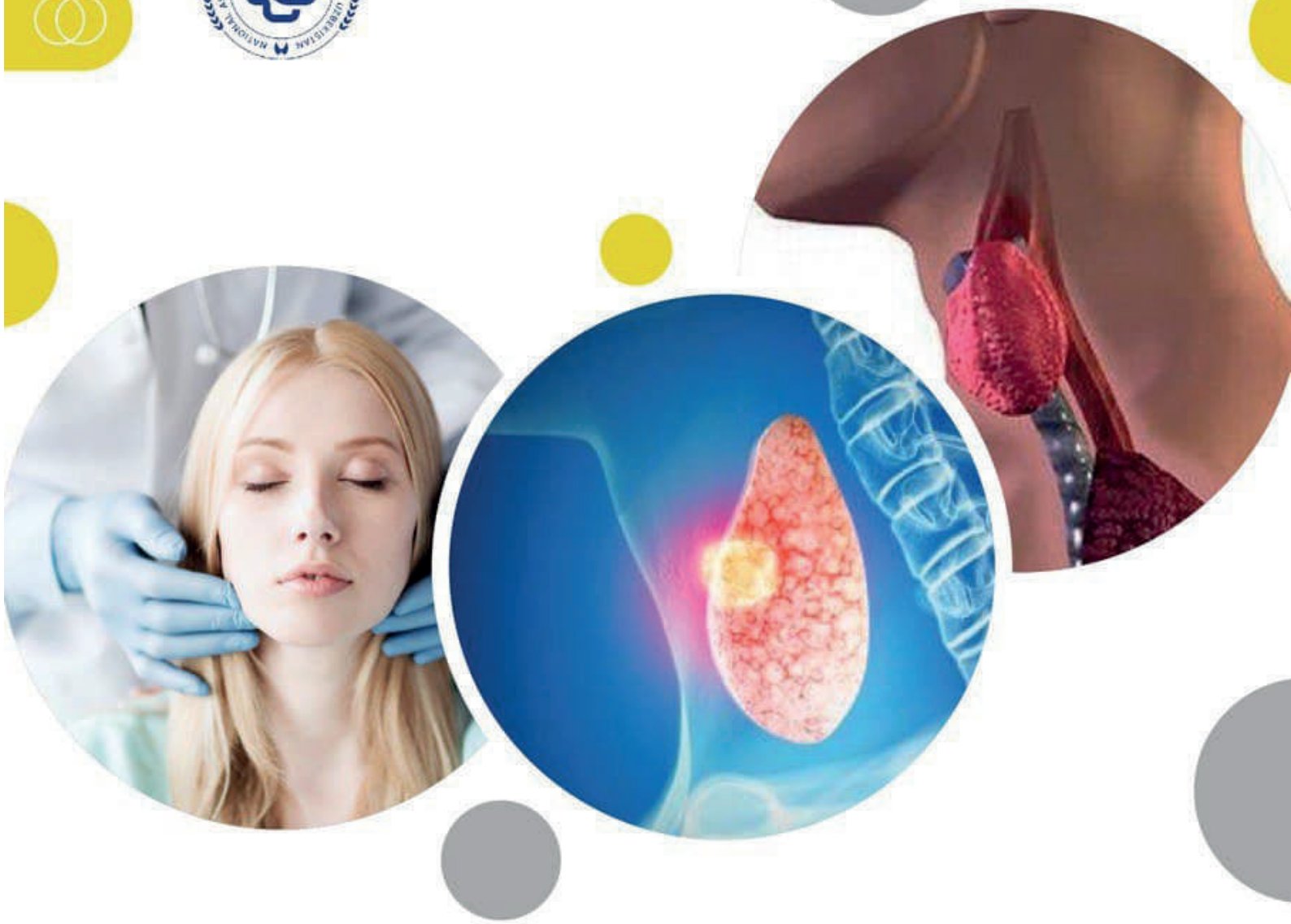

# O'RTA OSIYO ENDOKRINOLOGIK JURNAL
# ЦЕНТРАЛЬНО- АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ ЖУРНАЛ
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# O‘RTA OSIYO ENDOKRINOLOGIK

# ЦЕНТРАЛЬНО АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ

# CENTRAL ASIAN ENDOCRINOLOGICAL

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**ТОШКЕНТ – 2021**

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# VITAMIN D AS A RISK FACTOR FOR MINERAL DENSITY DISORDERS IN WOMEN

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**Резюме**
**Витамин D как фактор риска развития нарушений минеральной плотности у женщин**

**Аббосхужаева Л.С., Аллаярова Г.И.**

В обследованной группе (79 женщин) дефицит витамина D диагностировался у 41,8% женщин (в среднем 7,31 нг/мл), недостаточное содержание витамина D у 39,2% (в среднем 13,2 нг/мл), достаточное содержание при концентрации витамина у 19,0% (в среднем 30,2 нг/мл). По результатам двухэнергетической абсорбциометрии из 34 женщин у 1(2,9%) отмечается остеопороз (Т-критерий - -2,70; BMD шейки бедра 0,730 g/cm$^2$). У 5(14,7%) остеопения (в среднем Т-критерий - -1,46±0,31; BMD шейки бедра 0,888±0,09 g/cm$^2$).

**Summary**
**Vitamin D as a risk factor for mineral density disorders in women**

**Abboskhudzhayeva L.S., Allayarova G.I.**

In the examined group (79 women), vitamin D deficiency was diagnosed in 41.8% of women (average level 7.31 ng/ml), insufficient vitamin D level in 39.2% (average 13.2 ng/ml), sufficient vitamin content in 19.0% (average 30.2 ng/ml). According to the results of dual-energy absorptiometry of 34 women, 1 (2.9%) had osteoporosis (T-test -2.70; BMD of femoral neck 0.730 g/cm$^2$). Five (14.7%) had osteopenia (average T-criterion -1.46±0.31; BMD of femoral neck 0.888±0.09 g/cm$^2$).

Nowadays the problem of vitamin D deficiency is relevant, as many studies showed the relationship of its deficiency with development of a number of diseases.

The problem of vitamin D deficiency is one of the most urgent, because, according to the results of numerous studies, one third of the world's population is vitamin D3 deficient [2; 4; 8]. To date, it has been irrefutably proved that vitamin D is closely interrelated not only with parathyroid hormone and calcitonin in maintaining of phosphorus-calcium metabolism, but also with the secretion and biological effects of other hormones (insulin, estrogen), neurotrophic factors, as well as cytokines [3; 6; 13].

50% of postmenopausal women in Thailand and Malaysia, 75% in the USA, 74-83.2% in Russia, and 90% in Japan and South Korea have levels of 25(OH)D less than 30 ng/ml [5; 15]. There is an evidence of severe vitamin D deficiency (< 12ng/ml) in the Middle East and South Asia [12; 16].

There are no studies in Uzbekistan regarding the assessment of vitamin D status among the population, which does not allow us to accurately judge the true causes leading to the development of its deficiency and its contribution to the incidence of socially significant diseases.

In this regard, the study of the prevalence of vitamin D deficiency in various population groups will provide reduction of the risk of many chronic diseases.

**Objective**: to assess vitamin D levels in perimenopausal women.

**Materials and methods.** 79 women aged 40-50 years were examined. The average age was 46.1±3.28 years. In 34 of them, bone mineral density (BMD) was assessed using dual energy X-ray absorptiometry (DEXA).

Vitamin D and parathyroid hormone (PTH) levels were tested using electrochemiluminescent assay in an automatic analyzer.

According to the classification of the European Society of Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, vitamin D deficiency is diagnosed at a level of <10 ng/mL, insufficient vitamin D level – at <20 ng/mL, and sufficient vitamin content at 20-30 ng/mL.

Bone mineral density (BMD) was evaluated by dual energy absorptiometry (DEXA) on a Prodigy

bone densitometer, GE Lunar Corporation, USA.

The measurement results are presented in absolute values of BMD (g/cm$^2$) and in T- and Z-score (T- and Z-criterion), according to the generally accepted WHO criteria for diagnosis of osteoporosis. The measurements were performed in two standard areas of skeleton: the lumbar spine (vertebrae $L_1$-$L_4$) and the proximal femur. When interpreting data for the diagnosis of osteoporosis of the spine, the *Total* indicator was estimated in standard deviations.

According to the clinical recommendations on osteoporosis, diagnosis of osteoporosis or osteopenia was based on the values of the t-criterion – the number of standard deviations (SD) from the reference for the same age: ≤-2.5 SD was regarded as osteoporosis, -1.0 SD to -2.5 SD – as osteopenia, and >-1.0 SD as normal.

The data obtained were processed using computer programs Microsoft Excel, STATISTICA 6 and Biostat. Quantitative indicators are presented as M±SD, as well as medians (Me) and 25$^{th}$ and 75$^{th}$ percentiles (IQR). Differences between groups were considered statistically significant at $p<0.05$.

**Results and discussion.**

The average level of 25(OH)D was 13.95±9.41 ng/mL (Me 10.8; IQR 8.2-16.8). The trend line ranged from 13.6 to 14.01 ng/mL (Fig. 1.).

