone and any septa are removed. A Turkish saddle is identified on the posterior wall of the sphenoid sinus along the midline with a protrusion created by the lateral optic nerve, the internal carotid artery below the medial to the optic nerve and the optic-carotid artery between them, along both sides of the saddle bulge.

Sellar phase of the operation

The anterior saddle wall is removed to expose the dura mater (TMO). A cross-shaped incision of the dura mater is made to expose the adenoma. The tissue is taken for a representative biopsy. Tumor clearance is achieved using various suction curettes. The lower and lateral parts of the lesion are removed to the central and upper parts, otherwise the suprasellar cistern and the diaphragm of the sella turcica will fall out into the dura mater defect, hiding the lateral areas of the tumor. A Valsalva maneuver is performed to prolapse the diaphragm and control residual tumor tissue. It also helps in controlling liquorrhea. Auto fat, hemostatic sponges (Tachocomb,

Surgicellfibrillar) are placed in the tumor bed. The nasal flap is placed in such a way as to close the skull base defect. For strengthening, autologous bone is installed (obtained by removing the anterior wall of the sphenoid sinus) and fixed with bio glue (Bioglue®, Evicel®, DuraSeal®). Anterior nasal tamponade is performed with a bacteriostatic sponge.

Post-operative care

Hourly monitoring of vital signs and urine output is performed using serum electrolytes to detect diabetes insipidus. Patients were observed for signs of meningitis, nasal liquorrhea, focal neurological deficits, and epistaxis. The patients were prescribed broad-spectrum injectable antibiotics in anti-meningitis doses for 7 days. All patients received perioperative steroids, which were continued postoperatively if the patient required preoperative steroid replacement and decreased postoperative serum cortisol levels.

Observation

All patients continued observation after 6 weeks, then after 1 year, followed by annual observation for 6-7 years, in the absence of complaints requiring examination.

The hormonal profile was studied on the 2nd day after surgery and 6 weeks after surgery. Ophthalmic assessment was performed in the immediate postoperative period, 6 weeks and 3 months after surgery.

Postoperative radiological imaging (MRI) was performed 3 months after surgery to assess residual tissue. All data was recorded, based on which studies were collected and data analyzed.

Results

Endoscopic endonasal transsphenoidal removal of pituitary adenoma was performed in 950 patients. The age of treatment ranged from 4 to 73 years, the average age was 38.1 years. 582 (60%) patients were women and 386 (40%) were men.

Symptoms

The most common symptom was a headache in 873 (90.2%) patients, followed by visual impairment complaints in 605 (62.5%) patients. Clinical features of hormonal imbalance occurred in 409 (42.25%) patients. Of these, 42 (4.33%) patients had amenorrhea with increased prolactin levels, 258 (26.65%) patients had signs of acromegaly with increased levels of growth hormone, 106 (10.95%) patients had signs of Cushing's disease with increased levels of ACTH and cortisol. 531 (54.85%) patients presented with hormone-inactive pituitary adenomas, including craniopharyngioma 38 (3.92%), meningioma 12 (1.23%), tuberculosis 2 (0.2%).

Tumor invasiveness

Preoperative MRI revealed a macroadenoma (maximum diameter> 10 mm) in 835 patients (86.2%). The maximum tumor diameter ranged from 15 mm to 65 mm, with an average of 40 mm. According to preoperative MRI, in 236 (24.38%) patients, the adenoma was limited to the sella turcica, 659 (68.07%) patients had suprasellar enlargement, and 387 (39.97%) patients also had intracavernous enlargement. No one had intracranial intradural tumor spread.

Outcomes

Relief of headache was observed in all cases. Normalization of the altered hormonal background in patients with Cushing's disease was observed in 93 cases (88.2%), while in patients with acromegaly without invasion of the cavernous sinus, remission was observed in 100% of cases. An improvement in visual field defects was observed in 100% of cases.

Postoperative MRI revealed residual lesion, as well as relapse, in patients with tumor invasion into the cavernous sinuses. In patients with a lesion limited to the sella turcica, no residual tumor was observed.

Complications

Transient diabetes insipidus was noted in 4 cases (0.41%). Persistent diabetes insipidus occurred in 10 (1.03%) patients. Postoperative liquorrhea was observed in 29 (2.99%) patients. Fatal postoperative meningitis was observed in 7 patients (0.7%), fatal postoperative pulmonary embolism was observed in 3 patients (0.3%), while hemorrhage into the rest of the tumor with fatalities was observed in 2 cases (0.2%) - so the total mortality was 12 cases (1.2%). In our study,

there were no cases of vascular complications and focal neurological deficits. There were no cases of postoperative bleeding, atrophic rhinitis, impaired smell, or nasal flap necrosis in our study.

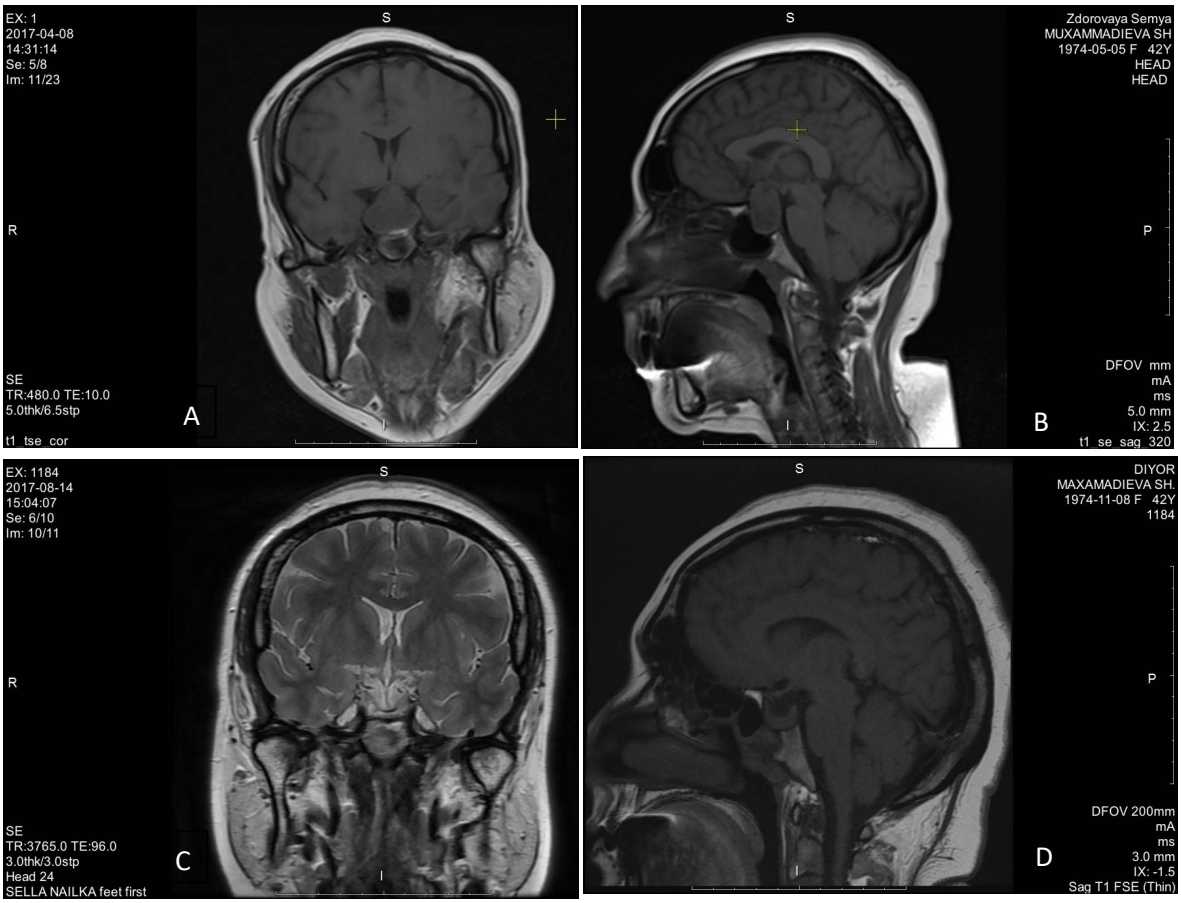

Figure: 2. MRI of a patient with pituitary adenoma with supra-infra-parasellar growth. **A, B** before surgery; **C, D** after surgery

Discussion

Our study noted the predominance of pituitary adenomas in women (60%) with an average age of 37.3 years. According to the observations of Ammirati et al. [8], in their meta-analysis, 54.49% were women and the mean age was 46 years.

It is reported that 35% of pituitary adenomas are clinically nonsecreting, and among secreting adenomas, prolactinoma (40%) is the most common, followed by growth hormone-secreting adenoma (20%) and ACTH-secreting (10%) [11]. In our study, in 528 (54.5%) cases, adenomas were clinically nonfunctional, whereas, among functional masses, the most common were STH-secreting (26.75%) and corticotropinomas(10.9%).

Headache and visual disturbances were the predominant features in our analysis. This may be because all our patients had a macroadenoma, with 29.4% showing the spread of the mass into the cavernous sinuses. Ammirati et al. [8] in their meta-analysis of 5643 patients with pituitary adenoma reported 79.75% cases of macroadenoma and 28% had intracavernous spread.

While preoperative MRI of the brain determines the exact size and location of the lesion as well as its neurologic and vascular relationships, CT scan of the sinuses serves as a guide for the operating surgeon by identifying anatomical variations. The pattern of wedge pneumatization is the most important for endoscopic transsphenoidal access; the sellar type is the most common and most favorable [12, 13], as in our series (91%). It is also important to note the presence of wedge-shaped septa attached to vital structures (e.g., internal carotid artery or optic nerve).

The four-handed bilateral access technique provides a sufficient surgical corridor for two surgeons to work "in two hands" and easily manipulate the instruments. This allows simultaneous

suction in the operating field and removal of the tumor, while the endoscope could be used while visualizing the anatomical features. This method is also suitable for operations on tumors with suprasellar spread, since one surgeon can mobilize the tumor dome upward (which tends to prolapse when the central part of the tumor is removed), while the other can remove the tumor from the lateral parts of the bed, thereby helping to reduce recurrence.

The posterior nasal flap (Hadad-Bassagasteguy) has been used for intra- or postoperative liquorrhea - it is an endonasal flap on the posterior septum of the sphenoid-palatal artery, without external incisions and with enough surface area to cover the entire anterior base of the skull [14]. The stem flap is kept in the nasopharynx during surgery and does not create any special obstacles for microinstruments. No cases of flap necrosis were noted in the postoperative period. Thus, this flap proved to be a convenient and reliable option for reconstruction of the skull base in limited anterior defects of the skull base.

The incidence of residual tumor noted by Ammirati et al. [8] in their meta-analysis of 38 studies was 33%. The residual tumor rate in our study was 40%. The higher recurrence rate in our study can be explained by the following facts. In our patient series, macroadenoma accounted for 86.2%, whereas the Ammirati et al. study included 20.25% of macroadenomas. 39.9% of our patients had intracavernous spread of the tumor, whereas Ammirati et al. in their study noted 28% of cases with intracavernous extension.

The residual tumour incidence was directly related to tumor size and spread, with the highest frequency in patients with tumors extending into the cavernous sinuses (Table 3). This relationship with tumor size and spread was also noted by Hofstetter et al. in their study of functionally active adenomas, where the rate of biochemical remission decreased in microadenomas (75%), in macroadenomas (51%) and with intracavernous spread (39%) (11).

In our study, the clinical and biochemical remission rate was 88.2% in Cushing's disease and 100% in STH-secreting adenoma without spread to the cavernous sinuses (Hofstetter et al. reported 60% in their series) [11].

Visual field defects arise due to displacement or pressure of the tumor on the optic chiasma. If optic nerve atrophy has not occurred, vision can rapidly improve within minutes or days after removing the adenoma [15]. 100% of our patients with perimeter visual field defects showed improvement after surgery. Previous studies have reported visual improvements ranging from 74.7 to 93.4% [16]. Early surgical intervention has a good prognosis for the elimination of visual impairment.

The most frequent complication in our study was postoperative liquorrhea. Transient nonsycharic diabetes is not considered a complication, but the result of excessive funnel manipulation during surgery and occurs within 24-48 hours of the postoperative period. The incidence of transient nonsycharic diabetes after transsphenoidal surgery ranges from 0.4 to 17% [17]. This was observed in 4 patients (0.41%) who received infusion therapy and Desmopressin drops in our study.

Persistent non-sugar diabetes probably represented damage to the pituitary stalk during surgery and was observed in ten (1.03%) of our patients. (2.31% in the Ammirati et al. study [8]).

A common cause of nasal liquorrhea is the diaphragm defect resulting from instruments such as curettes, forceps, or suction. The sellar diaphragm is often very thin and prone to injury. Besides, in front of the pituitary stalk, the upper part of the pituitary gland is connected directly to the spider sheath and the soft dura mater. The subarachnoid space here extends below the diaphragm and can be inadvertently damaged during tumor removal. Cappabianca et al. reported intraoperative lycraemia in 90 of 242 patients (37.1%) undergoing endoscopic pituitary surgery [18]. In our study, intraoperative lycvoria was observed in 11% of patients. Plasty of the defect was performed using autograsse tissue and broad femoral fascia with subsequent placement of the nasoseptal flap with fixation by biocele (Bioglue®, Evicel®, DuraSeal®).

Conclusions

Endoscopic transsphenoidal access is minimally invasive, providing direct access to the Turkish saddle. This eliminates the need for craniotomy and brain retraction and, therefore, prevents

complications due to cerebral edema and damage to vital structures during the skull base's exposure using cranial trepanation. In contrast to the microscope, which provides a funnel-shaped image, the endoscope provides a broader panoramic visualization. The angled optics allow you to see beyond the recesses, especially in the parasellar and supra- and retrosellar regions, thus providing maximum total tumor removal. Endoscopic access is also less traumatic for nasal structures.

Endoscopic access limitations are considered to be 2D imaging (although medical device manufacturers have recently started producing 3D optics), the employment of one hand in holding the endoscope, and the steep learning curve.

Endoscopic endonasal transsphenoidal access has now become the standard method for surgical treatment of pituitary adenomas. Although this study does not compare the endoscopic approach with the microscopic approach, our results in this study were very encouraging. Nevertheless, the importance of the learning curve and the use of interdisciplinary collaboration in endoscopic surgery cannot be overemphasized.

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EPIDEMIOLOGY, ETIOLOGY AND CLINICAL COURSE OF SUBCLINCAL HUPOTHYROIDISM

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ABSTRACT

Hypothyroidism – a disease caused by lack of thyroid hormones in the body. The disease is very widespread throughout the world. Hypothyroidism flows subclinical and manifest. The article is devoted to modern trends in the prevalence, etiopathogenesis, clinical course, diagnosis and treatment of hypothyroidism.

Keywords: hypothyroidism, subclinical, manifest, thyroid – stimulating hormone, autoimmune thyroiditis.

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ЭПИДЕМИОЛОГИЯ, ЭТИОЛОГИЯ И ТЕЧЕНИЕ СУБКЛИНИЧЕСКОГО ГИПОТИРЕОЗА

АННОТАЦИЯ

Гипотиреоз заболевание, вызванное недостатком в организме гормонов щитовидной железы. Заболевание очень широко распространено во всем мире. Гипотиреоз протекает субклинически и манифестно. Статья посвящена современным тенденциям в распространенности, этиопатогенезе, клиническом течении, диагностике и лечении гипотиреоза.

Ключевые слова: гипотиреоз, субклинический, манифестный, тиреотропный гормон, аутоиммунный тиреоидит.

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СУБКЛИНИК ГИПОТИРЕОЗ ЭПИДЕМИОЛОГИЯСИ, ЭТИОЛОГИЯСИ ВА КЕЧИШИ

АННОТАЦИЯ

Гипотиреоз – организмла тиреоид гормонлар етишмаслиги натижасида юзага келадиган касалликдир. Бу касаллик дунё бўйлаб жуда кенг тарқалган. Гипотиреоз субклиник ва манифест кўринишда кечади. Ушбу мақола гипотиреоз таркалиши, этиопатогенези, клиник кечиши, диагностика ва даволашнинг замонавий ёндашувларига бағишланган.

Калит сўзлар: гипотиреоз, субклиник, манифест, тиреотроп гормон, аутоиммун тиреоидит.

Diseases of the thyroid gland are the second most common endocrine diseases after diabetes mellitus. They develop as a result of disregulation of thyroid function, changes in the biosynthesis of thyroid hormones or their action in tissues [4]. Thyroid hormone function is vital to maintain whole body homeostasis. Thyroid hormones are the central regulator of many body functions [24]. One of the most common endocrine diseases is hypothyroidism.

Hypothyroidism is a clinical syndrome that is caused by a prolonged and persistent deficiency of thyroid hormones in the body. This is one of the most common endocrine diseases.

According to a number of epidemiological studies, the prevalence of hypothyroidism among the population is 0.1–2%, while women are 10 times more likely to suffer from hypothyroidism than men (1.5–2% in women, 0.1–0.2% in men), and taking into account subclinical forms, its frequency can reach 10–12% [11,26,27].

In recent years, data have appeared indicating an even higher prevalence of hypothyroidism - 4.8% among females and 0.9% among men [17] Among the adult population, hypothyroidism occurs in 1.5–2% of women and in 0.2 % of men; with age, its prevalence increases: among people over 60 years old - in 6% of women and 2.5% of men. Numerous studies indicate that changes characteristic of hypothyroidism can be determined already at the stage of subclinical hypothyroidism (SG) [20, 21].

Subclinical hypothyroidism, or minimal thyroid insufficiency, is a clinical syndrome caused by a persistent borderline decrease in the level of thyroid hormones in the body, in which the normal level of peripheral hormones is determined in combination with an increased level of thyroid stimulating hormone (TSH). However, the most common cause of FH in adults is autoimmune thyroiditis (AIT). Within a year, 5–10% of cases of latent (subclinical) hypothyroidism become manifest, and its frequency increases with the age of the surveyed and in the population of elderly people can reach 7–26% [5,6,7,8].

The relevance of studying the clinical and pathogenetic features of FH is determined, first, by its widespread prevalence, which varies from 8 to 10% among women and from 2 to 3% among men [7]. Second, the study of the features of the course of FH is relevant because of the possibility of developing a number of negative consequences of this condition, especially cardiovascular, the clinical and prognostic significance of which is confirmed by many studies [10,12,13,20]. The overall prevalence of FH is 7-10% among women and 2-3% among men. In women of an older age group, the incidence of both subclinical and overt hypothyroidism can reach 21% [8.16].

According to the results of other studies, the frequency of FH in the general population can be as high as 10-20%, depending on gender and age. The peak prevalence of FH is observed in the age group over 75 years (21% in women and 16% in men) [1,2,11,26,27].

Currently, FH is often detected in young and middle-aged people, it is assumed that this is due to the expansion of the use of thyroid hormones in clinical practice. In Japan, FH occurs in 4 to 8.5% of the population, and increases to 20 percent in women over 60 years of age [23].

An analysis of the thyroid function in adults living in the city of Wuwei, Gansu province (China) showed that FH occurs in 14.4% of 104 surveyed, and it is significantly higher in women and people with elevated levels of TgAb and TPOAb. epidemiological study in 8 major cities in

India. The prevalence of FH (normal fT4 and TSH> 5.50μIU / ml) was 8.02%, an increased level of antibodies to thyroid peroxidase (anti-TPO) was detected in 21.85% of cases [26].

In the Kantipur hospital (Kathmandu, Nepal), in the period from February 2010 to January 2011, 472393 people were examined, of which 16.9% had FH [22]. Another study was conducted at Charak Hospital (Pokhara, Nepal) from January 1, 2011 up to December 30, 2012 out of 1504 examined FH was detected in 10.50%, and the frequency of FH is higher in women and in the age group 41-50 years [28].

The authors suggest that the high prevalence of FH is due to the fact that the Himalayas and lowland regions of Nepal are iodine-deficient regions. Aminorroaya A. etal. [2009.] studied the prevalence of hypothyroidism in Isfahan (Iran) 15 years after universal salt iodization and found that overt hypothyroidism is detected in 2.85% of the examined, subclinical - in 5.83%. Moreover, the overall prevalence of hypothyroidism in men was 4.8% (95% CI 3.7-6.1), in women - 12.8% (95% CI 10.9-14.6).

According to the results of a large population study NHANES-III (National Health and Nutrition Examination Survey), the prevalence of hypothyroidism among US residents over 12 years of age was 4.6% (0.3% - overt, 4.3% - subclinical).Whereas in the group of people over 70 years old, the incidence of hypothyroidism reached 14%. Analysis of the data obtained showed that the prevalence of hypothyroidism is higher among whites (5.1%; 0.4% - overt, 4.8% - subclinical) than among African Americans (1.7%; 0.1% - overt, 1, 6% - subclinical) of non-Hispanic origin [18]. The incidence of hypothyroidism in the Russian Federation is 0.6-3.5 cases per 1000 population per year and increases with age [3].

Hypothyroidism is divided by the level of damage and by the severity.

In accordance with the pathogenesis of the disease, there are: primary (thyrogenic) (congenital and acquired, secondary (pituitary) and tertiary (hypothalamic).

In 90–99% of cases, the cause of hypothyroidism is damage to the thyroid gland itself (primary hypothyroidism). Acquired hypothyroidism is most often based on autoimmune processes in the thyroid gland or is a consequence of surgical interventions on the thyroid gland (with diffuse toxic goiter, thyroid cancer, benign thyroid nodules) with radioactive iodine or long-term administration of thyreostatics. Besides, hypothyroidism can develop with radiation therapy of malignant neoplasms of the head and neck area, including lymphoma, the use of tyrosine kinase inhibitors (iatrogenic hypothyroidism) - it induces hypothyroidism,

TPOAb determination can predict the risk of hypothyroidism in the presence of other autoimmune diseases:

- Diabetes mellitus type 1
- Addison's disease
- Chromosomal disorders like Down syndrome and Shereshevsky-Turner
- When treated with lithium, interferon-alpha, amiodarone, or excess iodine intake
- Multiple autoimmune endocrinopathies (MAE) types 1 and 2
- MAE type 1: hypoparathyroidism, Addison's disease, mucocutaneous candidiasis (as a result of a mutation in the autoimmune gene regulator - AIRE), autoimmune thyroiditis (in 10-15%)
- MAE type 2: Addison's disease, autoimmune thyroiditis, type 1 diabetes (known as Schmidt syndrome)

In the presence of adrenal insufficiency, the diagnosis of subclinical hypothyroidism is made after glucorticoid therapy. The presence of untreated adrenal insufficiency leads to an increase in TSH.

Other causes of subclinical hypothyroidism may be a previous operation on the thyroid gland or treatment with radioactive iodine for thyrotoxicosis. After surgery or treatment with radioactive iodine, a small amount of functioning thyroid tissue remains, leading to the development of FH. FH is more common in patients undergoing thyroidectomy than in patients undergoing hemistrumectomy. The incidence of hypothyroidism after surgery directly depends on the volume of surgery. A clear pattern was revealed between the volume of the thyroid residue and thyroid hormones and TSH level. FH was diagnosed when the left thyroid tissue volume was 4-7

cm3 in 8 out of 15 women. When the volume of the thyroid residue was more than 7 cm3, hypothyroidism was not detected, and when the volume of the stump was less than 4 cm3, all patients developed hypothyroidism, the severity of which negatively correlated with the size of the thyroid stump [15].

The main risk factors for the progression of FH to manifest are an increased level of thyroid antibodies and a relatively high baseline level of TSH (> 8); age and gender of patients do not significantly affect the likelihood of overt hypothyroidism manifestation [2]. Diez J., Iglesias P. [2004] provide data on spontaneous normalization of TSH levels in 40% of patients with FH examined within 12-72 months (TSH> 5 mIU / I and normal T4 values).

FH does not have clear clinical manifestations of the disease; nevertheless, 25-50% of patients have moderate, but characteristic signs of hypothyroidism, demonstrating disorders in many organs and systems. Often, SG is an accidental finding during the general examination of the patient. This syndrome is more common in older patients. As a rule, clinical symptoms are assessed retrospectively, after detection of laboratory changes characteristic of FH.

The clinical picture is of secondary importance.

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ASSESSMENT OF THE CLINICAL AND HORMONAL CHARACTERISTICS OF WOMEN WITH CAD, PCOS AND IH IN A COMPARATIVE ASPECT

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ABSTRACT

Hyperandrogenism syndrome (HS) is a group of endocrine diseases that occur due to various pathogenetic mechanisms but combined according to the principle of similar clinical symptoms due to secretion of excessive amounts and/or activity of male sex hormones in the female body. Among the specific disorders leading to the development of hyperandrogenemia, there is congenital adrenocortical dysfunction (CAD) with 21-hydroxylase deficiency, polycystic ovary syndrome (PCOS) and androgen-secreting tumours. It is often difficult to distinguish the first two of the above violations clinically, which determined our study's purpose. The purpose is to evaluate the analysis of clinical and hormonal indicators, especially menstrual and reproductive functions in women with a non-classical form of congenital adrenocortical dysfunction (NC CAD), polycystic ovary syndrome (PCOS) and idiopathic hirsutism (IH) in a comparative aspect. In our study, 1,512 women of childbearing age were screened. The data of 196 women identified during the screening were analyzed. All of them underwent a genetic study by PCR REAL-TIME method, on the basis of which the diagnosis of CAD was made. According to the results of the surveys, 196 women were divided into three groups: the first group included 23 women with NC CAD, the second - 82 patients with PCOS and the third - 91 women with IH. Hormonal status was investigated by determining the levels of 17-hydroxyprogesterone, total testosterone, dehydroepiandrosterone, adrenocorticotropic hormone, sex steroid-binding globulin, luteinizing hormone, follicle-stimulating hormone, an-corostlendin in the blood serum. Carbohydrate metabolism and ultrasound scans of the uterus and ovaries were also appraised.

Keywords: Hyperandrogenism syndrome, a non-classical form of congenital adrenocortical dysfunction, polycystic ovary syndrome and idiopathic hyperessence.

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ОЦЕНКА КЛИНИЧЕСКИХ И ГОРМОНАЛЬНЫХ ХАРАКТЕРИСТИК ЖЕНЩИН С ВДКН, СПКЯ И ИГ В СРАВНИТЕЛЬНОМ АСПЕКТЕ

АННОТАЦИЯ

Синдром гиперандрогении (СГ) - это группа эндокринных заболеваний, возникающих в силу различных патогенетических механизмов, но объединённых по принципу сходной клинической симптоматики в результате секреции избыточного количества и/или активности мужских половых гормонов в женском организме. Среди специфических нарушений, приводящих к развитию гипернадрогенемии, можно назвать, врожденную дисфункцию коры надпочечников (ВДКН) при недостаточности 21-гидроксилазы, синдром поликистоза яичников (СПКЯ) и андроген-секретирующие опухоли. Первые два из вышеперечисленных нарушений различить клинически зачастую бывает затруднительно, что и определило цель нашего исследования. Целью исследования оценка проведение анализа клинико-гормональных показателей, особенности менструальной и репродуктивной функций у женщин с Неклассической формой врожденной дисфункции коры енадпочечников(НК ВДКН), синдромом поликистоза яичников(СПКЯ) и идиопатического гирсутизма(ИГ) в сравнительном аспекте. В ходе нашего исследования скрининг прошли 1512 женщин фертильного возраста. Анализировались данные 196 женщин выявленных в ходе скрининга. Все они прошли генетическое исследование методом ПЦР REAL TIME, на основании которого ставился диагноз ВДКН.По итогам обследований, 196 женщин были разделены на 3 группы: в первую группу вошли 23 женщины с НК ВДКН, во вторую - 82 пациентки с СПКЯ и в третью – 91 женщины с ИГ. Гормональный статус исследовали путем определения в сыворотке крови уровней 17-гидроксипрогестерона, общего тестостерона, дегидроэпиандростерона, адренокортикотропного гормона, сексстероидсвязывающий глобулина, лютеинизирующего гормона, фоликулостиммулирующего гормона ,андростендиона и кортизола. Также проводилась оценка углеводного обмена, ультразвуковое сканирование матки и яичников.

Ключевые слова: Синдром гиперандрогении, неклассическая форма врожденной дисфункции коры надпочечников, синдром поликистоза яичников и идеопатический гирсутизм.

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АЁЛЛАРНИНГ ВДКН, СПКЯ ВА ИГ БИЛАН КЛИНИК ВА ГОРМОНАЛ ТАЖРИБЛАРИНИ СОЛИШТА БАҲОЛАШ

АННОТАЦИЯ

Гиперандрогения синдроми (ГС) – бу турли патогенетик механизмлар оқибатида келиб чиқадиган, аммо аёллар организмида эркаклар жинсий гормонлари ортиқча миқдорда ва/ёки фаоллиги натижасида ўхшаш клиник симтомлар тамойили бўйича бирлаштирилган эндокрин касалликлар гуруҳидир. Гиперандрогенемия ривожланишига олиб келувчи махсус бузилишлар орасида 21-гидроксилаза етишмовчилигида буйрак усти безлари пўстлоғи туғма дисфункциясини (БУБПТД), тухумдонлар поликистози синдроми (ТПКС) ҳамда андроген секретловчи ўсмаларни санаш мумкин. Юқорида саналган бузилишларнинг биринчи иккитасини клиник фарқлаш кўпинча қийин бўлиб, бизнинг тадқиқотимиз мақсадини белгилади. Тадқиқот мақсади буйрак усти безлари пўстлоғи туғма дисфункцияси ноклассик шакли (БУБПТД НК), тухумдонлар поликистози синдроми (ТПКС) ва идиопатик гирсутизм (ИГ) билан хасталанган аёллар ҳайз ва репродуктив функциялари хусусиятлари, клиник-гормонал кўрсаткичлар таҳлилини амалга оширишни қиёсий жиҳатдан баҳолаш. Бизнинг

тадқиқотимиз жараёнида фертил ёшдаги 1512 аёл скринингдан ўтди. Скрининг давомида аниқланган 196 аёл маълумотлари таҳлил қилинди. Уларнинг барчаси ПЗР REAL TIME усули бўйича генетик текширувдан ўтказилди, унинг асосида БУБПТД ташхиси қўйилди. Текширувлар якунига кўра, 196 аёл 3 гуруҳга бўлинди: биринчи гуруҳга БУБПТД НК бўлган 23 аёл, иккинчига – ТПКС бўлган 82 бемор ва учинчига – ИГ бўлган 91 аёл кирди. Гормонал статусни қон зардобида 17-гидроксипрогестерон, умумий тестостерон, дегидроэпиандростерон, адренокортикотроп гормон, сексстероид боғловчи глобулин, лютеинловчи гормон, фоликул стиммулловчи гормон, андростендион ва кортизол миқдорини аниқлаш йўли билан текширилди. Углевод алмашинуви баҳоланди, бачадон ҳамда тухумдонлар ультратовуш текшируви ҳам амалга оширилди.

Калит сўзлар: Гиперандрогения синдроми, буйрак усти безлари пўстлоғи туғма дисфункцияси ноклассик шакли, тухумдонлар поликистози синдроми, идиопатик гирсутизм.

Hyperandrogenism syndrome (HS) is a group of endocrine diseases that occur due to various pathogenetic mechanisms but combined according to the principle of similar clinical symptoms due to secretion of excessive amounts and/or activity of male sex hormones in the female body [1; 2].

An excess of androgens is found in approximately 10% of women. Symptoms of androgen excess include hirsutism, alopecia, acne, ovulatory dysfunction, and in extreme cases, androgenization and masculinization. Among the specific disorders leading to the development of hyperandrogenemia, there is congenital adrenocortical dysfunction (CAD) with 21-hydroxylase deficiency, polycystic ovary syndrome (PCOS) and androgen-secreting tumours. To distinguish violations clinically of the first two of the above is often difficult [3; 4; 5; 6; 7].

As a result, the purpose of our study was to evaluate the analysis of clinical and hormonal indicators, mainly the menstrual and reproductive functions in women with a non-classical form of congenital adrenocortical dysfunction (NC CAD), polycystic ovary syndrome (PCOS) and idiopathic hirsutism (IH) in a comparative aspect.

Research methods:

In our study, 1,512 women of childbearing age were screened. Before conducting epidemiological studies, we developed a female fertility questionnaire. All women gave informed consent to participate in the study.

According to the survey results, 233 women met the inclusion criteria, of which 25 (10.7%) of the examined patients had a subjective character. Besides, during the analysis of the results of the survey, 12 damaged profiles were identified. As a result, the data of 196 women identified during the screening were further analyzed.

The control group included 25 gynecologically and somatically healthy women of the corresponding age without signs of hyperandrogenism.

The degree of virilization of the genital organs was determined using the Prader scale [8].

The presence of PCOS was determined based on the classification of the European Association for Human Reproduction and Embryology (ESHRE) and the American Society for Reproductive Medicine (ASRM) (Rotterdam, 2003).

Idiopathic hirsutism (IH) was diagnosed in patients with hirsutism who had a regular menstrual cycle, a normal androgen concentration, and the causes of hirsutism were not identified.

All 196 women underwent a genetic study by PCR REAL-TIME method, based on which the diagnosis of CAD was made. A genetic study was conducted at The Scientific and Diagnostic Center Immunogen test at the Institute of Immunology and Human Genomics, Academy of Sciences of the Republic of Uzbekistan.

The severity of hirsutism was determined on a Ferriman-Hollway scale. [9; 10].

Hormonal status was studied by determining blood serum levels of such hormones as 17-hydroxyprogesterone (17OHP), total testosterone, dehydroepiandrosterone (DHEA), adrenocorticotropic hormone (ACTH), sex steroid-binding globulin (SHBG), lutein follicle-stimulating hormone (FSH), androstenedione and cortisol using the radioimmunological method

using standard IMMUNOTECH kits (Czech Republic).

To exclude false-negative results in connection with a circadian decrease in the concentration of 17OHP, the analysis was carried out early in the morning and in the early follicular phase of the menstrual cycle.

Evaluation of carbohydrate metabolism included determination of fasting glucose in capillary blood.

All women underwent ultrasound scanning of the uterus and ovaries on a Philips HD 11 XE using a transabdominal and transvaginal probe with a frequency of 5.0 MHz.

Bone mineral density was evaluated by dual-energy absorptiometry (DEXA) on a Prodigy bone densitometer from GE Lunar Corporation, USA.

Results:

As a result of the above examination methods, 196 patients were divided into three groups: the first group included 23 women with NC CAD, the second 82 patients with PCOS and the third 91 women with IH. The average age, menarche age, menstrual irregularity debut, and acne's appearance in the groups did not significantly differ (Table 1).

Table1.