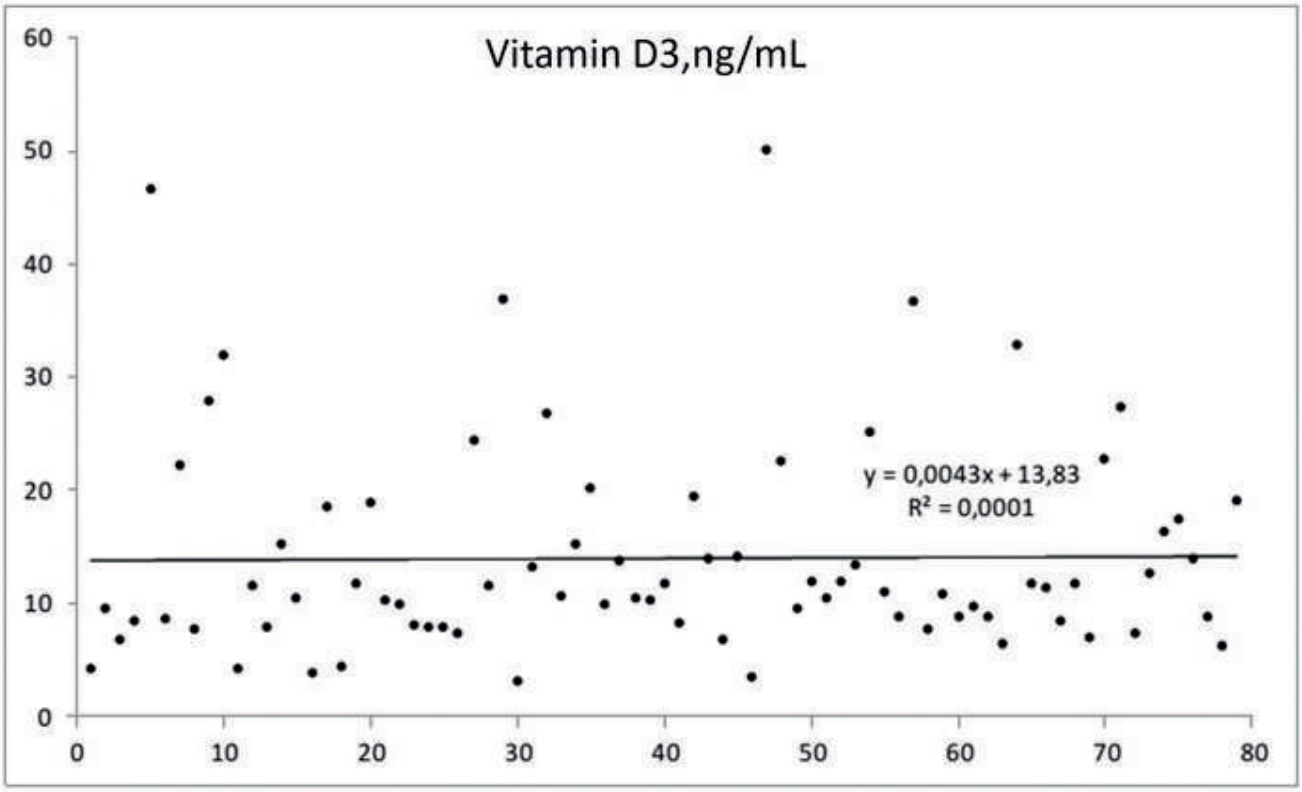


**Fig.1. 25(OH)D level in examined women**

According to classification of the European Society of Clinical and Economic Aspects of Osteoporosis and Osteoarthritis, vitamin D deficiency was diagnosed in 41.8% of women (average level 7.31 ng/ml), insufficient vitamin D level – in 39.2% (average level 13.2 ng/ml), and sufficient vitamin content – in 19.0% (average level 30.2 ng/ml).

In 81.0% of women, the level of 25(OH)D was within 2.5$^{th}$-90$^{th}$ percentiles in the range of 3.0-19.25 ng/ml. 5.1% of women had 25(OH)D level below the 5$^{th}$ percentile, and 7.6% of the examined women had the level above 93.5$^{th}$ percentile. Analysis of PTH in women of perimenopausal age showed that the average PTH level was 61.93±25.0 ng/ml (Me 55.9; IQR 43.3-73.1). The trend line ranged from 58.17 to 62.0 ng/ml (Fig. 2.).

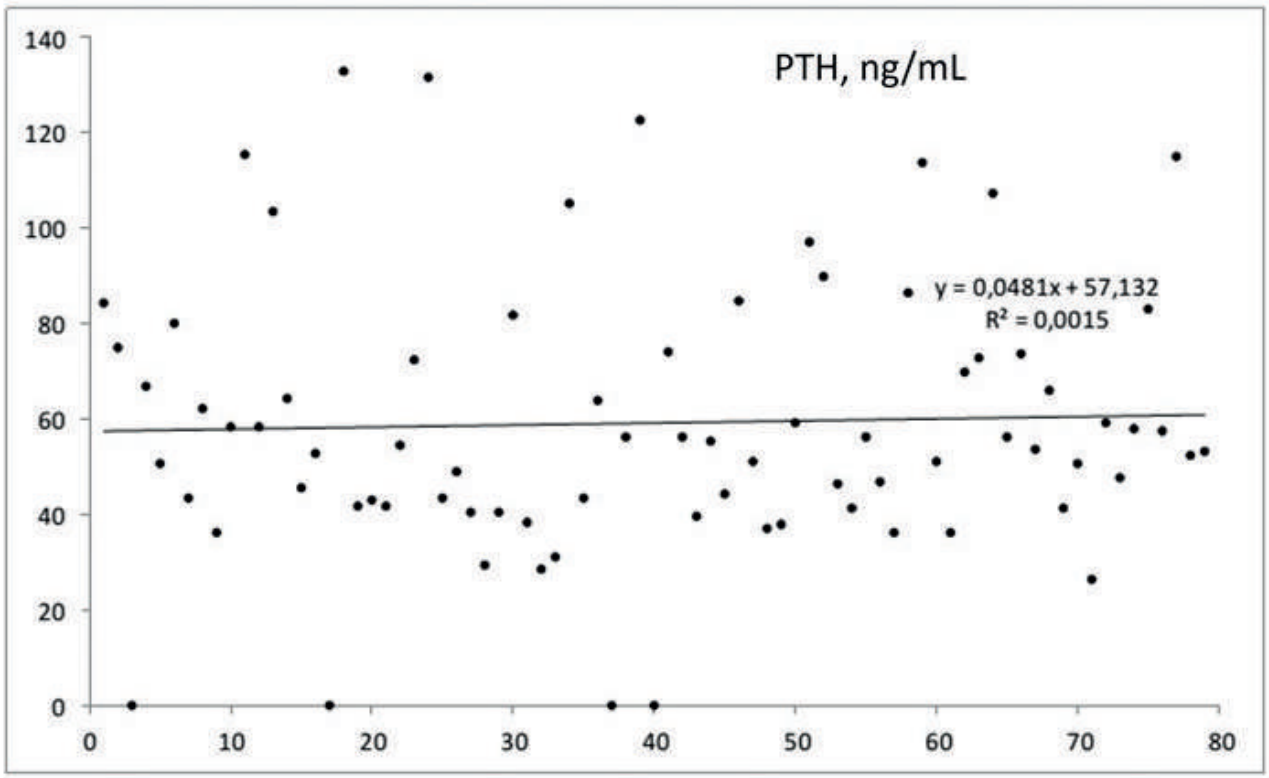


**Fig. 2. PTH level in examined women**

The average BMD of the femoral neck was 0.976±0.133 g/cm$^2$, the average T-score was 0.09±1.10. The average BMD of $L_1$-$L_4$ was 1.111±0.16 g/cm$^2$, the T-score was 0.14±1.20.

According to the results of dual-energy absorptiometry of 34 women, 1 (2.9%) had osteoporosis (T-test -2.70; BMD of the femoral neck 0.730 g/cm$^2$). Her level of vitamin D was 8.29 ng/mL, which, according to the classification, corresponds to severe vitamin deficiency. 5 women (14.7%) had osteopenia (average T-criterion -1.46±0.31; BMD of femoral neck 0.888±0.09 g/cm$^2$). Vitamin D level was 8.18±2.65 ng/ml, which also corresponds to severe vitamin deficiency. It should be noted that 16 (47.1%) women had severe vitamin D deficiency (3.0-9.73 ng/ml), in 15 (44.1%) women vitamin D level ranged from 10.2 to 17.3 ng/ml, which also indicates vitamin deficiency.

To date, there are various views on the reference and deficient levels of vitamin D. Testing for vitamin D is not routine, and the question of the exact rubrication of its levels is crucial. In a laboratory reference, vitamin D content of less than 10 ng/ml is defined as deficit, 10-30 ng/ml as insufficient level, and 30–100 ng/ml as sufficient, normal value [1; 9].

A number of experts propose the level of 20 ng/ml as the lower reference limit of 25(OH)D. It is believed that the risk of vitamin D deficiency is most likely at a serum level of 25(OH)D <30 nmol/L (<12 ng/ml). 25(OH)D level in the range of 30–50 nmol/L (12–20 ng/ml) is referred to as vitamin D insufficiency. Sufficient vitamin D concentration is ≥50 nmol/L (≥20 ng/ml). 25(OH)D level above 50 nmol/L covers vitamin D requirement in 97.5% of population [7; 10; 14].

Based on population studies conducted in different regions of the world and in different age groups, it is believed that concentration of 25(OH)D 30 ng/ml and higher ensures its adequate effect on calcium metabolism and parathyroid hormone levels [11; 13].

Our studies were conducted on a small group of women. All population-based studies on the prevalence of hypovitaminosis D in other medical centers were carried out on a large cohort of patients. This makes it reasonable to conduct further studies in this direction with the prospect of subsequent clinical application of the results obtained.

Thus, an average level of 25(OH)D (13.95±9.41 ng/ml) in women of perimenopausal age indicates its severe deficiency. 81.0% of women of the studied population had 25(OH)D levels below 20 ng/ml which shows that the majority of subjects had vitamin D deficiency of various severity.

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## CLINICAL CHARACTERISTICS OF ANDROGEN-SECRETING TUMORS IN ADRENALS IN GENDER AND AGE ASPECTS

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## КЛИНИЧЕСКАЯ ХАРАКТЕРИСТИКА АНДРОГЕН-СЕКРЕТИРУЮЩИХ ОПУХОЛЕЙ НАДПОЧЕЧНИКОВ В ГЕНДЕРНО-ВОЗРАСТНОМ АСПЕКТЕ

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**Аннотация:** Целью настоящего исследования явилось изучение клинических особенностей андроген-секретирующих опухолей надпочечников в зависимости от пола и возраста. Среди обследованных пациентов с различными образованиями надпочечников (n=282), которые находились на амбулаторном и стационарном лечении в РСНПМЦ Эндокринологии МЗ РУз в период с 2000 по 2018гг, андроген-секретирующие опухоли надпочечников были диагностированы у 9(3,2%) больных: 3(33,3%) мужчин и 6(66,7%) – женщин в возрасте от 1,7 лет до 34 лет. Как и в остальных группах образований надпочечников, наблюдалось преобладание женщин, в 2 раза. Однако соотношение отдельных возрастных подгрупп существенно отличалось. В этой группе пациентов возрос удельный вес детей (55,6%) по сравнению с взрослыми до 44 лет (44,4%). Анализ клинических проявлений андроген-секретирующих опухолей надпочечников у детей и взрослых, выявил некоторые различия, несмотря на сходную этиопатогенетическую основу. Так, проведенный анализ свидетельствует о наличии ряда симптомов у детей, не встречающихся у взрослого контингента. Напротив, соматические расстройства у взрослых выражены в большей степени, чем у детей.