Clinical characteristics of the examined women

Index	CAD,n=23	PCOS, n=82	IH,n=91	Control,n=25
Ageyears	24,4±6,6	25,8±6,9	26,2±6,8	25,0±5,2
Menarcheage, years	13,4±1,4	13,5±1,5	12,9±1,4	12,4±2,1
Menstrual Irregularities debut age, years	15,6±1,5	18,1±3,6	-	-
Ageofacne, years	16,8±2,9	16,9±1,9	17,8±3,3	-
The age of hirsutism, years	17,1±1,6	17,8±2,5	15,0±2,0●	-
Age of onset of sexual activity, years	20,8±2,4	20,1±3,8	20,9±2,0	21,1±2,3
BMI, kg/m²	24,2±3,4*	26,6±6,9●	23,8±5,1	21,7±3,41
SBP, mmHg	113,5±12,7	110,6±12,7	112,4±9,7	112,8±10,2
DBP, mmHg	76,1±7,8	73,3±9,1	73,5±8,6	75,2±8,2
Durationof MC, days	5,1±1,4	4,9±1,4	4,6±1,2	4,7±1,3
Hirsutenumber, points	9,1±4,9●	13,9±8,9*	8,8±5,2	4,92±1,38
Ovarianvolume, cm^3	6,8±1,3	9,9±2,5●	6,4±1,9	5,28±1,09

Note: * - the differences relative to the data of the CAD are significant (* - p <0.05, # - p <0.01, ● - p <0.001)

In the control group and with IH, no menstrual cycle disorders were detected, MC was retained in all examined patients. From the survey data, it was found that the average age of the appearance of excessive hair growth in hormone-dependent areas of the body is significantly less in the group with IH (15.0 ± 2.0 years). Age of onset of sexual activity did not have significant differences between groups. The BMI of patients with CAD was higher than that of women in the control group but had no differences than women with PCOS and IH. The SBP, DBP and MC duration among patients with CAD, PCOS, and IH did not differ significantly. The Hirsute number in the groups with CAD (9.1 ± 4.9 points) and PCOS (13.9 ± 8.9 points) was significantly higher compared to the control group. Ovarian volume (9.9 ± 2.5 cm^3) was higher in the group with PCOS.

We analyzed hereditary burden in parents and patients with CAD, PCOS and IH. It was found that more than a third of women with CAD have a parental marriage, whereas in the group with PCOS there were significantly less of them (34.8% versus 9.8%; OR 4.93; 95% CI 1.60- 15.2; p = 0.009).

In addition, cases of closely related marriages were significantly more common in women with CAD in comparison with patients with PCOS (17.4% versus 2.4%; OR 8.42; 95% CI 1.44-49.4; p = 0.03). Hereditary burden of diabetes in first-line relatives is more often observed in patients with PCOS (39.0% versus 13.0%; OR 4.27; 95% CI 1.17-15.5; p = 0.04).

When assessing the history data, menstrual irregularities are significantly more often observed in women with PCOS (80.5% versus 56.5%; OR 3.17; 95% CI 1.18-8.53; p = 0.04), in

comparison with those with CAD. Moreover, in both groups, MC disorders were of the type of oligomenorrhea. In the group with IH, no women with menstrual irregularities were identified (Table 2).

Hirsutism was diagnosed in almost a third (34.8%) of women with CAD, 56.1% of patients with PCOS and 50.5% of women with IH. There were no significant differences between the groups ($\chi2 = 3.28$; df = 2; p = 0.19).

When assessing excessive hair growth cases in androgen-sensitive areas, no significant differences between the groups were revealed ($\chi2 = 5.62$; df = 2; p = 0.06). Acne and hirsutism's appearance in almost a quarter (23.7%) coincided with the onset of menarche. The time of the appearance of hirsutism and a violation of the menstrual cycle were combined in 26.6%.

The frequency of infertility cases in the groups with CAD and PCOS do not differ (OR 1.41; 95% CI 0.55-3.62; p = 0.63). Infertility was much less common in women with IH (12.1%) compared with CAD (39.1%; OR 0.21; 95% CI 0.08-0.61; p = 0.006) and PCOS (47.6 %; OR 0.15; 95% CI 0.08-0.33; p <0.0001).

Table2.

Comparative characteristics of clinical manifestations hyperandrogenism in the studied groups

	CAD, n=23		PCOS, n=82		IH, n=91	
	n	%	n	%	n	%
Menstrualirregularities	13	56,5	66	80,5	-	-
oligomenorrhea	11	47,8	54	65,9	-	-
amenorrhea	2	8,7	12	14,6	-	-
Hirsutism (hirsutenumber ≥8 points)	8	34,8	46	56,1	46	50,5
SkinAcne	4	17,4	10	12,2	24	26,4
Infertility	9	39,1	39	47,6	11	12,1
primary	5	21,7	27	32,9	6	6,6
secondary	4	17,4	12	14,6	5	5,5
Alopecia	6	26,1	16	19,5	28	30,8
Undevelopedmammaryglands	2	8,7	0	0,0	0	0,0
Baryphony	3	13,0	5	6,1	10	11,0
Masculinization	8	34,8	9	11,0	9	9,9
Clitoromegaly	5	21,7	1	1,2		
Sexualdisorientation	5	21,7				
Osteopenia	5	21,7	1	1,2		
Osteoporosis	3	13,0			1	1,1
BMI ≥ 27 kg/m^2	4	17,4	21	25,6	23	25,3

Primary infertility was reported in one-third of women with PCOS. Significant differences between groups in the frequency of secondary infertility have not been established ($\chi2 = 4.98$; df = 2; p = 0.08).

Alopecia, to a large extent in the zone of the crown of the head and forehead as well as in the central parting with extension to the sides, was diagnosed in a quarter (25.5%) of the examined women. The frequency of alopecia among the groups do not differ ($\chi2 = 2.88$; df = 2; p = 0.24).

In two women with CAD, underdevelopment of the mammary glands was observed (small areas of glandular tissue in the area of the nipples were noted upon palpation), both of which had a violation of the MC as amenorrhea and, accordingly, infertility.

Decrease in voice timbre was slightly more often observed in the group with CAD ($\chi2 = 1.70$; df = 2; p = 0.43).

Signs of masculinization with an increase in the shoulder girdle were significantly more often observed in women with CAD (34.8%), compared with patients with PCOS (11.0%; OR 4.33; 95% CI 1.44-13.0; p = 0.02) and IG (9.9%; OR 4.86; 95% CI 1.62-14.6; p = 0.008).

In 5 (21.7%) women with CAD, clitoromegaly was noted.

In the form of osteopenia and osteoporosis, violation of bone mineral density was observed in 5 (21.7%) and 3 (13.0%), respectively. Among patients with PCOS, 1 case of osteopenia was

noted, IH - 1 case of osteoporosis. The incidence of BMI ≥ 27 kg/m2 is slightly lower in the group with CAD ($\chi 2 = 0.71$; df = 2; p = 0.70).

Somatic history was burdened mainly in women with CAD and PCOS. However, the frequency of occurrence of the groups did not differ significantly.

The levels of total testosterone and dehydroepiandrosterone (DHEA) in women with CAD (3.96 ± 1.5 nmol/l and 192.2± 72.4 μg/ml respectively) and PCOS (2.90±1.1 nmol/l and 170.7±48.0 μg/ml respectively) were significantly higher than in the IH and control groups.

The content of SHBG (50.7±17.7 nmol/l) in women with CAD was significantly lower compared with the indicators from the PCOS (64.6 ± 25.8 nmol/l) and IH (65.6 ± 19 6 nmol/l). The level of androstenedione (3.19±1.3 ng/ml) in women with CAD is significantly higher compared with indicators from the groups (Table 3).

The level of LH in the blood serum of women of the compared groups did not have significant differences. The average FSH value in women with PCOS (4.12 ± 2.4 IU/l) and IG (3.93 ± 1.7 IU/l) was significantly lower than in patients with CAD (7.04 ± 4.9 A piece of chalk). The ratio of LH/FSH turned out to be higher in women with PCOS (2.24 ± 1.3) than with CAD (1.54 ± 1.1) and IH (1.56 ± 0.8).

The average fasting glucose levels in all four groups were within normal limits, although in patients with PCOS, compared with those in women from other groups, they were elevated.

Table3.

The hormone content of the pituitary-adrenal system in women of the examined groups

Index	CAD, n=23	PCOS, n=22	IH, n=21	Control, n=25
17OHP, nmol/l	18,8±7,1●	4,14±1,2	2,63±0,7	3,51±1,1
Testosterone, nmol/l	3,96±1,5●	2,90±1,1*	1,84±0,4	1,46±1,08
DHEA, μg/ml	192,2±72,4●	170,7±48,0●	143,7±44,2	133,7±44,5
ACTH, ng/ml	66,3±19,7	41,8±21,7	34,3±11,1	32,2±14,1
Cortisol, nmol/l	218,8±61,9	307,2±70,2	328,9±93,0	334,9±140,1
SHBG, nmol/l	50,7±17,7#	64,6±25,8	65,6±19,6	59,9±20,1
Androstenedione, ng/ml	3,19±1,3●	1,86±0,9	1,72±0,9	1,77±0,61
LH, ME/l	9,13±7,6	7,93±4,5	6,26±2,3	9,79±9,6
FSH, ME/l	7,04±4,9	4,12±2,4*	3,93±1,7#	8,90±7,5
LH/FSH	1,54±1,1	2,24±1,3●	1,56±0,8	1,12±0,49
Note:	* - the differences relative to the data of the CAD are significant (* - p <0.05, # - p <0.01, ● - p <0.001)			

The highest HOMA-IR index was in obese women with PCOS. The average level of insulin and HOMA-IR in the group with CAD did not differ from women's parameters with PCOS and IH but was significantly higher than in the control group.

When analyzing the lipid spectrum, significant differences between the groups were not found. However, the levels of TH (1.52 ± 0.4 mmol/l) and HDL (3.55 ± 0.9 mmol/l) were significantly higher than in women with CAD (1.21 ± 0.5 mmol/l and 2.72 ± 0.9 mmol/l).

Conclusions:

1. In women of reproductive age, the frequency of hyperandrogenic cases is 13.0%. Among women with hyperandrogenemia, the rate of CAD is 11.7%; PCOS frequency - 41.8%, idiopathic hirsutism - 46.4%.

2. A comparative analysis of patients' clinical and medical history with CAD and PCOS showed that the clinical picture is similar in both cases. However, related marriage (34.8% versus 9.8%), clitoromegaly (21.7% versus 1.2%), baryphony (13.0% versus 6.1%), masculinization (34.8% versus 11.0%) is more often observed in patients with CAD, while menstrual irregularities (80.5% versus 56.5%) more commonly observed in patients with PCOS. The incidence of infertility, alopecia, acne, seborrhea, and hirsutism do not differ significantly.

3. The blood content in patients with CAD of 17-SNPs (82.6%) is significantly higher than in women with PCOS (36.4%).

4. Thus, non-classical congenital adrenal hyperplasia should be taken into account in the differential diagnosis of PCOS and IH, since neither the clinical manifestations nor the level of androgens is a reliable predictor disease.

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ЎЗБЕК ТИББИЁТ ЖУРНАЛИ
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THE IMPORTANCE OF DYSLIPIDEMIA IN THE PROGRESSION OF CHRONIC KIDNEY DISEASE AND ITS MANIFESTATION IN THE DYNAMICS OF RENAL ACTIVITY

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ABSTRACT

Chronic renal failure is a disease that results in severe uremic intoxication. The article presents a study that has 123 patients with the predialysis stage of chronic kidney disease. The blood lipid spectrum (cholesterol, LDL, HDL, triglycerides) was evaluated. The results showed that dyslipidemia in stage III of CKD is observed at least, and in stage IV, it is more pronounced and an increase expresses this in the levels of CS, LDL, TG and a decrease in HDL. When using the hypo-azotemic drug nephrotisin, there is an improvement in kidney function by optimizing dyslipidemia indicators.

Keywords: chronic kidney disease, glomerular filtration rate, dyslipidemia, LDL, HDL, TG.

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ВАЖНОСТЬ ДИСЛИПИДЕМИИ В ПРОГРЕССИРОВАНИИ ХРОНИЧЕСКИХ ЗАБОЛЕВАНИЙ ПОЧЕК И ЕЕ ПРОЯВЛЕНИЯ В ДИНАМИКЕ ПОЧЕЧНОЙ ДЕЯТЕЛЬНОСТИ

АННОТАЦИЯ

Хроническая почечная недостаточность - заболевание, приводящее к тяжелой уремической интоксикации. В статье представлены результаты исследования 123 пациентов с преддиализной стадией хронического заболевания почек. Проведена оценка липидного спектра крови (холестерин, ЛПНП, ЛПВП, триглицериды). Результаты показали, что дислипидемия в III стадии ХПН наблюдается как минимум, а в IV стадии более выражена, что выражается в повышении уровня холестерина, ЛПВП, ТГ и снижении ЛПВП. При применении гипоазотемического препарата нефротизин наблюдается улучшение функции почек с оптимизацией показателей дислипидемии.

Ключевые слова: хроническая болезнь почек, скорость гломерной фильтрации, дислипидемия, ЛПНП, ЛПВП, ТГ.

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БУЙРАК КАСАЛЛИКЛАРИНИ РИВОЖЛАНТИРИШДА ДИСЛИПИДИЯ ВА БУЙРАК ФАОЛИЯТИНИНГ ДИНАМИКАСИДАГИ МУҲИМЛИГИ

АННОТАЦИЯ

Сурункали буйрак етишмовчилиги — оғир уремик интоксикацияга олиб келадиган касаллик. Мақолада 123 беморни тадқиқот натижалари кўрсатилган. Қоннинг липид спектри баҳоланди. Натижалар шуни кўрсатдики, III босқичда дислипидемия камида кузатилади, IV босқичда эса анча ифодаланган бўлиб, бу холестерин, , ТГ даражасининг ошиши ва пасайиши билан ифодаланади. Нефротизиннинг гипоазотемик препаратини қўллашда дислипепидемия кўрсаткичларини оптималлаштириш орқали бурак функцияси яхшиланаётгани кузатилмоқда.

Калит сўзлар: сурункали буйрак касаллиги, гломер филтрация тезлиги, дислипидемия, ЛПНП, ЛПВП, ТГ.

Characteristics of chronic kidney disease (CKD) and problems in treatment have not yet been adequately addressed. [1; 2]. This is due to the multifactorial nature of the disease, i.e., rough and irreversible disruption of many pathogenetic joints, such as protein, water-electrolyte, and mineral metabolism acid-base imbalance, severe changes in blood composition qualitatively and quantitatively. One of the most important of these is dyslipidemia. According to the National Kidney Foundation, all patients with chronic kidney disease should be included in the high-risk group to develop cardiovascular disease, in which conventional factors do not play a major role [13]. The main mechanisms of SBK progression, which are directly or indirectly related to lipid metabolism, differ depending on the stage of the process. But there are some common symptoms. They are based on low levels of low-density atherogenic lipoproteins (LDAL), high levels of triglycerides (TG) and low levels of high-density lipoproteins (HDL) in the blood plasma [9; 14; 15].

According to our country's researchers, dyslipoproteinemia in nephrological patients leads to damage to the endothelium of the capillaries of the glomeruli and the accumulation of lipids in mesangial cells, which bind and oxidize LDAL, thereby accelerating mesenchymal proliferation and the development of glomerulosclerosis [2; 3]. Some data from foreign authors confirm this idea: hyperlipidemia increases the activity of mesangial cells with receptors for low-density lipoproteins, which enhances cell proliferation and increases the formation of macrophages, hemataxis factors, extracellular matrix components, plasminogen-1 activator, active forms of oxygen, etc. . [10; 11; 12; 13]. In doing so, lipoproteins accumulated in the basement membrane of cells bind glycosaminoglycans, increasing the membrane's permeability to proteins.

Besides, filtered lipoproteins in the glomeruli precipitate in the renal tubules, causing tubulointerstitial processes and sclerosis. Subsequently, high lipids levels lead to the fact that their epithelium occupies the tubules and leads to intracellular deposition. Accumulation of lipids in mesangiocytes and tubular epithelium gives cells a peculiar foamy shape; the lipid material occupies the intercellular space, leading to their dystrophy and atrophy [4; 7]. Therefore, in our study, we found that treating CKD patients with nephrocisine, a hypoazotemic drug that belongs to the group of bioflavonoids in the pre-dialysis period, reduces uremic intoxication, was the most appropriate way to treat the disease.

The purpose of the study. To study the dynamics of the lipid spectrum in patients with chronic kidney disease and to evaluate the effectiveness of the drug nephrocisin in renal function and dyslipidemia.

Materials and methods. 63 patients with stage III CKD 1 A (n-32) and 1 B (n-31) and 60 patients with stage IV CKD 2 A (n-30) and 2 B treated in the nephrology department of the multidisciplinary clinic of the Tashkent Medical Academy. (n-30) were divided into groups. Group A and 2 A were given conventional treatment and groups 1 B and 2 B were given nephrocisine 50 mg (6 tablets) in addition to conventional treatment for 3 months. All patients underwent serum analysis before and after 1 and 3 months of treatment to determine renal function: urea, creatinine,

BFR, total cholesterol (CH), LDL, HDL, and TG. The group's mean age was 38.63 ± 1.09 years, i.e., patients over 50 years of age and under 19 years of age and patients with metabolic disorders such as diabetes were not included in the study.

Results and their discussion.

Renal function status in groups 1, urea averaged 11.4 ± 0.28 before treatment; creatinine increased by an average of 191.1 ± 6.47, BFR 39.2 ±) .92 ml / min. decreased in value. On day 10 of treatment, urea averaged 10.6 ± 0.30 in group 1 A patients; creatinine decreased by an average of 180.2 ± 8.73, BFR by 40.9 ± 1.27 ml/min. value was observed. After 30 days, urea in group 1 A was 10.1 ± 0.24; creatinine decreased to 171.3 ± 7.74, BFR increased to 42.1 ± 1.26, and three months later urea increased to 16.6 ± 0.41; creatinine increased by 198.9 ± 8.98 and BFR decreased by 37.2 ± 1.30 ml/min. In group 1 B, urea averaged 10.5 ± 0.25 in patients on day 10 of treatment; creatinine decreased by an average of 179.6 ± 6.88, and BFR increased by 41.2 ± 1.14. On day 30, urea was 9.8 ± 0.20; creatinine decreased to 167.2 ± 5.83, BFR increased to 44.3 ± 1.23, and after 90 days, urea 9.4 ± 0.135; creatinine decreased to 154.7 ± 4.93 and BFR increased to 47.3 ± 1.68 ml/min.

Table 1

The state of renal function in patients with stage III CK

Parameters	Control group (n = 20)	Before treatmeNt	1 A group (n-31)			1 B group (n-32)		
			After 10 days	After 30 days	After 90 days	After 10 days	After 30 days	After 90 days
urea mmol / l	6,8±0,13	11,4±0,288***	10,6±0,30***	10,1±0,24***^^^	13,6±0,411***^^^	10,5±0,25***^	9,8±0,20***^^	9,4±0,135***^^^
Creatinine mkmol / l	71,6±1,53	191,1±6,47***	180,2±8,73***	171,3±7,74***	198,9±8,98***^^^	179,6±6,88***	167,2±5,83***	154,7±4,93***
BFR ml/min	104±4,82	39,2±0,92***	40,9±1,27***	42,1±1,26***	37,2±1,30***^^^	41,2±1,14***	44,3±1,23***^^	47,3±1,68***^^^

Note: * - differences are significant relative to the control group (*** - R <0.001); ^ - differences are significant relative to group values prior to treatment (^ - R <0.05, ^^ - R <0.01, ^^^ - R <0.001).

If we look at renal function assessment indicators, a slight decrease was observed on the tenth day of treatment in both groups. On day 30 of treatment, although the positive shift in renal function was almost the same in both groups, group 1B began to lead at a lower value. However, a significant decrease in urea and creatinine was evident in group 1B, which received nephrocisine compared to group 1 A after 3 months. This was also observed in the dynamics of BFR, which is the main criterion for assessing renal function. This was particularly noticeable in the 1 B group who received nephrocisine compared to the 1 A group on day 90 of treatment. In group 1 A, which did not receive nephrocisine, BFR was lower than at the beginning of treatment, indicating an increase in CKD.

In group 2, the average state of renal function before treatment was 16.9 ± 0.52 urea; creatinine averaged 347.2 ± 12.37, and BFR 21.8 ± 0.59 ml/min decreased in value.

On the tenth day of treatment, urea increased by an average of 17.8 ± 0.79 in group 2 A patients; creatinine decreased by 345.7 ± 19.31, and BFR increased slightly by 22.1 ± 0.80 ml / min. Urea 15.8 ± 0.54 in group 2 A for 30 days; creatinine decreased by an average of 338.9 ± 15.75, and BFR by 22.9 ± 0.69 ml / min. three months after the increase in value, urea 19.83 ± 0.561; creatinine increased to 379.8 ± 14.24, and BFR to 17.5 ± 0.31 ml / min. decreased in value. In group 2 B, on the tenth day, urea increased by 17.9 ± 0.42 in patients; creatinine decreased to 344.2 ± 10.38, BFR to 22.6 ± 0.72 ml / min. A slight increase in value was observed. One month sung urea 15.0 ± 0.52; creatinine decreased to 336.7 ± 11.23, BFR increased to 23.1 ± 0.56, and after three months urea 13.5 ± 0.293; creatinine decreased to 326.6 ± 10.67 and BFR increased to 24.6 ± 0.42 ml / min.

Table 2

The state of renal function in patients with stage IV CKD

Parameters	Control group (n = 20)	Before treatmeNt	Group A 1 (n-30)			Group B 1 (n-30)		
			After 10 days	After 30 days	After 90 days	After 10 days	After 30 days	After 90 days
urea mmol / l	6,8±0,13	16,9±0,52***	17,8±0,79***	15,8±0,54***	19,83±0,56***^^^	17,9±0,42***	15,0±0,52***^	13,5±0,29***^^^
creatinine mkmol / l	71,6±1,53	347,2±12,37***	345,7±18,82***	338,9±15,75***	379,8±14,24***	344,2±10,38***	336,7±11,2***	326,6±10,67***
BFR ml/min	104±4,82	21,8±0,59***	22,1±0,80***	22,9±0,69***	17,5±0,31***^^^	22,6±0,72***	23,1±0,56***	24,6±0,42***^^

Note: * - differences are significant relative to the control group (*** - R <0.001); ^ - differences are significant relative to group values prior to treatment (^ - R <0.05, ^^ - R <0.01, ^^^ - R <0.001).

If we look at the indicators that assess renal function, almost no dynamics were observed on the tenth day of treatment in both groups of creatinine and BFR. This indicates that as CKD escalates, it becomes increasingly difficult to influence processes. However, in the background of treatment, a significant increase in urea was observed in both groups. This is explained by the release of large amounts of urea and other residual nitrogen products into the peripheral blood at the beginning of the treatment process. BFR, which was the most essential criterion or indicator in the renal function assessment, also did not change significantly in the first month of treatment, only a positive shift was observed in group 2B who received nephrocisine compared to group2 A by the third month.

The dynamics of the lipid spectrum was 5.27 ± 0.043 with a mean value of CH in groups 1 with stage III of CKD; LDL averaged 2.6 ± 0.06; TG increased by 1.8 ± 0.01, while HDL decreased by 1.0 ± 0.01 on average. At first glance, CH, LDL, and TG appear to be slightly above the norm's upper limit or slightly below the HDL norm, but if we compare the indicators with the control group, we observe significant lipid spectrum change disturbances.

Besides, the literature suggests that dyslipidemia in renal disease begins before CKD complicates the disease, and this process deepens as CKD progresses [6; 14]. CH 5.1 ± 0.04 in group 1 A on day 30 of treatment; LDL 2.5 ± 0.09; TG decreased slightly to 1.7 ± 0.03, while HDL increased to 1.1 ± 0.01, and CH 5.4 ± 0.04 three months later; LDL 2.9 ± 0.08; TG increased by 2.041 ± 0.0268 and HDL decreased by 0.92 ± 0.0085.

Table 3

Lipid spectrum indicators in patients with stage III CKD

Parameters	Control group (n = 20)	Before treatmeNt	Group A 1 (n-31)		Group B 1 (n-32)	
			After 30 days	After 90 days	After 30 days	After 90 days
Cholesterol (mmol / l)	4,7±0,08	5,27±0,043***	5,1±0,04***^^^	5,4±0,04***^	5,1±0,04***^^	4,8±0,06^^^
LDL (mmol/l)	2,11±0,05	2,6±0,06***	2,5±0,09***	2,9±0,08***^^	2,4±0,04***^^	2,3±0,04**^^^
HDL (mmol/l)	1,35±0,027	1,0±0,01***	1,1±0,01***^^^	0,92±0,0085***	1,1±0,01***^^^	1,2±0,0294***^^^
Triglyceride (mmol / l)	1,5±0,04	1,8±0,02***	1,7±0,03***^^	2,041±0,0268***^^^	1,6±0,03***^^^	1,4±0,0294*^^^

Note: * - differences are significant relative to the control group (*** - R <0.001); ^ - differences are significant relative to group values prior to treatment (^ - R <0.05, ^^ - R <0.01, ^^^ - R <0.001).

In group 1 B, the one-month sung CH was 5.1 ± 0.04; LDL 2.4 ± 0.04; TG decreased by 1.6 ± 0.03 and HDL increased by 1.1 ± 0.01, while on day 90, the indicators CH were 4.8 ± 0.06; LDL 2.3 ± 0.04; triglycerides decreased by 1.4 ± 0.0294 and HDL increased by 1.2 ± 0.0294, and lipid

spectra showed normal results. Looking at the results, there was a positive shift in performance at the end of the first month of treatment, not only in group 1B but also in group 1A. Three months later, in group 1 B, who received nephrocisine, CH, LDL and TG's dynamics decreased and the value of HDL increased, and in group 1 A, who did not receive nephrocisine, the results were negative.

In group 2 patients with stage IV CKD, CH averaged 5.86 ± 0.045 before treatment; LDL averaged 3.0 ± 0.03; TG increased by 2.0 ± 0.02, while HDL decreased by an average of 0.98 ± 0.01. Now at this stage it is clear that CH, HDL and TG are significantly above the norm, that is to say, we are clearly observing dyslipidemia. Decreases in the concentration of antiaterogen HDL are also characteristic of CKD, which is caused by a decrease in the concentration and activity of lecithin-cholesterol-acyltransferase, which leads to disruption of HDL synthesis, transport and accelerated degradation of HDL [5; 8].

Thirty days later, the CH in group 2 A was 5.7 ± 0.06; LDL 2.9 ± 0.05; TG decreased by 1.9 ± 0.02 and HDL increased by 1.1 ± 0.02, while on day 90 CH increased by 6.0 ± 0.05; LDL 3.3 ± 0.05; TG increased by 2.209 ± 0.0267 and HDL decreased by 0.90 ± 0.0104.

Table 4

Lipid spectrum parameters in patients with stage IV CKD

Parameters	Control group (n = 20)	Before treatmeNt	Group A 2 (n-30)		Group B 2 (n-30)	
			After 30 days	After 90 days	After 30 days	After 90 days
Cholesterol (mmol / l)	4,7±0,08	5,86±0,045***	5,7±0,06***^	6,0±0,05***^	5,6±0,05***^^^	5,3±0,06***^^^
LDL (mmol/l)	2,11±0,05	3,0±0,03***	2,9±0,05***	3,3±0,05***^^^	2,9±0,05***	2,6±0,06***^^^
HDL (mmol/l)	1,35±0,027	0,98±0,01***	1,1±0,02***^^^	0,90±0,0104***^^^	1,1±0,02***^^^	1,2±0,0223***^^^
Triglyceride (mmol / l)	1,5±0,04	2,0±0,02***	1,9±0,02***^^^	2,209±0,0267***^^^	1,8±0,04***^^^	1,76±0,0338***^^^

Note: * - differences are significant relative to the control group (*** - R <0.001); ^ - differences are significant relative to group values prior to treatment (^ - R <0.05, ^^ - R <0.01, ^^^ - R <0.001).

In group 2 B, CH after one month was 5.6 ± 0.05; LDL 2.9 ± 0.05; TG decreased by 1.8 ± 0.04 and HDL increased by 1.1 ± 0.02, and after three months XS increased by 5.3 ± 0.06; LDL 2.6 ± 0.06; TG decreased by 1.76 ± 0.0338 and HDL increased by 1.2 ± 0.0223.

There was a slight improvement in the lipid spectrum in both groups on the thirtieth day of treatment. However, three months later, in group 2B who received nephrocisine, CH, LDL and TG's dynamics decreased, and the value of HDL increased, which showed positive results. In group 2 A, which did not receive nephrocisine, the opposite can be seen. Proper nephrocisin is not a drug with a hypoglycemic effect. Therefore, lipid spectrum indicators are not completely normal. However, we are witnessing that the process of dyslipidemia is relatively consistent with the improvement of BFR.

Comparing the groups of CKD III and IV, it was observed that in the relatively early III stages of CKD, CH, TG and LDL slightly exceeded the norm, and in the IV stage slightly increased. The study also found that in group 1 B, the positive shift returned to normal, while in group 2 B it decreased to the norm. HDL, on the other hand, was almost unchanged in stage III, decreased below the norm in stage IV patients, and remained unchanged in group 1 B, and was normalized in group 2 B patients. This leads to a decrease in the amount of lipoproteins that pass through the filter in the blood vessels inside the ball and into the renal tubules, which prevents tubulointerstitial processes and sclerosis. Occlusion of the capillaries of the balls with lipid deposits and foam cells reduces the filtration of the balls. [4]

Therefore, coordination of the lipid spectrum prevents an increase in systemic arterial pressure and also leads to a decrease in intracranial pressure in intact nephrons, thus slowing the progression to glomerulosclerosis. These processes are reflected in BFR and other biochemical analyses of renal function, including a positive shift in renal function improvement in groups receiving nephrocisine.

Conclusions:

1. Dyslipidemia is inextricably linked with CKD development, the effect of which is explained by both atherosclerotic damage of the renal vessels and the direct nephrotoxic effect of lipids.
2. The hypoazotemic properties of nephrocisine and its effect on lipid spectrum are more effective in stage III than in stage IV CKD.
3. Improving renal function with hypoazotemic drugs in the pre-dialysis stages of CKD, to some extent, harmonizes lipid spectrum indicators.
4. The drug nephrocisine slows the progression of CKD by reducing uremic intoxication and coordinating dyslipidemia.

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EPIGENETIC OVERVIEW OF THE PROLACTINOMAS

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ABSTRACT

This paper is dedicated to review a genetic and epigenetic study and provide a deep understanding of the molecular biology of prolactinomas. The pituitary gland consists of anterior (adenohypophisis) and posterior (neurohypophysis) parts. They differ in function. The adenohypophysis independently produces hormones, and the neurohypophysis only accumulates and activates them (Russell et al., 1998). Adenohypophysis is a large part of the pituitary gland and constitutes about 75% of its total mass, consisting of glandular cells. Glandular cells are divided into 5 main species according to the type of hormonal substances they produce: somatotrophs, lactotrophs, corticotrophs, thyrotrophes, gonadotrophes (Rizzoti et al, 2016). Pituitary adenomas are benign (non-cancerous) tumors of the pituitary gland, located on the lower surface of the brain. Adenomas make up about 80% of pituitary tumors (Mete et al., 2017). Prolactinoma is a non-cancerous tumor of the adenohypophysis, which cause hyperprolactinemia. It is the most commonly diagnosed tumor type in the pituitary that affects hormonal status. Most prolactinomas are thought to develop by chance without any known association to a genetic condition. (Cocks Eschler et al., 2018). However, there are some genetic alterations have been associated with prolactinomas.
Keywords: pituitary adenomas, prolactinoma, epigenetics.

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ЭПИГЕНЕТИЧЕСКИЙ ОБЗОР ПРОЛАКТИНОМОВ

АННОТАЦИЯ

Цель данной статьи - обеспечить эвакуацию генетических и эпигенетических исследований пролактиномы и объяснение яичной молекулярной биологии пролактиномов. Гипофиз состоит из 2 передних (аденогипофиз) и задних частей (нейрогипофиза). Хар имеет свою функцию. Если аденогипофиз активно разрабатывает гормоны, нейрогипофиз собирает и активирует их. 75% гипофизной железы составляют передние роды, то есть аденогипофиз,

состоящие из гландов. В зависимости от работы хозяйки подразделяются на 5 видов: соматотрофы, лактотрофы, кортикотрофы, тиреотрофы и гонаторофы. Аденомы гипофизной железы - гипофизическая опухоль, расположенная на нижней поверхности мозга. Аденомы составляют около 80% гипофиза. Пролактинома- опухоль без рака, гиперпролактинемия, аденогипофиза. Пролактинома является наиболее часто встречающейся аденимой и влияет на гормональный холат. Многие пролактиномы считаются холатами, не связанными с генетическими изменениями. Однако существуют самостоятельные генетические и эпигенетические изменения, связанные с пролактиномой.
Ключевые слова: аденома гипофиза, пролактинома, эпигенетика.

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ПРОЛАКТИННИНГ ЭПИГЕНЕТИК УМУМИЙ ШАРҲИ

АННОТАЦИЯ

Ушбу маколанинг максади пролактиномаларнинг генетик ва эпигенетик тадқиқотларини тахлил килиш ва пролактиномаларнинг чукур молекуляр биологиясини тушунтиришни таъминлаш. Гипофиз 2 олдинги (аденогипофиз) ва орқа бўлакдан (нейрогипофиздан ташкил топган. Хар бир бўлакни ўзига хос функцияси мавжуд. Аденогипофиз гормонларни актив ишлаб чиқса, нейрогипофиз уларни тўплайди ва фаоллаштиради.

Гипофиз безини 75% фоизини олдинги бўлак, яъни аденогипофиз ташкил қилади ва у гландулар хужайралардан ташкил топган. Хужайралар ишига қараб 5 турга бўлинади: соматотрофлар, лактотроф лар, кортикотрофлар, тиреотрофлар ва гонаторофлар. Гипофиз бези аденомалари- бу миянинг пастки юзасида жойлашган гипофиз ўсмаси. Аденомалар гипофиз ўсмаларининг тахминан 80% ни ташкил этади. Пролактинома- саратон бўлмаган, гиперпролактинемия келтириб чикарадиаган, аденогипофиз ўсмаси. Пролактинома энг кўп учрайдиган аденма булиб, гормонал холатга таъсир этади. Аксарият пролактиномалар генетик ўзгаришларга боглиқ булмаган холатлар деб хисобланади. Аммо, пролактинома билан боглик булган бъзи генетик ва эпигенетик ўзгаришлар мавжуд.
Калит сўзлар: гипофиз аденомаси, пролактиномалар, эпигенетика.

Genetic mutations in prolactinomas.

Up to 2.6% of individuals with a prolactinoma and no other symptoms may have a mutation in the MEN1 gene, which causes a genetic condition known as multiple endocrine neoplasia type 1 (MEN1). The chance of a prolactinoma being associated with MEN1 increases if the tumor is large or affects surrounding tissues (is invasive), or if the individual develops multiple tumors, especially in other glands such as the parathyroids or pancreas (Gérard et al., 2015). Prolactinomas have also been associated with another, a rare genetic condition called AIP-Related Familial Isolated Pituitary Adenomas, caused by mutations in the AIP gene; only 50 families with this condition have been described in the medical literature (Carty et al., 2020).

Recent studies showed that alteration of the genes PRL, POMC, DRD2 are the main cause of the development of the prolactionamas (Li et al, 2017).