**Ключевые слова:** опухоли надпочечников, андроген-секретирующие опухоли

## АНДРОГЕН ИШЛАБ ЧИҚАРУВЧИ БУЙРАК УСТИ БЕЗИ ЎСМАЛАРИНИНГ ГЕНДЕР-ЁШ ЖИҲАТДАН КЛИНИК ТАВСИФИ

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**Аннотация:** Мазкур тадқиқотнинг мақсади: андроген ишлаб чиқарувчи буйрак усти бези ўсмаларининг ёш ва жинсга боғлиқлиги нуқтаи назаридан клиник хусусиятларини ўрганиб чиқиш. ЎзРССВ РИЭИАТ Марказида 2000 йилдан 2018 йилгача амбулатор ва стационар назоратда турган, буйрак усти безининг турли хил ўсмалари билан касалланган (n=282) беморлар текширувдан ўтказилганда, буйрак усти безининг андроген секреция қилувчи ўсмалари 9(3,2%) нафар беморда аниқланди: 3(33,3%) эркак ва 6(66,7%) – аёл, ёши 1,7дан 34ёшгача. Буйрак усти бези ўсмаларининг бошқа гуруҳларидаги каби аёлларда 2 баравар кўп учраши кузатилди. Бироқ бу нисбат алоҳида ёшли подгруппаларда жиддий равишда фаркланди. Бу гуруҳдаги беморларда болаларнинг нисбий оғирлиги (55,6%) катталарникига нисбатан 44 ёшгача (44,4%) юқори бўлди. Болалар ва катталарда андроген ишлаб чиқарувчи буйрак усти бези ўсмаларининг клиник кўринишларини таҳлил қилинганда этиопатогенез негизининг ўхшашлигига қарамай,

баъзи бир тафовутларни аниқлади. Ўтказилган таҳлил натижалари болаларда учрайдиган бир қатор симптомларнинг катталар контингентида учрамаслигини кўрсатди. Аксинча, соматик ўзгаришлар катталарда болаларга нисбатан яққолроқ намоён бўлди.
**Калит сўзлар: буйрак** усти бези ўсмалари, андроген ишлаб чиқарувчи ўсмалар

**Annotation:** The objective of this research was to study clinical peculiarities of androgen-secreting tumors in adrenals dependent on age and gender. Among the patients with various neoplasms in adrenals (n=282), who received out-patient and in-patient treatment in the Republican Specialized Scientific Practical Medical Center of Endocrinology of the Uzbekistan Public Healthcare Ministry within the period from 2000 to 2018, androgen-secreting tumors were diagnosed in 9(3.2%) patients: 3(33.3%) men and 6(66.7%) women aged from 1.7 to 34 years old. As well as in the other groups with adrenal neoplasms, there was double prevailing of women. However, correlation of separate age subgroups was significantly different. In this group of patients specific weight of children increased (55.6%) compared to adults under 44 years old (44.4%). In spite of similar etiopathogenetic basis analysis of clinical manifestations of adrenal androgen-secreting tumors in children and adults revealed some differences. So, performed analysis confirms the presence of several symptoms in children, symptoms which are not observed in adults. On the other hand, somatic disorders in adults are more expressed than in children.
**Key words:** adrenal tumors, androgen-secreting tumors

Adrenal androgen-secreting tumor is a rare pathology. Being hormonal active tumor of reticular area of adrenal cortex these neoplasms are characterized by increased production of androgens and its metabolites. According to the basic series of publications for the last 20 years the prevalence of adrenocortical tumors among the patients studied due to clinical hyperandrogenism is equal to 0.1% (4 out of 3695 patients) [4]. Recent population study included the analysis of the prevalence of adrenal androgen-secreting tumors among the patients whose level of androgens was measured independently of the presence of signs and symptoms of hyperandrogenism. The prevalence of adrenocortical tumors was equal to 1.7% (20 out of 1205 patients) [5]. In a French study including 801 adrenalectomies performed from 1970 till 2003, only in 21(2.4%) cases adrenal androgen-secreting tumors were revealed [7]. Androgen-secreting tumors more often develop in women, mostly in the age from 35-40 years old [3]. There was notable high percent of malignant tumors in children population, where tumors were observed more often in girls, than in boys [1,2]. Totally, among the patients with androgen-secreting tumors 75% of the cases (18/24 tumors) were classified to be adrenocortical cancer by means of histological tests, while the others were adenomas [4]. It should be noted that, androgen-secreting tumors producing only androgens were met relatively rarely. More often together with androgens tumors also secrete other hormones, and particularly glucocorticoids [3,8]. Clinical manifestations of a tumor are conditioned by virilizing and anabolic properties of androgens. Virilization degree depends on hormonal activity of the tumor and term of disease [3,6]. Virilization is often observed with tumors in children and represent the most prevalent characteristics of adrenocortical carcinomas in patients of that age group. However, relative data of adults population are diverse.

**The objective of the research** was to study clinical characteristics of adrenal androgen-secreting tumors dependent on age and gender.

**Materials and methods**

Among the studied patients with various adrenal neoplasms (n=282), who received out-patient and in-patient treatment in the Republican Specialized Scientific Practical Medical Center of Endocrinology of the Uzbekistan Public Healthcare Ministry within the period from 2000 to 2018 adrenal androgen-secreting tumors were diagnosed in 9(3.2%) patients: 3(33.3%) men and 6(66.7%) women aged from 1.7 to 34 years old.

All patients with adrenal neoplasms had common clinical, biochemical, hormonal, and instrumental tests. Common clinical tests included careful collection of complaints, history of life and disease, assessment of somatic and endocrine status, complete clinical investigation with measurement of arterial pressure (AP) and definition of body mass index (BMI); common blood and urine tests. Biochemical blood tests included definition of serum potassium, sodium, chlorine, calcium, lipid spectrum, fasting glycemia, glycemia in two hours after meal, and in some cases oral glucose tolerance test (OGTT), glycated hemoglobin, coagulogram, creatinine, and urea. We performed the study of hormonal status, including definition of plasma aldosterone concentration and rennin activity, ACTH, cortisol in blood, plasma metanephrines, normetanephrines, testosterone, and DHEAS. MSCT of adrenals was performed as a special instrumental method. The complex of compulsory research methods included ECG and ophthalmoscopy. For the assessment of clinical manifestations, we used parameters of average and standard deviations (M ± SD), and also prevalence of the studied signs. We assessed the correspondence of numerical data to the normal distribution law. Differences between

the compared average values of dependent and independent samples were determined in compliance with «ANOVA» single-factor analysis. For the analysis of difference reliability between qualitative parameters $\chi 2$ criterion was used. Reliable level for all applied tests was $p<0.05$.

**Results and discussion**

Adrenal androgen-secreting tumors were diagnosed in 9(3.2%) patients, among them 3(33.3%) men and 6(66.7%) women aged from 1.7 to 34 years old. As well as in the other groups of adrenal neoplasms, there was double prevailing of women. However, correlation of certain age subgroups differed much. In this groups of patients specific weight of children increased (55.6%) compared to adults under 44 years old (44.4%) (Table 1).

**Table 1 Age and gender distribution of the patients with adrenal androgen-secreting tumors (WHO, 2017)**

| Age | Men, n=3 | | Women, n=6 | | Total, n=9 | |
|---|---|---|---|---|---|---|
| | abs. | % | abs. | % | abs. | % |
| Children under 18 | 3 | 100.0 | 2 | 33.3 | 5 | 55.6 |
| Young from 18 to 44 | 4 | 67.7 | 4 | 44.4 | | |
| Average 45-59 | | | | | | |
| Old 60-74 | | | | | | |
| Senile, 75-90 | | | | | | |

**Note** * statistically significant values within groups

Further clinical analysis was performed separately in the group of adult patients (n=4) and children (n=5). So, in the group of adult patients there were only women aged from 14 to 44 years old (with average age 27.5±5.2). It should be noted that, it is extremely difficult to determine the presence of symptoms, caused by androgen excess, in male patients, as clinical presentation does not have any specific manifestations. In men these tumors can develop like hormonally inactive adrenal tumors.

Among four patients 3(75%) were initially treated by gynecologist due to amenorrhea, sterility, and two of these three were also followed by local physician due to arterial hypertension (AH). One of these four patients had independent US investigation due to menstrual dysfunction, where adrenal neoplasm was determined.

All the patients were diagnosed in the term above one year after the start of the disease. Average duration of the disease was equal to 2.0±0.8 years. Three patients did not relate the start of the disease with any event, and only one patient indirectly linked it with previous surgical intervention. When we studied life history of the patients, we revealed that, 3(75%) patients had low physical activity, 3(75%) had irrational nutrition, and one (25%) patient smoked. Analyzing family history of the patients we revealed cardiovascular diseases in a woman (25%) under 65, and particularly hypertonic disease, oncologic disease in two cases (50%), and renal pathology in one patient (25%).

Among the early symptoms of the disease frequent ones were disorders of menstrual cycle (amenorrhea or opsomenorrhea) and hirsutism, which were observed in 100% cases. Besides menstrual dysfunctions and hirsutism at the moment of application to clinic patients most often complained about acne (75%), head hair loss (50%), headache (50%), stomachache (50%), lumbar pain (50%), muscular pain and numbness (25%), voice change (25%), decrease in acuity of vision (25%). Twenty-five percents of the patients had total weakness and fatigability. Two (50%) patients complained about increased libido.

Objective investigation showed that, two (50%) patients had masculine type change in body architectonics. Alterations on the dermal surface such as folliculitis combined with acne vulgaris were observed in 75%. Hyperpigmentation in the area of external genitals, axillary area, shins, and elbows was also observed in 75% of the patients. Excessive hair growth on face, spine, chest, and femor was noted in all (100%) patients. Two (50%) patients had various degrees of diminishing of mammary glands. It should be noted, that one patient had a change of voice timbre worth paying attention. None of the studied patients had notable clitoris hypertrophy.

We observed 5 children with androgen-secreting tumors in the age from 1.7 to 7 years old (average age 5.2±1.9 years old). Different from adult population, in pediatric population adrenal androgen-secreting were observed similarly often among boys and girls, with some prevalence in boys (60% and 40%, respectively).

Within the assessment of the duration of the disease we noted that, children with adrenal androgen-secreting tumors were diagnosed within 1-7 years after occurrence of the initial manifestations of the disease; in two children duration of the disease was 1 year, two other children suffered for two years, and, finally, one more child had 7 years duration of the pathology. Average duration of the disease was 2.6±2.5 years. Relatively low prevalence rate of adrenal tumors in children and absence

of clear understanding of clinical manifestations are the main reasons of incorrect diagnostics, choice of inadequate therapy, delay in surgery, and, as a result, non-satisfactory results of the therapy.

Prior to final diagnosis two 2(40%) children were treated due to adrenogenital syndrome, and one (20%) was treated due to preterm puberty. One more girl was incorrectly diagnosed with Cushing disease. Only in one case of a patient (1.7 years old), who came with parents complaining about child's enlargement of stomach combined with enlargement of penis and scrotum, pubic and axillary hair growth, change of voice timbre, US imaging revealed adrenal neoplasm 8.4 cm, so the primary diagnosis was correct and corresponding surgical treatment was indicated.

Similar to adults, etiology of adrenal cortical tumors in children is not clarified yet. However, some facts revealed at the study of patients' histories deserve paying attention. For example, a mother of one patient during pregnancy had long-term and severe toxicosis, while another patient received a great number of medications, including hormones, due to pregnancy pathology. These data suggest that, pathologic pregnancy and birth could probably be considered to be the reasons of adrenal tumor occurrence.

Clinical manifestations of adrenal androgen-secreting tumors in children are diverse and have certain characteristics. Three (60%) boys had a start of disease with symptoms of pre-term puberty, clinical manifestations of which are enlargement of penis and scrotum (60%), pubic hair growth (60%), acne (20%), and voice alteration (60%). One of them (20%) had gynecomastia, in other words, together with hyperandrogenism manifestations there were feminization symptoms (description of the case is herein below). In girls initial stages of the disease were characterized by pre-term pubic and axillary hair growth. At the same time one girl had very expressed hirsutism. Another patient with 7 years duration of the disease, besides hirsutism had clitoris hypertrophy and voice timbre change. Both girls had acne on their face. Besides that, mothers of the studied children noted complaints such as stomachache (20%), anxiety (20%), irritability (20%), total weakness (20%), polyuria (20%), nighturia (20%), and polydipsia (20%).

Two (22.2%) out of all patients with adrenal androgen-secreting tumors we studied (n=9) had AH. Average age of the patients at the moment of AH debut was 25.5±2.1 years old, which was statistically different from the parameters of control groups with and without AH ($p<0.0001$). Fluctuations of systolic AP (SAP) and diastolic AP (DAP) varied from 140-150 to 90-100 mmHg. Average levels of maximal SAP/DAP were 123.3±16.6/80.0±12.2 Hg.mm, which was significantly different from the parameters in the group with AH. Both patients with androgen-secreting tumors had AH I stage. One case of AH had a stable character, while another case had a periodic rise of AP. Average duration of AH was equal to 1.5±0.71 years and was significantly lower, than in the control group with AH ($p<0.05$) (Table 2).

**Table 2 Clinical characteristics of the studied groups (single-factor dispersive (ANOVA) and paired analysis)**

| Parameters | Control, n=46 | | Androgen-secreting tumors, n=9 | p |
|---|---|---|---|---|
| | Without AH, n=24 | With AH n=22 | | |
| Age | 39.6±11.1 | 41.3±6.9 | 15.1±12.3## | **<0.0001** |
| SAP (max) mmHg | 122.4±5.4 | 157.7±13.1# | 123.3±16.6# | **<0.0001** |
| DAP (max) mmHg | 77.1±4.6 | 98.2±8.0# | 80.0±12.2# | **<0.0001** |
| SAP (mean) mmHg | 119.6±6.9 | 143.6±7.9# | 113.3±14.1# | **<0.0001** |
| DAP (mean) mmHg | 69.3±4.8 | 91.8±3.9# | 72.2±10.5# | **<0.0001** |
| AH duration | - | 3.3±2.0 | 1.5±0.71* | **0.01** |
| Age at the moment of AH | - | 38.0±7.0 | 25.5±2.1# | **<0.0001** |
| Duration of the disease, years | - | - | 2.33±1.9 | |
| BMI, kg/m$^2$ | 23.8±2.6 | 24.5±2.7 | 20.4±5.5*● | **0.009** |

Note: data are presented in M±SD values; * differences related to the data with and without AH are significant (* - $p<0.05$, ●- $p<0.01$, #- $p<0.001$)

Both patients with AH received a mono therapy with hypotensive agents, and particularly, ACE inhibitors, and had a positive effect of the performed therapy. It should noted that, average values of BMI in cases of adrenal androgen-secreting tumors were statistically significantly lower than in comparison groups without AH($p<0.05$) and with AH($p=<0.01$), but were within the range of normal weight 20.4±5.5 kg/m$^2$. There were three (33.3%) patients with adrenal androgen-secreting tumors had increased body mass with BMI≥25. Average age of patients with adrenal androgen-secreting

tumors was reliably less, than in both control groups ($p<0.001$).

ECG of two (50%) patients revealed metabolic changes. ECG did not register any deviations from the age-specific normal parameters in children.

None of the children had registered rise of AP. Average SAP/DAP in children was 104.0±5.5/64.0±5.5 mmHg.

**Conclusions**

In spite of similar etiopathogenetic basis, analysis of clinical manifestations of adrenal androgen-secreting tumors in children and adults revealed certain differences. Thus, performed analysis confirmed the presence of several symptoms in children, which are not observed in adult population. On the other hand, somatic disorders are more expressed in adults, than in children. Similarity of clinical presentation of adrenal androgen-secreting tumors in children with some other endocrine pathologies makes its early diagnostics significantly more difficult. At the same time during careful observation it is worth to pay attention to clinical data suggesting excessive androgen secretion in children, which can be noted before puberty. It is extremely difficult to differentiate the symptoms caused by androgen excess in male patients, as clinical presentation has no specific manifestations, which probably explains low detection rate of these tumors in men.

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# WOMEN OF REPRODUCTIVE AGE WITH CONGENITAL ADRENAL CORTEX DYSFUNCTION (ADRENOGENITAL SYNDROME): THEIR QUALITY OF LIFE AND PSYCHOSOCIAL CHARACTERISTICS

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**Резюме:** Установлено достоверное снижение качества жизни у женщин с ВДКН по сравнению показателями группы контроля. Самые низкие показатели качества жизни при ВДКН отмечались по шкалам: ролевое физическое функционирование (у 74,1% женщин), общее состояние здоровья (у 59,3% пациенток), физическая активность (у 48,1% пациенток), ролевое эмоциональное функционирование (у 44,4% женщин), жизненная активность (у 37,0% женщин) и психическое здоровье (у 33,3% женщин). Выявленные особенности психосексуального статуса женщин обосновывают необходимость тесного взаимодействия медицинских психологов и психотерапевтов для эффективной работы специально-ориентированной психологической программы для пациентов с ВДКН.

**Ключевые слова:** врожденная дисфункция коры надпочечников, качество жизни, стигма

**Резюме:** Буйрак усти бези пўстлоғи туғма дисфункцияси (БУБПТД) бўлган аёлларда назорат гуруҳига нисбатан ҳаёт сифати ишончли камайиши ўрнатилган. БУБПТД да ҳаёт сифати энг паст кўрсаткичлари шкалалар бўйича қайд қилинган: ролли жисмоний фаолият (74,1% аёлда), умумий саломатлик ҳолати (59,3% беморда), жисмоний фаоллик (48,1% беморда), ролли эмоционал фаолият (44,4% аёлда), ҳаётий фаоллик (37,0% аёлда) ва руҳий саломатлик (33,3% аёлда). Аёлларда аниқланган психосексуал ҳолатнинг хусусиятлари БУБПТД беморлари учун махсус йўналтирилган психологик дастурнинг самарали ишлаши учун тиббий психологлар ва психотерапевтлар ўртасида яқин ўзаро ҳамкорлик зарурлигини асослайди.

**Калит сўзлар:** буйрак усти бези пўстлоғи туғма дисфункцияси, ҳаёт сифати, стигма

**Summary**: the control group parameters analysis indicated a significant decrease in the quality of life for women with congenital adrenal cortex dysfunction (adrenogenital syndrome). The lowest quality of life indicators for women with congenital adrenal cortex dysfunction, (adrenogenital syndrome), were observed on the following scales: role-physical functioning (74.1% of women), general state of health (59.3% of women), physical activity (48.1% of women), role-emotional functioning (44.4% of women), vitality (37.0% of women) and mental health (33.3% of women). The revealed peculiarities of the psychosexual status of women justify the necessity of close collaboration between medical psychologists and psychotherapists for the effective work with a specially-oriented psychological program for women-patients with congenital adrenal cortex dysfunction (adrenogenital syndrome).

**Key Words:** congenital adrenal cortex dysfunction, quality of life, stigma

The birth of a child with genital ambiguity (the so-called intersexuality), “sexual development disorder” raises the question of the appropriate gender-based correlating – this may cause misery and suffering for parents. It is considered that the sexual status may put a child at risk of social stigmatization. A classical (intra-uterine) congenital adrenal hyperplasia in karyotype 46, XX is the most common of the classic intersexuality syndromes and, of course, requires the most thorough research in terms of endocrinology and psychology. The degree of incidence connected with the congenital adrenal cortex dysfunction (adrenogenital syndrome) – according to various authors – varies from 1: 5000 to 1: 67000 and is on an average 1: 10000 - 1: 15000 newborns in Russia – 1: 8662; and in the Republic of Bashkortostan - 1: 8974 [1 ; 4].

In Uzbekistan, according to investigations of F.A. Khaidarova, the congenital adrenal cortex dysfunction (adrenogenital syndrome) makes appearance among 5.4% of women with hyperandrogenemia; its non-classical form makes appearance among 8% of women [5].

The social conflict of patients has been determined by the anomalous anatomical structure of the

external genitalia, by hormonal insufficiency, by the inability to reproduce offspring. These factors led to the formation of severe psychological disorders. The psychosexual development of children may be influenced by many factors, such as the effects of androgens, sex chromosome genes, brain structures, as well as social and family circumstances. Many girls who have the congenital adrenal cortex dysfunction (adrenogenital syndrome) and a severe course of the disease due to certain mutations, and also, accordingly, a more pronounced masculinization, often play with toys for boys. A row of psychological characteristics, such as maternal interest and sexual orientation, are associated with the prenatal effects of androgens. Very recent evidence suggests that bisexual/homosexual orientation may be associated with prenatal exposure to androgens and masculinization of a child behavior.

Happenings of untimely disease diagnosis, late feminizing plastic surgery, often gender reassignment, postnatal hyperandrogenism, as a result of decompensation, can create uncertainty in the chosen field in parents and the patient and impede the process of sex education. Women with the congenital adrenal cortex dysfunction (adrenogenital syndrome) are less likely to get married, show less interest in motherhood, which is probably associated with difficulties in compensation, complications of feminizing operations, and the development of secondary polycystic ovary. The increase in the ratio of homo- and bisexual relationships among women with the congenital adrenal cortex dysfunction (adrenogenital syndrome) is caused, first of all, by unsatisfactory outcomes of feminizing genitoplasty [2; 3]. Another debating point is the question of the interaction of psychiatrists, psychotherapists and medical psychologists with this disease. Who should provide psychological assistance to these patients and whether mental disorders are possible in patients with the congenital adrenal cortex dysfunction (adrenogenital syndrome) who need the help of a psychiatrist?

According to Kanhere M. etal. [6] the family and other social and psychological support are correlated with positive prospects in childhood and improved quality of life during young adulthood. Most patients denied a desire to become a man, and 60% indicated that they had a sexual preference only for men, while the minority had sexual contact with another woman.

As part of the study conducted in Sweden using structured surveys revealed a decrease in the quality of life in 62 women with 21-hydroxylase deficiency. Both the genotype and the surgical procedure that these women underwent affected the quality of life [10]. A decrease in the quality of life was also observed in another cohort of 40 women with 21-hydroxylase deficiency (33 of them had classical the congenital adrenal cortex dysfunction (adrenogenital syndrome). The main reasons for the decline in the quality of life of such patients are psychological trauma due to tedious diagnostic procedures, the chronic nature of the disease and psychological complications. Women with the congenital adrenal cortex dysfunction (adrenogenital syndrome) have a higher level of anxiety about sexual contacts and partners, as well as in connection with a change in the appearance of their body. However, as soon as a partner appeared in such women, they considered their connection with him as more stable and satisfactory than healthy women in the control population [7].