Moreover, according to the Gürlek et al (2007), molecular, immunohistochemical, and genetic studies have demonstrated insight into the prolactinomas development. High Ki-67/MIB-1 labelling index and polymorphism in the cyclin adenine (A)/guanine (G) gene have been associated with invasive prolactinomas. Reduced expression of the E-cadherin/catenin complex and increased expression of the polysialylated neural cell adhesion molecule (NCAM) suggests a contribution to altered cellular migration cell-to-cell adhesion. Matrix metalloproteinases (MMPs) and their inhibitors, play essential roles in invasion and angiogenesis. The promotion of vascular endothelial

growth factor and fibroblast growth factor by oestrogen-induced overexpression of novel genes (PTTG, hst and Edpm5) promotes cell growth, angiogenesis and proliferation contributing to invasiveness in prolactinomas (Del Basso De Caro et al., 2017).

Although mutations in proto-oncogenes like Ras are uncommon, loss of tumour suppressor genes at loci 11q13, 13q12–14, 10q and 1p seem to be associated with invasiveness. Of the described mechanisms, only reduced E-cadherin/catenin expression and overexpression of hst gene seem to be relatively specific markers for prolactinoma invasiveness compared with other pituitary adenomas (Seltzer et al., 2016).

Genetic studies demonstrate a mutation. However, this research could not provide any prognostic approach of prolactinomas. Thus, the epigenetics' novel methodologies can suggest potential early prevention of the prolactinomas and future studies are required to understand the epigenetics of prolactinomas better.

Epigenetics.

The term epigenome is derived from the Greek word «epi» which means "above" the genome. The epigenome consists of chemical compounds that modify, mark, the genome in a way that tells it what to do, where to do it, and when to do it. Different cells have different epigenetic marks. These epigenetic marks, which are not part of the DNA itself, can be passed on from cell to cell as cells divide, and from one generation to the next (Angarica et al., 2017).

The epigenome is the collection of all of the epigenetic marks on the DNA in a single cell. The epigenomic marks different between different cell types. Thus, a blood cell will have different marks or modifications than a liver cell (Deans et al, 2015).

The epigenomic modifications, the whole collection of all of the epigenetic marks on the first sample blood cell DNA should be more similar to all of the marks on the second sample blood cell DNA than to collect all the marks on first sample liver cell DNA. Thus, this is a way of defining a particular type of cell. Now due to individual differences, epigenome will differ from the first sample epigenome even in the same tissue. Those differences make us all individuals, and we'll see even greater changes in a state of disease. Therefore, a comparison of a normal cell and all of its epigenetic marks, or the epigenome of that cell, will differ from the diseased state of that same cell type. Hence, these differences can be used to figure out disease mechanisms (Cai et al., 2019).

Gene expression is controlled by epigenetics that is not caused by DNA sequence alterations but are Trans generationally and mitotically heritable. Inappropriate epigenetic reprogramming has been identified as contributing to common diseases with fetal origins such as type 2 diabetes (Martin-Gronert et al., 2005), and prostate cancer (Ho et al., 2006), suggesting it may also contribute to PCOS, given that PCOS is a common disease with both reproductive and metabolic abnormalities.

At least three systems, including DNA methylation, histone modifications and non-coding RNAs (ncRNA) are considered to play fundamental roles in epigenetic regulation. Epigenetic regulations play an important role in a variety of human disorders and diseases. Besides, age, environment, lifestyle, and other factors influence epigenetic states, which might play a fundamental role in regulating gen expression or preventing genetic modification (Costa-Pinheiro et al, 2015). Epigenetic regulation of gene expression has been linked to discrete mechanisms that affect the stability, folding, positioning, and DNA organisation (Fontecha-Barriuso et al., 2018). The most studied of these mechanisms includes DNA methylation and chromatin remodeling, which work synergistically to organize the genome into transcriptionally active and inactive zones.

The most studied mechanism for epigenetic regulation of gene activity is the methylation process, which involves the addition of a methyl group to the cytosine bases of DNA CpG. (Ooi et al., 2009). Hypermethylation of promoter CpG island is commonly associated with transcriptional silencing. Methylation can affect gene activity in several ways. In particular, methyl groups can physically interfere with transcription factor contact (a protein that controls the process of synthesis of information RNA on a DNA matrix) with specific DNA sites (Volloch et al., 2019).

On the other hand, they work in conjunction with methylcytosine-binding proteins, participating in the process of remodelling chromatin - the substance, from which chromosomes consist, a

repository of genetic information. DNA methylation is relevant in blood tests as the non-invasive test for screening, prognosis and therapeutic strategies (Bogdanović et al., 2017).

To better understand the bioinformatics approaches to studying the epigenetic changes in cells, it is crucial to understand the biology and the molecular assays used in researching these regulatory mechanisms.

Epimutation in prolactinomas.

Numerous genes involved with cell growth and signaling show altered methylation status for pituitary tumors, including cell cycle regulators, components of signal transduction pathways, apoptotic regulators, and pituitary developmental signals (Sapienza et al, 2016).

According to the recent studies, high levels of methylation have been identified in large and invasive pituitary tumors (Kober et al, 2018).

Moreover, DNA methyltransferase overexpression has been detected in pituitary tumors, especially in macroadenomas. Methylation differences at CpG sites in promoter regions may distinguish several types of tumors from normal pituitary tissue. Histone modifications have been linked to increased p53 expression and longer progression-free survival in pituitary tumors. Further investigations stated that sirtuins are expressed at higher values in GH-expressing adenomas compared to nonfunctional adenomas and correlate inversely with size in somatotrophs (Hauser et al, 2019).

Regarding to the prolactinomas, recent researchers explored that upregulation in citrullinating enzymes may be an early pathogenic marker of prolactinomas (DeVore et al, 2018).

Peptidylarginine deaminase (PAD) enzymes facilitate histone citrullination, which can modulate chromatin expression (Bozdag et al., 2013). Increased PAD prevalence in prolactinomas and somatoprolactinomas has been associated with increased mRNA targeting of oncogenes HMGA, Insulin-like Growth Factor 1 (IGF-1), and Neuroblastoma MYC Oncogene (N-MYC) by miRNAs, which may yield insight into the etiology of the affected tumor subtypes (DeVore et al., 2018).

Normal human pituitaries and pituitary adenomas found that PAD2, PAD4, and citrullinated histones are highest in prolactinomas and somatoprolactinomas. In the somatoprolactinoma-derived GH3 cell line, PADs citrullinate histone H3, attenuated by a pan-PAD inhibitor. RNA sequencing and chromatin immunoprecipitation (ChIP) studies show that the expression of microRNAs (miRNAs) let-7c-2, 23b, and 29c is suppressed by histone citrullination (DeVore et al, 2018). According to the recent studies (Young et al, 2016), miRNAs directly target the mRNA of the oncogenes encoding HMGA, insulin-like growth factor 1 (IGF-1), and N-MYC, which are highly implicated in human prolactinoma/somatoprolactinoma pathogenesis. Our results are the first to define a direct role for PAD-catalyzed histone citrullination in miRNA expression, which may underlie the etiology of prolactinoma and somatoprolactinoma tumors through regulation of oncogene expression.

Conclusion.

According to the last, studies prediction of benign or aggressive behave of prolactinomas are not well understood. Classification methods are poorly characterized and the cellular pathways that drive transformation in pituitary neoplasms are unknown. Thus, new techniques in epigenetics, which helps to investigate activity of genes and their expression without changes to the genetic code, can provide a novel approach to tumors characteristic, and it suggests a prophylactic management. Moreover, epigenetic biomarkers can explore the predictive measures of prolactinomas.

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FEATURES OF THE CURRENT OF HYPERPROLACTINEMIA IN WOMEN FERTILIZED AGE WITH COMORBIDITY WITH BREAST CANCER

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ABSTRACT

In this article, we aimed to study the features of the clinical course of hyperprolactinemia associated with breast cancer in women of fertile age. The study's object was 56 women with breast cancer aged from 27 to 40 years (mean age 37.2 ± 1.3 years). The patients were divided into 2 groups, following the assigned tasks. Group I (main) consisted of 36 patients with breast cancer without hyperprolactinemia and Group II (comparison) consisted of 20 women with breast cancer with hyperprolactinemia. In our analysis the comorbidity of hyperprolactinemia in breast cancer is a serious factor that worsens the diagnosis of breast cancer in the early stages, and the often dominant symptomatology of hyperprolactinemic syndrome is a "distracting" mask for the course of breast cancer, especially in women of fertile age.

Keywords: breast cancer, hyperprolactinemia, benign breast dysplasia.

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ОСОБЕННОСТИ ТЕЧЕНИЯ ГИПЕРПРОЛАКТИНЕМИИ У ЖЕНЩИН ФЕРТИЛЬНОГО ВОЗРАСТА ПРИ КОМОРБИДНОСТИ С РАКОМ МОЛОЧНОЙ ЖЕЛЕЗЫ

АННОТАЦИЯ

В данной статье мы преследовали цель изучить особенности клинического течения гиперпролактинемии ассоциированного с раком молочных желез у женщин фертильного возраста. Объектом исследования были 56 женщин с раком молочной железы в возрасте от 27 до 40 лет (средний возраст 37,2 ±1,3 года). Больные в соответствии поставленными задачами были разделены на 2 группы. I группа (основная) состояла из 36 больных с раком молочной железы без гиперпролактинемии и II группа (сравнения) состояла из 20 женщин с раком молочной железы с гиперпролактинемией. В нашем анализе коморбидность гиперпролактинемии при раке молочной железы является серьезным фактором, ухудшающим диагностику рака молочной железы на ранних стадиях и зачастую доминирующая симптоматика гиперпролактинемического синдрома является «отвлекающей» маской течения рака молочной железы, особенно у женщин фертильного возраста.

Ключевые слова: рак молочной железы, гиперпролактинемия, доброкачественная дисплазия молочной железы.

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КЎКРАК БЕЗИ САРАТОНИ ҚЎШИМЧА КАСАЛЛИКЛАР БИЛАН БУЛГАН ФЕРТИЛ ЁШДАГИ АЁЛЛАРДА ГИПЕРПРОЛАКТИНЕМИЯНИНГ КЕЧИШ ХУСУСИЯТЛАРИ

АННОТАЦИЯ

Ушбу мақолада биз туғруқ ёшидаги аёлларда кўкрак бези саратони билан боғлиқ бўлган гиперпролактинемия клиник курсининг хусусиятларини ўрганишни мақсад қилдик.

Тадқиқотимизда текшириш учун 27 ёшдан 40 ёшгача (ўртача ёши 37,2 ± 1,3 ёш) бўлган 56 аёл олинди. Белгиланган вазифаларга мувофиқ беморлар 2 гуруҳга бўлинган. И гуруҳ (асосий) гиперпролактинемиясиз кўкрак бези саратонига чалинган 36 касалдан ва ИИ гуруҳ (таққослаш) гиперпролактинемия билан оғриган 20 аёлдан иборат эди. Бизнинг таҳлилимизга кўра, кўкрак бези саратонини гиперпролактинемия билан қўшилиб келиши кўкрак бези саратони диагностикасини ёмонлаштирадиган жиддий омил бўлиб, кўпинча гиперпролактинемик синдромнинг доминант симптоматологияси кўкрак бези саратони учун, айниқса, туғиш ёшидаги аёлларда "чалғитувчи" ниқоб ҳисобланади.

Калит сўзлар: кўкрак бези саратони, гиперпролактинемия, кўкрак дисплази.

Relevance: Breast cancer is a malignant tumor of the glandular tissue of the breast. It is the most common cancer among women globally, with an incidence rate of 99.4 per 100,000 (4) women aged 13 to 90 years. It is also the second most common cancer after lung cancer in the general population (including the male population; since the mammary gland is composed of the same tissue in men and women, breast cancer (BC) sometimes occurs in men, but cases of this type of cancer in men make up less than 1% of the total number of patients with this disease).

Human prolactin (PRL) secreted by the pituitary gland plays a central role in breast development and lactogenesis, and the PRL receptor is expressed in the mammary gland (1, 2). BPD contributes to the initiation, progression, and invasion of breast cancer in rodents and humans (2). It is unknown whether endocrine or autocrine/paracrine mechanisms mediate these effects, but epidemiological data indicate that high levels of circulating PRL in healthy women are associated with an increased risk of breast cancer (3). This association was found to be strongest in postmenopausal women with estrogen receptor-positive breast cancer (3).

Prolactin plays an irreplaceable role in breast cancer initiation and development by inducing cell proliferation and inhibiting apoptosis (8). Moreover, prolactin also functions to enhance angiogenesis and cell migration, contributing significantly to cancer metastases (7). Indeed, elevated plasma prolactin levels are often found in advanced and late cancer patients. Consistent with this, the results of several lines of research showed that the expression levels of prolactin and prolactin receptors from breast cancer cells and tissues were much higher than in normal tissues (6).

Additional studies also report that, in addition to reliable tumor function, prolactin may serve to increase the number of cells in the S-phase, increase the frequency of cell proliferation, and increase cyclin D1 levels in breast cancer cell lines (5).

Objective: To study the features of the clinical course of hyperprolactinemia associated with breast cancer in women of fertile age.

Materials and methods of research: The study's object was 56 women with breast cancer aged from 27 to 40 years (mean age 37.2 ± 1.3 years). The patients were divided into 2 groups in accordance with the assigned tasks. Group I (main) consisted of 36 patients with breast cancer without hyperprolactinemia and Group II (comparison) consisted of 20 women with breast cancer with hyperprolactinemia. In the work used clinical (examination of the somatic, endocrine and mammological status), biochemical, hormonal (radioimmune analyzes of the levels of luteinizing (LH), follicle-stimulating (FSH), thyroid stimulating (TSH), free thyroxine (T4 sv), estradiol (E2), progesterone prolactin), instrumental (ultrasound of the mammary glands, internal organs; mammography in two projections, MRI of the brain with coverage of the pituitary gland and, if necessary, other organs). The studies were carried out in patients on outpatient and inpatient treatment in the conditions of the RSSMPCacad. Ya. Kh. Turakulova and the Tashkent city branch of RSSMPCOandR. Clinical manifestations of women in the group I were characterized by the presence of local cutaneous edema in the mammary glands in 32 (89%), nipple edema in 16 (44.4%), nipple retraction in 5 (14%), deformation and tightness of the nipple areola in 4 patients (11 %), changes in the skin in the form of an "orange peel" in 2 (5.5%) and changes in breast size in 1 (2.7%).

While in women of group II, complaints of discharge from the breasts from light to dirty and bloody in 12 (60.9%), menstrual dysfunction in 17 (85%), the presence of heaviness and pain in the

breasts in 13 (65%), the presence of a seal in the mammary glands in 7 (35%), changes in the skin under the mammary glands in 4 (20%), headaches in 12 (60%), edema in 10 (50%), problems with the onset of pregnancy in 8 (40%).

As can be seen from this analysis, the comorbidity of hyperprolactinemia in breast cancer is a serious factor that worsens the diagnosis of breast cancer in the early stages, and the often dominant symptomatology of hyperprolactinemic syndrome is a “distracting” mask of the course of breast cancer, especially in women of fertile age.

On ultrasound diagnostics of the mammary glands in patients of group I, fibrocystic mastopathy occurred in 19 (52.7%), in 4 (11%) there was a site of breast sclerosis, and in 13 (36%) a breast tumor with infiltration of the surrounding tissue and the presence of a hyperechoic rim of the tumor in 3 patients including. Out of 36 patients, a normal background of the mammary gland was found in 6 (16.6%) patients.

While in group II patients, 16 (80%) had a normal background of the mammary glands with dilated milk ducts, with the phenomenon of milk stagnation, 7 (35%) had fibrocystic mastopathy, 11 (55%) had fibroadenomas, and only 3 (15%) patients had a suspicion of breast cancer.

Comparative analysis of the results of mammographic studies in patients of the study groups revealed the following: in group I, focal infiltration prevailed in 45% versus 34% in group II ($p < 0.01$) diffuse infiltration in 9 (25%) versus 3 (15%) ($p < 0.05$), presence of microcalcifications in 11 (30%) versus 2 (10%) ($p < 0.01$), respectively. In 12 (60%) patients of group II, breast tissue had a glandular nature, and in 22 (61%) women in group I, gross fibrous, cystic changes.

So, the instrumental-visualization studies of the examined groups of women with breast cancer revealed clear boundaries, differentiating the presence of hyperprolactinemia, were characterized by a predominance of the normal background of the mammary glands with a glandular character with the phenomena of stagnation and expansion of the milk ducts, which suggest the presence of hyperprolactinemia and the moment to level (erase) the process of early diagnosis and aggravate the outcomes of the disease. Further, following the tasks set, we analyzed the hormonal status of two groups of women in a comparative examination (Table 1) Comparative characteristics of hormonal parameters in women with breast cancer and associated with hyperprolactinemia (n = 56)

	Hormones						
	Prolactin	FSH	LH	Estradiol	Progesterone	TSH	freeT4
Group I (main) Breast cancer without hyperprolactinemia (n=36)	7,3 ±0,8	9,2±0,7	15,4±0,6	192±17	4,8±0,7	4,4±0,8	9,9±2,1
Group II (comparisons) Breast cancer with hyperprolactinemia (n=20)	97,3±11,2	6,8±1,1	13,1±1,6	168±12	3,6±0,3	3,3±0,9	12,3±0,9
Credibility	p<0,0001	p<0,5	p<0,05	p<0,01	p<0,05	p>0,5	p>0,5

As can be seen from the table, the patients of group II were characterized by significantly increased prolactin levels ($p < 0.0001$), with a significant decrease in the indicators of gonadotropins, estradiol and progesterone. While in patients of group I, hyperestrogenism ($p < 0.01$), an increase in LH, FSH and progesterone compared with the second, came to the fore.

The levels of thyroid hormones did not differ significantly and remained within the normal range.

Conclusions.

Thus, breast cancer associated with hyperprolactinemia in women of fertile age has its clinical features of the manifest and course, is characterized by the blurring of both subjective symptoms and objective, visualization characteristics. The hyperprolactinemic breast cancer mask is a serious factor that aggravates timely diagnosis and treatment.

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EVALUATION OF EFFICIENCY OF CARRYING OUT NEONATAL SCREENING IN RKK, DEPENDING ON VARIOUS DIAGNOSTIC CRITERIA

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ABSTRACT
The article is devoted to prolonging TSH diagnostics' status to identify children born with button hypothyroidism between 1997-2019 in the Republic of Karakalpakstan child screening of marcasite.
Keywords: born hypothyroidism, The Republic of Karakalpakistan diagnosis

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ОЦЕНКА ЭФФЕКТИВНОСТИ ПРОВЕДЕНИЯ НЕОНАТАЛЬНОГО СКРИНИНГА В РКК В ЗАВИСИМОСТИ ОТ РАЗЛИЧНЫХ ДИАГНОСТИЧЕСКИХ КРИТЕРИЕВ

АННОТАЦИЯ
В статье приведена информация о состояние изменения диагностического уровня ТТГ с целью выявления детей с врожденным гипотиреозом, в Центре скрининга матери и ребенка Республики Каракалпакстан с 1997 по 2019 годы.
Ключевые слова: Врожденный гипотиреоз, диагностика Республики Каракалпакстан.

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ҚОРАҚОЛПОҒИСТОН РЕСПУБЛИКАСИНИНГ ТУРЛИ ХИЛ ДИАГНОСТИК КРИТЕРИЯЛАРИГА БОҒЛИК ХОЛДА НЕОНАТАЛ СКРИНИНГ САМОРАДОРЛИГИНИ БАХОЛАШ

АННОТАЦИЯ

Маколада Қорақолпоғистон Республикаси она ва бола скрининг марказида 1997-2019 йил оралигидаги тугма гипотиреоз билан тугилган балаларни аниклаш максадида ТТГ диагностик даражасининг узгариши холати хакидаги маълумотлар келтирилган.

Калит сузлар: тугма гипотиреоз, Қорақолпоғистон Республикаси диагностикаси.

Relevance. Neonatal screening for congenital hypothyroidism is an effective method for early diagnosis and timely treatment of the disease, preventing the development of disabling complications [1].

The incidence and prevalence of congenital hypothyroidism vary significantly in different world countries depending on the geographical location, race [9], and the severity of the country's iodine deficiency [7]. Despite the development of more accurate screening test programs, in about 5% of cases, congenital hypothyroidism can be skipped in any screening program. The reasons may be unsuccessful in collecting the sample, unsatisfactory samples, incorrect interpretation of the samples, the state of subclinical hypothyroidism, inability to detect infants with central congenital hypothyroidism [3]. Also, the diagnostic level of TSH is set separately for each laboratory, depending on the chosen method and laboratory kits [2].

ESPE in 2014 made recommendations for the diagnosis of congenital hypothyroidism in neonatal TSH screening > 40 mIU / ml [6]. Over the past 30 years, many screening programs have reduced TSH's level for diagnosis from 20 - 50 mIU / ml to 6-15 mIU / ml [4]. In Russia, for the diagnosis of congenital hypothyroidism in neonatal screening, a TSH level of > 20 mIU / ml is used [2], in Brazil a TSH> 5 mIU / ml [10], and in the UK a TSH> 10 mIU / ml [5]. During the neonatal screening program, a decrease in TSH levels increases the number of children with congenital hypothyroidism and improves long-term results concerning general health and intellectual development [11]. Based on the previous, given the severe iodine deficiency in Uzbekistan, since 2006 Director of the Republican Screening Center "Mother and Child" prof. Sharipova M.K. decided to reduce the diagnosis of congenital hypothyroidism in the first stage in neonatal screening to TSH> 10 mIU / ml.

The study aimed to study the prevalence of congenital hypothyroidism in RKK, depending on changes in diagnostic criteria in congenital hypothyroidism.

Research material and methods.

In retrospect, a copy was made of outpatient records of patients with congenital hypothyroidism identified during neonatal screening in the Republic of Karakalpakstan for two periods from 1997-2005 and 2006-2019. In the Republic of Karakalpakstan [RKK], screening has been carried out since 1997. For the period 1997-2002, there is no data on the number of newborns examined, since screening was carried out jointly with the Khorezm region, from 2003 to 2019. 383018, newborns were examined.

In the RKK for 1997-2005. the diagnostic level of TSH from capillary blood on day 4-5 was> 20 mIU / ml whole blood, then a repeated full blood retest was recommended. From 2006 to the present, the diagnostic level of TSH from capillary blood on day 4-5 was recommended > 10 mIU / ml of whole blood, after which a repeated retest in (after the results of the first sample) of whole venous blood was recommended. If the TSH during retest is higher > 5 mIU / ml, it is necessary to begin treatment with thyroxine immediately.

From 1997 to the present, 124 children with congenital hypothyroidism have been identified, of which 8 (9.9%) were transferred under the supervision of an endocrinology clinic, 1 (1.2%) refused treatment, 4 (4.9%) moved, 3 died (3.7%). Among the patients, 87 (70.1%) girls dominated; 37 (29.8%) boys. In two families, repeated cases of congenital hypothyroidism were recorded (3.2%). Among patients, 35 (28.2%) patients had a social status of a disabled child since childhood.

Evaluation of the effectiveness of neonatal screening, according to ESPE (2014) recommendations is carried out on the coverage of newborns, on coverage by retesting.

Results and discussion. In neonatal screening in the RKK, there are 2 time periods for changing the TSH diagnostic criteria: 1st period 1997 - 2005. the diagnostic level of TSH was > 20 mIU / ml, then a repeated serum retest was recommended. 2nd period - from 2006 to 2019. The diagnostic level of TSH is > 10 mIU / ml. In the 1st period, with a TSH level > 20 mIU / ml of neonatal screening, 16 (13%) children with congenital hypothyroidism were identified; in the 2nd period, with a TSH level > 10 mIU / ml, 108 (87%) children were detected. Disease prevalence in RKK for 2019 It is an average of 1.9 per 100,000 children.

Table 1

The prevalence of congenital hypothyroidism in RKK depending on the screening period

Year coverage	newborns Revealed %		Revealed cases of CH	Frequency of CH
		1997-2005		
1997	-		1	-
1998	-		2	-
1999	-		2	-
2000	-		4	-
2001	-		4	-
2002	-		0	-
2003	22		0	-
2004	-		-	no reactive
2005	70.4		3	1:7601
		2006-2019		
2006	24.5		2	1:4320
2007	86.3		6	1:5267
2008	77.1		5	1:5984
2009	51		4	1:5120
2010	74.8		9	1:3271
2011	87.7		7	1:4400
2012	94.1		8	1:4367
2013	79.8		7	1:4426
2014	49.9		13	1:1489
2015	48.2		7	1:2742
2016	32.2		8	1:1563
2017	45		7	1:2324
2018	83		13	1:2473
2019	94.4		12	1:3075
Totally	60.6		124	1:3089

For the period from 1997 to 2002. there was a joint neonatal screening in the RKK together with the Khorezm region, for this period. Unfortunately, there is no data on the number of examined newborns. In 2003 screening coverage of newborns was 22%; it was low; there were no identified children with congenital hypothyroidism. In 2004 due to the lack of reagents, screening for congenital hypothyroidism was not conducted all year.

To identify the significance of a decrease in the TSH diagnostic criterion > 10 mIU / ml, the incidence rate was compared in the periods with the highest coverage of newborns: at the first stage in 2005, where coverage was 70.4%, and at the second period the highest coverage was in 2019 (94.4%). In 2005, the prevalence of congenital hypothyroidism was 1: 7601, and in 2019, the prevalence of congenital hypothyroidism was 1: 3075.

Table 2

The prevalence of congenital hypothyroidism, depending on the periods of the study (changes in diagnostic criteria) and coverage

	1 period TSH > 20 mIU/ml	2 period > TSH 10 mIU/ml	P
Year	2005	2019	
Maximum reach. %	70.4	94.4	<0.05
RKK frequency	1:7601	1:3075	<0.05

Thus, we revealed a significant improvement in the diagnosis of congenital hypothyroidism by lowering the diagnostic criterion for TSH. Improving diagnostics for the period from 2006 - 2019. 2.5 times better than for the period from 1997-2005.

Table 3

The frequency of identified patients with congenital hypothyroidism, consisting of "D" registration in the regions of the Republic of Karakalpakstan, depending on changes in diagnostic criteria

Cities and districts		1997 - 2005 TSH> 20 mIU / ml n = 16	2006 - 2019 TSH > 10 mIU / ml n = 108	Totally n=124
	Over RKK %	13(16)	87 (108)	
	Amudarya %	6.3 (1)	9.3(10)	8.9 (11)
	Ellikkalla %	6.3(1)	8.3(9)	8.1 (10)
	Turtkul %	6.3 (1)	14.8(16)	14(17)
	Beruniy %	13 (2)	6.6 (7)	7.3 (9)
	Kungrat %	13 (2)	2.8 (3)	4(5)
	Moynak %	-	1.9 (2)	1.6 (2)
	Shomanai %	-	3(3)	2.41 (3)
	Kanlikul %	-	2(2)	1,6(2)
	Karauzyak %	-	-	-
0	Kegeyli %	6,3 (1)	4,6(5)	4,8(6)
1	Taxtakupyr %	13 (2)	0,9 (1)	2,4(3)
2	Chimbay %	13 (2)	9,3 (10)	9,7 (12)
3	Nukus %		6,5 (7)	5,6 (7)
4	Xojeli %	6,3 (1)	3,7 (4)	4(5)
5	Takhiatash %	-	0.92 (1)	0,8 (1)
6	Nukus city %	19 (3)	26 (28)	25 (31)

When analyzing data on the incidence of congenital hypothyroidism in the RKK, it should be noted that when lowering the diagnostic criterion for TSH, more children with congenital hypothyroidism were diagnosed in the regions of Muynak 1,9%, Shumanai 2.8%, Kanlikul 1.9%, Nukus 6.5%, Takhiatash 0.9%.

Thus, based on the preceding, a decrease in the diagnostic level of TSH during neonatal screening for congenital hypothyroidism significantly improved the diagnosis of congenital hypothyroidism in the RKK by 2.5 times. During neonatal screening for the 2nd period, cases of diagnosis of congenital hypothyroidism were observed in areas wherein the 1st period was not a single case of congenital hypothyroidism. The data obtained are consistent with data from the UK,

where also the diagnostic level was reduced by TSH> 10 mIU /ml [5; 10]. A decrease in TSH levels during the neonatal screening program increases children's detection rate with congenital hypothyroidism. It improves early diagnosis and long-term results related to physical, sexual, and intellectual development [11], especially in severe iodine deficiency conditions.

Conclusions.

1. In RKK, with a decrease in the diagnostic criterion of TSH> 10 mIU / ml since 2006, in the first period of neonatal screening for congenital hypothyroidism (in maternity hospitals), 2.5 times more children with manifest congenital hypothyroidism were detected. A change in the diagnostic criterion of TSH revealed children with congenital hypothyroidism in areas of the RKK, where previously there was no case of diagnosis of congenital hypothyroidism.
2. In RKK in recent years, there has been an improvement in neonatal screening for congenital hypothyroidism. In 2019, neonatal screening coverage for neonatal screening in the PKK + reached 94.4%.

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PREDICTION OF DIABETIC COMPLICATIONS BASED ON GENETIC MARKERS

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ABSTRACT

It is interesting that some patients can have severe complication while others with the same duration and similar progression of disease do not. Besides that, different people have diverse complications. For example, if one patient can have mostly macroangiopathy, another suffers microangiopathies; sometimes there is combination of these two complementary states, in both cases with or without development of severe stages. This article provides literature review of genetic markers of some of diabetes mellitus complications.

Keywords: diabetes mellitus, genetic markers, diabetic complications.

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ПРОГНОЗИРОВАНИЕ ДИАБЕТИЧЕСКИХ ОСЛОЖНЕНИЙ С УЧЁТОМ ГЕНЕТИЧЕСКИХ МАРКЁРОВ

АННОТАЦИЯ

Вызывает интерес факт наличия или отсутствия тяжелых стадий осложнений у лиц с одинаковой продолжительностью заболевания и примерно одинаковым течением заболевания, кроме этого у разных людей развиваются различные осложнения, т.е. если у одного пациента развиваются преимущественно макроангиопатии, то у другого микроангиопатии, а иногда встречается сочетание этих двух взаимоотягощающих состояний, в обоих случаях с развитием или без развития тяжёлых стадий. В статье приведен литературный обзор данных по генетическим маркёрам некоторых осложнений СД.

Ключевые слова: сахарный диабет, генетические маркёры, диабетические осложнения

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ГЕНЕТИК МАРКЁРЛАРНИ ҲИСОБГА ОЛГАН ҲОЛДА ДИАБЕТ АСОРАТЛАРИНИ ПРОГНОЗ ҚИЛИШ

АННОТАЦИЯ

Касалликнинг давомийлиги бир хил бўлган ва тахминан касалликнинг бир хил босқичида бўлган қандли диабет беморларида жиддий асоратларнинг мавжудлиги ёки йўқлиги қизиқтиради, бундан ташқари, турли беморларда турли хил асоратларни келиб чиқади, яъни бир беморда асосан макроангиопатия ривожланса, бошқасида микроангиопатия ривожланади, баъзан эса бу икки ҳолатни оғирлаштирадиган ҳолатларнинг комбинацияси юзага келади. Мақолада диабетнинг баъзи асоратларини генетик маркёрлари тўғрисидаги маълумотларнинг адабий шарҳи берилган.

Калит сўзлар: қандли диабет, генетик маркёрлар, диабет асоратлари

The number of patients with diabetes mellitus (DM) is growing in the whole world, mostly due to the number of patients with DM type 2. Similar situation is observed in Uzbekistan; considering the situation on the 01.01.2020 there are 257 457 people registered with 93% (239 565) of the patients suffering DM type 2. It is known that, the burden of DM in health care system is conditioned by its severe complications. It was noted that, more than 60% of the patients with DM type 2 had cardiovascular diseases, and exactly these pathologies serve to be the cause of the most patients' death [1]. Lethal outcome rate due to MI among the patients with DM type 2 is notably higher, than among patients without DM, both in acute stage and in a long-term follow up [20]. Lesion of heart in diabetes mellitus cases is often associated with diabetic nephropathy in the form of cardionephral syndrome [21]. Chronic renal failure due to diabetic nephropathy can be the reason for hem dialysis in 50% of the cases [8]. Diabetic nephropathy significantly increases cardiovascular risk in patients with DM [17]. As cardiovascular diseases and DM type 2 are often observed in the same person a study was performed to reveal that these pathologies can have a common reason with genetic associations [27].

Genetic associations often vary between populations due to the difference in ethnic characteristics, age, place of living, and other factors, effecting not only dominance of genetic risk factors of the disease prevalence, but also appearance of risk factors associated with behavior or environment (for example, smocking, alcohol, diet, physical exercises). Hence, prognostic value and possibility of clinical application of genetic tests depends on population where it is to be used and disease to be prognozed. With the appearance of large scale genome researches hundreds of genetic polymorphism types with possible effect on diabetic cardiovascular complications were identified [Farbstein D., 2010]. J.Rani et al performed integrative analysis of genes associated with DM type 2 complications by means of automated processing of a text with manual cycle, and also analysis of gene expression from Gene Expression Omnibus (https://www.ncbi.nlm.nih.gov/geo/), international database of genetic studies, presence of negative or protective impact on the development of complications, interrelation with risk factors. T2DiACoD database contains 650 genes and 34 micro RNA associated with DM type 2 complications. Seven genes AGER,

TNFRSF11B, CRK, PON1, ADIPOQ, CRP and NOS3 were associated with all complications. Obesity was a dominant risk factor, interrelating with DM type 2 complications genes [26].

For risk stratification optimal is creation of a model considering genetic risk and phenotypic manifestations simultaneously, and that significantly improves the quality of the model. Quantitative assessment of genetic risk promotes personalization of prophylactic strategies. One of the basic instruments for prognosis and primary prophylaxis of CVD is estimation of summary cardiovascular risk (CVR). Existing systems for assessment of CVD risk were designed both for patients with DM and general population. However, there are only few for patients with DM. Guidelines on CVD therapy, as a rule, suggest assessment of individual cardiovascular risk, as insurance medical treatment is provided for patients with a high CVD risk [Winocour P.H. et al, 2003, Ul Haq I. et al, 1996, 13]. Systems for CVD risk assessment were designed as a result of the analysis of large population studies. Totally 17 studies were performed for that purpose (15 in USA and Europe and 2 in China). The number of analyzed cohorts varied from 1500 to 205178 patients, lasting from 4.7 to 25 years. Eight studies were performed among the patients with DM type 2 and nine studies in the general population. Most of the systems for risk assessment included classic factors such as age, gender, smocking, arterial pressure, and cholesterol level [Chamnan P. et al., 2009].

There are several models of estimation of summary CVR, created on the basis of prospective studies and named similarly. Framingham scale is the first model of summary CVR, worked out on the basis of the longest Framingham Heart Study (1949–1984), due to which IHD, stroke, sudden death, and cardiac failure risk factors were determined. Designed scale provides prognosis of these events within the closest 10 years both in men and women. Estimation of the risk was done with taking into account 5 factors, two of which were non-modified ones (age and gender) and three modified (smocking, systolic arterial pressure, and total cholesterol). More accurate data on the definition of summary risk is provided by mathematical model PROCAM (Prospective Cardiovascular Münster) in a computer software CERCA (Coronary Events Risk Calculator), designed on the basis of prospective study with similar title. That model assesses the risk of IHD complication development, and particularly myocardial infarction and sudden death within the closest eight years in men and postmenopausal women. There were already nine isolated factors: non-modified age, myocardial infarction in history, heredity, and five modified ones including smocking, systolic AP, total cholesterol, low HDL, DM [Assmann G., 2002]. On the basis of the results of prospective studies performed in 12 European countries and Russian Federation with participation of 205 thousand patients lasting totally for 27 years European Cardiology Society worked out Systematic Coronary Risk Evaluation (SCORE). Different from Framingham study evaluating 10-years risk of development of both lethal and non-lethal coronary events, SCORE determines 10-year risk of all lethal events associated with atherosclerosis and arterial hypertension, including myocardial infarction, stroke, and lesion of peripheral arteries. The factors used for the estimation of the summary risk were similar with Framingham study [13].