Since women with the congenital adrenal cortex dysfunction (adrenogenital syndrome) are not equally responsive to their functional abnormalities, assessing the level of quality of life is essential until standard assessment methods are developed that are highly sensitive to specific psychosocial aspects in patients with the congenital adrenal cortex dysfunction (adrenogenital syndrome) and sexual development disorders, especially in light of the outcome of her treatment.

***Goal of Research*** is a study of the quality of life, psychosocial characteristics in women of reproductive age with the congenital adrenal cortex dysfunction (adrenogenital syndrome), as well as the identification of stigma associated with structural features of the genitals in the context of sexual and psychological adaptation.

***Materials and Methods***. A questionnaire survey of 27 women in the age of 18 to 43 years (average age 24.9 ± 6.8 years) who have the congenital adrenal cortex dysfunction (adrenogenital syndrome) has been conducted. This group – in addition to 23 women with the congenital adrenal cortex dysfunction (adrenogenital syndrome) – also included three patients with polycystic ovary syndrome and one with idiopathic hirsutism, in which CYP21A2 mutations were found in a genetic study. More than half (55.6%) of women were between the ages of 20 and 30 years.

The control group included 23 women with a regular ovulatory menstrual cycle without signs of hyperandrogenemia. The average age of women was 31.3 ± 7.3 years.

All studies were conducted at the Republican Specialized Scientific and Practical Medical Center for Endocrinology (Tashkent, Republic of Uzbekistan). Period: from January 2014 to September 2016. The study protocols were approved by an independent ethics committee and biomedical ethics

commissions. Patients gave written informed consent to participate in the project in accordance with the Helsinki Declaration (2013).

Statistical processing of the obtained results was carried out using STATISTICA 6.0 programs (Stat Soft, 2003). Quantitative indicators are presented as M ± SD. The differences between the groups were considered statistically significant at $p < 0.05$. Quality of life was assessed using Quality of Life (QoL) assessmentby-ShortFormSF-36® Health Survey, as well as the determination of the sexual orientation of women with UCD using the Klein Sexual Orientation Grid, KSOG.

***Results and Argumentation:*** When evidence-based analysis, it has been found that a significant proportion of patients complained of headache (19 - 70.4%), excessive hair growth on the body (14 - 51.9%), overweight (8 - 29.6%), and the presence of acneiform rash (8 - 29.6%). From the anamnesis it has been found that 6 women (22.2%) were born in closely related marriages. Hereditary burden of diabetes was found in 7 women (25.9%). Age at menarche averaged 13.6 ± 1.6 years. An early onset of menstruation was revealed in 1 woman (11 years old), later onset of menstruation in 12 women (44.4%) (14-18 years old). Menstrual disorders were observed in 15 patients (55.6%). Violation of the menstrual cycle by the type of opsomenorrhea and amenorrhea was observed in seven women (25.9%) and eight women (29.6%) of the examined group. Pregnancy occurred in seven women (25.9%). The average number of pregnancies was 2.1 ± 1.6. 71.4% of all pregnancies have ended in childbirth, 7.4% - in artificial abortions, and 11.1% - in spontaneous miscarriages.

The study of the social status of women with the congenital adrenal cortex dysfunction (adrenogenital syndrome) showed that the level of education is mainly secondary and secondary special level of education (17 - 63.0%). More than a quarter of patients had higher education (7-25.9%). No education had 3 women (11, 1%). As far as the social status is concerned, almost half of patients, (13-48.1%), had working specialties. Almost the same numbers of women were students and office workers (5-18.5% and 6-22.2%, respectively). And three women (11.1%) were housewives. With regard to marital status, more than half of the patients were married (14-51.9%). More than a third of women under study (10-37.0%) were never married. Three women (11.1%) were divorced. It should be noted that 5 women (35.7%) who were married and three women (66.7%) who were divorced were childless.

As a result of the analysis of indicators of the quality of life in women with the congenital adrenal cortex dysfunction (adrenogenital syndrome), we revealed the presence of a significant decrease in the quality of life compared with the indicators of the control group (Table 1).

The lowest indicators of quality of life of women with the congenital adrenal cortex dysfunction (adrenogenital syndrome), which did not exceed 50 points, were noted on the following scales: role-based physical functioning (in 74.1% of women), general health status (in 59.3% of patients), and physical activity (in 48.1% of patients).

Table 1

Indicators of the Physical and Psychological Components of Health and Quality of Life of patients with the Congenital Adrenal Cortex Dysfunction (Adrenogenital Syndrome). According to SF-36. In points:

| **SF-36** | Control, **n=23** | CACD, n=27 | % |
|---|---|---|---|
| Physical Functioning, PF | 76,7±9,0 | 50,2±12,7* | -34,5 |
| Role-Physical Functioning, RP | 74,5±11,7 | 40,7±11,7* | -45,4 |
| Bodily Pain, **BP** | 79,7±8,8 | 56,0±7,8* | -29,7 |
| General Health, **GH** | 83,0±8,4 | 47,0±9,5* | -43,4 |
| Physical HealthComponent | 74,5±5,7 | 46,1±4,9* | -38,2 |
| Vitality,**VT** | 83,7±8,7 | 52,4±12,5* | -37,4 |
| Social Functioning, **SF** | 86,3±10,4 | 61,0±11,6* | -29,3 |
| Role-EmotionalFunctioning, **RE** | 80,9±9,9 | 53,6±15,4* | -33,8 |
| Mental Health **MH** | 79,0±10,0 | 54,3±9,5* | -31,3 |
| Mental HealthComponent | 78,4±5,2 | 52,5±8,5* | -32,9 |

Note: *p<0,0001 reliability in relation to control

To a lesser extent, the changes affected the indicator of physical pain (in 22.2% of women). And an integrated indicator of the physical component of health less than 50 points was observed in 66.7%

of patients.

The analysis of the components of the physical health component showed that the congenital adrenal cortex dysfunction (adrenogenital syndrome) had an impact on the ability to perform various physical activities (decrease in PF compared to the control group by 34.5%), on daily role-playing activities (RP compared to the control group by 45.4%), on the ability to engage daily activities (BP - by 29.7%). Thus has reflected also a decrease in patients' subjective assessment of their health (GH - by 43.4%).

The presence of clinical manifestations of the congenital adrenal cortex dysfunction (adrenogenital syndrome) had an impact on the psychological component of health. Indicators not exceeding 50 points were noted on a scale of role-based emotional functioning (in 44.4% of women), vitality (in 37.0% of women), and mental health (in 33, 3% of women). An integrated indicator of the psychological component of health of less than 50 points was observed in 40.7% of patients.

When analyzing the components of the psychological component of health, a significant decrease in the vital activity indicator was observed. It reflects the subjective feeling of cheerfulness (37.4% lower compared with the clinical control), and emotional-role functioning (33.8%). A reduced VT (vitality) level indicates that patients have problems (anxiety about their health, decreased mood) that have a significant negative impact on their social activity (SF decrease of 29.3% of women) and daily role-playing activities. Mental health self-esteem decreased by 31.3%.

A typical result for girls with severe pathology is the dubious (unclear) masculine external genitalia with periodontal hypospadias, with a curved penis and with undescended testicle (cryptorchism). But not all women with hypergenetic teratosis have an equally pronounced degree of doubtfulness of the genitals. When considering the effect of prenatal sex hormones on a person, it is necessary to distinguish between a sexual role, sexual orientation, and sexual identity of a person [12].

The distribution of sexual roles involves stereotypical sexual behavior – the choice of toys by children, for instance. During the survey, the parents of three girls with the congenital adrenal cortex dysfunction (adrenogenital syndrome) aged 15-18 years reported that their daughters in childhood preferred toys and games more for boys than for girls. In addition, four women with congenital adrenal cortex dysfunction (adrenogenital syndrome) reported a low interest in maternal behavior, beginning with rare doll games in early childhood and a growing lack of interest in older behavior.

The stereotyped image of certain phenomena and stereotyping in general are often necessary to determine which group a certain person or phenomenon belongs to. Different stereotypes help those who have a generalized piece of information about various phenomena. Nevertheless, myths and prejudices always stand next to stereotypical representations. For the first time and more often in medicine, the term "stigma", "stigmatization" began to be used in relation to patients with various mental disorders. Later, issues of stigma began to be considered in the context of other diseases. At the present stage of the development of medicine, the broad involvement of the therapist in solving various psychological problems, a lot of scientific research has appeared on the stigmatization of patients with somatic diseases [8].

The presence of structural features of the genital organs, where the women with the congenital adrenal cortex dysfunction (adrenogenital syndrome) are concerned, that occurred in the study group, as well as the fact that 35.7% of married women and 66.7% of divorced women were childless, prompted us to think about possible stigma in the studied group of women.

Different structural changes in the external genitalia of varying severity were noted in 6 patients (22.2%). The main focuses of the study were the study of gender behavior, sexual orientation, sexual behavior and sexual dysfunction, as well as the identification of possible mental disorders.

A detailed interview was conducted with each patient under the participation of a female psychotherapist. A specially designed interview scheme was used during interviewing. We were using specific tests to identify sexual orientation and gender behavior. All questions were open during the interview, and the explicit terms "stigma" or "difference" were not used, but they were formulated so that the messages from the patients reflected stigmatic feelings and images.

Our study identified three types of stigma:

1. Experienced or accepted stigma. This is the stigma that was accepted by sexual partners. This kind of stigma was detected in 8 patients (40.0%). Thus, all women who have had sexual experience have been stigmatized.

2. Expected stigma. In other words: stigma of feelings about an upcoming marriage or sexual intimacy. This stigma started to form when patients began to turn to doctors with complaints about

the absence of menstruation or menstrual irregularities, or other complaints of a gynecological or endocrinological nature. Later, the necessary examinations and consultations were conducted. After staging and diagnosing the disease and explaining the diagnosis, this stigma started to form. This stigma has adverse effects on the dating and future expectations of a long-term partnership and marriage, seven women, (35.0%), mentioned that the heritability of the disease also added barriers to marriage.

3. Social stigma. Nine patients (45.0%) – age range: 21- 42 years – perceived their disease as an illness in which it is impossible to lead a full productive life. These patients did not have sexual experience, social contacts were sporadic, and their life was limited only to the family circle. As a rule, they did work at home. However, most of the women surveyed were shy of their appearance. The main reason is associated with severe hirsutism and masculinization.

Only three women (11.1%) among the women studied had one stigma. 17 women (85.0%) had a number of stigmas. It was common to all patients that they had recollections of the negative comments of their sexual partners regarding genital signs, such as general appearance, clitomegaly, clitoral erections, as well as non-genital somatic symptoms, especially hirsutism. Some of women's sexual partners directly questioned the true gender of women. The effects of stigma on women were diverse. According to their reports, the stigma introduced into romantic / sexual life led to immediate and violent emotional reactions – such as tragedy, embarrassment, and shame. Trying to avoid the risk of direct stigmatization, women resorted to hiding their body, and especially their sexual area, from the eyes and touch of partners even during sexual contact. All women surveyed showed increased caution in choosing the sexual partner. They tried to maintain a secret status. The expected stigma is notable by low self-esteem. Three women, (15.0%), reported their self-esteem as "abnormal". Such self-esteem can help raise the level of psychiatric problems: such as depression, which was discovered by some of our researchers. Six women reported that they often resorted to drinking of alcohol in order to level their problems.