Population studies [Donnan P.T., 2006, Shen J., 2008] of the patients with DM isolated the following additional CVD risk factors: age at the moment of DM diagnosis, DM duration, parameters of DM compensation (glycated hemoglobin and fasting glycemia). However, the search for models prognozing CVR in patients with DN type 2 is still going on. ADVANCE study proposed a model for 4-years assessment of CVD risk. 7168 participants, who did not have CVD, were selected for the analysis. At the time of observation there were 473 registered basic cardiovascular events. The age at the moment of diagnosis, duration of diabetes, gender, hypertension therapy, arrhythmia, retinopathy, HbA1c, urinary albumin/creatinine ratio and original HDL cholesterol served to be significant predictors of cardiovascular events [13]. According to the UKPDS results a calculation engine for cardiovascular risk was worked out for patients with DM type 2 (UKPDS Risk Engine), considering not only gender, age, duration of diabetes, smocking, glycated hemoglobin, systolic arterial pressure (SAP), total cholesterol, albuminuria, but also ethnicity of the patients (Asian-Indian and Afro-Caribbean regions). With the help of the engine it is

possible to estimate 10-year risk of non-fatal and fatal IHD, and fatal and non-fatal stroke (https://www.dtu.ox.ac.uk/riskengine/).

On the basis of all aforesaid it can be concluded that, in most cases assessment of CV risk involves lethal cardiovascular events within the closest 8-10 years. At the same time, risk factors supposed to be modified are chronic progressing severe pathologies such as arterial hypertension, DM, and dyslipidemia. From this point of view, it is difficult to speak about primary early prophylaxis of arterial hypertension, IHD, and atherosclerosis with other localization. There is emergency of CVD prognosis at preclinical stages. All that indicates the necessity of the search for new biochemical and genetic markers of CVD. The interest in the latter appears due to the possibility of using the obtained results in earlier age, even before the development of initial stages of the disease, in other words performance of the primary prophylaxis of CVD in patients with DM type 2. In the literature there is active discussion of the role of polymorphic markers in the increase of IHD risk.

According to Taiwan researchers' data [12] DD genotype of I/D polymorphism of ACE gene is an independent risk factor of coronary syndrome, and particularly myocardial infarction. Besides that, it is a marker of severe stage and high probability of sudden death. The association between ACE gene and IHD was revealed in Saudi Arabia [4] and India [13] populations. Researchers from India detected the association between that kind of polymorphism and IHD in patients with DM type 2 [25]. A.Moradzadegan et al found out that in Iranian patients with DM type 2 ACE gene is an important risk factor of IHD development [23]. S.Sahin et al reported that, I/D polymorphism of ACE gene was associated with IHD risk factors and effects development of IHD in Turkish nation [12]. Researchers from Bulgaria [3] together with the ACE gene effect revealed the impact of eNOS gene on IHD development. E.F. Muslimova reported the importance of eNOS gene in IHD development in the population of Western-Siberian region of Russian Federation [24]. Egypt researchers did not reveal any association between eNOS gene and IHD [Steinthorsdottir V. et al, 2007]. Researchers from Brasilia studied severity of ischemic heart disease progression in patients with metabolic syndrome and recent acute coronary syndrome in relation to the presence of some genes polymorphism and the results of their study revealed that, ACE and TCF7L2 genes polymorphism was associated with the severity of the pathology, though in relation to eNOS gene there was no association revealed [16]. Development of the terminal stages of diabetic nephropathy also had ethnic differences [9].

Etiopathogenesis of vascular complications involves disorders in micro circulation, lipid exchange, coagulation and fibrinolytic blood systems, antioxidation protection, ion and acidic-alkali homeostasis, vascular protein components exchange and vascular permeability. Common root of all diabetic micro and macro angiopathies and the earliest manifestation is alteration of vascular endothelial cells function or endothelial dysfunction [Karimova I.A., 2005]. Endothelial cells covering the lumen of all blood vessels provide regulation of vascular tension (change of vascular lumen due to contraction or relax of smooth muscles cells) and, respectively, regulation of arterial pressure, redistribution of blood, oxygen and metabolic products supply to tissues and organs, dependently on the demand. Endothelium takes an active part in many local and systemic metabolic processes, regulation of homeostasis, proliferation and migration of various types of cells, provision of vascular wall integrity, selective permeability, restoration of damaged vessels, and neovascularization of tissues in ischemia. These endothelial functions are realized via various mechanisms, and first of all with the help of vessel-constricting factors of blood coagulation, components of fibrinolytic system produced by endothelium itself, which makes it possible to classify endothelium as paracrine organ [Karimova I.A., 2004].

Metabolic disorders in DM cause n functional shifts in vascular endothelial cells, which further lead to severe structural changes both in small and in large vessels. In the first it is thickening of basal membrane, disorders in its selective permeability, and proliferation of the smooth muscle cells, while in the second it is diminishing of vascular lumen mostly due to atherosclerotic alterations in vascular walls. Poor control of glycemia is the major, but not the only etiological factor of all chronic complications of diabetes [5]. Chronic hyperglycemia has

immediate damaging effect and can directly lead to structural alterations in various components of endothelial vascular cell membranes and intercellular substance (glycation, cross sectional protein and lipid oxidation), the more irreversible and causing unfavorable outcomes, the higher is the concentration and term of glucose impact, and the longer is the half- life of the protein. As vascular endothelial cells consumption of glucose is independent of insulin, in hyperglycemia there is steep increase of intracellular glucose, so the cells become dominant glucose toxicity targets [6].

In the development of vascular pathology in DM metabolic and genetic factors can have close interrelation presenting both synergic and antagonist effect, as clinical manifestation and speed of vascular complications progression in DM do not always correlate with the carbohydrate exchange compensation rate, duration of diabetes, and the therapy [11]. As a result of their study A.V. Jeleznyakova et al detected that, development of CRP in DM type 2 was genetically determined. They revealed a reliable association of CRP risk with genes encoding endothelial factors (NOS3), lipid exchange factors (APOB), and insulin secretion factors (KCNJ11, TCF7L2), expression products of which participate in the basic pathogenic mechanisms of renal lesion in DM. Crucial one in complex analysis of the studied markers was accumulation of risk genotype: with presence of just protective genotypes CRP risk was very low and progressively increased in case of accumulation of risk genotypes. So the authors concluded that, it suggests application of the panel of polymorphic markers as genetic diagnosticum for prognosis of CRP and formation of risk groups of pathology development at preclinical stages [19].

As it is known that, not all patients with DM have terminal stages of diabetic nephropathy with similar progression of the disease. That made many researchers think, that probably, development of these complications was genetically determined, and the search for genetic markers can lead to development of the methods of its early prognosis. A research performed in Saudi Arabia showed the importance of ACE gene in the development of DN [3]. Researchers from Egypt revealed the impact of ACE gene on the development of DN in patients with DM type 2 in their population [14]. Berstneva et al reported the impact of ACE and eNOS genes on the development of DN in the studied nationality [7]. Like ACE gene, eNOS gene was initially studied in relation to arterial hypertension [Karimova I.A., 2005, Karimova I.A., 2004, 30]. Z.Fan et al performed meta-analysis dedicated to the study of TCF7L2 gene in the DN development and concluded that, that gene contributes to the development of the complication, but further study is required [13]. The rise of the number of confirmed correlations between genetic markers and clinical presentations leads to more descriptive assessment of individual human genome. Besides that, it is interesting which clinical characteristics of a patient and complication risk factors can be determined by genetic markers. It should be noted, that established genetic predispositions to the development of certain diseases are realized during the whole life. However, the manifestation of these is observed in various periods and in different stages, and it depends not only on genome, but also environmental conditions, nutrition, and lifestyle. That suggests performance of various prophylactic and rehabilitation activities in relation to the revealed negative genetic predispositions within the whole life, taking into account age and developing deviations in health status.

Conclusion. Thus, analyzing literature data it can be concluded that, almost all researchers noted the necessity of the study of DM type 2 genotypes taking into account geographic region and sexual dysmorphism of a patient. Detection of these mechanisms will assist the understanding of the pathophysiological basis of DM type 2 and definition of the groups of people with high DM type risk and development of complications in that category of patients. It will also provide the possibility to work out the methods of its early prognosis for prophylactic purposes. In Uzbekistan the importance of genetic markers was studied in the development of myocardial infarction and chronic renal failure (CRF) in Uzbek population in patients with DM type 2. These studies showed that, C/T polymorphism of TCF7L2 gene can effect development of myocardial infarction [28, 2], while I/D polymorphism of ACE gene can serve to be prognostic factor for myocardial infarction [28, 29], and CRF [28, 1].

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ЎЗБЕК ТИББИЁТ ЖУРНАЛИ
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SOCIO-ECONOMIC ASPECTS OF DIABETIC GASTROPARESIS

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ABSTRACT

This review article presents data on the prevalence and socio-economic significance of complications of diabetes mellitus - diabetic gastroparesis. Diabetic gastroparesis is a component of autonomic neuropathy resulting from prolonged, poorly controlled type 1 and 2diabetes. Gastroparesis is manifested by a significant decrease in the quality of life in patients with diabetes mellitus. Timely and early diagnosis of this complication allows improving the quality of life of patients and the course of the underlying disease. Also, preventing the development of this complication reduces the disease's economic burden and shortens the hospitalization period for patients with diabetes. In connection with the increasing spread of diabetes mellitus, the number of patients with various complications of this pathology is also growing, which requires a more thorough approach to the timely diagnosis and prevention of complications.

Keywords: Diabetes mellitus, gastroparesis, quality of life, abdominal pain, diabetic complications.

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СОЦИАЛЬНО-ЭКОНОМИЧЕСКИЕ АСПЕКТЫ ДИАБЕТИЧЕСКОГО ГАСТРОПАРЕЗА

АННОТАЦИЯ

В данной обзорной статье представлены данные о распространенности и социально – экономическом значении осложнения сахарного диабета – диабетического гастропареза. Диабетический гастропарез является компонентом вегетативной нейропатии, возникшей в результате длительного, плохо контролируемого диабета 1 и 2 типа. Гастропарез проявляется значительным снижением уровня качества жизни у пациентов сахарным диабетом. Своевременная и ранняя диагностика данного осложнения позволяет не только улучшить качество жизни пациентов, но и течение основного заболевания. Также предупреждение развития данного осложнения уменьшает экономическое бремя болезни и сокращает сроки госпитализации больных с сахарным диабетом. В связи с увеличивающимся распространением сахарного диабета, растет и количество больных с

различными осложнениями данной патологии, что в свою очередь требует более тщательного подхода к своевременной диагностике и профилактике осложнений.

Ключевые слова: Сахарный диабет, гастропарез, качество жизни, боль в животе, диабетические осложнения

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ДИАБЕТИК ГАСТРОПАРЕЗНИНГ ИЖТИМОИЙ ИҚТИСОДИЙ АСПЕКТЛАРИ

АННОТАЦИЯ

Ушбу шарх мақоласида кандли диабетнинг асорати – диабетик гастропарез тарқалиши ва ижтимоий ва иктисодий ахамияти кўрсатилган. Диабетик гастропарез узок муддатли, яхши назорат қилинмаган 1 ва 2 тур диабет натижасида келиб чиқадиган вегетатив нейропатиянинг таркибий қисмидир. Гастропарез қандли диабет беморларда хаёт сифатининг сезиларли пасайиши билан намоён бўлади. Ушбу асоратни ўз вақтида ва эрта ташхислаш нафақат беморларнинг хаёт сифатини, балки асосий касалликнинг ривожланишини яхшилашга имкон беради. Шунингдек, ушбу асоратнинг ривожланишига йўл кўймаслик касалликнинг иқтисодий юкини камайтиради ва қандли диабет билан касалланганларни касалхонага ётқизиш муддати қисқартиради. Қандли диабетни тарқалиши тобора кўпайиб бораётганлиги сабабли, ушбу патологиянинг турли хил асоратлари билан касалланганлар сони хам кўпаймоқда, бу эса ўз навбатида асоратларни ўз вақтида аниқлаш ва олдини олишга пухта ёндашишни талаб қилади.

Калит сўзлар: Қандли диабет, гастропарез, хаёт сифати, корин оғриғи, диабет асоратлари.

Introduction

Traditionally, the term diabetic gastroparesis is used to describe the manifestations of complications of diabetes mellitus (DM) from the upper gastrointestinal tract (GIT). Gastroparesis is a syndrome characterized by delayed gastric emptying (GO) and upper gastrointestinal symptoms that are not associated with the gastric outlet's obstruction. It is a well-known diabetic complication in type 1 and types 2 diabetes mellitus (DM). However, some diabetic patients may have gastrointestinal symptoms with normal OB or no symptoms with abnormal OB. These gastrointestinal symptoms can also arise from the stomach and the small intestine [8]. Therefore, diabetic gastroenteropathy is a broader term to describe the gastrointestinal manifestations of diabetes. In addition to gastroparesis, diabetic gastroenteropathy also includes diabetic dyspepsia (i.e. indigestion), which is characterized by upper gastrointestinal symptoms and a normal, rapid or slightly delayed OB and a low or asymptomatic delayed OB. The latter accounts for up to 40% of patients with diabetes with delayed OB [3]. In some patients, the distinction between dyspepsia and gastroparesis can be difficult because the boundaries based on symptoms and voiding are poorly defined [8].

Clinical manifestations

There are many clinical features that may be associated with gastroparesis, including nausea and vomiting, and early satiety, often associated with bloating and epigastric pain and impairment of glycemic control combined with increased glucose variability. [5] Up to 53% of patients may experience weight loss, while up to 24% of patients may gain weight. Symptoms can be acute, with 65% of chronic symptoms with periodic exacerbations or chronic progressive symptoms [3]. According to Soykan et al. among 146 patients with gastroparesis, nausea was present in 92%, vomiting in 84%, bloating in 75%, and early satiety in 60% [11]. Although similar gastrointestinal symptoms may occur with oral antidiabetic agents such as metformin and alpha-

glycosidase inhibitors (flatulence, diarrhea, and pain), symptoms improve upon discontinuation of the drug [12]. Interestingly, in a retrospective study of 186 patients (56% of type 1 diabetes) from the Netherlands, dyspeptic symptoms, except for early satiety and abdominal pain, were not associated with delayed gastric emptying [13]. In a Talleyetal study. Patients with dyspepsia [14], the prevalence and severity of symptoms did not distinguish between delayed or normal gastric emptying patients. Assessment of the clinical condition of patients with gastroparesis is based on identifying symptoms and determining their severity. To quantify symptoms in clinical practice, the index of gastroparesis's main symptoms (GCSI-Gastroparesis Cardinal Symptom index) is widely used, which is the result of interviewing a patient with gastroparesis [9]. According to the severity of the clinical course, three degrees of severity of gastroparesis are determined. The first severity of gastroparesis is characterized by mild intermittent symptoms controlled by dietary modification and prevention of trigger factors. The second degree of gastroparesis severity proceeds with mild symptoms, but without weight loss of the patient, and prokinetic drugs and antiemetics are required for control. In the third degree, symptoms are not treatable, patients cannot maintain adequate oral nutrition, require enteral or parenteral nutrition, and are often in urgent need of care
[16, 17].

Prevalence and diagnosis of gastroparesis

The pathogenesis of gastroparesis is not fully understood, but autonomic neuropathy of the gastrointestinal tract is one of the important factors. [3,4] The prevalence is unknown, but various studies have suggested 30–65% in patients with long-term diabetes. Many patients with diabetic gastroparesis (BPH) suffer from gastrointestinal symptoms associated with reduced quality of life, which sometimes contribute to poor nutritional status caused by inadequate oral nutrient intake and vomiting and/or diarrhea. The association between gastrointestinal symptoms and the degree of delayed gastric emptying varied between studies, but bloating postprandial fullness, and abdominal pain is significantly correlated with the presence of gastroparesis. [7,9,11] Upper motor function parts of the gastrointestinal tract are critical in determining postprandial glucose levels. Many patients with delayed gastric emptying have unstable plasma glucose, and studies have also confirmed that glycated hemoglobin (HbA1c) levels are higher in these patients. [4,6] Since good metabolic control is important to prevent further diabetic complications, it is therefore important that patients with gastroparesis were correctly diagnosed and received adequate care.

It is widely believed that gastroparesis is rare and often underestimated, inadequately investigated, and poorly controlled. Gastric scintigraphy is the gold standard for measuring gastric emptying and diagnosing gastroparesis. However, this method is expensive and not always available. [17,18] Other methods for measuring gastric emptyings, such as breath tests, a wireless capsule, [18] and determination of gastric emptying using radiopaque markers [19], are also not available to all physicians. Therefore, it would be useful to have clinical parameters that would allow clinicians to suspect gastroparesis and act as a screening tool. Moreover, a test that the patient himself could perform would be even more beneficial. Recent research demonstrates that postprandial plasma glucose influences gastric emptying. [5,9,12]. Based on the presence of abnormal postprandial glucose levels and upper gastrointestinal symptoms in diabetic gastroparesis, we hypothesized that this information could be used clinically to identify gastroparesis suspicion.

The description of gastroparesis in many studies was mainly carried out, emphasising patients observed in specialized medical centers [1-3]. In this regard, various literature data more often describe patients with more severe gastroparesis symptoms or patients with multiple concomitant diseases that require referral for additional examination and treatment. These patients probably represent a small percentage of the gastroparesis population. The NIH Gastroparesis Consortium Gastroparesis Patient Register illustrates some of the disease burden, reduced quality of life, and gastroparesis comorbidities [4]. Idiopathic gastric paresis primarily affects young women, with acute onset in half of these patients [4]. Suddenly, many patients are overweight. [4]. Patients with diabetic gastroparesis have a more severe form of belching and vomiting than idiopathic gastroparesis [3]. Most patients do not improve over time [4]. Studies have also shown that gastroparesis patients have a reduced quality of life (QOL) [3–6]. These data, however, come from

studies of cohorts of patients who participated in clinical trials, often at specialized health centers. Factors such as specificity of symptoms, the severity of symptoms, and duration of gastroparesis symptoms that affect the quality of life are unclear.

Patients admitted with diabetic gastroparesis (DG) require more procedures, longer hospital stays, and higher costs than average. There is currently insufficient data on gastroparesis predictors in patients with diabetes and the relationship between them. The deceleration of the stomach's motor-evacuation function in patients with type 2 diabetes is attracting more and more attention, scientific and clinical interest as one of the key mechanisms for the development of gastroparesis [12,15,16]. Lack of compensation for carbohydrate metabolism, as well as the labile course of diabetes usually accompanies a number of chronic complications of the disease. Asymptomatic DH may manifest itself exclusively as a violation of glucose control, since slow gastric emptying reduces the peak postprandial glucose and insulin requirements [2,5,8,7]. According to the results of clinical studies aimed at determining the risk of mortality among patients with diabetes, taking into account all complications, gastroparesis is not associated with an increase in mortality. Several studies aimed to determine the prevalence of gastroparesis and gender differences among patients with diabetes [2,8] proved that the presence of comorbid factors (age, smoking, alcohol consumption) significantly reduces the quality of life of patients. Jung et al. (2009) found that DH is associated with increased morbidity and hospitalization, as well as health care costs and mortality rates in the working-age population [7,11,14]. Although gastroparesis has multiple etiologies, in a large single center study, of 146 patients with gastroparesis, 29% had diabetes, 13% developed symptoms after gastric surgery, and 36% had idiopathic gastroparesis. [9,12] It has been estimated that about 4% the adult population suffers from this disease, and the consequences of the Epidemiological Study showed that the incidence of gastric paresis in the United States is 24.2 cases per 100,000 population: 37.8 cases per 100,000 inhabitants for women and 9.6 cases per 100,000 inhabitants for men [11] Indeed, up to 40% of patients with DH may be asymptomatic. The prevalence of gastroparesis in type 2 diabetes varies widely. An analysis of a population study in Olmstead County (Minnesota, USA) demonstrated that gastroparesis is diagnosed only in 0.1% of individuals without diabetes, in 4.8% of patients with type 1 diabetes and 1.0% of patients with type 2 diabetes [3,12]. According to the scintigraphy results, a slowdown in the motor-evacuation function of the stomach is characteristic of 25–55% of patients with type 1 diabetes and 18–30% of patients with type 2 diabetes [3,6,7]. The prevalence of delayed gastric emptying in diabetic patients has been between 28% and 65%. Gastroparesis affects 20-50% of diabetics, especially with type 1 diabetes or long-term (> 10 years) type 2. It is usually associated with retinopathy, neuropathy and nephropathy, as well as poor glycemic control, as noted in the DCCT-EDIC study [12, 14.15]

Unfortunately, in our country, the actual prevalence of, as well as the social and economic significance of gastroparesis in patients with diabetes is currently not defined, since late diagnosis, the severe clinical course is determined by scientists, but not doctors at the stage of primary health care [11,14,18]. Most clinicians still believe that the early manifestations of gastric paresis in patients with diabetes are symptoms of various gastrointestinal tract diseases, and gastroenterologists often do not detect any organic changes in the stomach, and this complication is diagnosed too late. Severe DH has an unfavorable prognostic value. Timely medical correction of the stomach's motor-evacuation function in patients with moderate bradygastria contributes to the normalization of carbohydrate metabolism and prevents the labile course of the underlying disease. The predictors of DH remain poorly understood.

Socio-economic burden of gastroparesis

Hospital admissions data from the Nationwide Inpatient Sample, which includes a representative sample of 5 million to 8 million hospitalizations in the United States, suggest that gastroparesis rates did not change significantly between 1996 to 2000 and 2000 to 2006. [17,19] In contrast, in another study conducted between 1995 and 2004, the number of hospitalizations associated with gastroparesis increased by 138%, and the number of patients in whom gastroparesis was the main diagnosis for hospitalization increased by 158% [19]. The proportion of these patients

with diabetes increased from 21% in 1995 to 26.7% in 2006. This figure was greater than the corresponding changes in hospitalizations associated with diabetes (+ 58%), all hospitalizations (+13) and hospitalizations for other diseases associated with the gastrointestinal tract, i.e. gastroesophageal reflux disease (GERD), stomach ulcer, gastritis or nonspecific nausea/vomiting as the main diagnosis (3% to 76%). [16,17] Several factors may explain the increased morbidity and hospitalization for gastroparesis. These include an increased prevalence of diabetes or gastroparesis, changes in diagnostic criteria, severity and/or treatment of gastroparesis, better recognition and/or diagnosis of this disorder, or changes in hospital coding practices.

a nationwide inpatient sample, the data are not separated separately into idiopathic idiopathic gastroparesis. [17] At the National Institute for the Study of Diabetes, Digestive and Kidney Diseases (NIDDK), patients with type 1 diabetes mellitus required more hospitalizations, mainly for vomiting and dehydration, than for patients with Iresdiopathic Disease. SD type 2. In another study of patients with diabetes and upper gastrointestinal symptoms, patients with delayed gastric emptying spent more days in hospital than patients with normal gastric emptying.

Quality of life of patients with gastroparesis

The assessment of physical and mental components using the SF-36 questionnaire is lower in patients with idiopathic and diabetic gastroparesis, which indicates deterioration in the quality of life (QOL) [10,12]. There are no reliable data on the difference in QOL between patients with idiopathic and diabetic gastroparesis. In general, the effect of gastroparesis on quality of life is comparable to that of active inflammatory bowel disease [12, 15]. Physical quality of life is comparable to rheumatoid arthritis, but the mental quality of life is lower than in patients with rheumatoid arthritis [12]. Deterioration in quality of life, anxiety and depression were higher in patients with more severe abdominal pain [15]. Although a cross-sectional study of 135 diabetic patients with gastrointestinal tract symptoms showed that their quality of life is lower than in patients with normal or delayed gastric emptying [15], it is not entirely clear if this deterioration in the quality of life is due to gastrointestinal symptoms or co-morbidities (such as depression) and/or medications (such as opiates)

Our understanding of the impact of gastroparesis on quality of life in the community is limited. Among the cohort of people with predominant type 2 diabetes in the population, physical and mental assessments of the SF-36 scale were lower in patients with symptoms of diabetes and gastrointestinal tract compared with the general population [10,12]. The decrease in QoL was more pronounced in patients who had more gastrointestinal symptoms but did not depend on age, gender, smoking, alcohol consumption and type of diabetes. Surprisingly, the absolute SF-36 scores in the population-based study were about twice as high as the NIDDK Study, which included patients from specialized medical centers [9,12,15]. Gastroparesis is also associated with varying degrees of unemployment, declining income, and absenteeism. [13,15]

Some studies have questioned the effect of delayed gastric emptying (OB) on typical symptoms because many patients have no symptoms of delayed gastric emptying [17,19] and because symptom profiles are similar in patients with diabetes and gastrointestinal symptoms. with normal or delayed coolant. [9,14]. Also, in therapeutic trials of prokinetic agents for gastroparesis treatment, OB improvement and reduction in symptoms were not correlated [1,4]. However, some of these findings can be explained by the limitations of the methods used to measure OB in these studies. A meta-analysis of cross-sectional studies assessing the relationship between symptoms and OB retention identified only two studies in patients with diabetes in which OB was assessed using optimal techniques. [11.16]

In these studies, early satiety and fullness were associated with coolant retention in DM, but other symptoms (i.e., nausea, vomiting, abdominal pain, or bloating) were not associated with coolant retention. In comparison, all these symptoms were associated with a delayed OB among all patients (i.e., with and without diabetes). Why delayed coolant in people with diabetes may be asymptomatic is unclear. One possible explanation: afferent dysfunction of the vagus nerve [7]. Supporting this hypothesis, hyperglycemia (ie, higher HbA1c) correlates with less severe symptoms

during the study and during the perfusion of intestinal lipids.5,8 Similar discrepancies between symptoms and objective results exist in other diseases (eg, Crohn's disease)

Differential diagnosis

By definition, gastroparesis symptoms are similar to benign or malignant gastric outlet obstruction [8], which can be easily ruled out with endoscopy. Gastroparesis is easily treatable, unlike most other organic causes of upper gastrointestinal symptoms (eg, acute cholecystitis) [11,14]. There is a bi-directional relationship between diabetes mellitus and pancreatic cancer (adenocarcinoma). [10] Long-term type 2 diabetes is a risk factor for pancreatic cancer. Conversely, robust epidemiological studies suggest that diabetes may be a manifestation of overt or latent pancreatic cancer. Indeed, ~ 1% of people with new-onset diabetes over 50 years of age have been diagnosed with pancreatic cancer within 3 years [10]; patients have hyperglycemia for an average duration of 30 to 36 months before a cancer diagnosis. Similar findings have been reported among US veterans [10]. Therefore, the clinician should carefully investigate (especially food-related) gastrointestinal symptoms in newly diagnosed diabetic patients and there should be a low threshold for examining these symptoms. Diabetes mellitus is also associated with chronic intestinal pseudo-obstruction, which results in abnormal motility and enlargement of the small intestine [10,14]. When the stomach is involved in this process, coolant retention can occur. If necessary, to detect chronic intestinal pseudo-obstruction, visualization of the small intestine's abdominal cavity and/or manometry is performed.

Differentiating gastroparesis from other inorganic gastrointestinal disorders associated with nausea and vomiting may be more challenging [13,15,17]. Except for weight loss, which is more common in patients with delayed OB, upper GI symptoms do not differentiate between diabetic patients with normal, delayed, or rapid OB. [2,11,16,19] Similarly, in the NIDDK cohort of patients with gastroparesis and diabetes, non-diabetic patients with chronic nausea and vomiting, patients with normal and delayed OB were practically indistinguishable [17,19]. Careful history taking is important to differentiate the regurgitation in GERD from vomiting that occurs with gastroparesis [10]. This distinction is critical because regurgitation is easily and efficiently managed through behavioral intervention (i.e. diaphragmatic breathing).

Other possible explanations for gastrointestinal symptoms (e.g., alcohol or drugs such as nonsteroidal anti-inflammatory drugs or opioids) should also be sought [7,17] In rare cases, metabolic, endocrine disorders can also mimic gastroparesis. Adrenal insufficiency can lead to symptoms similar to gastroparesis, as well as associated with delayed OB [4,17]. Physical signs such as hyperpigmentation of the mucous membranes, skin scarring, and abnormally low cortisol levels or abnormal response of cortisol to adrenocorticotropic hormone suggest this condition. Renal tubular acidosis (in children) [15] and hypercalcemia have been mistaken for gastroparesis; basic laboratory testing, including pH, chloride, and calcium levels should rule out this possibility.

Nutrition for gastroparesis.

Most patients with BPH have a caloric intake below the recommended level, as well as a deficiency of macro- and micronutrients [21]. The calorie requirement can be calculated by multiplying 25 kcal by your current body weight in kilograms. The American Diabetes Association (ADA) standard dietary composition for diabetes mellitus is low in carbohydrate and high in fiber and may not be suitable for gastroparesis patients. Dietary recommendations should be based on measures that promote gastric emptying or, at least in theory, do not slow gastric emptying. Fats and fiber tend to delay emptying, so intake should be kept to a minimum [22]. One nutritional option is a phased approach, starting with clear liquids with nutritional value, followed by soups and smoothies, and then adding solids that do not increase gastroparesis [23]. Small, low-fat meals are recommended four or five times a day. Avoid carbonated liquids to limit stomach distension, eliminate insoluble fiber, high-fat foods, and stop using tobacco and alcohol [4]. Patients are instructed to take fluids throughout the meal, sit or walk for 1–2 hours after meals [7]. If the above measures are ineffective, the patient may be advised to consume most of the calories in the form of liquid, as patients with gastroparesis often retain fluid emptying [4]. Also, hyperglycemia can reduce the accelerating effects of prokinetic agents. Glucose levels must be maintained below 180

mg / dL to avoid suppression of myoelectric control and gastric motility [11]. A retrospective study of diabetic patients who underwent gastric scintigraphy showed that higher HbA1c levels were significantly associated with higher delay of food in the stomach after 4 hours [22].

Conclusion

The prevalence of diabetes is increasing worldwide, with global economic implications associated with the disease's complications. Today, the development of diabetic gastroparesis is considered a serious problem. This complication not only aggravates the course of the underlying disease but also worsens control and treatment. The symptoms associated with diabetic gastroparesis impact the patient's quality of life and increase the economic burden of the disease. This is why it is so important to diagnose and treat diabetic gastroparesis in time. This complication should be detected at the level of tertiary health care and be in the focus of attention of primary care. This requires the development of available methods for identifying risk groups for DH, as well as an algorithm for diagnosing gastroparesis at an early stage.

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DYNAMICS OF ANTHROPOMETRIC INDICATORS IN WOMEN OF FERTILIZED AGE WITH CUSHING SYNDROME AFTER SURGICAL AND MEDICINAL TREATMENT

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ABSTRACT

We studied anthropometric indicators' dynamics in 153 women of fertile age with Cushing's syndrome, who applied for excess weight, lack of menstruation and infertility in the RSSPMC of Endocrinology of the PHM of the Republic of Uzbekistan, from 2000 to the present. The control group consisted of 20 women with obesity of varying degrees and without menstrual irregularities. According to the American Association of Endocrinologists' classification from 2012, all female patients with SC registered since 2000 (the dead are not included) were distributed according to etiology as follows: 1 g. - patients with ACTH-dependent CS– 115 (75.2%), 2 g. - with ACTH-independent CS - 35 (22.9%) and group 3 - patients with ACTH-ectopic CS - 3 (1.9%). 6 months after surgical and drug treatment, in groups 1 and 2 of patients, there was a significant improvement compared with the average OT, OB, OT / OB data before treatment. In contrast, in patients of 3 groups, there were significant changes in the average OT, OB, OT values / OB after 6 months of treatment not established.

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ДИНАМИКА АНТРОПОМЕТРИЧЕСКИХ ПОКАЗАТЕЛЕЙ У ЖЕНЩИН ФЕРТИЛЬНОГО ВОЗРАСТА С СИНДРОМОМ КУШИНГА ПОСЛЕ ХИРУРГИЧЕСКОГО И МЕДИКАМЕНТОЗНОГО ЛЕЧЕНИЯ

АННОТАЦИЯ

Изучена динамика антропометрических показателей у 153 женщин фертильного возраста с синдромом Кушинга, обратившихся за лишним весом, отсутствием менструации и бесплодием в РСЦПМЦ Эндокринологии РНЖМ Республики Узбекистан с 2000 года по

настоящее время. Контрольная группа состояла из 20 женщин с различной степенью ожирения и без нарушений менструального цикла. По классификации Американской ассоциации эндокринологов с 2012 года, все пациентки с ЗК, зарегистрированные с 2000 года (мертвые не включены), были распределены по этиологии следующим образом: 1 г. - пациентки с АКТГ-зависимым ГК - 115 (75,2%), 2 г. - с АКТГ-независимым ГК - 35 (22,9%) и 3-я группа - пациентки с АКТГ-эктопическим ГК - 3 (1,9%). Через 6 месяцев после хирургического и медикаментозного лечения в 1-й и 2-й группах пациентов наблюдалось значительное улучшение по сравнению со средними данными ОТ, ОТ, ОТ/ОБ до начала лечения. Напротив, у пациентов 3-х групп наблюдались значительные изменения средних значений ОТ, ЛО, ОТ/ЛО после 6 месяцев лечения, которые не были установлены.

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КУШИНГ СИНДРОМИ БЎЛГАН ФЕРТИЛ ЁШДАГИ АЁЛЛАРДА ХИРУРГИК ВА ТИББИЙ ДАВОЛАНИШДАН КЕЙИНГИ АНТРОПОМЕТРИК КЎРСАТЧИЛАРНИНГ ДИНАМИКАСИ

АННОТАЦИЯ

Антропометрик курсаткичларнинг динамикаси 2000 йилдан то хозирги кунгача РСНПМЦЭ МЗРУзда ортикча вазн, хайз куришининг етишмаслиги ва бепуштлик учун мурожат килган Кушинг синдроми булган тугрук ешидаги 153 аелда урганилган. Назорат гурухи турли даражадаги семириб кетган ва хайз пайтида носимметрикликлар булмаган 20 аелдан иборат эди. Америкалик эндокринологлар ассоциациясининг 2012 йилги таснифига кура, 2000 йилдан бери руйхатга олинган Кушинг синдроми билан касалланган барча аел беморлар (улим хисобга олинмайди) этиология буйича куйидагича таксимланган: 1 гр. – АКТГ га боглик булган Кушинг касаллиги булган беморлар - 115 (75,2%), 2 гр. -АКТГ дан мустакил Синдром Кушинг билан- 35 (22,9%) ва 3 гурух – АКТГ эктопик Синдром Кушинг билан касалланганлар - 3 (1,9%). 1 ва 2 гурухларда жаррохлик ва дори-дармон билан даволашдан 6 ой утгач, беморлар даволанишдан олдин ОТ,ОБ, ОТ / ОБ уртача курсаткичларига нисбатан курсаткичларини сезиларли даражада яхшиланганлигини курсатди, 3-гурухдаги беморларда эса ОТ,ОБ уртача кийматларида сезиларли узгаришлар юз берди. 6ойлик даволанишдан кейин ОБ аникланмаган.