The danger of so called "self-stigmatization" is that it masks the patient's true problem, directing his efforts in the wrong direction. Therefore, to achieve the greatest success in overcoming the disease and building a full productive life, a process called "destigmatization" is very necessary. The main goal of the patient in this process is to realize himself as a person independent of the disease [9; 11].

***Conclusions***: The practical value of this study is the development of specially-oriented psychological programs for clinics. The undertaken stigma-revealing-interview has an important social context. This is an imported stigma screening tool specific for individuals with somatic intersexuality. It may be used for clinical and research purposes. This study also showed that close interaction between medical psychologists and psychotherapists is necessary for the effective operation of specially-oriented psychological programs for patients with congenital adrenal cortex dysfunction (adrenogenital syndrome).

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## ДИАБЕТИЧЕСКАЯ НЕФРОПАТИЯ И ЛЕЧЕБНОЕ ПИТАНИЕ.

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Хроническая болезнь почек наглядно демонстрирует уровень начала лечебного питания или нутритивной поддержки. Состояние питания является важным фактором, который оказывает влияние на заболеваемость и смертность у больных с заболеваниями почек, особенно в терминальной стадии. Избыточное потребление белка с пищей обсуждается как один из факторов прогрессирования диабетической нефропатии (ДН). Анализ многочисленных публикаций о роли компонентов диеты и диетического рациона в целом в предотвращении и задержке прогрессирования ДН свидетельствует, что правильно подобранный рацион питания в сочетании с адекватной медикаментозной терапией обеспечивают достаточно выраженный эффект по сохранению фильтрационной способности почек.

***Ключевые слова:*** *хроническая болезнь почек, лечебное питание.*

## ДИАБЕТИК НЕФРОПАТИЯ ВА ТИББИЙ ОВҚАТЛАНИШ

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Сурункали буйрак касаллиги терапевтик овқатланиш ёки озуқавий ёрдам бошланиш кераклигини кўрсатади. Озиқланиш холати буйрак касаллиги бўлган беморларда, айниқса терминал босқичда, касалланиш ва ўлимга таьсир қилувчи мухим омилдир. Озиқ –овқат билан оқсилни ортиқча истеъмол қилиш диабетик нефропатия (ДН) ривожланишининг омилларидан бири сифатида мухокама қилинади. ДН нинг ривожланишини олдини олиш ва кечиктиришда пархез таркибий қисимлари ва умуман пархезнинг рўли тўғрисидаги кўплаб наширларнинг тахлили шуни кўрсатадики,тўғри танланган пархез етарли дори терапияси билан биргаликда буйракнинг фильтрацион барқарорлигини сақлашга аниқ тасир кўрсатади.

***Калит сўзлари****: сурункали буйрак касаллиги, тиббий овқатланиш*

## DIABETIC NEPHROPATHY AND CURATIVE NUTRITION

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Chronic kidney disease clearly demonstrates the onset of therapeutic nutrition or nutritional support. Nutritional status is an important factor that affects morbidity and mortality in patients with kidney disease, especially in the terminal stage. Excessive protein intake with food is discussed as one of the factors in the progression of diabetic nephropathy (DN). An analysis of numerous publications on the role of diet components and the diet in general in preventing and delaying the progression of DN indicates that a properly selected diet in combination with adequate drug therapy provides a sufficiently pronounced effect on preserving filtrational stability of the kidneys

**Key words:** chronic kidney disease, curative nutrition.

Diabetic nephropathy (DN), the morphological basis of which is nodular or diffuse glomerulosclerosis, is one of the most serious late complications of diabetes mellitus (DM). Developing in a third

of patients, diabetic kidney damage leads to the loss of the ability of the kidneys to purify the blood of toxic products of protein metabolism: urea, creatinine and other products of nitrogen metabolism, the development of chronic kidney disease (CKD) and, in the terminal stage, death of patients from uremic intoxication.The severity of chronic kidney disease is assessed by glomerular filtration rate (GFR). Based on the experience of pharmacotherapy,primarily the use of angiotensin-converting enzyme inhibitors and angiotensin 1 receptor blockers, three stages of nutritional correction can be distinguished:

-preventing the development of DN:

-slowing the progression of existing DN (GFR 90-60 ml/min);

-an increase in the pre-dialysis period of an already existing DN (GFR 60-15ml/min).

The achievements of recent decades include the allocation of staging in the development of DN and the allocation of the early preclinical stage of this complication.

**Stage diabetic nephropathy [13.11]:** stage microalbuminuria; stage proteinuria with preserved nitrogen excreting renal function; stage of chronic renal failure. Hyperglycemia is a leading, but not the only factor in the cascade of reactions leading to structural and functional impairment of the kidneys in diabetes.

Synergistic with hyperglycemia, damage to the renal tissue is also caused by other metabolic factors: hyperketonemia, overproduction of glucagon and growth hormone, imbalance of prostaglandins, high protein intake (more than 1.5 g / kg body weight). As a rule, very little attention is paid to the dietary component in the pathogenesis of DN and its correction in the treatment of this complication. At the same time, food rich in protein of animal origin, in itself, has a pronounced nephrotoxic effect. The damaging effect of a high-protein diet, in which the protein content is more than 1.5 g per 1 kg of body weight, occurs through a number of mechanisms that are largely involved in the pathogenesis of DN.

**Nephrotoxic effect of high protein food [4]:** development of glomerular hypertension and hyperfiltration within; the development of dyslipoproteinemia as an additional factor in kidney damage; increased filtration load with protein; increased activity of tissue growth factors. We will consider the features of the diet for patients with diabetes at different stages of DM.

**The role of low protein diets in slowing the development and progression of chronic kidney disease.**

At the earliest stages of development of diabetic kidney damage, at the stage of hyperfiltration and microalbuminuria (MAU - daily protein loss with urine of 30-300 mg), the restoration of intrarenal hemodynamics can be achieved not only by conventional medication methods (ACE inhibitors, antagonists of receptor antagonists) II). A moderate restriction of animal protein with food should also be attributed to this effect. The most optimal at the MAU stage is the use of protein, not exceeding 12-15% of the total calorie content of food, which is not more than 1 g of protein per 1 kg of body weight [1]. Such a restriction of protein in food at the stage of MAU can eliminate the effects of a number of important pathogenetic mechanisms in cases of DN. The ability of the patient to independently take into account protein in food gives the table.1, which provides information on the protein content in staple foods.

Starting from the MAU stage, in the case of arterial hypertension, an important factor in the correction of blood pressure is a diet with sodium chloride limited to 3-5 g per day. This implies the exclusion from the diet of foods rich in salt (pickles, tomatoes, cabbage, mushrooms, fish, sparkling mineral water, etc.). Food should be prepared from natural products without salting (it should be remembered that 1 teaspoon contains 5 g of table salt, and a healthy person's diet contains on average 10-15 g of salt per day).

In full, the concept of a low-protein diet should be used in the treatment of DN at the stage of proteinuria. At this stage, along with such important factors of DN progression as impaired systemic and intra glomerular hemodynamics in combination with impaired carbohydrate and lipid metabolism, proteinuria directly affects the renal parenchyma, has a damaging effect on the tubular apparatus of the kidneys, accelerating nephroangiosclerosis as through the process of protein deposition in mesangia and proliferation of the mesangial matrix, and through the process of protein reabsorption in the tubules and the development of interstitial sclerosis [9]. Thus, proteinuria plays the role of an additional powerful factor in the further progression of renal pathology in diabetes with an outcome in chronic renal failure. Based on the pathogenetic role of proteinuria in DN, a low-protein diet should be considered not only as a method of symptomatic therapy, but, which is especially important, and as

a pathogenetic effect. The effectiveness of a low-protein diet has been shown in a number of clinical studies. A. Ciavarella noted that in patients with DN at the stage of proteinuria, the appointment of a low-protein diet (0.7 g of protein per 1 kg of body weight) allowed after 4.5 months. significantly reduce urinary albumin excretion. Moreover, the level of glycated hemoglobin did not significantly change [8].

Later data confirmed the effectiveness of limiting the protein to 0.7-0.8 g per 1 kg of body weight in patients with DN, which was expressed in a decrease in proteinuria, a decrease in the rate of decrease in glomerular filtration [7,4]. This restriction of protein in the diet does not lead to an increase in catabolism in combination with an increase in calorie intake due to carbohydrates and careful monitoring of carbohydrate metabolism. In addition, the restriction of animal protein contributes to a significant decrease in the intake of cholesterol, which is a powerful factor in the progression of diabetic glomerulosclerosis.

Such restrictions should be recommended not only to patients with moderate proteinuria, but also to patients with nephrotic syndrome and proteinuria of more than 3 g per day [13]. With the development of nephrotic syndrome, it is advisable to limit salt to 2-2.5 g per day, which is accompanied by a significant decrease in blood pressure and edema. In practice, such a restriction of salt means not only the exclusion of salting when cooking, but also the mandatory transition to salt-free bread and other products without salt. Products containing a minimum amount of salt include rice, oatmeal and semolina, cauliflower and white cabbage, carrots, beets, potatoes, pike perch, carp, pike, perch, veal.

***Table 1***

| Protein content in animal and vegetable products | |
|---|---|
| **Product name. (per 100 g of the finished product or the number of pieces)** | Protein, g |
| **Meat (1 fried entrecote)** | 30 |
| **Poultry (1/4 chicken)** | 20 |
| **Fish** | 20 |
| **Dairy products** | |
| **Curd** | 15 |
| **Milk (1 cup)** | 7 |
| **Sour cream (1/2 cup)** | 3 |
| **Cheese, curd (1 pc.)** | 7 |
| **Dutch cheese** | 23 |
| **Butter** | 6 |
| **Egg (1 pc.)** | |
| **Starch-containing products** | 2 |
| **Bread (25 g.) 1 piece 1 cm thick** | 4 |
| **Oatmeal, semolina, millet porridge (1 cup)** | 6 |
| **Rice, buckwheat porridge (1 cup)** | 10 |
| **Pasta** | 2 |
| **Potato** | |
| **Vegetable products** | 1 |
| **Cucumber (1), tomato (2), zucchini (1), apricots (4), pear (1), apple (1), carrots (2), 1 cranberries and lingonberries (1 cup), raspberries (1/2 cup), currants (3/4 cup).** | |
| **White cabbage, Brussels sprouts, cauliflower (1), sweet pepper (4), radish (12), beets (1), banana (1), sweet cherry (1 cup), strawberries (3/4 cup)** | 2 |
| **Fresh mushrooms** | 2 |
| **Mushrooms dried** | 30 |
| **Soybean** | 34 |
| **Nuts (hazelnuts)** | 16 |

**Features of the diet at the stage of chronic renal failure**.

The role of the low-protein diet in the progression of DN is most fully studied at the stage of chronic renal failure. Moreover, conservative therapy of chronic kidney disease consists largely in the application of certain dietary regimes and their modifications [11]. The nature of dietary recommendations is determined by the pathogenetic features of kidney damage at the stage of chronic kidney disease. Given that the daily urea production in the body is proportional to protein intake, it is possible to reduce urea production by limiting its consumption. The main principle of dietary therapy for chronic renal failure is a significant limitation of animal protein in the diet: up to 0.6-0.3 g per 1 kg of body weight per day. For the first time, the influence of protein content in food on the progression

of chronic kidney disease was detected experimentally: a direct relationship was found between the degree of restriction of dietary protein and the slowing of the progression of chronic kidney disease.