Калит сузлар: АКТГ га боглик ва АКТГ га боглик булмаган Кушинг синдроми, гиперкортицизм, репродуктив еш, гиперкортизолемия, гипогонадизм, аменорея.

Relevance. The leading pathogenetic factor in developing the clinical picture in endogenous corticorticism is hypercortisolemia, which is proved by similar symptoms with long-term treatment with synthetic glucocorticoids (Cushing's drug syndrome). In this regard, the clinical manifestations in various forms of endogenous hypercortisolism (ACTH-dependent and ACTH-independent) are of the same type and can be considered together [1-5].

The clinical picture of hypercortisolism includes dysplastic obesity, trophic changes in the skin, arterial hypertension, systemic osgeoporosis, myopathy, steroid diabetes mellitus, hypogonadism, secondary immunodeficiency, steroid encephalopathy, and emotional and mental disorders. Most researchers note the relative rarity of all symptoms in the advanced stage and the disease's relapse [6-10].

Dysplastic obesity is one of the most striking and common symptoms in endogenous hypercortisolism (observed in 90% of patients). Excessive fat deposition is noted in the body, abdomen, and face. On the upper and lower limbs, on the contrary, there is a decrease in body fat, the limbs are "thin" in comparison with other parts of the body. In patients with a severe disease

course (usually young people), obesity may be absent. However, a characteristic redistribution of the subcutaneous fat layer is observed to one degree or another [11].

Thus, changes in patients' appearance during the initial examination (increase in body weight, redistribution of adipose tissue, skin manifestations) suggest the presence of SC. Simultaneously, the dynamics of changes in the patient's appearance at the stages of treatment indicate remission or relapse of the disease even before a more detailed examination [12].

A decrease in body weight and a decrease in adipose tissue redistribution is one of the main indicators of the effectiveness of the treatment. and macronodular hyperplasia of the adrenal glands, excess body weight remains. This may be due to the hypothalamic genesis of obesity (with ACTH-CGS), as well as the use of unreasonably high doses of glucocorticoids during replacement therapy [12-15].

In almost all patients, after corticosteroma removal (in the absence of malignant growth and distant metastases), body weight and distribution of subcutaneous adipose tissue are normalized in the first 6 months [16-18].

Based on the foregoing, early diagnosis, the study of long-term treatment results and the development of optimal diagnostic and treatment algorithms, monitoring quality of life is relevant both in scientific and practical terms [19-20].

The foregoing determines the relevance of studies aimed at developing an integrated approach to the treatment of obesity in young women with SC, taking into account the characteristics of metabolic and hormonal imbalance, eating behavior and reproductive disorders, which can improve the quality of life of patients and reduce the risk of diseases associated with obesity.

In the literature, there are very few publications devoted to assessing the effectiveness of SC's surgical treatment, taking into account the study of anthropometry indicators. A stimulating factor for this work was the lack of sufficient information about patients' state after surgical treatment in terms of anthropometric parameter dynamics. These data can solve the problems of rehabilitation of patients and their return to a full-fledged lifestyle.

All of this was the reason for this study.

The study aimed to study anthropometric parameters' dynamics in women of fertile age with SC before and 6 months after treatment.

Materials and research methods. The dynamics of anthropometric indicators were studied in 153 out of 212 women with Cushing's Syndrome, who applied for excess weight, lack of menstruation and infertility in the PSSPEMC MH RUz, starting from 2000 to the present. The control group consisted of 20 women with varying degrees of obesity and without menstrual irregularities.

According to the 2012 classification of the American Association of Endocrinologists, all female patients with KS who have been registered since 2000 (deaths not included) were distributed by etiology as follows: 1 gr. - patients with ACTH-dependent CK - 115 (75.2%), 2 gr. - with ACTH-independent SC - 35 (22.9%) and group 3 - patients with ACTH-ectopic SC - 3 (1.9%). 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. The age of patients in group 1 ranged from 20 to 39 years and was 28.3 ± 0.64 years. In group 2, 22–37 years old, on average 30.4 ± 0.51 years, and in group 3 - on average, 29.4 ± 0.51 years.

All patients underwent a complex of studies, which included general clinical (general blood and urine analysis), biochemical (blood glucose, electrolytes of blood, urea, creatinine, lipid spectrum), hormonal (ACTH, LH, FSH, prolactin, free testosterone, blood cortisol, free testosterone, estradiol, progesterone, insulin, etc.), ultrasound of internal and genital organs, as well as magnetic resonance imaging (MRI) of the Turkish saddle and computed tomography (CT) of the adrenal glands, chest x-ray, spinal X-ray densitometry.

The patients also underwent a study of the rhythm of daily cortisol secretion in the blood, determination of free cortisol in daily urine, and a large test with dexamethasone. If necessary, a glucose tolerance test was performed.

Anthropometric study - was carried out immediately during the initial examination, in dynamics and included the determination of height, MT, determination of body mass index (BMI) (Quetelet index), calculated by the formula: BMI (kg / m2) = (MT, kg) / (height, m) 2. The degree of obesity was determined following the BMI values recommended by the WHO (1997). Determination of the nature of the distribution of adipose tissue was carried out per the ratio (ratio) of the waist circumference (OT) to the length of the thigh circumference (OB). OT / OB ratio more than 0.85 was regarded based on WHO recommendations (1997) as abdominal obesity (AO), less than this value - as gluteofemoral (GFO).

When prescribing therapy regimens, we primarily relied on various international guidelines - Managementofobesity 115, NationalGuldeline (ScottishIntercollegiate GuidelinesNetwork, PartofNHSQualityScotland, 2010, 96 pages) .; etc.

The methods of treatment for ACTH-ZSC were surgical (TAG and AE, surgical treatment of ACTH ectopic foci), radiation therapy (RT) and drug therapy (MT), as well as combination therapy (CTe).

All patients with KS received treatment at the Department of Neuroendocrinology and Neurosurgery of the RSNPMTSE MH RUz named after acad. J.H. Turakulova. Transnasal adenomectomy of the pituitary gland (TAG) was performed primarily in 107 (50.5%) patients with ACTH-CGS, of which the second - in 10 (9.3%) (Prof. Powell M.P. (Great Britain, London), Ph.D. Fayzullaev.R.B., Ph.D. Makhkamov K.I.). Adrenalectomy was performed in only 43 (20.3%) patients, including 11 patients with ACTH-BSC. All patients with surgical treatment developed compensation of the condition against the background of HRT (they were prescribed prednisolone therapy at a dose of 5 to 15 mg).

The patients were prescribed non-drug therapy and drug therapy. Non-drug therapy included general recommendations for measuring weight every day before and after exercise therapy, counting daily calories, and avoiding easily digestible carbohydrates. Drug therapy included the following schemes:

Group 1 was prescribed a combination of Siofor 1000 mg per day + veroshpiron 100 mg twice a week + iodmarine 100 mg in the morning + levothyroxine 50 mg in the morning + antidepressants in courses (amitriptillin, phenibut, resetin, etc.).

Group 2 was prescribed a combination of Siofor 1000 mg per day + veroshpiron 100 mg twice a week + iodmarine 100 mg in the morning + levothyroxine 50 mg in the morning + reduxin 15 mg in the morning after meals + antidepressants in courses (amitriptillin, phenibut, resetin, etc.).

Group 3 was prescribed a combination of iodmarine 100 mg in the morning + levothyroxine 50 mg in the morning.

The data obtained were processed using Microsoft Excel and STATISTICA_6 computer programs. The mean values (M) and standard deviations of the means (m) were calculated. The significance of differences in the level between the groups was assessed by the value of the confidence interval and the Student's test (p). Differences were considered statistically significant at $p < 0.05$.

Research results. It was found that remission was achieved in 82.4 ± 5.63% of patients of fertile age, and in 17.6 ± 5.63% of patients, in general, remission was not achieved. Table 1 shows the activity of the process of hypercortisolism in various forms of the disease.

Table 1

Characteristics of the state of patients with KS according to the register (n = 153)

	Patient condition	AKTH-ZSK (%±m) n= 115	AKTH-NSK (%±m) n= 35	ACTH ESC (%±m) n= 3	Total (%±m) n= 153
	Remission n=126	n=89 77,4±3,22	n=34 97,1±4,12***	n=3 100,0±2,83	n=126 82,4±5,63

	Active (NDR, R) n=27	n=26 22,6±2,63	n=1 2,9±1,83**	n=0	n=27 17,6±5,63

Note: - reliability of differences compared to ACTH dependent SC, where *** p <0.001. (PDR-patients who did not achieve remission, R-patients who developed a relapse)

As can be seen from Table 1, a high remission rate was found in patients with ACTH-NZSC, which amounted to 97.1 ± 4.12% of cases, and only in 1 case (2.9%), a relapse of the disease developed due to an unfavorable outcome. with the development of metastases after surgery for adrenal carcinoma.

According to the research results of Narimova G.D., in 2018, 71% of patients with SC in RUz achieved remission [7]. Moreover, the smallest remission was observed in patients with ACTH – ZSK and amounted to 65.3%, consistent with the literature data.

Table 2 presents anthropometry data by the group before treatment. As can be seen from Table 2, the most common patients with BMI grade 1 in all groups.

Further, to carry out the study, we calculated other anthropometric data for the groups before treatment. As shown in Table 2, in our study, persons with grade 2 obesity prevailed - 104 cases out of 153 (67.9)%. In second place in frequency was obesity of the 1st degree - 35 cases (22.8%) and the third - obesity of the 3rd degree - 15 cases (9.8%).

Table 2.

Average BMI by the group before treatment.

№	Group	30,0-34,9 kg/m^2		35,0-39,9 kg/m^2		≥40 kg/m^2	
1	Group 1	n= 25	33, 5 ± 3,8	n= 91	37,8 ± 3,2	n= 4	41,2 ± 4,6
2	Group 2	n= 9	34, 3 ± 4,5	n= 12	37,6 ± 4,1	n= 9	42,3 ± 3,5
3	Group 3	n= 1	34, 6 ± 4,4	n= 1	38,5 ± 3,7	n= 1	42,9 ± 3,7
	Total	35		104		15	

Table 3 presents the data on OT, OT, OT / OV by groups before treatment. As shown in Table 3, the mean values of OT, OT, OT / OV corresponded to the degree of BMI in groups and increased with its increase.

Table 3.

Average values of OT, OT, OT / OV by groups before surgical treatment

Group	30,0-34,9 kg/m^2			35,0-39,9 kg/m^2			≥40 kg/m^2		
	OT	OB	OT/OB	OT	OB	OT/ OB	OT	OB	OT/ OB
Group 1	85,1± 13,8	89, 9 ± 11,6	0,95± 0,03	87,4± 12,4	93, 7 ± 12,8	0,93± 0,05	105,6± 13,3	110, 4 ± 13,8	0,95± 0,07
Group 2	86,3± 11,5	88, 7 ± 10,9	0,97± 0,02	89,7± 14,7	94, 8 ± 12,8	0,94± 0,06	107,8± 12,4	111, 9 ± 12,8	0,98± 0,06
Group 3	87,2± 11,3	89, 2 ± 10,9	0,97± 0,03	88,7± 11,6	95, 7 ± 12,9	0,92± 0,02	103,1± 12,5	112, 9 ± 11,9	0,91± 0,07

In the postoperative period, the patients were prescribed non-drug and drug therapy according to the above schemes in groups.

Table 4 presents anthropometry data by groups 6 months after treatment.

Table 4.

Average BMI indices by groups 6 months after treatment.

№	Group	30,0-34,9 kg/m^2	35,0-39,9 kg/m^2	≥40 kg/m^2

1	Group 1	n=106	26, 7 ± 3,5*	n= 14	34,2 ± 2,9*	n= 0	-
2	Group 2	n= 22	28, 1 ± 3,2*	n= 7	33,4 ± 3,2*	n= 1	37,5 ± 3,6
3	Group 3	n= 3	32, 8 ± 3,9	n= 0	0	n= 0	-
	Total	131		21		1	

Note: * - reliability of differences p <0.5 compared with the data before treatment.

As shown in Table 4, there was a significant decrease in BMI of 1 and 2 degrees 6 months after surgical and drug treatment in all groups of patients. Simultaneously, in patients of group 3 with a BMI of grade 3 after 6 months, a tendency towards a decrease in BMI was achieved.

Besides, restoration of fertility and pregnancy was achieved in group 1 without stimulation treatment - in 23.0% of cases (in 30 patients).

Table 5 shows the data on OT, OB, OT / OB by groups 6 months after treatment.

As can be seen from table 5, in the 1st and 2nd groups of patients, there was a significant improvement in indicators compared to the mean values of OT, OB, OT / OB before treatment, while in patients of the 3rd group, there were significant changes in the mean values of OT, OB, OT / OB after 6 months of treatment not established.

Table 5.

Average values of OT, OT, OT / OV by groups 6 months after treatment.

Group		**30,0-34,9 kg/m^2**			**35,0-39,9 kg/m^2**			**≥40 kg/m^2**		
		OT	**OB**	**OT/OB**	**OT**	**OB**	**OT/OB**	**OT**	**OB**	**OT/OB**
1	**Group 1**	**80,1± 6,4 ***	**85, 4 ± 7,8***	**0,94± 0,04**	**82,1± 8,3 ***	**89, 4 ±9,2***	**0,92± 0,05**	**100,4± 8,9**	**107, 8 ± 9,3**	**0,93± 0,06**
2	**Group 2**	**79,1± 4,3 ***	**86, 5 ± 6,7 ***	**0,91± 0,03**	**83,2± 8,4***	**89, 3 ±8,4***	**0,93± 0,04**	**105,4± 8,9**	**109, 4 ± 9,3**	**0,96± 0,05**
3	**Group 3**	**89,4±,9 ,4**	**91, 7 ± 9,7**	**0,97± 0,02**	**91,5± 12,3**	**97, 8 ±11,2**	**0,93± 0,03**	**106,7± 11,7**	**116, 5 ± 12,7**	**0,91± 0,04**

Note: * - reliability of differences p <0.5 compared with the data before treatment.

Discussion of the results obtained. Like many pathological conditions, SC contributes to developing other complications, including obesity and reproductive dysfunction [7]. Despite this functional state of the gonads in KS, at the same time, the issues of overweight therapy in KS, the combination of drug and non-drug treatment in the postoperative period have not been sufficiently studied. In the literature, there are only separate works devoted to this issue in which they are limited to the study of the level of total estrogens [15, 17, 18].

Back in 1990, Manusharova R.A, Veĭnberg M.E described the main parameters of the reproductive system in 121 women with Itsenko-Cushing's disease and 87 with primary obesity before and after therapy. Itsenko-Cushing's disease was treated with agents affecting the adrenal glands (chloditan, destruction of one or both adrenal glands, unilateral or bilateral adrenalectomy) and the hypothalamic-pituitary zone (parlodel, peritol, nakom, X-ray therapy). Combination therapy for primary obesity included a low-calorie diet (about 1200 kcal) with 1-2 fasting days a week, a set of therapeutic exercises, physiotherapy and balneotherapy.

The results obtained allowed the authors to conclude that pathogenetic therapy leading to a stable clinical and hormonal remission of Itsenko-Cushing's disease and a decrease in body weight in primary obesity, as a rule, leads to the restoration of the functioning of the reproductive system in such patients [129].

According to our research, after 6 months. after the surgical treatment and the implementation of the drug, as well as non-drug treatment, significant shifts from the initial data appeared in groups I and II. Namely, a significant decrease in BMI, OT, OB, OT / OB was observed. Simultaneously, in patients of group 3, no significant changes in BMI, OT, OB, OT / OB were found after 6 months of treatment. Also, positive changes in weight had an effect on the

reproductive function of patients: spontaneous restoration of fertility was observed and pregnancy was achieved in patients of group 1 - in 23.0% of cases (in 30 patients).

Conclusions: 1) Thus, the inclusion in the traditional treatment of patients with SC of various groups in the postoperative period of drug and non-drug treatment contributes to a significant improvement in clinical parameters - a decrease in BMI, which indirectly indicates that in the studied groups of women obesity is one of the markers of reproductive disorders function.

2) Optimization of the treatment of obesity in women of reproductive age with SC is based on the compilation of individual programs, the choice of which is determined by the values of anthropometric indicators, the state of hormonal and metabolic status, the characteristics of eating behavior and personality-emotional sphere, the state of menstrual and reproductive function.

3) A complex of therapeutic measures, taking into account the developed algorithm for the individual selection of therapy for obesity, makes it possible to effectively reduce and maintain the achieved body weight and improve somatic and reproductive health in women of childbearing age with SC.

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ЎЗБЕК ТИББИЁТ ЖУРНАЛИ
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MODERN APPROACHES OF THE TREATMENT OF PROLACTINOMAS IN WOMAN WITH HYPERPROLACTINEMIA

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ABSTRACT

Hyperprolactinemia syndrome is one of the most common neuroendocrine disorders. Hyperprolactinemia syndrome – a symptom complex that develops against the background of hyperprolactinemia and is accompanied by menstrual and reproductive disorders in women. In women aged 25 – 34 years, the incidence of hyperprolactinemia is 23,9 per 100000 population per year. In 60% of cases,hyperprolactinemia outside lactation is caused by lactotrophic adenomas of the pituitary gland (prolactinomas), which account for about 40% of all pituitary adenomas. The incidence of prolactinomas, on average, ranges from 6 to 10 new cases per 1 million adult population per year. The article is dedicated to topical issues of the treatment of prolactinomas.

Keywords: Prolactin, hyperprolactinemia, hypophysis, macroprolactinoma, microprolactinoma,cabergolin, clomiphene citrate.

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СОВРЕМЕННЫЕ ПОДХОДЫ ЛЕЧЕНИЯ ГИПЕРПРОЛАКТИНЕМИИ ПРИ ПРОЛАКТИНОМАХ У ЖЕНЩИН

АННОТАЦИЯ

Гиперпролактинемия является одним из наиболее часто встречаемых расстройств гипоталамо-гипофизарной системы. Синдром гиперпролактинемии – симптомакомплекс, который развивается на фоне гиперпролактинемии и сопровождается нарушениями менструальной и репродуктивной функций у женщин. У женщин в возрасте 25-34 лет частота встречаемости гиперпролактинемии составляет 23,9 на 100000 население в год. В 60 % случаев гиперпролактинемия вне лактации вызывается лактотрофными аденомами гипофиза (пролактиномами), на долю которых приходится около 40% всех аденом гипофиза. Заболеваемость пролактиномами, в среднем, колеблется от 6 до 10 новых случаев на 1 миллион взрослого населения в год. Статья посвящена актуальными вопросами лечения синдрома гиперпролактинемии опухолевого генеза.

Ключевые слова: Пролактинома, гиперпролактинемия, гипофиз, макропролактинома, микропролактинома, каберголин, кломифен цитрат.

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ПРОЛАКТИНОМАДА АЁЛЛАРНИ ГИПЕРПРОЛАКТИНЕМИЯ ХОЛАТЛАРДА ДАВОЛАШНИНГ ЗАМОНАВИЙ ЁНДАШУВЛАРИ

АННОТАЦИЯ

Гиперпролактинемия гипоталамо-гипофизар тизимнинг кенг тарқалган бузилишларидан бири ҳисобланади. Гиперпролактинемия синдроми − гиперпролактинемия фонида ривожланувчи, аёлларда менструал ва репродуктив бузилишларга олиб келувчи симптомакомплекс ҳисобланади. 25− 34 ёшли аёллар орасида гиперпролактинемиянинг учраш частотаси йилига 100000 аҳолига 23,9 ни ташкил этади. 60% дан ортиқ ҳолатларда лактация давридан ташқари гиперпролактинемияга гипофизнинг лактотроф аденомалари (пролактинома) сабаб бўлиб, барча гипофиз аденомалари ичида тахминан 40% ни ташкил этади. Пролактинома билан касалланиш кўрсаткичи йилига 1 миллион аҳолига 6 тадан 10 тагача ҳолатни ташкил қилади. Ушбу мақола пролактиномани даволашнинг актуал саволларига бағишланган.

Калит сўзлар: Пролактинома, гиперпролактинемия, гипофиз, макропролактинома, микропролактинома, каберголин, кломифен цитрат.

Hyperprolactinemia syndrome, characterized by excessive pathological secretion of prolactin, accompanied by the development of hypogonadism in men and women, and possibly pathological discharge from the mammary glands, is a very common pathology [1]. In women aged 25-34 years, the incidence of hyperprolactinemia is 23.9 per 100,000 population per year [2, 3]. The incidence of hyperprolactinemia in women of reproductive age is 24.2% and ranges from 11 to 47% in various individual studies [4].

Diagnosis of hyperprolactinemia is a difficult task, requiring the determination of the content of prolactin (PRL) and its isoforms with high biological activity, a thorough study of the historical exclusion of various somatic, endocrine and neuroendocrine disorders [5, 12, 14].

Prolactinoma is the most common pituitary tumor (about 40%). The annual incidence ranges from 6-10 to 50 cases per 1 million population, and its average prevalence in women is 30 cases per 100,000 population [1]. The disease in women is often recorded at the age of 20-50 years (the peak prevalence is 25-34 years). More than 90% of prolactinomas are microprolactinomas (<1.0 cm in diameter), while the rest are macroprolactinomas (≥1.0 cm) [2, 15].

The goals of treatment of patients with prolactinoma are as follows: normalization of prolactin levels; reduction in the size of the tumor; elimination of symptoms of hyperprolactinemic hypogonadism and restoration of fertility; prevention of recurrence and resumption of tumor growth, evaluation of the results of laboratory and instrumental research methods in women with hyperprolactinemia of various origins.

In the treatment of hyperprolactinemic conditions, 3 generations of drugs can be distinguished. The first generation of drugs is Bromocriptine, Lizurid, Pergolid, Tergurid, Abergin [7, 11].

Materials and methods: Examination of patients was performed based on the PSSPEMC named after academician Y.H.Turakulov in 2018-2020. 90 women were examined with hyperprolactinemia. All examined patients were divided into 3 groups: 30 patients with prolactinomas, 30 patients with polycystic testicles syndrome and 30 patients with hypothyroidism. All patients underwent conventional research methods (general clinical and biochemical blood tests, radioimmunological hormonal blood tests, MRI of the pituitary gland, ultrasound of the pelvic organs). The age of the patients in our study at the time of treatment was 33.5 ± 11.5 years,

minimum - 17.0 years, maximum - 49.0 years. The duration of the disease ranged from 6 months to 16 years. The age gradation of patients by group is shown in Figure 1.

Diagnosis of hyperprolactinemia syndrome consists of the following stages: laboratory confirmation of hyperprolactinemia, exclusion of symptomatic forms of the disease, exclusion of the phenomenon of macroprolactinemia, visualization of the hypothalamic-pituitary region, visualization of the pelvic organs and assessment of sexual function [6, 7, 12].

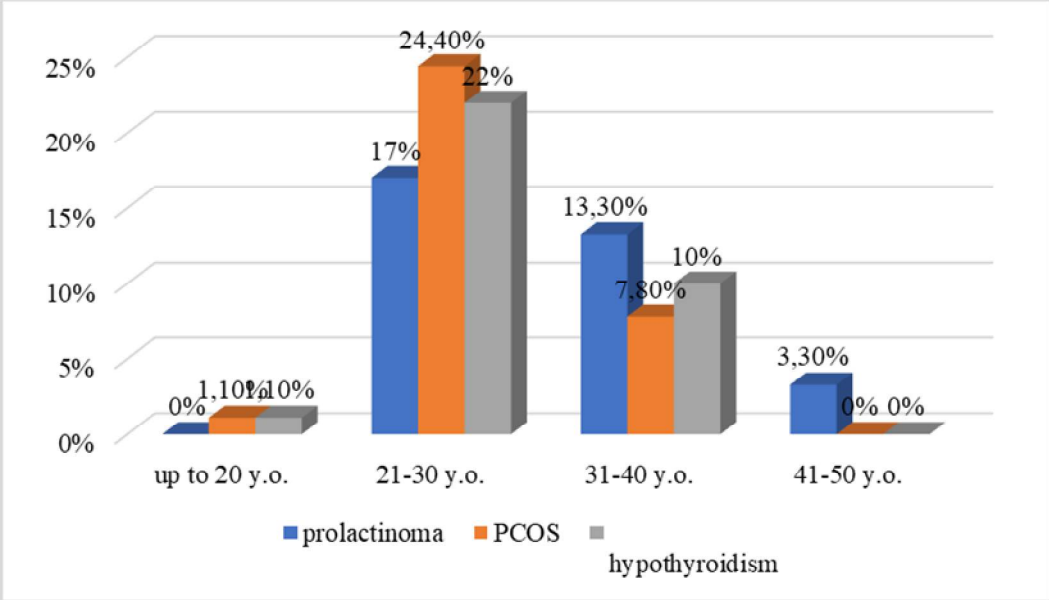

Figure: 1. Age gradation of women with hyperprolactinemia syndrome by groups

Determination of the basal prolactin level for the diagnosis of hyperprolactinemia syndrome

According to the latest clinical guidelines for the diagnosis and treatment of hyperprolactinemia syndrome released in 2011, to establish hyperprolactinemia, it is sufficient to determine the level of prolactin in the blood serum once. Currently, from the standpoint of evidence-based medicine, dynamic testing of the prolactin content for the diagnosis of hyperprolactinemia is considered inappropriate [8, 9, 15]. A higher than normal level of PRL confirms the diagnosis, provided that venipuncture is performed without undue stress for the patient and taking into account all possible physiological influences on prolactin secretion [10, 16, 17].

According to the literature, with hyperprolactinemia of tumor genesis, the level of prolactin in the blood serum is significantly higher than with hyperprolactinemia of non-tumor genesis, since, according to international expert recommendations published in 2006, basal prolactin levels can be used to judge the genesis of hyperprolactinemia [11, 18, 19].

The content of the basal level of total prolactin in the total group of examined patients is presented in Table 1.

Table №1.

The level of total prolactin in the examined patients depending on the genesis of hyperprolactinemia

	Prolactinoma	PCOS	Hypothyroidism
Number of patients	30	30	30
Median	1812	963	958
Lower quartile	1224	588	551
Upper quartile	2973	1488	1115
Kruskal-Wallis criterion p =	p_{1-2}<0,001	p_{2-3}=0,990	p_{1-3}<0,001

An increased level of prolactin is observed in all patients with prolactinoma (30, 100%), in 21 with PCOS (70%) and 24 with hypothyroidism (80%). When assessing the dependence of the level of total prolactin on the cause of hyperprolactinemia, between tumor hyperprolactinemia

(prolactinoma) and non-tumor genesis (PCOS, hypothyroidism), significant differences were obtained (Kruskal-Wallis criterion, p1-2 <0.001, p1-3 <0.001), but in the group among women with hypothyroidism between patients with PCOS, no significant differences were obtained p2-3 = 0.990, Fig. 2.

Determination of gonadotropic, thyroid hormones, testosterone and progesterone in blood serum in patients with hyperprolactinemia

To obtain a comprehensive hormonal characterization of patients, we used the spectrum of hormonal studies. The levels of hormones in the serum of the examined women are presented in Table 2.

When assessing the dependence of testosterone levels in women with hyperprolactinemia on its cause, significant differences were obtained between 2 (PCOS) and 1 (prolactinoma) (Kruskal-Wallis test, p1-2 <0.001) and between 2 (PCOS) and 3 (hypothyroidism) groups (p2-3 <0.001), that is, testosterone levels in women with PCOS are much higher compared to women with prolactinoma and hypothyroidism.

Statistical analysis of the level of FSH, LH and progesterone in tumor and non-tumor hyperprolactinemia did not reveal significant differences, p> 0.05.

Elevated FSH levels are observed in 3 women with prolactinoma, and in 6 patients with hypothyroidism. With PCOS, there is no increase in FSH levels. Elevated LH levels are observed in 3 women with sprolactinoma, 3 with PCOS. In patients with hypothyroidism, an excess of the LH level from the reference values is not observed.

Table 2.

Levels of gonadotropic, thyroid hormones, testosterone and progesterone in the blood serum of the examined women (on day 21 MC)

	Prolactinoma(n=30)	PCOS(n=30)	Hypothyroidism (n=30)	P
FSH IU/l (up to)	4,7 (1,9-6,92)	3,6 (2,4-6,6)	2,36 (2,2-6,88)	0,728 P1-2=1,0 P1-3=0,77 P2-3=0,77
LH IU/l (up to)	6 (1,9-7,9)	5,1 (3,2-10,2)	3,28 (1,2-9,8)	0,231 P1-2=0,82 P1-3=0,677 P2-3=0,163
LH/FSG	1,276	1,417	1,389	0,128 P1=0,91 P2=0,68 P3=0,175
Progesterone ng / ml (before)	3,85 (0,608-5,7)	1,8 (0,4-3,01)	1,8 (0,8-2,35)	0,277 P1-2=0,499 P1-3=0,256 P2-3=0,955
Testosterone ng / ml (before)	0,99±0,85	2,2±1.04	0,5±0,23	0,001 P1-2<0.001 P1-3=0.063 P2-3<0.001
TSH mIU / ml (up to)	2,63±1,78	2,03±1,0	12,2±5,56	0.001 P1-2=0.323 P1-3<0.001 P2-3<0.001
Sv-T4 nmol / l (up to)	14,7±3,12	11,1±3,04	4,2±3,16	0.001 P1-2<0.001 P1-3<0.001 P2-3<0.001

Low FSH levels are observed in 8 patients with prolactinoma, 7 with PCOS, and 6 with hypothyroidism. Low LH levels are observed in 1 patient with prolactinoma, 1 with PCOS, and 6 with hypothyroidism. According to LH and FSH levels, it can be concluded that with hyperprolactinemia syndrome, normogonadotropic hypogonadism develops mainly.

It was noted that 9 women with prolactinoma, 18 women with
PCOS and in 3 women with hypothyroidism, the ratio of LH to FSH exceeds the reference values (LH / FSH> 1.5).

14 women with prolactinoma, 23 with PCOS, and 18 with hypothyroidism have low progesterone levels in the middle of the luteal phase of the menstrual cycle, which means chronic anovulation in women with hyperprolactinemia syndrome.

Increased testosterone levels are mainly found in patients with PCOS (observed in 17 patients). In 3 patients with prolactinoma, this indicator is higher than the reference values.

Low levels of free T4 are found in 14 women with hypothyroidism (overt hypothyroidism).

Study of the hypothalamic-pituitary-gonadal function in women with hyperprolactinemia syndrome

Hyperprolactinemia is one of the most common causes of ovulation disorders, menstrual disorders and infertility in women. Hyperprolactinemia is a heterogeneous group of neuroendocrine disorders from a clinical and pathogenetic perspective [13, 14, 20].

To study the structural changes of the ovaries and uterus, to assess ovulatory function and to diagnose gynecological diseases, tumors of the uterus, appendages, to identify abnormalities in the development of the uterus, the patients underwent ultrasound of the pelvic organs on days 14 and 16 of the menstrual cycle. An ultrasound examination of the pelvic organs (n = 90) showed signs of sexual infantilism in 43 patients. These were mainly patients with tumor-induced hyperprolactinemia (prolactinoma). 21 patients had signs of polycystic ovaries (an increase in ovarian volume> 10 ml, the number of antral follicles in one cut ≥ 12, with sizes of 2-9 mm, thickening of the ovarian stroma) (PCOS-21), 16 had signs of a multifollicular structure of the ovaries (prolactinoma - 5, PCOS - 8, hypothyroidism - 3). Among patients with hyperprolactinemia of non-neoplastic genesis, 3 revealed small uterine fibroids, 2 had signs of adenomyosis, 4 patients had signs of chronic inflammatory disease of the pelvic organs without exacerbation, and one patient had a dermoid cyst of the right ovary. LH and FSH levels are presented in Table 2.

Evaluating the clinical signs in patients with tumor hyperprolactinemia, depending on the level of total prolactin, it was shown that in women with amenorrhea, the prolactin level was significantly higher (Kruskal-Wallis criterion p = 0.01). Thus, evaluating the clinical signs, the levels of prolactin, FSH, LH and progesterone, as well as on the basis of ultrasound of the pelvic organs, it can be concluded that with hyperprolactinemia of tumor genesis, the severity of menstrual irregularities depends on the level of prolactin (with the exception of the phenomenon of macroprolactinemia).

MRI of the hypothalamic-pituitary region in the diagnosis of prolactinomas

MRI of the hypothalamic-pituitary region was performed in all patients with prolactinoma to visualize and determine the size of the tumor, the state of chiasm, and to exclude other changes in the hypothalamic-pituitary region. The characteristics of the MRI results are presented in Table 3.

Table 3.

Results of MRI in patients with prolactinoma

Tumor volume, mm3	Microprolactinomas N = 25 (p=0,23)	Makroprolactinomas N = 5 (p=0,001)
Mediana, mm^3	42,39	1778,86
Lower quartile, mm3	22,30	900,34
Upper quartile, mm3	118,90	4056,78

Thus, MRI examination, a highly informative non-invasive method of radiological diagnosis, revealed pituitary microadenomas in 25 cases (83.3%), macroadenomas in 5 (16.7%) cases.

Using MRI of the hypothalamic - pituitary region, we determined the size of the pituitary gland and the tumor, the nature of tumor growth, the state of the chiasm and other structures of the

brain. Given the relatively high cost of MRI studies, this method should be carried out strictly according to indications in the presence of clinical signs, as well as for dynamic monitoring of patients with prolactinoma against the background of treatment with dopamine agonists [21].

Bromocriptine - an ergoline agonist of D1 - dopamine receptors, have a non-selective effect. The drug was for many years the gold standard in the treatment of patients with hyperprolactinemia syndrome [1, 13]. However, in addition to dopaminomimetic properties, it also possesses an adrenergic blocking antiserotonergic activity, due to which in 65 - 75% of patients treated with bromocriptine, nausea, headache, dizziness, and arterial hypotension develop [3, 4]. Another disadvantage of bromocriptine is its short half-life (up to 4 hours), which requires multiple daily intake. The use in practice of other drugs of the first generation of dopaminomimetics did not show significant clinical advantages over bromocriptine, and the tolerance of these drugs was much worse, therefore they were not widely used in practice [5]. Imperfection of the first generation dopamine agonists led to the creation of new (selective for D2 receptors) agonists of the second - Chinagolide (Noprolac) and the third - Cabergoline (Dostinex) generations [6].

Quinagolide is a non-ergoline selective dopamine receptor agonist. It is a long-acting drug. Its biological activity exceeds that of bromocriptine by almost 50 times. Normalization of prolactin levels, reduction of adenomas were achieved in 50-60% of cases, including in one third of patients resistant to bromocriptine treatment. There was a better tolerance of quinagolide compared to bromocriptine, but the data on the fact that this drug has a teratogenic effect and increases the frequency of spontaneous abortions, limited its use in obstetric and gynecological practice [7, 9].

In 1982, a third generation dopaminomimetic, **cabergoline**, appeared. It is an ergoline selective agonist of D2 - dopamine agents with a long reception period and a pronounced prolactin-inhibiting activity. The drug has a prolonged decrease in the level of PRL in the blood plasma is observed 3 hours after administration and persists for 7–28 days in patients with hyperprolactinemia. The initial dose is 0.5 mg (1 tablet) in two doses (1/2 tablet 2 times a week) with food intake for 4 weeks, followed by monitoring the level of PRL blood and, if necessary, titrating doses [7, 8, 9].