Later it was found that a diet with phosphate restriction also has a positive effect. Phosphorus, like a protein, affects renal hemodynamics, enhances hyperfiltration in the remaining nephrons. The maximum attention to the issue of protein restriction and understanding of the importance of this problem in progressive nephropathies came after the publication of the diet of S. Giovannetti and Q. Maggiore in 1964 [6]. The proposed principle was the daily introduction of protein at a dose of 22-25 g (0.3 g per 1 kg of body weight), while 50% of this amount was complete animal protein. The lower calorie limit of food should not be less than 2500 kcal per day. This diet has been widely recognized and distributed, supplemented by various modifications, taking into account the national characteristics of nutrition. When using this diet, a significant improvement in the general condition, a decrease or disappearance of dyspeptic phenomena, a significant decrease in azotemia and acidosis were noted.

A number of more recent studies have confirmed the effectiveness of a low-protein diet to inhibit the progression of chronic kidney disease. And although this diet only slows down, and does not prevent the development of chronic kidney disease, for elderly patients it should be considered as an alternative treatment method, which allows to reduce intoxication symptoms for a long period [10]. The effectiveness of a low-protein diet is determined by the rate of decrease in glomerular filtration rate (GFR) before starting dietary treatment. At an initially fast rate of GFR decline (1 ml / min per month), a low-protein diet can extend the pre-dialysis period by several months; with a slower initial deterioration in the filtration function of the kidneys, the need for dialysis may be delayed by more than 1 year. At the same time, the use of a low-protein diet has several limitations: 1) the risk of developing malnutrition syndrome increases; 2) difficult for a number of patients; 3) reduces the quality of life in the perception of patients.

To eliminate the protein fasting syndrome, drugs containing essential amino acids (EA) are added to treatment at the stage of chronic kidney disease. The Swedish diet, which includes a combination of low-protein foods with EA additives, without the need for the introduction of complete proteins, has become widespread [2]. This diet has greatly expanded the possibilities of using the principle of protein restriction in the treatment of progressive nephropathy. Replacement of a complete animal protein can also be carried out by keto analogs of amino acids, which differ from amino acids by substitution of an amino group by a keto group. With the help of keto analogs, it is possible to replace most EA, but not all. Therefore, ketoanalogue additives along with ketoanalogs contain irreplaceable EA [6]. The founder of the developed principle of protein restriction in the treatment of progressive nephropathy S. Giovannetti as a result of a twenty-year study of this problem formulated a modified principle of dietary treatment.[18-19]

The goal of treatment is to slow the progression of chronic kidney disease and to delay the use of substitution dialysis treatment, to improve the function of residual nephrons. Two diet options have been proposed: one at a plasma creatinine level of 2 to 5 mg% (177 - 442 μmol / L), and the second at higher levels of creatininemia.[14] The first option, called the traditional diet, prescribes a protein content of 0.5-0.6 g per 1 kg of body weight per day, high calorie content (35 kcal per 1 kg of body weight), phosphate content of 8 to 12 mg per 1 kg of body weight body per day. The second option, the so-called artifact diet, recommends a sharp restriction of protein in the diet to 0.3 g per 1 kg of body weight, up to 18-20 g / day, a significant restriction of phosphates to 6-7 mg per 1 kg of body weight. An obligatory component of the artifical diet is the addition of EA and keto analogs in an amount of 14–16 g / day [5]. When developing dietary recommendations, one should take into account the pathogenetic features of DN, which is characterized by an early, not proportional to the degree of glomerular filtration disturbance development of hyperkalemia (increased serum potassium concentration> 5 mmol / l).[15]

Often this is due to the development of hyporeninemic syndrome of hypoaldosteronism. A decrease in the production of aldosterone, which regulates potassium metabolism, leads to the development of hyperkalemia. Increased metabolism (infection, fever, trauma, surgery), hemolysis, excessive intake of potassium from food, intake of potassium-sparing diuretics, acidosis can aggravate hyperkalemia in chronic kidney disease. A potassium concentration of 7 mmol / L or more is considered life threatening, and more than 8.5 mmol / L in the absence of emergency measures leads to cardiac arrest. With the development of hyperkalemia, potassium-rich foods should be excluded from the diet and switch to foods low in potassium (Table 2). The kidneys play a leading role in the regulation of calcium-phosphorus metabolism.[16] Sclerosis of the renal glomeruli, accompanied by the develop-

ment and progression of chronic kidney disease, leads to hyperphosphatemia, which in turn leads to increased secretion of parathyroid hormone (PTH).

***Table 2***

| **Potassium content in plant products** | |
|---|---|
| **Potassium content** | Product type |
| **High** | Nuts, yellow peas, Brussels sprouts, red cabbage, potatoes, rhubarb, radish, spinach, sorrel, raisins, dried apricots, prunes, peaches, apricots, pineapple, bananas, cornel, dates, mulberry, black currant |
| **Average** | Green peas, zucchini, eggplant, cauliflower, green onions, leek, radish, turnip, salad, beets, tomatoes, carrots, cherries, plums, persimmons, cherries, apples, blackberries, gooseberries, raspberries, red currants , oranges, grapefruit |
| **Low** | Cabbage, onions, cucumbers, sweet peppers, asparagus, watermelon, melon, cherry plum, pumpkin, pears, lingon berries, blueberries, strawberries, cranberries, rosehips, blueberries |

At the same time, the formation of calcitriol is disrupted in the kidneys, which leads to a decrease in calcium absorption in the intestine and the development of hypocalcemia. Hypocalcemia additionally stimulates the secretion of PTH, triggering the destruction of bone tissue. To correct these disorders, an increase in the intake of calcium with food is used along with the restriction of phosphates in the diet and their binding in the gastrointestinal tract.[17] Adequate calcium intake is due to products with its high content (table. 3). However, it is impossible to practice the intake of the required amount of calcium (at least 1,500 mg per day) only through diet and additional calcium salts are introduced - carbonate, lactate, gluconate.

**Table 3**

| **Calcium content in food products** | |
|---|---|
| ***Product name (per 100 g of product)*** | ***Ca, mg*** |
| **Beef 10-30** | 10-30 |
| **Sardines with bones 350** | 350 |
| **Boiled fish 20-30** | 20-30 |
| **Dairy products Cottage cheese 95** | 95 |
| **Milk 1% 120** | 120 |
| **Milk 3% 100** | 100 |
| **Sour cream 100** | 100 |
| **Hard cheese 600** | 600 |
| **Cream cheese 300** | 300 |
| **Yogurt 120** | 120 |
| **Fruits and nuts Dried apples 45** | 45 |
| **Dried apricots 170** | 170 |
| **Raisins 56** | 56 |
| **Figs 57** | 57 |
| **Oranges 35** | 35 |
| **Peanuts 70** | 70 |
| **Almonds 254** | 254 |
| **Sesame seeds 1150** | 1150 |
| **Sunflower seeds 100** | 100 |
| **Vegetables and bread Celery 240** | 240 |
| **Lettuce 83** | 83 |
| **Cabbage 60** | 60 |
| **Onions 60** | 60 |
| **Beans 40** | 40 |
| **Olives 77** | 77 |
| **Rye bread 60** | 60 |
| **Wheat bread 30** | 30 |

The use of a low-protein diet for diabetic kidney is an effective method of treatment, it inhibits the progression of the sclerotic process in the kidneys. However, with this method of treating DNs, it

is necessary to take into account the diversity and individual characteristics of the clinical course of the disease. The most important condition for the successful use of a low-protein diet should be the achievement and maintenance of stable compensation for carbohydrate metabolism, and correction of systemic blood pressure.[20] When using a low-protein diet in the complex of treatment for patients with DN, a systematic monitoring of the level of albumin, calcium, phosphorus, potassium in plasma, the absolute number of peripheral blood lymphocytes and red blood cells, daily excretion of urea, and body weight should be carried out. An important component of treatment is maintaining a "food" diary for the patient, discussing it with a doctor and a nutritionist. [21]

Based on the steady progression of DN at the stage of chronic kidney disease (CKD) with the outcome in the terminal uremic stage, requiring immediate and lifelong treatment with hardware-based methods of blood purification, the use of a low-protein diet should be considered as an essential component of the complex pathogenetic therapy of patients with DN. This measure will significantly improve the clinical status, delay the development of terminal renal failure.

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## РОЛЬ ВРАЧЕЙ И МЕДСЕСТЕР ПЕРВИЧНОГО ЗВЕНА В ВЫЯВЛЕНИИ ПЕРЕЛОМОВ ПРОКСИМАЛЬНОГО ОТДЕЛА БЕДРЕННОЙ КОСТИ У ЛЮДЕЙ СТАРШЕГО ВОЗРАСТА В РЕСПУБЛИКЕ УЗБЕКИСТАН

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Точные данные о частоте остеопорозных переломов проксимального отдела бедра (ППОБ) в популяции имеют неоценимое значение для планирования медицинской помощи и создания национального клинического инструмента оценки риска переломов FRAX. В Узбекистане такие данные до настоящего времени отсутствовали. Цель. Создать в Узбекистане систему выявления ППОБ для оценки их инцидентности и определить роль врачей и медсестер общей практики в выявлении пожилых пациентов с низкоэнергетическими переломами. Материалы и методы. В 2011-2017 гг. в Папском районе Узбекистана выполнено популяционное когортное исследование. После изучения системы регистрации ППОБ в ходе проспективного наблюдения осуществлялся мониторинг записей о ППОБ в официальных медицинских источниках, проводилось выявление неучтенных случаев ППОБ с привлечением врачей всех специальностей, медицинских сестер общей практики и волонтеров. Результаты. При ППОБ в районе госпитализировались 34 % больных, 26 % пациентов лечились амбулаторно у травматолога, 29 % — получали помощь исключительно у врачей общей практики, 11 % больных не получали врачебной помощи — они были выявлены благодаря привлечению специально обученных медсестер и волонтеров (все больные старше 80 лет, 87 % — женщины). Стандартизированная инцидентность ППОБ у лиц старше 40 лет в Узбекистане составила 357,7 для женщин и 190,2 для мужчин на 100 000 населения в год. Заключение. Показана важная роль врачей и медицинских сестер общей практики в создании системы выявления ППОБ. Полученные показатели будут включены в национальную модель FRAX для Узбекистана.