Control of the PRL level is carried out after 4 weeks, followed by dose titration if necessary: if the PRL level has not returned to normal, the weekly dose is increased by 0.5 mg with an interval of 4 weeks until the prolactin level normalizes. Usually, the average therapeutic dose is 0.5-1.5 mg per week. Side effects include nausea, headache, decreased blood pressure, dizziness, abdominal pain, dyspeptic symptoms, weakness, and constipation. Usually these symptoms are moderate or mild, appear within the first two weeks of admission and then go away on their own, not being a reason for stopping treatment. Many authors have shown that cabergoline normalizes the blood prolactin content in women and men in 86-92%, causes regression of microadenomas of the pituitary gland in 16 - 74%, macroadenomas - in 44-91%, helps to restore ovulation in 67-89% of cases [10, 12]. Cases of the effectiveness of cabergoline in giant prolactinomas and adenomas have been described mixed genesis. Taking cabergoline normalizes metabolism, improves the lipid spectrum of blood, decreases weight [14,15]. The average frequency of undesirable effects when taking cabergoline in different studies is different - from 13 to 70% [6, 16].

Among patients with prolactinomas, there is a certain number of patients with tumor resistance to dopamine agonists. Clinically, this is manifested by the preservation of an increased level of bioactive PRL against the background of the maximum tolerated doses of dopamine agonists and the absence of a decrease in tumor size by 50% from the initial value. In patients with resistant prolactinomas, it is recommended to increase the dose of the drug to the maximum tolerated. If bromocriptine is intolerant, it should be replaced with cabergoline or another dopamine agonist [15, 16].

Surgery is required in a small number of patients and is not the treatment of choice for prolactinomas. The indications for surgical intervention are: an increase in the size of the tumor, despite the optimal treatment regimen; pituitary apoplexy; intolerance to drug therapy; macroprolactinoma resistant to dopamine agonist treatment; macroadenoma in patients planning pregnancy; compression of the optic chiasm, which persists against the background of drug treatment; prolactinoma with a cystic component, resistant to treatment; liquorrhea while taking

dopamine agonists; macroadenoma in patients with mental illness in the presence of contraindications to the appointment of dopamine agonists [16, 17]. Removal of the tumor can be performed by transcranial or transsphenoidal approach [16].

In the case of partial removal of adenomas, a combination treatment is indicated: the appointment of dopamine agonists or radiation therapy [3,14]. Since the positive effect after irradiation of the adenoma of the pituitary gland develops gradually and for the development of the full effect lasts up to 12-18 months, as well as due to complications (necrosis of the brain tissue, damage to the optic nerves, in the long-term period - hypopituitarism as a result of radiation damage to the hypothalamus), radiation therapy with prolactinomas is used in exceptional cases: as an additional effect after surgery in patients when a large volume of tumor tissue remains; ineffectiveness and intolerance to drug therapy; in patients for whom surgery is contraindicated or who refuse surgical treatment [15, 17].

The use of pathogenetic therapy - the dopamine agonist cabergoline in hyperprolactinemia effectively restores fertility: in 72% of patients treated with this drug within 24 weeks, ovulation is restored and pregnancy occurs, and in 90% - with therapy up to 40 weeks. In prolactinomas, the duration of therapy with dopamine agonists is 2 years. In patients with prolactinomas, an increase in treatment duration is due to the achievement of the maximum tumor shrinkage before pregnancy [17, 13].

The effectiveness of treatment with pregnancy onset is lower in women with hyperprolactinemia lasting more than 10 years [17]. When the content of PRL in the blood is normalized, but there is no ovulation, ovulation is induced - clomiphene, 50-100 mg from the 5th to the 9th day of the menstrual cycle. In the absence of ovulation, an ovulatory dose of human chorionic gonadotropin is additionally prescribed - 7500-10,000 units. in the presence of a dominant follicle 18-20 mm. Given the decrease in progesterone levels in hyperprolactinemia, it is advisable to prescribe gestagens in phase II of the cycle (dyufaston 20 mg / day or morning 200 mg / day from the 16th to the 25th day of the menstrual cycle). In the absence of pregnancy, operative laparoscopy (PCOS, endometriosis) is indicated. The effectiveness of infertility treatment in hyperprolactinemia is determined by the level of gonadotropins. The maximum effect of infertility treatment was obtained with a low level of gonadtropins - 80.6%, in patients with a high level of gonadotropins, reproductive function is not restored [18, 19]. In patients with hyperprolactinemia of childbearing age, receiving therapy with dopamine agonists and wishing to exercise fertility, pregnancy planning should be carried out [20]. When pre-conceptional preparation for pregnancy, all women planning a pregnancy should undergo imaging of the pituitary gland (MRI or CT), as well as an assessment of the visual fields. When treating with dopamine agonists, contraception with barrier agents is recommended, since with normalization of the PRL level, fetality is quickly restored. In patients with micro- and macroprolactinomas resistant to dopamine agonists or intolerance to this treatment, it is advisable to consider the possibility of surgical treatment before pregnancy [18, 20].

The growth of macroprolactin during pregnancy occurs in 31% of cases, and after pre-gestational surgical treatment decreases to 2.8 - 4.3%. Optimal for conception is a stable normalization of the PRL level in the blood and a decrease in tumor size (less than 10 mm). In this situation, contraception is canceled and pregnancy planning is carried out. If such patients have menstrual irregularities or hypogonadism at pregravid preparation stage, this pathology is treated [17, 19].

The method of choice in patients with hyperprolactinemia of tumor genesis is the use of drug treatment - **dopamine agonists.** A number of patients with microadenomas and asymptomatic course of the disease may not need to prescribe drug therapy due to the low probability of tumor growth [20].

The examination of patients was carried out on the basis of the RSSMPSE, named after E.Kh. Turakulov in 2018-2020. 90 women with hyperprolactinemia were examined. All examined patients were divided into 3 groups: 30 patients with prolactinomas, 30 patients with polycystic testicles syndrome and 30 patients with hypothyroidism. All patients underwent conventional

research methods (general clinical and biochemical blood tests, radioimmunological hormonal blood tests, MRI of the pituitary gland, ultrasound of the pelvic organs).

The age of the patients in our study at the time of treatment was 33.5 ± 11.5 years, minimum - 17.0 years, maximum - 49.0 years. The duration of the disease ranged from 6 months to 16 years.
Of all patients with prolactinoma, including those operated on, 27 women received cabergoline. 3 women with prolactinoma received cabergoline and bromocriptine. Among women with prolactinoma, 25 had microadenoma (microprolactinoma), 5 had macroadenoma (macroprolactinoma).

The selection of the dose of cabergoline was individual. The scheme for selecting the optimal dose is as follows: an initial dose of 0.25-0.5 mg 2 times a week at 20.00, after a meal for 4 weeks, followed by monitoring the PRL level and titrating the dose, if necessary, increasing the weekly dose by 0.25 , 0.5 mg per week with an interval of 4 weeks and the selection of the optimal dose (the minimum, against the background of which the PRL level normalizes with good tolerance). The control was carried out according to the level of total PRL and subsequently the optimal therapeutic dose was maintained.
The total prolactin level in women with prolactinoma is shown in Table 4.

Table 4.

Prolactin levels before and after cabergoline therapy in women with prolactinoma

PRL mIU/L	Up to treatment	After 3 months	After 6 months	After a year
Median	1812	656	495	368
Lower quartile	1224	515	231	230
Upper quartile	2973	1095	856	610

Normalization of the total prolactin level to the reference values during treatment with cabergoline (dostinex) in the group, in general, occurred in 66.7% of patients with prolactinoma. The dynamics of the total prolactin level in the examined group is shown in Fig. 16.
Restoration of the menstrual cycle in women was observed in 70.0% (21) cases, in 22.7% (5) women with infertility, pregnancy occurred, galactorrhea decreased or disappeared in 56.7% (17) women with prolactinoma.
On the background of treatment with cabergoline, a decrease in the pituitary tumour volume was noted. In women with prolactinoma, the median tumor volume is 95.58 mm3 (lower quartile 18.32 mm3, upper quartile 783.15 mm3), after treatment 58.64 mm3 (lower quartile 6.11 mm3, upper quartile 224.43 mm3), differences in the tumor volume are statistically significant, p = 0.00002, Fig. 17.

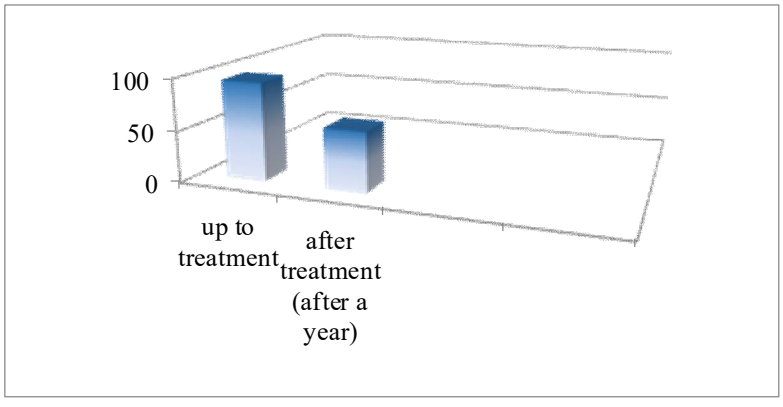

Figure: 17. Changes in tumor volume (mm3) during treatment with cabergoline

In our study, the duration of cabergoline intake in women was 6 months to 4 years, the median and interquartile range of 2 years (1 year, 3 years).
Doses of cabergoline required to normalize total prolactin levels in women ranged from 0.125 mg/week to 3 mg/week. Median and interquartile range 2 mg (0.5 mg; 1 mg). Resistance to

cabergoline treatment was 3.33% (in 1 patient). Complete remission was achieved in 73.3% (21), incomplete remission in 10.0% (3).

In our study, the duration of cabergoline intake in women was 6 months to 4 years, the median and interquartile range of 2 years (1 year, 3 years).

In 17 women with prolactinoma who complained of infertility, after treatment with cabergoline for at least 1 year, pregnancy did not occur, we prescribed Clomiphene citrate to induce ovulation and restore fertility. The treatment regimen for Clomiphene citrate is as follows: Clomiphene citrate (Clofit) 50 mg 1 tablet 1 time per day at 20.00 from the 2nd to the 6th day of the menstrual cycle for 2 cycles, then 2 tablets 1 time per day at 20.00 from the 2nd to 6th day of the cycle for 2 cycles. Considering the decrease in progesterone levels in hyperprolactinemia, we prescribed gestagens in phase II of the cycle (duphaston 20 mg/day or morning 200 mg/day from the 16th to the 25th day of the menstrual cycle). In case of pregnancy, we canceled clomiphene citrate and prescribed Dufaston 20 mg / day or Utrozhestan 200 mg / day during the first 12 weeks of pregnancy to prevent spontaneous abortions and miscarriages. We also gradually canceled cabergoline, reducing the dose of the drug by 0.5 mg per week. 12 patients became pregnant during treatment with Clomiphene citrate (40.0% of the total number of women with prolactinoma). 5 patients with prolactinoma who, after treatment with Clomiphene citrate for 4 months, did not become pregnant, about which we sent to a gynecologist to induce ovulation using human chorionic gonadotropin.

Against the background of the treatment, there was a significant increase in progesterone level ($p = 0.0002$) in the middle of the luteal phase of the cycle, apparently associated with the recovery of ovulation in women with prolactinoma.

Conclusions:

1. From the results obtained, we concluded that cabergoline effectively reduces the level of total prolactin in patients with prolactinoma, while simultaneously reducing the tumour's size. And also against the background of treatment with cabergoline, in women with prolactinoma, there is a recovery of the biphasic menstrual cycle and pregnancy onset at a fairly high frequency. In women with prolactinoma and infertility, if pregnancy does not occur spontaneously after treatment with cabergoline for at least 1 year, Clomiphene citrate is the drug of choice for restoring ovulation and fertility.
2. When assessing the dependence of the level of total prolactin on the cause of hyperprolactinemia, between tumor hyperprolactinemia (prolactinoma) and non-tumor genesis (PCOS, hypothyroidism), significant differences were obtained (Kruskal-Wallis criterion, $p1\text{-}2 < 0.001$, $p1\text{-}3 < 0.001$).
3. Testosterone levels in women with PCOS are much higher compared to women with prolactinoma and hypothyroidism.
4. Assessing clinical signs, levels of prolactin, FSH, LH and progesterone, as well as based on ultrasound of the pelvic organs, it can be concluded that in hyperprolactinemia of tumor genesis, the severity of menstrual irregularities depends on the level of prolactin (except for the phenomenon of macroprolactinemia).
5. MRI examination of the hypothalamic-pituitary region - a highly informative non-invasive method of radiation diagnostics revealed pituitary microadenomas in 25 cases (83.3%), macroadenomas in 5 (16.7%).

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THE MODERN DIRECTIONS IN PATHOGENESIS, DIAGNOSIS AND PROGNOSIS OF INACTIVE PITUITARY ADENOMAS

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ABSTRACT
The paper presents an analysis of data from 138 recent sources. The study of developmental factors of inactive pituitary adenomas remains one of the topical problems of modern medicine. The development of various instrumental and laboratory diagnostics of pituitary adenomas, including advances in genetics and molecular biology, has significantly changed the ideas about etiopathogenesis and, consequently, the possibility of diagnosis, treatment, and prevention of many tumor diseases of the brain. The study of pituitary adenoma pathophysiology can include many directions. Some scientists have highlighted molecular and signaling abnormalities within the human body. These bodily molecular genetic abnormalities are numerous because of the complexity of the pituitary gland itself. Some of the discoveries have led to the experimental use of new treatments, such as tyrosine kinase inhibitors, to resolve genetic damage. Another research line has focused on the inheritance of endocrine neoplasia syndromes, such as multiple endocrine neoplasia type 1 (MEN1) and the Carney complex (CNC). These studies have found that multiple clinical syndromes are caused by a germline of genetic mutations that affect many tissues and cause multiple endocrine tumors, including pituitary adenomas, as a characteristic feature. Examining these disrupted genes and the effects of missing or incorrect protein on cellular signal transduction and regulation may also provide information on the normal pituitary physiology and pathophysiology of pituitary adenomas appearing outside of these defined genetic settings. These data provide an important clinical opportunity, namely, to allow early diagnosis of pituitary adenomas.
Keywords: inactive adenoma of a hypophysis, diagnosis, pituitary, genetic.

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СОВРЕМЕННЫЕ НАПРАВЛЕНИЯ В ПАТОГЕНЕЗЕ, ДИАГНОСТИКЕ И ПРОГНОЗИРОВАНИИ НЕАКТИВНЫХ АДЕНОМ ГИПОФИЗА

АННОТАЦИЯ

В работе приведен анализ данных по 138 источникам последних лет. Изучение факторов развития неактивных аденом гипофиза остается одним из актуальных проблем современной медицины. Развитие различных методов инструментальной и лабораторной диагностики образований гипофиза, в том числе достижения генетики и молекулярной биологии значительно изменили представления об этиопатогенезе и, как следствие, возможность диагностики, лечения, профилактики многих опухолевых заболеваний головного мозга. Исследование гипофизарной патофизиологии аденомы может включать в себя много направлений. Некоторые учёные выдвинули на первый план молекулярные и сигнальные отклонения в пределах человеческого организма. Эти телесные молекулярные генетические аномалии многочисленные из-за сложности самой гипофизарной железы. Некоторые из открытий привели к экспериментальному использованию новых методов лечения, таких как ингибиторы киназы тирозина в урегулировании генетических повреждений. Другое направление исследований были направлены в сферу унаследованния эндокринных синдромов неоплазий, таких как многожественные эндокринные неоплазии тип 1 (MEN1) и комплекса Карни (CNC). Эти исследованиями были выявлены, что разносторонние клинические синдромы вызваны зародышевой линией генетических мутаций, которые влияют на многие ткани и вызывают множественные эндокринные опухоли, включая гипофизарные аденомы как характерная особенность. Исследование этих разрушенных генов и воздействие отсутствующего или неправильного белка на клеточной передаче сигналов и их регулирование могут также предоставить информацию о нормальной гипофизарной физиологии и патофизиологии гипофизарных аденом, появляющихся вне этих определенных генетических параметров настройки. Эти данные обеспечивают важную клиническую возможность, а именно, позволять ранней диагностике аденом гипофиза.

Ключевые слова: неактивная аденома гипофиза, диагностика, гипофиз, генетика.

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ГИПОФИЗ НОФАОЛ АДЕНОМАЛАРИНИНГ ПАТОГЕНЕЗИДА, ТАШХИСЛАШДА ВА ПРОГНОЗЛАШДА ЗАМОНАВИЙ ЙУНАЛИШЛАР

АННОТАЦИЯ

Ушбу маколада охирги йилларда чоп этилган 138 адабиётлар тахлили келтирилган. Гипофиз нофаол аденомалари ривожланишига сабаб буладиган омилларни урганиш замонавий тиббиётнинг долзарб муаммоларидан биридир. Гипофиз усмаларини инструментал ва лаборатор ташхислаш усулларининг ривожланиши, жумладан молекуляр биология ва генетика сохасида эришилган ютуклар бош мия усма касалликлари этиопатогенези, диагностикаси, давоси ва профилактикаси тугрисидаги тасаввурларимизни анчагина узгартирди. Гипофиз аденомаларининг патофизиологияси узининг таркибига куплаб йуналишларни камраб олиши мумкин. Баъзи бир олимлар одам организмидаги молекуляр ва

сигнал тармоклардаги бузилишларни биринчи уринга куйишади. Бу молекуляр-генетик аномалиялар гипофиз безининг мукаммалиги туфайли куплаб микдордадир. Баъзи бир янгиликлар даволашнинг янги усулларини экспериментал тадбик этишга, яъни генетик бузилишларнинг олдини оладиган киназа ингибитори тирозинни кулланилишига курсатма булди. Тадкикотларнинг бошка бир йуналиши 1 турдаги куплаб эндокрин неоплазиялар (MEN1) ва Карни комплекс (CNC) каби касалликларнинг наслдан-наслга берилишига йуналтирилди. Бу тадкикотларда аникландики, генетик мутациялар оркали турли хил клиник синдромлар келиб чикиши булиб, улар шунингдек куплаб эндокрин усмаларнинг, шунингдек гипофиз аденомаларининг келиб чикишига сабабчидир. Бу маълумотлар гипофиз аденомаларини эрта ташхислаш учун клиник пойдевор булиб хизмат килади.
Калит сўзлар: гипофиз нофаол аденомалари, каберголин, усма хажмлари.

Predicting tumor diseases of the pituitary gland, diagnosing and elucidating the reasons underlying the mechanisms of their formation is one of the urgent problems in modern neuroendocrinology [14, 21, 27, 104, 112]. Molecular, genetic, and clinical features in the pathogenesis of familial functionally inactive pituitary adenoma are fundamental and applied to this problem [126, 127, 130]. Clinically, these benign tumor formations are, in fact, hormonally inactive pituitary adenomas (NAG) and, according to individual authors, make up from 25 to 43% of all pituitary adenomas and, according to the modern IHCI classification, which belongs to 0-cell adenomas, oncocytomas [14, 27.35, 70.105]. Due to the manifest clinical course of the brain's pathological process, the diagnosis of NAH is difficult, which affects the process of progression, timely treatment, and prognosis of the disease [41,84,116].

As the literature of recent years shows, the main methods for diagnosing NAG are clinical-biochemical, cyto-immunochemical, radio-immunological, molecular-genetic, X-ray (craniography), computed tomography and MRI - studies [3, 21, 37, 47, 49, 58]. It is important to note that if NAG is suspected, radiography in two projections and tomography of the Turkish saddle areas is performed [9, 23, 54]. In this case, the characteristic features are the double-contour of the bottom of the sella turcica, the process's intrassellar volume [79, 85, 97]. Simultaneously, the presence of a tumor, features of its structure, the direction of spread and size can be determined by CT with contrast enhancement [23, 122, 138].

The tumor size is important for the clinical presentation and diagnosis of NAG [27, 56, 134]. Tumors up to 10 mm in size with intrasellar growth are referred to as microadenomas, with a diameter of more than 10 mm with suprasellar spread - to macroadenomas and giant ones larger than 20 mm [63, 65]. Using CT and MRI studies, NAG is diagnosed in 55-75% of cases [61, 85]. In 80-85% of cases, NAG with a tumor size of up to 1 mm is not diagnosed and is only detected at autopsy [58, 68, 87]. The diagnosis of NAH, as a rule, is established already when the tumor reaches a significant size, causing visual impairment, headache, autonomic disorders associated with the pressure of the structures of the anterior pituitary gland [18, 55, 56, 75]. In this regard, the diagnosis and prediction of the risk of developing NAH are among the difficult problems for neuroendocrinologists since it is diagnosed late, usually at the stage of the onset of symptoms of extrasellar tumor spread [4, 9, 50, 77].

In most cases, as noted, in several studies, due to the small size and intrasellar location, incapable of invasive-infiltrative growth of NAG, the practical impossibility of their visualization using CT and MRI tomography with a tumor size of up to 1 mm, as well as the absence of blood of reliable biochemical tumor markers, it is difficult to assess the tactics of therapy reliably, the dynamics of the course of the disease, the effectiveness of the treatment [65, 70]. In this regard, the diagnosis of NAG is necessarily carried out comprehensively with the participation of a neuroendocrinologist, radiologist, neurosurgeon, ophthalmologist, gynecologist, urologist, psychologist [8, 9, 43, 104].

This formulation of the question is due to the variety of NAG clinical manifestations, which complicates its diagnosis [9, 22, 116]. For this reason, there remains a high frequency of erroneous diagnoses, the most important of which are psychosomatic overdiagnosis, vegetative-vascular

dystonia, paroxysmal states, hemodynamic disorders [12, 24, 125]. The lability of the psychoemotional system in patients with NAH is often diagnosed as a breakdown of the central nervous system, and the resulting visual disturbances - as a decrease in visual fields, visual acuity, manifestations of ophthalmological diseases [22, 28, 38]. Disorders in the genital area are diverse - amenorrhea, menstrual irregularities, decreased libido, impotence, which gynecologists and urologists regard as menopause manifestations neurodystonia, functional disorders associated with hormonal and endocrine-metabolic manifestations [9, 10, 16, 128].

Headache, dizziness, nausea, and transient visual impairment occupy an important place among the symptoms in 10-15% of patients with NAH with macro- and giant adenomas [27, 40, 122, 131, 134]. They are, to a greater extent, combined with permanent vegetative-vascular disorders. Such patients do not tolerate physical and mental stress, change of weather, often disturbed by palpitations, especially attacks of pain in the region of the heart of the type of unstable angina pectoris, feeling short of breath, shortness of breath increased sweating, lability of blood pressure, increased heart rate, which is diagnosed by cardiologists as ischemic heart disease [69, 98, 120]. The identified subjective and objective symptoms are more often combined with various psychoemotional disorders - a feeling of heaviness throughout the body, weakness, weakness, sleep disturbances, decreased quality of life, and work capacity [72, 93, 109].

Among the possible reasons for the development of NAG to date, researchers associated with the staging of tumor growth, including the initiation, promotion and progression of neoplasms [63, 70, 115]. Molecular biological studies have shown that an activating mutation of the polyclonal pituitary tissue primarily occurs in tumor cells of patients with NAH, leading to the monoclonal expansion of a single transformed cell [61, 137]. These data are supported by the presence of gene mutations in the original cells, for example, allelic loss in 11q13, found in 28% of corticotropin and/or mutations of the gsp type (in 6%) [103, 116]. Some opinions mixed polyhormonal cells arise from multipotent progenitor cells de novo [80, 106]. In this case, in combination with local growth factors, hypothalamic hormones play promoters in activated and already transformed pituicites in the processes of hyperplasia and tumor growth [63, 64]. This process can be facilitated by some excess secretion of releasing hormones, a defect in inhibitory hormones that stimulate cell proliferation and promote tumor progression [58, 61].

In recent years, it has been shown that such local growth factors as a vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), cytokines-interleukin-1, interleukin-6, factor suppressing leukemia, gremlin can play an important role in the development of NAG [51, 53, 59]. There is a hypothesis that the influence of growth factors on pituicites is mediated through transmembrane receptors [93, 94, 132]. Growth factors control the expression, determination, and proliferation of pituitary cells [124, 136]. According to a number of authors, overexpression of growth factors can lead to uncontrolled reproduction of pituicites, while the production and activity of factors with antiproliferative function decrease, including corticotropin-inhibiting factor, somatostatin, dopamine [112, 113]. The opinion is preserved about the important role of hypothalamic factors in the pathogenesis of NAG, since in the process of tumor growth, receptors of pituicite cells acquire an abnormal sensitivity to a nonspecific stimulus for hypothalamic neurohormones, such as thyroliberin, gonadoliberin, arginine-vasopressin, vasoactive-intestinal peptide, dopamine [2, 19, 71, 111]. After their binding to these receptors of the corresponding ligands, active synthesis of precursors occurred, as well as differentiation and increased proliferation of cells [5, 42, 120].

Somatostatin and dopamine play a significant role in regulating the pituitary gland function, causing a decrease in hormone hypersecretion and a decrease in cell proliferation due to G-proteins' effect and a decrease in the normal cAMP concentration [136]. As studies show, these processes are disrupted in a tumour due to changes in the composition of G-proteins (gsp-mutations) and functional communication between receptor molecules and effectors [103]. The role of somatostatin and dopamine receptors in pituicites and other proliferating cells of the pituitary gland in NAH is still poorly understood [14, 71]. In the pituitary gland tissues with NAG, the effect of factors inhibiting tumor growth is weakened. There is some information that in NAG, embryonic mutations

in genes can be detected in familial neoplasms and sporadic tumors without hereditary transmission [127, 135].

Somatic mutations in the MEN1 gene have been described in 25% of pulmonary carcinoids [73, 104, 105]. Overexpression of growth factors such as TFN- &, NFR, VEGF, which promotes endocrine and endothelial cells' proliferation, plays an important role in developing lung tumors [89, 108, 124]. Some studies have demonstrated that NAG can be induced by the protein oncogene Bcl-2, which leads to inhibition of apoptosis in the tumor [26, 30, 53]. For benign tumors, including pituitary adenomas, mutations in the RAS family genes are characteristic, accompanied by the loss of the mechanism of negative autoregulation of cell growth [14, 21]. In most cases, this disrupts the work of signaling pathways associated with PRL proteins and the p53 proto-oncogene [1, 52, 133], which leads to a loss of control over the cell cycle and non-stop cell division [13, 46, 103, 123] ... In the pituitary tissue of patients with NAH, activation of BCL-2 oncogenes is often observed in biopsy material, which is associated with inhibition of the apoptosis process in tumor cells [7, 100, 129].

During immunohistochemical studies, with the help of which it is possible to determine markers of tumors' biological behavior, to establish the prognosis of the disease's further course, high content of Ki-67 was revealed in the tissues of the pituitary gland in patients with NAH [106]. This protein is known to be expressed by dividing cells during all active phases of the cell cycle and is absent in resting cells [34, 44, 99, 101]. Ki-67 is considered a specific proliferation marker used to determine the growth fraction of the tumor [26, 101]. Some reports indicate that Ki-67 is significantly more often detected in invasive pituitary adenomas than in non-invasive ones and is more often detected in recurrent tumors than in primary foci [106, 124]. With the development of tumor processes in the blood, vascular endothelial growth factor (VEGF) is detected - heparin-binding glycoprotein - one of the most significant vascular growth factors [35, 51, 124]. It increases vascular permeability due to their dilation by activating NO synthase in the endothelium [15, 78, 81, 121], promotes vascular wall remodeling [36, 59], cell migration and inhibits endothelial apoptosis [6, 24, 128, 133] ... Among the possible markers of immunohistochemical research methods in NAG, an important place is occupied by the endothelial factor of platelet adhesion (DM 31) [35, 62, 136]. It is a protein located on the surface of endothelial cells, platelets, monocytes, macrophages, neutrophils and some lymphocytes, belongs to the family of globulins [45, 89]. Diabetes mellitus 31 is responsible for intercellular interactions and plays an important role in many biological processes, including inflammation and angiogenesis [51, 90]. Diabetes mellitus 31 affects endothelial cells' mobility and promotes association in the vasculature, thus taking an active part in angiogenesis [90]. Several studies have shown a relationship between the presence of markers of VEGF and DM 31 with the size of the tumor, the degree of invasion, and, in some cases, with the development of hemorrhage in the adenoma [32, 35, 62].

In this regard, some researchers believe that the study of the immunohistochemical expression of markers of biological behavior VEGF, KI-67, SD31 opens up prospects for the diagnosis of NAH, clarification of the progression of the tumor process, and further prognosis of the disease [33, 47, 51, 116]. In recent years, researchers' efforts to study the etiopathogenesis of NAG are aimed at elucidating molecular genetic factors [48, 62, 103]. The widespread introduction of modern advances in genetics and molecular biology into fundamental and clinical medicine has significantly changed the concept of etiopathogenesis and, as a result, the possibility of diagnostics, treatment, and prevention of many brain tumor diseases [47, 66, 70].

In the endocrine system, genes are related to implementing various functions, coding for protein hormones, receptors, steroid biosynthetic enzymes, intracellular signaling molecules, transport proteins, ion channels, transcription factors and other molecules [2, 8, 31]. It is currently known that many endocrine diseases are hereditary, including NAG [11, 12, 20], associated with a defect in a particular gene or characterized by a polygenic type of inheritance [25, 33, 29, 67]. Simultaneously, during the development of NAG, there are no data on the causes of inheritance at the level of gene groups, based on the structure and biological function of encoded or protein molecules [82, 86]. Based on these results, some researchers believe that the prevalence of NAH

appears at the age of 20-50 years, is equally common in both men and women, and the disease mainly occurs in 75% of cases in working age, which is of great importance not only medical but also socio-economic [60, 88]. According to the literature, famous cases of pituitary adenomas have been known for many years and now account for from 1-2% to 5% of all cases [64, 69, 106]. Currently, the molecular, genetic and clinical features of familial pituitary adenoma are well characterized in multiple endocrine neoplasias of type 1 (MEN-1) and Carney complex (CNC), which account for the majority of familial cases of NAH [73, 88, 126]. As the literature sources show, the conditions caused by MEN-1 and the PRKARIA gene mutation, in fact, and the clinical and pathogenetic features of the pituitary gland pathology in these diseases, differ from sporadic pituitary tumors [83, 98, 127]. The frequency of MEN-1 syndrome is 1 observation per 30 thousand population [62, 69]. Simultaneously, the disease can develop at any age, but the clinical manifestation is most often noted in the 4th decade of life [61, 66, 114]. In large families, where the hereditary transmission of MEN-1 syndrome is reliably traced, the manifestation of symptoms in subsequent generations and the appearance of neoplasms occur at an increasingly young age, and atypical and malignant tumors develop more often [86, 92, 125].

Clinical manifestations of MEN-1 syndrome are very diverse and primarily due to morphological changes in benign adenoma or malignant neoplasia [126, 130, 132]. Over the past decades, the concept of familial MEN-1 / CNC tumors of the pituitary gland has been significantly expanded to include the entire condition known as a familial isolated pituitary adenoma (FIPA) [107, 130]. It has been established that tumors in FIPA can present homogeneous (the same phenotype) or heterogeneous (tumors of different types within the same family [74, 108, 127]. Compared with individual adenomas, patients with FIPA are young at the time of diagnosis and usually have large tumors [76,96] At the same time, it was revealed that the existing signs of FIPA differ from MEN-1 in terms of a higher incidence of growth hormone and a lesser degree of prolactin [8,9,21].

The recent discovery of the involvement of mutations in the aryl-hydrocarbon-interacting protein (AIP) gene receptor combined with a pituitary tumor has provided new information on the potential mechanism of neoplastic transformation in FIPA patients [76,82,102]. It has been noted that in sporadic pituitary tumors, it is infrequent, approximately 15% of FIPA patients have AIP mutations. It should be noted that MEN-1 syndrome is an autosomal dominant disease caused by a mutation in the MEN-1 gene on chromosome 11q13, which encodes minin proteins [100,110]. A combined study of tumor maps and relationships indicated the genome's location in the long arm of chromosome 11q13 as the genetic locus that causes MEN syndrome [103]. It has been shown that this locus can encode the suppression of a tumor gene that normally coordinates cell reproduction [102]. The proband inherits the allele predisposing to MEN-1 from the affected parent, while the normal allele comes from the unaffected parent [82].

Moreover, when a somatic mutation inactivates the normal allele, the suppressive function is lost, allowing the development of hyperplasia [106,128]. Mutations are not identified in 20% of sporadic and familial MEN-1 with the MEN-1 phenotype [14,103].

Many studies have noted that from the functional point of view of the biological role of MEN-1 acts as a tumor of suppressor genes, although it develops a series of interactions at the transmembrane level [57, 58, 62]. It has been reported that approximately 40% of patients with MEN-1 have pituitary adenomas and 17% with true pituitary tumors [126]. Among patients with the familial form of MEN-1, pituitary diseases are more common than in sporadic MEN-1 (59 versus 34%, respectively) [103, 137]. MEN-1, pituitary tumors are larger, associated with more local tumor effects, and more difficult to treat [56, 85]. For the MEN-1 tumor, prolactinomas (macroadenomas) are most common [12, 55, 68, 70, 119].

Some researchers recommend that the genetic defect's asymptomatic carriers should be identified first, then the prevalence of organ damage should be determined [73, 102]. So far, the method for determining the 11q13 chromosome in parents with MEN-1 is not widespread [14]. Therefore, the best alternative for detecting MEN-1 disease is determining hormones in affected relatives [3, 21, 76]. It has been noted that the manifestations of MEN-1 syndrome occur sharply

before the age of 15. Therefore, persons from the risk group should not be subjected to endocrinological examination earlier than this age [70, 105].

Almost all at-risk individuals develop the disease by age 40; the examination is unnecessary for people over 50 years of age who have not previously shown signs of this disease [77]. In recent years, some researchers studying the development of MEN syndrome in patients with NAH have associated this disease with a defect in the allele of the p53 suppressor gene [73, 123]. Families with this syndrome have an increased risk of early NAH [61, 114, 116]. However, these studies require theoretical and practical support [62, 64].

In general, at present, the concepts of the genetic nature of the development of NAG are very hypothetical, diverse, and based on assumptions about the existence of candidate genes, the normal regulation of which is associated with the suppression of the tumor process [69]. Such genes are called tumor suppressor genes [7,123]. Defects in these genes lead to progression, and restoration of function leads to a significant slowdown in proliferation or even equilibrium in tumor development [63,70].

Due to the high incidence of NAH, due to the expansion of modern diagnostic equipment - MRI and CT, methods of molecular genetic studies, in recent years, interest in the role of gene mutations in the emergence of familial NAH has significantly increased. In many countries, the question of the influence of genetic mutations and the importance of the apoptosis process on the development of benign tumors is widely discussed [1,7,8], including the incidence and prevalence of the functionally inactive form of NAG [20, 124]. It has been established that the incidence of both sporadic and familial NAH can be influenced by various etiological factors that worsen the prognosis of NAH [111]. These factors include, first of all, primary hypogonadism, intracranial hypertension, early traumatic brain injury, brain infections pre- and postnatal pathology, adverse environmental influences, drugs, radiation [3, 27, 38, 57, 114, 130] Psycho-emotional stress and the use of narcotic substances play an essential role in the induction of gene mutations [32, 47, 112, 125].

Simultaneously, as the extensive literature on the etiopathogenesis, clinic, diagnosis and prognosis of NAH shows, despite the increase in the number of people with this disease, there is still no root cause that underlies the formation of sporadic and familial susceptibility to NAH. The identified external and internal factors environments that affect the unfavorable prognosis of NAH indicate that the solution to the problem of prevention of this disease lies precisely through protecting the internal environment of the body from the effects of mutagenic environmental factors [49, 91, 117].

Consequently, an analysis of the literature of recent years has shown that there is a NAG problem, which arises both sporadically and in the family form (hereditary). However, there is no consensus in the interpretation of the cause of this disease. There is not enough information about families with heredity to NAG, which are observed by neuroendocrinologists in the literature. In this regard, in recent years, most researchers have been proposing to create special registers of hereditary NAG [14, 73, 76, 88, 118]. Undoubtedly, the registration forms of territorial or hospital registries for NAH should contain the appropriate columns of recommendations for observation connected with a hereditary predisposition to this disease. Most researchers consider gene mutation as one of the negative effects of this influence [21, 93, 103]. It is emphasized that if the constituent unfavorable conditions of the external and internal environment can act directly on the cells of the pituitary gland and cause transcriptional differentiation in the individual exposed to this effect, then the mutation of the genes of the germ cells, being inherited, determines the risk of NAG for subsequent generations [74, 100,136].

Thus, the identification of the role of heredity in the origin of NAG is one of the urgent problems of modern neuroendocrinology. Aspects of identifying the frequency of NAH cases among the relatives of probands remain important, which is of great importance for the choice of treatment tactics for these patients, the development of methods of prevention and prognosis in families of the population with a genetic predisposition to this disease. Finding out the reasons for

the development of NAG, which can provoke this disease, also remains relevant, and the question remains: due to what factors does NAG develop in probands among relatives in panmixia.

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A CASE OF A MEDIASTINAL TUMOR WITH ACTH ECTOPIC CUSHING'S SYNDROME

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ABSTRACT
A description of a clinical case of a mediastinal tumor in a 37-year-old man with manifestations of Cushing's syndrome is presented. This case's presentation describes the features of the course, the difficulties of diagnosis and the outcome of treatment in a young patient with ACTH-dependent Cushing's syndrome, of an ectopic nature.
Keywords: Cushing's ectopic cider. Mediastinal formation.

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СЛУЧАЙ ОПУХОЛИ СРЕДОСТЕНИЯ С АКТГ ЭКТОПИРОВАННЫМ СИНДРОМОМ КУШИНГА

АННОТАЦИЯ

Представлено описание клинического случая опухоли средостения мужчины 37 лет, с проявлениями синдрома Кушинга. В презентации данного случая описаны особенности течения, трудности диагностики и исхода лечения у молодого пациента с АКТГ зависимым синдромом Кушинга, эктопической природы.

Ключевые слова: эктопический сидром Кушинга. Образование средостения.

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KUKS ORALIGI USMASI BILAN EKTOPIRLANGAN AKTG GA BOGLIQ KUSHING SINDROMINI KECHISHI (KLINIK HOLAT)

ANNOTASIYA

37 eshli erkak kishida Kushing sindromi bilan namoyon bolgan kuks oraligi usmasining klinik holati tavsirlab berilgan. Mazkur holatni yoritib berishta yosh bemorda ektopik tabiyatli AKTGga bogliq bolgan Kushing sindromining uziga hos kechuvi, ,tashhislashtagi qiyinchiliklari , davolash va kassalik oqibati bayon qilingan.

Kalit so'zlari: Ektopir Kushing sindromi, kuks oralig usmasi.

Relevance. Cushing's syndrome is a complex of clinical symptoms characterized by high levels of corticosteroids in the blood (hypercortisolism). Hypercortisolism is a dysfunction of the endocrine system. The most formidable and prone to steady progression pathogenetic forms of Cushing's syndrome remain its classic variants: pituitary (associated with the development of a corticotropin-secreting pituitary tumor), - occupies at least 70% of all cases of the disease, adrenal Cushing's syndrome (due to autonomous, i.e. independent of the stimulating action of corticotropin, hypersecretion of cortisol by the adrenal glands due to their tumor lesion or hyperplasia) - covers 15-20% of cases and ACTH hormone or corticoliberin) - a rare condition that provides 10-15% all cases of hypercortisolemia [1]. Ectopic SC is more common in males aged 40-60. Of the variants of ectopic ACTH production, one is due to malignant tumors, more often lungs. These patients have clear signs of metastatic tumor: weight loss, hypertension, hypokalemia, and hyperpigmentation. Another type is caused by more slowly growing neuroendocrine tumors, designated as carcinoids (bronchus, thymus, pancreas). Patients with carcinoid tumors producing ACTH may have the same clinical manifestations and biochemical changes as in patients with pituitary KS [4]. Chronic administration of exogenous corticosteroids in various clinical conditions can induce the

development of exogenous CS. Cushing's syndrome is associated with a 2-5-fold increase in mortality compared to the general population, mainly due to cardiovascular complications. Cushing's syndrome is indeed characterized by a special clinical picture, complicated by several concomitant diseases, including systemic arterial hypertension, as well as visceral obesity, impaired glucose tolerance and dyslipidemia, metabolic syndrome [2]. However, hypertension associated with Cushing's Syndrome is not just a component of KS-related metabolic syndrome. Hypertension associated with KS exhibits several features, develops early, and can persist several years after clinical and hormonal remission of the disease [2]. AH in KS in a number of patients persists or recurs at various times after radical treatment, which has led to recent interest in the study. the state of the cardiovascular system in these patients. The search for ways to reduce vascular accidents and coronary complications is a task of paramount importance in the management of patients with arterial hypertension in CK.CK is associated with increased mortality from multisystem risk, which is already elevated several years before diagnosis, suggesting that it is caused by excess cortisol. Compared with the control control in patients with active disease, the risk degree is 6.0 (2.1-17.1) for heart failure and 2.1 (0.5-8.6) for acute myocardial infarction (AMI). An increased prevalence of left ventricular hypertrophy and concentric remodeling is consistently found in CS [3]

CK causes a number of systemic complications, such as metabolic obesity, refractory hypertension, diabetes mellitus, osteoporosis and low-energy bone fractures, which contribute to a 4-fold increase in cardiovascular mortality compared to the population. In this case, the main causes of death from cardiovascular complications are AMI, stroke, congestive heart failure, and PE. Further involvement of the skeletal system is also the cause of increased disability and mortality from bone fractures, including the spine.

In March 2019, the Department of Neuroendocrinology of the Republican Scientific and Practical Center for Endocrinology named after acad. Ya. Kh. Turakulova, a patient born in 1985 (Fig. 1-2) was admitted with complaints of: increased blood pressure, up to a maximum of 200/120 mm. rt. Art. , moon-shaped face, pasty lower extremities, numbness and pain in the lower extremities, a feeling of suffocation, pain in the lumbar region, a sharp and pronounced darkening of the skin, dry mouth, thirst, frequent urination.

From viva's anamnesis: I didn't have anything other than ARVI. Upon admission, according to the patient: he considers himself ill since March 2017, when pain first appeared in the epigastric region and in the chest, about which he consulted a doctor at his place of residence. The therapist recommended a gastroduodenoscopy, which did not reveal any pathological abnormalities. On chest X-ray an aneurysm of the aortic arch was suspected. mm, density - +43 + 65 N units), as well as nodular compaction of the pulmonary parenchyma at the level of C 3 and C 6 of the right lung and C 3 of the left lung. Lymphadenopathy. Ultrasound examination of internal organs revealed: moderate hepatomegaly, pronounced diffuse liver changes. A consultation with a surgeon was recommended, but the patient, due to family circumstances, refused the operation and went to work in Russia. And only in June 2018, when a swelling formed in the left supraclavicular region, he turned to a surgeon in the Russian Federation, where a biopsy of this tumor was performed with suspicion of a tumor. ... On June 25, 2018, under local anesthesia with a solution of lidocaine 1% - 20.0, with an incision up to 3 cm long in the left supraclavicular region, the lymph node was isolated and removed. Lymph node biopsy revealed cancer macrometastasis consisting of relatively small elongated cells. To clarify the histogenesis of the formation, an immunohistochemical study was performed with the setting of reactions with antibodies to BCC, synaptophysin, chromogranin, CD 56, Ki 67 (20%), which were positive in tumor cells. And the reaction with antibodies to napsin, CK 8, CK 5/6, CK7, TTF1 turned out to be negative. On this basis, the patient was exposed to a pathomorphological diagnosis: "Metastasis of neuroendocrine cancer in the lymph node". In this regard, on the basis of a consultation of an oncologist and an endocrinologist, the patient was examined tumor markers: alpha-fetoprotein 0.3 IU / ml (0-10 IU / ml), Cancer - embryonic antigen - 0.61 ng / ml (0-10 ng \ ml), Total PSA - 0.9 ng / ml (0-4 ng / ml), neuroendocrine enolase - 29.5 μg / L (0-13 μg / L) Hormonal tests: Blood cortisol at 8.00-981.0 nmol / L (at a rate of 260-720 nmol / L), TSH-1.07 μIU / ml (0.4-4.0 μIU / ml), Aldosterone-315.4 pg / ml (8-172 pg / ml). Potassium -

3.5 mmol / L, Sodium-140 mmol \ l, Calcium - 2.3 mmol / L, blood glucose - 6.8 mmol / L. Studies have shown an increase in the level of basal cortisol and aldosterone, as well as hypokalemia and hyperglycemia. The patient underwent MRI, which did not reveal structural changes in the brain and chiasmatic-sellar region. In view of the detected changes, the patient was recommended surgical treatment, to which the patient again did not consent. Since June 2018, the patient's condition began to deteriorate, the skin darkened sharply, fine-grained rashes appeared on the upper and lower extremities, and the A / D began to increase to 200/100 mm Hg. , there were swelling on the face, dry mouth and thirst. The patient returned to his homeland and was sent by an endocrinologist at the place of residence to the RSSPMC of Endocrinology for further examination. And only a few months later, in March 2019, he entered the neuroendocrinology department of the Endocrinology Center.

Objective examination: The general condition of the patient upon admission was of moderate severity., Clear consciousness, active position, answered questions in essence. Asthenic constitution. The skin and visible mucous membranes are dark in color with a purple tint, palmar folds, nipples, mucous membranes of the mouth are hyperpigmented, there are small-dot rashes all over the body. The face is puffy, moon-shaped. The lower limbs are pasty. Hairiness of the skin, axillary and groin areas is scarce. The sclera are icteric. The patient is dehydrated; severe hyperkeratosis of the elbows, knees and external ankles with significant hyperpigmentation. There are no striae. He makes active movements, but with difficulty due to general and muscular weakness. The symptom of "myopathic landing" is positive. Breathing is shallow, frequent, 24 times per minute. Catches air, constantly complains of a feeling of lack of air. Severe pallor of the nasolabial triangle and tip of the nose. In the lungs, breathing is weakened, fine bubbling rales in the lower parts of the lungs. A / D 170/100 mm Hg Pulse-90 beats per minute. rhythmic, pronounced filling and tension. Heart sounds are weakened, the emphasis of the second tone on the aorta and apex, single extrasystoles. The abdomen is enlarged due to swelling, sensitive around the navel and in the right hypochondrium with deep palpation. The liver is enlarged +2 cm, protrudes from under the edge of the costal arch. He urinates freely, Pasternatsky's symptom is negative. The stool is prone to constipation.

A preliminary diagnosis was made: Cushing's syndrome, ACTH ectopic form. Tumor of the mediastinum.

Fig.-1 (2016 before illness)

Fig-2 (2019 March month 1st appeal

On examination: hemoglabin - 133 g / l (130-160), erythrocytes - 4.29 mln (4.0-5.0), leukocytes - 8.1 thousand (4.0-9.0), lymphocytes - 24% (19-39), platelets - 216 thousand (180-320), ESR-10 Mm / h (0-10), that is, there were no deviations in the UAC. In the general analysis of

urine, proteinuria, leukocytes -10-15 / in the field of view, salts-oxalates. In biochemical analyzes from 18.03.2019 - hypoproteinemia (total protein - 59.3 g / l at a rate of 65-85 g / l.) Without violations of the ratio of blood proteins (albumin - 39.3 g / l (35-55)), hypokalemia and hypocalcemia. In the coagulogram there was a tendency to hypercoagulation: Hematocrit -42% (up to 40%) - increased, APTT -21 (20 "-30"), Fibrinogen-3.0 g / l (2-4), PTI-103% (80-100) - increased, TV-20 (15 "-20").

In other analyzes, there were no deviations - ALT-23 U \ L (12-14), AST-25 U \ L (8-35), total bilirubin-20.3 μmol / l (up to 25), Creatinine-78 μmol / l (62-115), Urea-7.3 mmol / L (2.5-8.3), Calcium -1.99 mmol / L (2.1-2.6) -low, Hypokalemia - 3.3 mmol / L (3.5-5.4), Sodium-138.5 mmol / l (130-150), Chlorides-99 mmol / l (95-110), Uric acid - 357 μmol / l (200-420). Triglycerides - 1.46 mmol / l (up to 1.7), Total cholesterol -4.4 mmol / l (3.4-5.2).

It should be noted that the patient already had diabetes mellitus: HbA1C - 7.8%. Glycemia 7: 00-7.3 mmol / L, 10: 00-12.0 mmol / L. Sugar in daily urine: specific gravity -1017, Amount-1813 ml, sugar in daily urine - 0.7%.

Hormonal examination revealed a threefold increase in the basal level of ACTH - up to 176 ng / ml (up to 50 ng / ml), Cortisol at 8:00 - 1100 nmol / L (260-720 nmol / L), 24:00 - 910 nmol / L (50- 350 nmol / L), i.e. hypercortisolism with disturbances in the rhythm of secretion; cortisol in daily urine is also increased - 210 nmol / L (38-208 nmol / L) Due to a significant increase in ACTH levels, baseline blood cortisol and daily urinary cortisol, the patient underwent a large dexamethasone suppression test (DPPD) - 2 mg.

Dexamethasone 4 times a day for 48 hours, after which cortisol was not suppressed - 958.0 nmol / L, which indicated the presence of an ectopic focus of ACTH hypersecretion. At the same time, the levels of aldosterone - 61.1 pg / ml (norm 8.0-172.0 pg / ml), and renin-7.9 pg / ml (norm 3.18-32.61 pg / ml) were within the normal range. Further, to determine the localization of the focus and differential diagnosis, we performed MSCT of the chest, which revealed a solid mass of the upper external mediastinum (thymoma?), Nodular compaction of the pulmonary parenchyma at the level of C 3 and C 6 of the right lung and C 3 of the left lung. Lymphadenopathy (Fig. 3,4,5) and MRI of the pituitary gland - MRI of the pituitary gland - in which no pituitary gland formations were detected (Fig. -6)

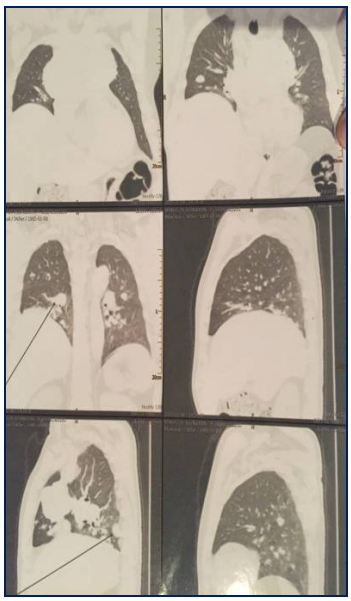

Fig-3

Fig-4

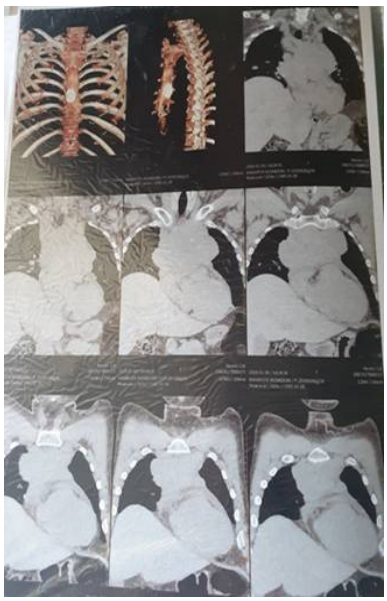

Fig-5

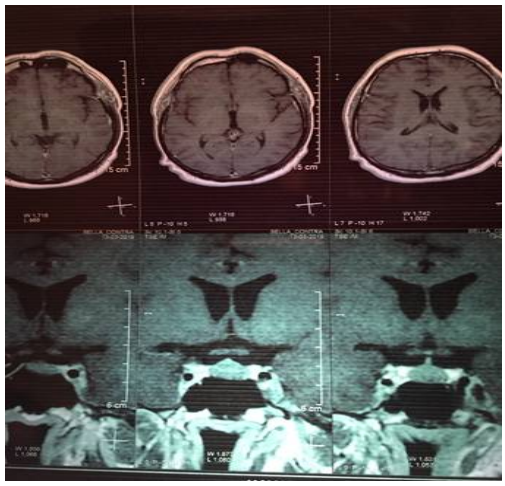

Fig-6

X-ray of the chest organs - X-ray picture of the volumetric formation of the upper external mediastinum.

ECG: Sinus tachycardia with a heart rate of -125 beats per minute. With moderate dystrophic changes in the myocardium of the left ventricle.

Ultrasound: Enlargement of the thyroid gland I st. with an autoimmune component. Left-sided lymphadenopathy. Hepatomegaly (+2.0 cm) Hepatosis of the liver. Chronic cholecystitis. Compaction of the PMS of both kidneys. Moderate pyelectasis of the left kidney.

MSCT of the abdominal region: There is a large infiltrative space-occupying mass in the anterior mediastinum with multiple nodules in both lungs, in the vertebrae and in the sternum (mts?). Hepatomegaly. Massive formations and structural changes in the adrenal glands were not revealed.

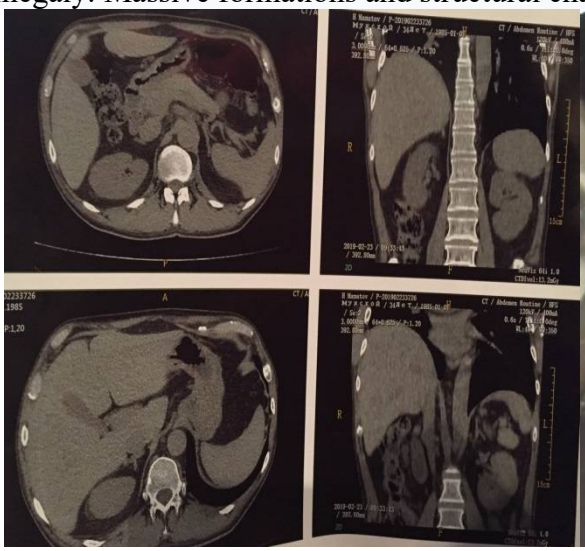

Fig-7

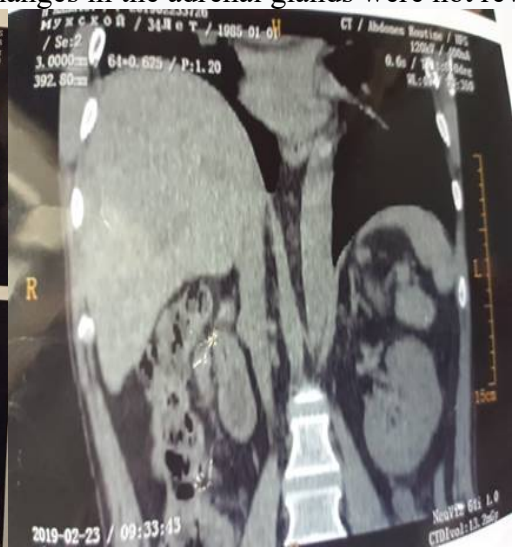

Fig-8

The patient was examined by narrow specialists and identified:

Ischemic heart disease. Stable exertional angina FC - II according to NYHA. Distal polyneuropathy 3 tbsp. sensory motor form. Syndrome of neuropathic diabetic foot. Urinary tract infection, complicated form.

The patient was examined by an oncologist and diagnosed with a malignant tumor of the mediastinum with mts in the regional lymph nodes. A council was organized, which included professors of neuroendocrinologists Ashley Grosman, Halimova Z.Yu. , Prof. Neurosurgeon Michael Powell, MD Narimova G.J. On the basis of laboratory and instrumental examinations, the diagnosis was made:

Main: ACTH ectopic Cushing's syndrome arising from the formation of the upper external mediastinum with metastases to regional lymph nodes.

Osl: Symptomatic arterial hypertension II. AG-III. Steroid diabetes. Urinary tract infection, complicated form.

It was recommended:

Staged bilateral adrenalectomy, followed by chemotherapy. To correct glycemia, the drug Metformin 2000 mg per day was prescribed, antihypertensive therapy: tab. Bisoprolol 5 mg, tab. Telmisartan 80 mg in the morning, tab. Adipin 10 mg 1 tab. in the evening. Antiplatelet therapy: tab. Thrombotic ACC 100 mg 1 ton x 1 time in the evening.

For a staged adrenalectomy, the patient was referred to the surgical department of the TMA, where on May 18, 2019, the operation “Retroperitoneascopic adrenalectomy on the left.” , 0 ml / min. Hormone levels continued to remain high ACTH - 89.0 ng / ml, blood cortisol 8: 00-856.0 nmol / l, blood cortisol 24: 00-638.0 nmol / l, daily urine cortisol - 345.0 nmol / L (38-208 nmol / L). That is,

despite the operation, remission was not achieved. The patient's condition remained stably severe, A / D increased to 160/100 mm Hg, pulse -120 beats per minute, respiratory failure increased, body weight decreased, skin darkening increased

In October 13, 2019, he underwent a second planned "Retroperitoneascopic adrenalectomy on the right", after which the A / D began to decrease to 80/50 mm. rt. Art., continued hyperpigmentation of the skin, nausea, loss of appetite, weight loss, an increase in body temperature to 37-38 C, postural hypotension, weakness of the legs, local edema in the legs and arms, which indicated the development of adrenal insufficiency, in connection with than 29.10.2019 was hospitalized in the neuroendocrinology department in serious condition, worried about: weakness, increasing shortness of breath, feeling short of breath, aversion to food, nausea, weight loss. The patient's position due to respiratory failure was forced, moved with outside help, answers questions essentially. Breathing is shallow, frequent, 24 r / min. A / D 80/50 mm Hg. Pulse-120 beats per minute. rhythmic, pronounced filling and tension. Supraclavicular, cervical, axillary, ulnar lymph nodes are enlarged.

When examining:

Complete blood count: Anemia progressed - hemoglabin - 104 g / l (130-160), erythrocytes - 3.5 (4.0-5.0), white blood cells suppressed - Leukocytes - 6.3 (4.0-9.0), Lymphocytes - 20% (19-39), Platelets-309 (180-320), ESR-28 Mm / h (0-10). Protein in urine - traces, leukocytes -5-7 / 1, bacteria ++. (Proteinuria, bacteriuria)

Nechiporenko's test: Leukocytes - 1.250, erythrocytes - 1.500, cylinders - 1000.0.

From biochemical analyzes (30.10.2019): Albumin - 30.4 g / L (35-55), Total protein - 57.2 g / L (65-85) (protein spectrum is lowered), toxic hepatitis phenomena ALT-254 U \ L (12-14), AST-303 U \ L (8-35), total bilirubin - 39.6 μmol / L (up to 25), Creatinine-76 μmol / L (62-115), Urea-4.2 mmol / L (2.5- 8.3), Calcium -1.93 mmol / L (2.1-2.6), Potassium - 5.3 mmol / L (3.5-5.4), Sodium-142 mmol / L (130-150), the examination revealed hypoproteinemia with a significant increase in the levels of liver enzymes (toxic hepatitis with cirrhosis), hypocalcemia, hyperkalemia. Sodium and glycated hemoglobin are normal. HbA1C - 6.5%. Glycemia began to decrease without glucose-lowering drugs: Fasting blood glucose -4.2 mmol / l, after 2 hours - 4.7 mmol / l. Sugar in daily urine - relative density -1015, Amount - 1400 ml, sugar in daily urine - abs.; Triglycerides - 1.43 mmol / L (up to 1.7), Total cholesterol -4.0 mmol / L (3.4-5.2). (Indicators in norm).

Coagulogram: Hematocrit -40% (up to 40%), APTT -24 (20 "-30"), Fibrinogen-1.3 g / l (2-4), PTI-89% (80-100), TB-20 (15 "-20"). (The level of hematocrit and thrombin time in the upper limit of the norm)

Hormonal examination: ACTH - 72.0 ng / ml (up to 50 ng / ml), Cortisol at 8:00 - 140 nmol / L (260-720 nmol / L), 24: 00-25.0 nmol / L (50 -350 nmol / l), cortisol in daily urine - 33.0 nmol / l (38-208 nmol / l) (decreased levels of blood cortisol and urine cortisol)

ECG: Sinus tachycardia with a heart rate of 90 beats per minute. Dystrophic changes in the myocardium. Decreased coronary blood flow. As shown by the results of analyzes after a staged 2-sided adrenalectomy, the patient's condition was aggravated by adrenal insufficiency, although the levels of ACTH continued to be high. HRT was recommended: Cortef 10 mg, 1 tab in the morning, ½ tab at 13.00 and at 16.00 after meals, prednisolone 5 mg at 16.00.

Further, in accordance with the treatment plans, the patient was referred to an oncologist at the place of residence for chemotherapy (CT). The patient underwent 2 courses of chemotherapy in an oncological dispensary at the place of residence according to the FOLFIRINOX scheme (March - June 2020), 2 courses of CT according to the Gemcitabine + Abraxan scheme (July -August 2020), which further aggravated the condition due to the toxicity of drugs in general and hypocorticism, which manifested itself in nausea, lack of appetite, a decrease in A / D to 70/50 mm Hg, and therefore dexamethasone was prescribed in / m 4 mg 2-3 times a day. The condition progressively worsened, the patient was cachectic (Fig. 9-12), was on parenteral nutrition. Respiration is shallow, frequent, 26 r / min. Heart sounds are muffled. A / D 90/50 mm Hg Pulse-100 beats per minute. rhythmic, weak filling and tension.

From the results of the analysis after chemotherapy from 16.06.2020.
Complete blood count: Hemoglabin - 87 g / l (130-160), Erythrocytes - 3.0 (4.0-5.0), Leukocytes - 9.0 (4.0-9.0), Lymphocytes - 40% (19-39), Platelets - 280 (180- 320), ESR - 70 Mm / h (0-10). (Decrease in the level of hemoglabin, erythrocytes in the blood, lymphocytosis, increased ESR)

General urine analysis: Quantity - 100 ml, specific weight - 1018, protein in urine - traces, leukocytes - 4-6 / 1. (Proteinuria). Nechiporenko's test: Leukocytes - 5200, erythrocytes - 1700, cylinders - 1400. (Increase in the level of leukocytes, urine cylinders).
Biochemical analysis: Total protein - 64.6 g / L (65-85) Albumin - 35.5 g / L (35-55) (Protein spectrum is normal) ALT-172 U \ L (12-14), AST-167 U \ L (8-35) (Increased liver enzymes), total bilirubin - 16.8 μmol / L (up to 25), Creatinine - 146 μmol / L (62-115), Urea - 11.0 mmol / L (2.5-8.3) (Creatinine level , urea is increased), Calcium -2.14 mmol / L (2.1-2.6), Potassium - 5.2 mmol / L (3.5-5.4), Sodium-133 mmol / L (130-150), (The electrolytes are normal); Triglycerides - 1.14 mmol / l (up to 1.7), total cholesterol -4.5 mmol / l (3.4-5.2). (Indicators are normal) HbA1C - 5.9%.

Fasting blood glucose 4.5 mmol / l, 2 hours after - 5.1 mmol / l. Sugar in daily urine - relative density -1010, Amount-1400 ml, sugar in daily urine – avc.

Coagulogram: Hematocrit -40% (up to 40%), APTT -19 (20 "-30"), Fibrinogen-5.4 g / l (2-4), PTI-80% (80-100), TB-23 (15 "-twenty"). (Indicators of hematocrit, fibrinogen are increased).

Hormonal examination: ACTH - 63.0 ng / ml (up to 50 ng / ml), Cortisol at 8:00 - 40.0 nmol / L (260-720 nmol / L), 24:00 - 10.0 nmol / L (50-350 nmol / L), cortisol in daily urine - 77.0 nmol / L (38-208 nmol / L) (The rhythm of blood cortisol secretion is lowered, this indicates the decompensation of hypocorticism).

ECG: Sinus tachycardia with a heart rate of 105 beats per minute. Dystrophic changes in the myocardium. Left ventricular hypertrophy.

The patient's respiratory failure was growing. Pulmonary heart failure. Chronic heart failure against the background of post-radiation intoxication and paraneoplastic syndrome. The need for corticosteroids increased and the dose of HRT increased: Cortef 10 mg to 30 mg per day, Prednisalone 5 mg to 10 mg per day against the background of 12-16 mg / day parenteral dexamethasone. 8 months after bilateral adrenalectomy, 3 months after chemotherapy. Severe paraneoplastic syndrome against the background of progression of heart failure were the predisposing factors of death.
Thus, this example clearly illustrates the difficulties in the diagnosis and treatment of ACTH-ectopic SC, which often affects males at a young age. Failure to follow the sequence of stages of diagnosis and treatment in treatment tactics causes a high incidence of fatal outcomes.


Fig-9


Fig-10

Fig-11

Fig-12

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CLINICAL AND NEUROLOGICAL COMPLICATIONS IN PATIENTS WITH CHRONIC BRAIN ISCHEMIA WHO HAVE HAD COVID-19

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ABSTRACT

The article presents the results of a study of patients with COVID-19 with chronic brain ischemia. The earliest and most common clinical symptom of the disease is cognitive impairment. Even at the earliest stages of CIM, 85-90% of patients are diagnosed with cognitive disorders of varying severity, which progress with COVID-19 disease. Studies have shown the risk of cognitive impairment associated with COVID-19 is higher in the elderly or with previous cognitive impairment, as well as in those with vascular risk factors (hypertension) and previous comorbidities. Patients with prior neurological impairment and acute respiratory symptoms have a higher risk of developing neurological complications with COVID-19.

Keywords: Chronic brain ischemia, COVID-19, neurological complications, moderate cognitive disorders.

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КЛИНИКО-НЕВРОЛОГИЧЕСКИЕ ОСЛОЖНЕНИЯ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ ИШЕМИЕЙ МОЗГА, ПЕРЕНЕСШИХ COVID-19

АННОТАЦИЯ

В статье приводятся результаты исследования больных с COVID-19 с хронической ишемией мозга. Самым ранним и наиболее распространенным клиническим симптомом заболевания является нарушение когнитивных функций. Уже на самых ранних стадиях ХИМ у 85-90% пациентов выявляются когнитивные нарушения различной степени выраженности, которые при заболевании COVID-19 прогрессируют. Исследования показали, что риск когнитивных нарушений, связанных с COVID -19, выше у пожилых людей или у людей с предыдущими когнитивными нарушениями, а также у людей с сосудистыми факторами риска (гипертония) и предыдущими сопутствующими заболеваниями. Пациенты с предыдущими неврологическими нарушениями и острыми респираторными симптомами имеют более высокий риск развития неврологических осложнений, связанных с COVID -19.

Ключевые слова: Хроническая ишемия мозга, COVID-19, неврологические осложнения, умеренные когнитивные расстройства.

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COVID-19 ЎТКАЗГАН, СУРУНКАЛИ МИЯ ИШЕМИЯСИ БЎЛГАН БЕМОРЛАРДА КЛИНИК ВА НЕВРОЛОГИК АСОРАТЛАР

АННОТАЦИЯ

Мақолада COVID-19 билан хасталанган бош мия сурункали ишемияси бор беморларда текширув натижалари келтирилган. Белгилардан энг биринчи бўлиб беморларда когнитив бузилишлар намоён бўлмоқда. Сурункали бош мия ишемиясининг эрта босқичларида 85-90% беморларда хар хил кўринишдаги когнитив бузилишлар кузатилади ва COVID-19 таъсирида кучайиб боради. Тадқиқотлар шуни кўрсатдики, COVID -19 билан боғлиқ бўлган когнитив бузилиш хавфи кекса одамларда ёки илгари когнитив бузуқлиги бўлган одамларда, шунингдек қон томир хавф омиллари (гипертония) ва олдинги касалликларга чалинган одамларда юқори. Аввалги асаб касалликлари ва ўткир нафас олиш аломатлари бўлган беморларда COVID -19 билан боғлиқ бўлган неврологик асоратларни ривожланиш хавфи юқори.

Калит сўзлар: сурункали бош мия ишемияси, COVID-19, неврологик асоратлари, енгил когнитив бузилишлар.

Relevance: The 2019-2020 coronavirus infection pandemic has shown to the world not only the high aggressiveness of the new virus, but also its ability to cause severe neurological and cardiovascular complications. Studies have shown the risk of cognitive impairment associated with COVID-19 is higher in the elderly or with previous cognitive impairment, as well as in those with vascular risk factors (hypertension) and previous comorbidities. Patients with prior neurological impairment and acute respiratory symptoms have a higher risk of developing neurological complications with COVID-19. The formation and progression of cerebrovascular insufficiency is, as a rule, multifactorial, and in patients of older age groups there is a connection with the involutional changes in the brain tissue itself. As a rule, several risk factors are combined in one patient, and none of them can fully explain either the severity of neurological disorders or the nature of the course of the disease, which confirms the complexity of the mechanisms of the onset and

progression of both acute and chronic cerebral vascular insufficiency [1, 2]. Patients with COVID-19 suffer from severe hypoxia, which is a risk factor for encephalopathy. There is a decrease in compensatory capabilities due to prolonged exposure to ischemia, nonspecific stress resistance is weakened, which contributes to the further aggravation of the pathological process [1].

Chronic cerebral ischemia (CCI) is a chronic progressive form of cerebrovascular insufficiency associated with small focal or diffuse brain damage and manifested by a complex of neurological and neuropsychological disorders [1, 3,4].

It has now been established that the main reason for the development of chronic vascular non-stroke brain damage is microangiopathy, and not only chronic cerebral ischemia, but also repeated acute cerebrovascular accidents without clinical signs of stroke, the so-called silent heart attacks and / or hemorrhage [5,6]. The manifestations of CCI depend on the severity and / or extent of the process and include the presence of asthenic, cognitive, neuropsychiatric and focal neurological disorders. The earliest and most impaired cognitive function is a common clinical symptom of the disease. Already at the earliest stages of CCI, 85-90% of patients have cognitive impairments of varying severity. Cognitive deficits, in this case “vascular cognitive mental disorders”, is a symptom of the disease that develops one of the first, almost always combined with emotional disorders [1,2,7].

The aim of the study was to assess cognitive functions on the basis of clinical and neurological examination of patients with 1-st, 2-nd stages of CCI who had undergone caronovirus disease.

Materials and methods of research: 60 patients with 1-st, 2-nd stages of CCI were included in the study. The inclusion criteria for the study were the patients' age from 55 to 75 years, the established diagnosis of 1-st, 2-nd stages of CCI, corresponding to the ICD-10 criteria; stable course of the disease for at least 12 months before screening. According to the distribution by sex, among the 60 surveyed, there was a predominance of men over women (35 (58%) versus 25 (42%)). Clinical symptoms in 19 (32%) patients corresponded to stage 1 of CCI, in 41 (68%) patients - stage 2 of CCI with mild to moderate cognitive impairment. The main group consisted of 30 patients with CCI who had undergone caronovirus disease, the comparison group consisted of 30 patients with 1-st, 2-nd stages of CCI.

The state of the cognitive sphere was studied using a short test for assessing the mental sphere - Mini Mental State Examination (MMSE), which allows to quantify the general cognitive deficit, the state of the psycho-emotional sphere was determined by the results according to the Hamilton Depression Scale (HDG).

Research results: At the time of inclusion in the study, psychoemotional disorders prevailed among patients' complaints, signs of asthenization in the form of weakness and decreased performance in 100% of patients in the main group and 97% of the comparison group, rapid fatigue in 100% and 93%, patients complained of headache in 97% and 92%, dizziness in 68% and 60%, disturbance of night sleep in 80% and 67%, excessive irritability and nervousness in behavior in 73% and 67%, respectively, withdrawal in 20% of the examined patients with CCI who underwent caronovirus disease.

Analysis of focal neurological symptoms showed: central paresis of the 7th pair of cranial nerves was detected in 90% and 80%, central paresis of the 12th pair of cranial nerves occurred in 50% and 30% of the examined, respectively. Reflexes of oral automatism were found in 30% and 20%, respectively, anisoreflexia was diagnosed in 67% and 62% of patients, unsteadiness in the Romberg position in 67% and 57%, and an intention when performing a finger test in 32% and 20%, respectively, in patients with CCI after caronorvirus disease and CCI. During the observation process, the patients of the main group had a total MMSE score of 21.7 ± 0.02, while in the comparison group it was 23.8 ± 0.04, which confirms the negative effect of caronovirus disease on the cognitive sphere.

At the time of inclusion in the study, all patients had disorders in the emotional sphere. The study of psycho-emotional state using clinical scales of depression showed that depressive syndrome is characteristic in the group of patients with CCI, but prevails in the main group. The

results on the Hamilton Depression Scale (HHD) averaged 10.3 ± 2.1 points in the comparison group, which corresponds to mild depression (8-16 points), while in the main group of patients with CCI who underwent caronovirus disease it was 7.8 ± 1.2 points.

Conclusions and suggestions: In CCI, an increase in neurological symptoms is combined with a deepening of cognitive and depressive disorders. The formation of cognitive and depressive disorders is associated with more extensive focal brain damage and more pronounced vascular disorders due to caronovirus disease. Early diagnosis of cognitive impairment in CCI in patients with caronovirus infection will improve the quality of life of patients with neurological complications.

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IMPROVING THE EFFICIENCY OF HEALTH CARE IN MODERN CONDITIONS

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ABSTRACT

The Republican Scientific and Practical Conference with International Participation "Bioethics and Evidence-Based Medicine" was held on December 1-3, 2020 on the State Educational Institution "Belarusian Medical Academy of Postgraduate Education" online format. More than 500 participants, including representatives of the Republic of Belarus, the Russian Federation, the Republic of Uzbekistan, USA, France, Norway and Japan took part in the series of webinars held in the format of the online conference. The conference's uniqueness was in the formation of joint international approaches to the development of evidence-based medicine and bioethics, improving preventive medicine and the implementation of control of diabetes and other metabolic diseases in the modern world.

Keywords: bioethics, organization, global health, evidence-based medicine, diabetes, technology, roadmap.

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ПОВЫШЕНИЕ ЭФФЕКТИВНОСТИ ЗДРАВООХРАНЕНИИ В СОВРЕМЕННЫХ УСЛОВИЯХ

АННОТАЦИЯ

С 1 по 3 декабря 2020 г. на базе государственного образовательного учреждения «Белорусская медицинская академия последипломного образования» в онлайн-формате состоялась Республиканская научно-практическая конференция с международным участием «Биоэтика и доказательная медицина» в ходе которой была принята данная резолюция. В серии вебинаров, которые прошли в online-формате в рамках конференции, приняло участие более 500 человек, включая представителей из Республики Беларусь, Российской Федерации, Республики Узбекистан, США, Франции, Норвегии, Японии. Уникальность проходящей конференции состояла в формировании совместных международных подходов к развитию доказательной медицины и биоэтики, совершенствованию профилактической медицины и осуществлению контроля за ростом сахарного диабета и иных метаболических заболеваний в современных условиях.

Ключевые слова: биоэтика, организация, глобальное здравоохранение, доказательная медицина, сахарный диабет, технологии, дорожная карта.

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ЗАМОНАВИЙ ШАРОИТЛАРДА СОҒЛИҚНИ-САҚЛАШ ТИЗИМИНИ САМАРАДОРЛИГИНИ ОШИРИШ

АННОТАЦИЯ

2020 йил 1 дан 3 декабрга қадар “Белоруссия тиббиёт академияси постдиплом таълими” давлат таълим муассасида онлайн-форматда “Биоэтика ва даллиларга асосланган тиббиёт” номли Республика илмий-амалий анжуман бўлиб ўтди ва унинг асосида ушбу резолюция қабул қилинди. Онлайн-форматда ўтказилган вебинарларда 500та дан ортиқ иштирокчилар қатнашди, шу қатори Беларус Республикаси, Россия Федерацияси, Ўзбекистон Республикаси, АҚШ, Франция, Норвегия ва Япония мамлакатларидан вакиллар қатнашди. Ўтказилган анжуман мақсади замонавий шароитларда даллиларга асосланган тиббиёт ва биоэтикани ривожлантиришда хамкор ҳалқаро ёндашувларни шакллантириш, профилактик тиббиётни такомиллаштириш ва қандли диабет ва бошқа метаболик касалликлар билан касалланиш сонини назорат қилиш.

Калит сўзлари: биоэтика, ташкиллаштириш, глобал соғлиқни сақлаш тизими, даллилларга асосланган тиббиёт, қандли диабет,технологиялар, йўл харитаси.

Changes in the structure of morbidity and mortality of the population, as well as social, economic, political and technological changes in the modern world, lead to the need to search and develop new approaches and technologies that allow effective management of public health in the created conditions. Obviously, in response to the time challenges, various attempts are being made to form algorithms for managing public health, eventually providing variants of health systems with different degrees of effectiveness. In an analysis of 30 countries in Western Europe, the researchers obtained 27 health care systems grouped into 5 clusters along three dimensions: the regulatory system, financing, and the structure of health care delivery. Interestingly, the medical technologies used, their safety, effectiveness, clinical and economic efficiency were not considered either in this or in most other works devoted to health management [1].

Part of the researchers' focus on financial flows in health care is explained by a significant increase in healthcare costs in general and modern medical technologies (interventions), which occupy an increasing share of total funding. Simultaneously, researchers often underestimate the fact that the use of these technologies influences the quantitative changes of financial flows and the changes in the quality, quantity, and distribution of information in the decision-making process in health care. Formation in most countries of Health technology Assessment agencies (hereinafter - HTA agencies), responsible for the expertise of clinical and economic characteristics of medical interventions, indicates the urgent need to create new supporting models of decision-making in the field of medicine, based on the development and rational use of appropriate methods of prevention, diagnosis, treatment and rehabilitation [2].

The creation of PHC agencies is a significant step forward, allowing the inclusion of interventions that will not prove critical to the health care system, as well as a more comprehensive consideration of the benefits and risks associated with the use of these interventions in funding systems. At the same time, it is becoming apparent that using HTA agencies as tools for making the ultimate decision about the use or non-use of a particular medical technology does not solve all the issues of building effective and rational health care.

As a result, several contradictory concepts of the influence of medical technologies on health care efficiency are forming, each of which has supporting evidence and taken as a whole these concepts contradict one another. In particular, the emergence of new medical technologies is associated with an unconditional increase in the effectiveness of their use (without conducting clinical and economic research and cost accounting). However, a detailed analysis of the statistical and clinical significance of the clinical trials results shows that only about 5% of the new drugs introduced in the market of European countries meet these expectations [3]. On the other hand, the increase in the number of new drugs (according to INN classification) does correlate with treatment outcomes in cancer patients, which suggests the role of the drug availability factor as one of the main mechanisms influencing the performance of medical technologies [4].

Research evidence suggests the need to form additional algorithms for population health management, built around evidence-based information about the benefits and risks associated with the use of medical technologies and allowing a rapid (and, if possible, pro-active) response to the emergence (or forecast) of public health risks. First of all, such algorithm concerns consistent formation of evidence base about existing and prospective healthcare technologies in connection with current or expected morbidity structure, and development of scenario models based on these data depending on possible managerial decisions. Such a model must be combined with the financial and managerial structure of health care regulatory bodies, with a legal mechanism for supporting medical technologies. Otherwise, no matter how wonderful and trustworthy the generated solutions may be, they will not be implemented.

At the expert forum "Health Care of Russia: Organizational and Economic Features and Trends, Strategic and Tactical Tasks for Further Development," which took place on February 26, 2019, with the participation of representatives of the World Health Organization (WHO), United Nations Educational, Scientific and Cultural Organization (UNESCO), the Russian Academy of Sciences (RAS), state authorities and management bodies, the League of Patient Advocates, scientific organizations and public associations, the main provisions for the development of health protection in modern conditions were formed, including for the first time the principle of pro-active risk management in health protection was presented to the general public [5].

Further development of this principle, including the structuring of information flows and interaction of expert blocks in the model for supporting effective managerial decision-making in health care, is presented in Fig. 1.

The proposed model assumes the development and presentation of probabilistic scenarios of events development, their medical, social and economic consequences to the authorized authorities. The model is based on a comprehensive analysis of the results of monitoring and forecasting public health and health care technologies with the formation of the evidence-based on their effectiveness, safety, clinical and economic efficiency. Most elements of this model are already used in practice, for example, in the formation of programs of prevention, diagnosis, treatment, rehabilitation and reduction of medical, social and economic consequences of non-communicable diseases [6].

The presented model of proactive risk management in public health has become an integral part of the World Health Organization's draft Resolution "Integration and Collaboration in the Development of Guidelines for Research to Improve Health". The draft Resolution assumes the holistic, continuous, consistent and successive formation of data on medical technologies at different stages of their life cycle, including preclinical, clinical and clinical-economic research, systematic reviews and clinical guidelines following WHO requirements, monitoring and forecasting of public health risks, as well as a direct connection with health system requests for preparation of scenarios and models of public health development in making regulatory decisions.

The draft resolution also takes into account that each element of the information block:
- firstly, is represented by infrastructure and financing, qualified personnel, their basic training and continuous development of relevant key competences,
- Secondly, it addresses bioethical and conflict of interest management issues within the limits of its mandate,
- Thirdly, it ensures the participation of all interested parties, especially patients,
- Fourth, it establishes a coherent, continuous, consistent and successive connection with other units and regulatory bodies.

It is worth emphasizing that each information block interacts with other blocks both directly (when forming an evidence base on the benefits and risks associated with medical technologies) and along the lines of work within blocks, providing a functional link in such areas as structure and financing, provision of qualified personnel, compliance with bioethics norms, and management of conflicts of interest.

The Draft Resolution draws special attention to the need to create and support structures to ensure the coordination and integration of evidence into regional and international cooperation, practice, implementation of WHO recommendations, international requirements and standards. International cooperation allows exchanging the created information on the structure of morbidity, peculiarities of application of health care technologies, scientific research methodology, information processing and decision making. One of the advantages of broad international collaboration is the possibility of investing available resources from each of the participants, so that everyone has full access to joint developments and can apply them according to their own needs and local conditions.

The Republic of Uzbekistan, being one of the initiators of the WHO Resolution, based on national institutions, is starting to form project offices for structuring international cooperation on evidence-based medicine within the CIS. Such approach makes it possible to significantly expand the volume and improve the quality of evidence, to create a national evidence base corresponding to high world standards through linking evidence with the needs of the national health care system of the Republic of Uzbekistan, as well as the peculiarities of its infrastructure and financing.

As a result of project offices functioning, there will be a roadmap on introducing a pro-active risk management model into the Republic of Uzbekistan's health care system to improve citizens' health.

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ЎЗБЕК ТИББИЁТ ЖУРНАЛИ
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ASSESSMENT OF TYPE 1 DIABETES MELLITUS COMPENSATION IN CHILDREN AND ADOLESCENTS IN THE REPUBLIC OF UZBEKISTAN

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ABSTRACT

The study evaluates carbohydrate metabolism in children and adolescents with DM 1 in the Republic of Uzbekistan. The study's object is a type 1 DM register database - 14 regions of the RUz included in the online registration system. When assessing glycated hemoglobin, it was found that overall in Uzbekistan, the optimal parameters of carbohydrate metabolism (HbA1c) <7.5% in children were 36.8%, and in adolescents 22.4%. The best indicators in children were in the RKK (54%) and Andijan region (56%). Assessment of fasting and postprandial glycemia in children and adolescents was also carried out for RUz. The average fasting glycemia in RUz was 7.8 mmol/l, and postprandial glycemia in children and adolescents was 10.3 mmol/l. The frequency of hypoglycemia among children and adolescents with type 1 diabetes was 8.7% according to RUz. The frequency of ketosis and ketacidosis in RUz was 10.5%.

Keywords: diabetes mellitus, compensation, glycated hemoglobin, children.

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ОЦЕНКА СТЕПЕНИ КОМПЕНСАЦИИ САХАРНОГО ДИАБЕТА 1 ТИПА У ДЕТЕЙ И ПОДРОСТКОВ ПО РЕСПУБЛИКИ УЗБЕКИСТАН

АННОТАЦИЯ

Цель исследования – провести оценку углеводного обмена у детей и подростков с СД 1 по Республики Узбекистан. Объектом исследования является база данных регистра СД 1

типа – 14 регион РУз, включенный в систему онлайн-регистра. При оценке гликированного гемоглобина, было выявлено, что в целом по Узбекистану оптимальные показатели углеводного обмена (HbA1c) <7,5%у детей составили 36,8%, а уподростков 22,4%. Наилучшие показатели у детей были в РКК (54%) и в Андижанской области (56%) областях. Также проведена оценка гликемии натощак и постпрадиальной гликемии у детей и подростков по РУз. По РУз средняя гликемия натощак составила – 7,8 ммоль/л, постпрандиальная гликемия у детей и подростков составила 10,3 ммоль/л. Частота гипогликемий среди детей и подростков с СД 1типа составил по РУз 8,7%. Частота кетозов и кетацидозов по РУз составила 10,5%.

Ключевые слова: сахарный диабет, компенсация, гликированный гемоглобин, дети.

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ЎЗБЕКИСТОН РЕСПУБЛИКАСИДА БОЛАЛАР ВА ЎСМИРЛАРДА 1-ТУР ҚАНДЛИ ДИАБЕТНИ КОМПЕНСАЦИЯ ДАРАЖАСИНИ БАҲОЛАШ

АННОТАЦИЯ

Тадқиқотнинг мақсади: Ўзбекистон Республикасида қандли диабет билан касалланган болалар ва ўсмирлар орасида углевод алмашинувини баҳолаш. Тадқиқот объекти - интернет реестр тизимига киритилган Ўзбекистон Республикасидаги барча 14та худудларидан йиғилган қандли диабет 1 тури рўйхатга олиш маълумотлар базаси. Гликирланган гемоглобинни баҳолашда, умуман олганда Ўзбекистонда углевод метаболизмининг оптимал кўрсаткичлари (HbA1s) -7,5% болаларда 36,8%ни, ўсмирларда эса 22,4%ни ташкил этганлигини аниқланди. Болаларда энг яхши кўрсаткичлар ҚҚРда (54%) ва Андижон вилоятида (56%) бўлган. Шунингдек, Ўзбекистон Республикаси бўйлаб болалар ва ўсмирларда наҳордаги ва постпрандиал гликемияни бахолаш ишлари олиб борилди. ЎзРда нахордаги ўртача гликемиянинг миқдори 7,8 ммоль/л, постпрандиал гликемия миқдори эса ўртача болаларда ва ўсмирларда 10,3 ммоль/л ташкил этди. Биринчи турдаги қандли диабет билан касалланган болалар ва ўсмирларда гипогликемияларнинг сони ЎзРда 8,7%ни ташкил этди. Кетоз ва кетоацидознинг сони ЎзРда 10,5%ни ташкил этди.

Калит сўзлар: қандли диабет, компенсация, гликирланган гемоглобин, болалар.

Introduction. Type 1 diabetes is characterized by chronic, immune-mediated destruction of pancreatic β-cells, which leads to partial or in most cases, absolute insulin deficiency.

There is currently no question that effective glycemic control in patients with diabetes mellitus (DM) is the basis for preventing the occurrence and progression of long-term complications. Management of diabetes in the pediatric age group involves many difficulties due to objective and subjective reasons [1].

Management of diabetes in children is complicated by factors such as hormonal changes characteristic of normal growth and development (e.g., rapid growth, insulin resistance during puberty, psychosocial and cognitive developmental features), family traditions (including socioeconomic status, cultural traditions and a parent or guardian views on parenting), and the provision and quality of care and support outside home (such as school or college).

The use of genetically engineered insulins and their analogues intensified insulin therapy, the use of pump insulin therapy, regular self-monitoring, and the opportunity to improve their

knowledge in a diabetes school setting are the keys to good disease compensation and, consequently, to reducing the risk of future complications.

The study aimed to evaluate carbohydrate metabolism and acute complications in children and adolescents with DM 1 in the Republic of Uzbekistan.

Materials and methods.

The study's object was the DM1 type 1 registry database - 14 regions of the RUz included in the online registration system. The level of glycated hemoglobin (HbA1c) was determined in all regions of RUz, the daily requirement for insulin, the presence and nature of complications, and anthropometric characteristics were evaluated. The age of the examined children ranged from 2 to 18 years, and the average duration of the disease was 3.8 ± 2.9 g. The analysis was carried out according to several parameters: duration of DM1, level of compensation of the disease, method of insulin therapy. According to the latest ISPAD guidelines, HbA1c ≤ 7.5 % was considered to be compensation, HbA1c 7.6-9.0 % was subcompensation, and HbA1c > 9 % was decompensation [1].

Results and Discussion.

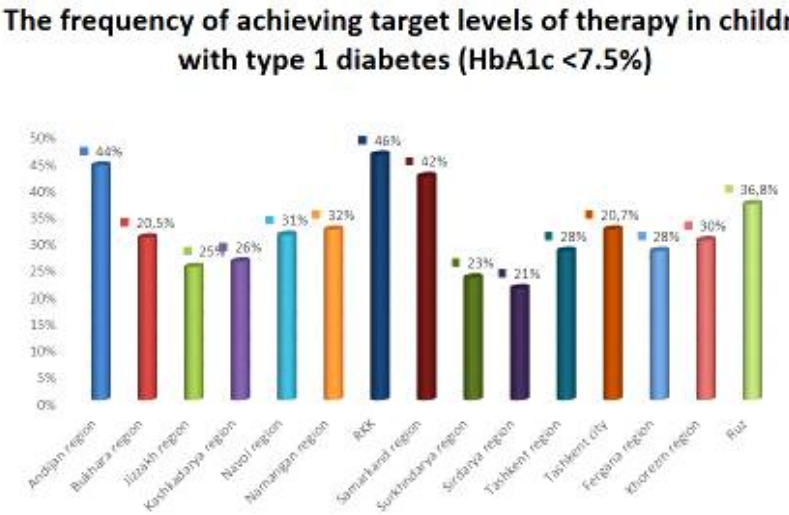
When assessed by age composition, children aged 10 to 14 years comprised the largest group -66.6%, those aged 0-4 years the smallest (5.0%), and patients aged 5-9 years comprised 28.3%. Similar ratios of the age structure were observed both among boys and girls and over the registry period.

In terms of disease duration, the largest group consisted of children with type 1 diabetes with a duration of less than 5 years (70.9%) and the smallest (2.1%) with a duration of more than 10 years.

Studying the age structure of child morbidity in RUz was the study of the general trend of morbidity with increasing age of children. For this purpose the dynamics of type 1 DM morbidity in three age groups were analyzed: younger (0-4 years), middle (5-9 years), and older (10-14 years). During the study period, the incidence of type 1 DM in children varied in different age groups. It was the highest in the older age group and exceeded the incidence in the middle and younger age groups.

The main criteria for the effectiveness of insulin therapy are achievement and maintenance of normoglycemia, absence of severe hypoglycemia and ketoacidosis episodes, as well as normal rates of physical and sexual development in children and adolescents (International Society for Pediatric and Adolescent Diabetes, 2017). It should be noted that the goals of self-monitoring, in some cases, should be individualized depending on the characteristics of the individual child. In 2020, an analysis of the level of compensation in children and adolescents by HbA1c level was carried out in all regions. It was found that in Uzbekistan as a whole, the optimal values of carbohydrate metabolism (HbA1c) <7.5% in children were 36.8% (Fig. 1).

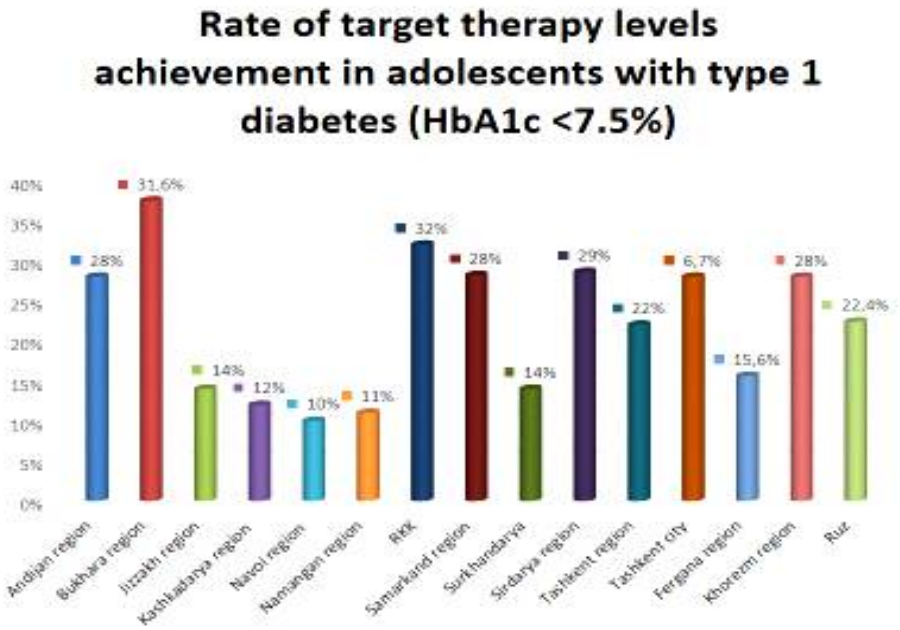
Fig. 1



A high percentage of children in decompensated condition was found in Syrdarya (79%) and Surkhandarya regions (75%). The best rates were in RKK (54%) and Andijan province (56%).

Analysis of the level of compensation in adolescents showed that overall in Uzbekistan, the optimal indices of carbohydrate metabolism (HbA1c) in adolescents were significantly worse than in children and amounted to 22.4% (Figure 2).

Fig. 2



When analyzing the degree of compensation in adolescents, it was found that a high percentage of decompensation was noted in Navoi (10%), Namangan (89%) and Kashkadarya regions (88%). The best rates were observed in the Bukhara region (68.4%) and RKK (68%).

Considering the permissible target level of HbA1c for children and adolescents <7.5%, one may note unsatisfactory results of this parameter with only 36.8% of children and 22.4% of adolescents reaching the target level. Worse HbA1c values in adolescents may be due to the objective difficulty of glycemic control during puberty. The data obtained indicate the priority importance of educating children and adolescents in "Schools for diabetes patients" and the need for more thorough glycemic monitoring and, consequently, providing the means of self-monitoring to an appropriate extent. The course of DM1 in childhood and adolescence is characterized by the greatest instability of carbohydrate metabolism parameters. The degree of compensation worsens by a factor of almost 6 as the duration of the disease increases, despite increasing insulin doses. Similar data are presented in the studies of Russian and foreign authors [6, 8].

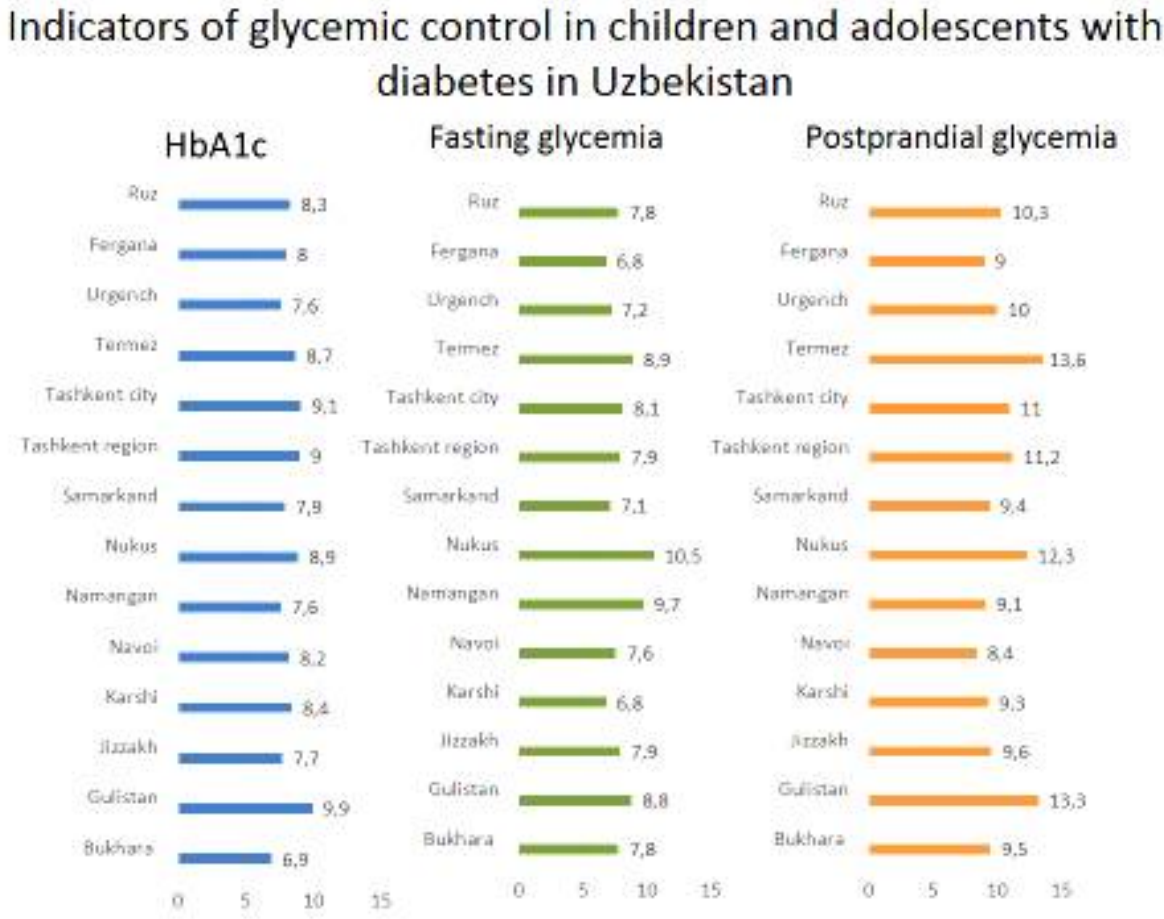
Control of HbA1c is a study that is necessary to monitor patients with diabetes, both clinically - to assess the effectiveness of insulin therapy and timely decision-making on the need for its correction, and organizationally - as a target indicator of the quality of nutritional care. To this end, it is necessary not only to improve the quality of HbA1c data entry in the register (in 100% of patients) and to increase the frequency of measurement of this parameter. Considering that in children - a special risk cohort - the targets should be individualized to avoid severe hypoglycemia, this issue becomes even more urgent.

The average level of HbA1c, fasting and postprandial glycemia in children and adolescents across RUz was analyzed in 2020 (Figure 5). Optimal glycated hemoglobin values were observed in the Bukhara region (6.9%).

When assessing fasting glycemia, the vast majority of patients had a fasting glycemic level of up to 7.9 mmol/l. The average fasting glycemia for RUz was 7.8 mmol/l. The optimal values were in Ferghana (7.8 mmol/l), Kashkadarya (6.8 mmol/l) and Samarkand regions (7.1 mmol/l). A high percentage of children and adolescents in the decompensated state was noted in RKK (10 mmol/l).

When assessing postprandial glycemia in children and adolescents across RUz, the figures were 10.3 mmol/l. High indices were observed in the Surkhandarya region (13.6 mmol/l), Syrdarya region (13.3 mmol/l) and RKK -12.3 mmol/l (Figure 3).

Fig. 3



The quality of care is characterized by the prescription of the correct insulin therapy regimen, 100% provision of insulin in the required daily dose, training in self-monitoring, prevention and treatment of late vascular complications.

During the analysis, it was found that in general, among children and adolescents in RUz, IIT's prescription was 100%.

In 19.04.2019 the Decree of the President of the Republic of Uzbekistan from. № PP -4295 "On approval of the National Program to improve endocrinological care for the republic's population for 2019-2021". In this decree, the main set of measures is the provision of analogue insulin for children and adolescents with type 1 DM in the Republic of Uzbekistan, providing centralized purchase and distribution of analogue insulin through regional endocrinology dispensaries. In 2020, all children and adolescents with type 1 diabetes across Uzbekistan were provided with analogue insulin.

As part of the online registry, the dynamics of the prevalence of acute complications of type 1 DM was assessed. The incidence of hypoglycemia among children and adolescents with type 1 diabetes was 8.7% in RUz. The highest frequency of hypoglycemia was observed in Surkhandarya region 36.3%. In Jizzak and Kashkadarya regions, no hypoglycemia was observed (Fig. 4).

The incidence of ketosis and ketacidosis among children and adolescents with type 1 DM in RUz was also assessed. The incidence of ketosis and ketacidosis in RUz was 10.5%. The highest frequency of ketosis and ketacidosis was found in Surkhandarya province (38.5%) and in Navoi province (24.4%). The incidence of ketosis and ketoacidosis was not observed in Jizzak, Namangan and Kashkadarya regions (Figure 5)

Fig.4.

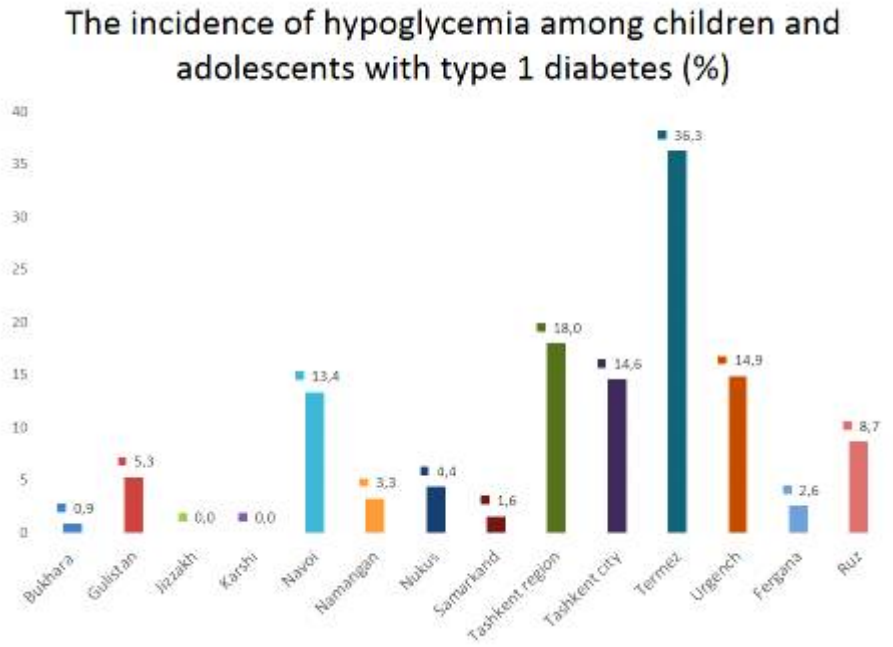
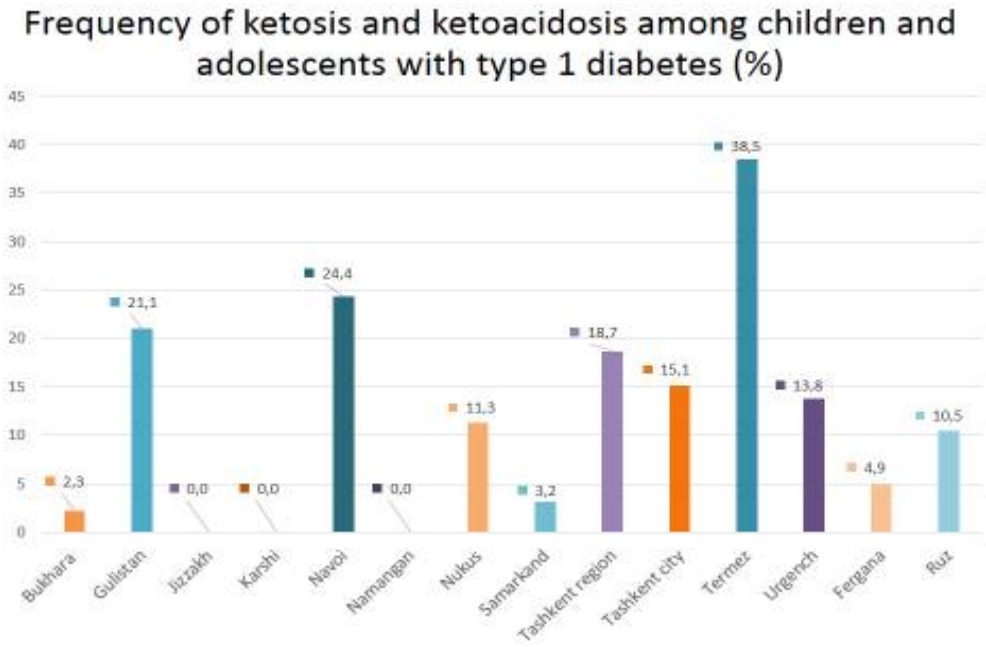


Fig.5.



Conclusions:

1. Over the period of the National Registry from 2018-2020, there has been an increase in the prevalence and incidence of type 1 DM among children against the background of decreasing mortality.
2. For the National Register period, it was revealed that Uzbekistan in terms of incidence of children DM 1 type belongs to the region with the lowest risk.
3. We assessed the extent to which children achieve target glycated hemoglobin therapy levels for 36.8%, depending on the regions. The worst compensation rates are in Syrdarya and Surkhandarya regions.

4. The incidence of DCAN in children in RUz reaches 10.5%. To diagnose it in time, patients with unsatisfactory compensation of carbohydrate metabolism, a long and complicated course of the disease need special examination.

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