**Ключевые слова:** врачи общей практики; медицинские сестры; остеопороз; эпидемиология; перелом проксимального отдела бедра.

## ЎЗБЕКИСТОН РЕСПУБЛИКАСИДАГИ КЕКСА ОДАМЛАРДА СОН СУЯГИ ПРОКСИМАЛ ҚИСМИ СИНИШЛАРИНИ БИРЛАМЧИ БЎГИМ ШИФОКОРЛАРИ ВА ХАМШИРАЛАРИНИН РОЛИ

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Сон суяги проксимал қисмини остеопоротик синишлари хакида аник маълумотлар тиббий ёрдамни режалаштириш ва синишлар хавфини бахолаш учун FRAX миллий клиник услубини яратишда катта ахамиятга эга. Ҳозирга қадар бундай маълумотлар Ўзбекистонда мавжуд емас еди. *Мақсад:* Ўзбекистонда сон суяги проксимал қисмини остеопоротик синишларини аниқлаш тизимини яратиш ва кам қувват синиши бўлган кекса беморларни аниқлашда шифокорлар ва умумий ҳамшираларнинг ролини аниқлаш. *Материаллар ва услублар:* 2011-2017 йилларда. Ўзбекистоннинг папал минтақасида популяцион когорт тадқиқоти ўтказилди. Сон суяги проксимал қисмини остеопоротик синишларини рўйхатга олиш тизимини ўрганиб чиққандан сўнг, потенциал кузатув пайтида биз расмий тиббий манбаларда сон суяги проксимал қисмини остеопоротик синишлари ёзувларини кузатдик, барча мутахассислик шифокорлари, умумий ама-

лиёт шифокорлари ва кўнгиллилар иштирокида сон суяги проксимал қисмини остеопоротик синишлари қайд этилмаган ҳолатлар аниқланди. *Натижалар:* ПОП туманида беморларнинг 34 фоизи туманда касалхонага ётқизилган, беморларнинг 26 фоизи травматолог томонидан амбулатория шароитида даволанган, 29 фоизи фақат умумий амалиёт шифокорларидан ёрдам олган, беморларнинг 11 фоизи тиббий ёрдам олмаган - улар махсус ўқитилган ҳамшираларва кўнгиллиларнинг жалб қилиниши туфайли аниқланган (барчаси). 80 ёшдан ошган беморлар, 87% аёллар). Ўзбекистонда 40 ёшдан ошган одамлар орасида ўртача даражадаги касалланиш даражаси ҳар 100000 аҳолига аёллар учун 357,7 ва еркаклар учун 190,2 ни ташкил қилди. *Хулоса:* Сон суяги проксимал қисмини остеопоротик синишларини аниқлаш тизимини яратишда умумий амалиёт шифокорлари ва ҳамшираларининг муҳим роли кўрсатилган. Олинган кўрсаткичлар Ўзбекистон учун FRAX миллий моделига киритилади.

**Калит сўзлар:** умумий амалиёт шифокори; ҳамширалар; остеопороз; эпидемиология; проксимал бўғиннинг синиши.

## GENERAL PHYSICIAN'S AND PRIMARY CARE NURSE'S CONTRIBUTION TO THE OSTEOPOROTIC HIP FRACTURE IDENTIFICATION IN THE REPUBLIC OF UZBEKISTAN

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Precise population-based data on the osteoporotic hip fracture (HF) rate play an invaluable role in the assessment of burden of osteoporosis as well as in development of the national clinical fracture risk prediction tool (FRAX). Currently, these data in Uzbekistan is unavailable. Aim. To create a system for the all HF detection to calculate their incidence in Uzbekistan, and to assess the general physician's (GP) and primary care nurse's role in this system. Materials and methods. Cohort study was carried out in 2011-2017 in the Pap district of Uzbekistan We had revealed the national trauma care records peculiarities and then organized the prospective study. The trauma care records were monitored. Besides, all medical specialists including GPs, GP nurses and the community leaders were actively involved into the search and verification of non-hospitalized hip fracture patients escaping trauma care statistics. Results. Overall, among HF patients, only 34% were hospitalized, and 26% took outpatient trauma care. Additional 29% of HF patients were found only with the help of GPs. GP nurses in collaboration with the community leaders disclosed additional 11% patients who had been staying at home without any medical care. The annual standardized HF incidence in people older than 40 years enriched 357.7 for women and 190.2 for men per 100 000. Conclusion. Collection of epidemiological information on HF incidence in Uzbekistan was possible only with the help of GPs and GP nurses as key figures of primary care. The obtained epidemiological data will be incorporated into the first created Uzbek national FRAX model to assess the 10-year risk of osteoporotic fracture in clinical practice.

**Keywords:** general practitioners; nurses; osteoporosis; epidemiology; hip fracture

### Introduction

Osteoporosis is chronic non-infectious disease associated with aging, characterized by fragility of bone tissue and occurrence of fractures even in cases of insignificant injures. Social and economical expenses on osteoporosis grow constantly [1]. Possession of reliable information about the incidence and risk of osteoporotic fractures in population, and first of all about the most dangerous of those being fracture of proximal part of femoral bone (FPPF), has invaluable importance for planning of medical service system organization. Taking into account that, according to the world Health Organization and UN prognosis, the part of adults above 70 in Uzbekistan will increase three times by 2050 [2, 3], the study of epidemiological and clinical aspects of osteoporosis is one of the priority problems

of health care system in this country.

It is important to note, that the system of traumatological service in Uzbekistan does not provide compulsory hospitalization and early surgical intervention for all patients with FPPF. That is why documentation data of traumatological clinics cannot be used as a single source of information about the number of patients with FPPF. A similar problem was noted in other countries of the region, where EVA (Epidemiology of Osteoporotic Fractures in Eurasian Countries) study was performed on the Russian Osteoporosis Association initiative [4, 5]. In these conditions the number of osteoporotic fractures can be more accurately estimated with the creation of FPPF detection system from the maximal possible number of references including medical staff of the primary line in health care system with compulsory further verification of fractures [5].

The objective of the study was to create FPPF detection system in Uzbekistan for the assessment of the incidence and to determine the contribution of general practice doctors and nurses in the general practice of revealing old-age patients with low energetic fractures.

Materials and methods

The study was performed in the frames of international multicenter epidemiological project EVA (Epidemiology of Osteoporotic Fractures in Eurasian Countries) supported by International Osteoporosis Fund. For registration of proximal part of femoral bone fractures (FPPF) incidence Pap district of Uzbekistan was chosen due to its convenient geographical location and administrative structure. Its square area was equal to 2941 $km^2$, where at the start of the study there were 193 267 residents, 29 % of them above 40, and that was compatible to the results in the country as a whole. Inclusion criteria was FPPF (fracture of the neck of femoral bone, petrochanteric and subtrochanteric fractures, IDC-10 S72.0, S72.1, S72.2) in patients of 40 years old and elder living in the study area.

The study was performed in three stages. The first preliminary stage was study of the system of FPPF official registration in Pap district of Uzbekistan within 2011-2012 with detection of possible additional sources of information about the patients with the pathology.

In 2015 the second prospective pilot stage of the study was started. For four months from 01.09.2015 till 31.12.2015 we performed an active detection of new FPPF cases among adults above 40, verification, search, and assessment of the significance of additional, earlier not used sources of medical information about low energetic fractures. Before the start of the prospective stage a short training course on the problems of osteoporosis was held for doctors of different specialties with the explanation of the objective of the study. After that 27 general practitioners, radiologists, forensic experts, ambulance personnel, traumatologists, surgeons, physicians received special registration forms for filling in cases of detection of a patient with clinical manifestations of FPPF within a protocol regulations. These forms contained items like age, gender, residence, data and character of trauma, and IDC-10 code of the fracture. Within 4 months trained doctors registered all new cases of FPPF in these forms.

Besides that, within the pilot stage we performed monitoring of journal registration in reception unit and medical cards of patients (forms № 003/y-07) in traumatological unit of the only in-patient facility in the district, statistical cards of the patients discharged from the clinic (form № 066/y-07), ambulance call registration journals, out-patient visits in polyclinic, traumatologist visits to patients homes, out-patient cards, forensic documentation to reveal the cases encoded in IDC-10 as S72.0, S72.1, S72.2. The information from all the sources were included to one common database for exclusion of data duplication. Exclusion criteria were fractures in patients with severe somatic pathologies (oncologic diseases with metastases to bone, myeloma disease) and fractures resulting from high energetic trauma (traffic accidents, falling from height above one's own height, work injuries).

Since 01.04.2016 a basic prospective stage of data collection of new FPPF cases had started and continued till 31.03.2017. Besides doctors at that stage we involved general practice patronage nurses. As the pilot stage showed, the latter ones were assistants of general practitioners and in Uzbekistan they are medical professionals most informed about family aspects of the patients. After the training, nurses started providing written information about every new case of detection of old immobile patients or patients with limited mobility. Later orthopedic surgeon consulted all these patients at home. We also searched for patients with FPPF in Pap district among surgical patients in the clinic of Namangan city, which is administrative center of Namangan region.

One more direction in our work was involving of seven traditional healers – tabibs (chiropractors) practicing in Pap district and very popular among the villagers. Prior to the study tabibs did not register their medical activity. From the time of the study they started registration of hip fracture cases

in their patients and sending that information to general practice (GP) nurses, who, in their turn, sent that data to the research center. The search for FPPF patients also involved volunteers, the elders in administrative units covering 1350-1500 people, called mahalla. Those elders, whose activity was irrelevant to medical issues, anyway have information on health status of all residents of their units. Within the research period with the help of representatives they also organized an active search for actual information about old people, who stopped going out. All the information provided by the leaders of mahalla was sent to patronage GP nurses, they checked the data and similarly to tabib practice here also they involved traumatologists to examine immobile old people at home. In cases of clinical verification of FPPF traumatologists filled registration forms and sent those forms to the chief researcher. The chief researcher in his turn checked the fulfillment of the forms and composed FPPF master database for the district. After that, using Uzbekistan State Statistics Committee demographical data the incidence of FPPF was estimated for men and women living in the district, age-specific incidence, and standard values of FPPF prevalence for the whole country with 5-year intervals.

Mathematical and statistical processing was performed using applied software Gretl for MS Windows (http:// gretl.sourceforge.net/ru.html). Symptom frequency and confidence intervals were calculated using Wilson method. Comparison of the age structure of the studied samples was performed using chi-square criterion.

**Results**

**Table 1**

**Population, number, and estimated incidence of femoral bone proximal part fractures in Pap district of Uzbekistan according to the results of 4-months pilot stage of the study in 2015.**

| Age, years | Population | | | New cases of hip fractures within 4 months | | | Estimated incidence of FPPF a year per 100 000 of population | | |
|---|---|---|---|---|---|---|---|---|---|
| | Men | Women | Total | Men | Women | Total | Men | Women | Total |
| 40-44 | 6152 | 6685 | 12837 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| 45-49 | 5132 | 5441 | 10573 | 2 | 0 | 2 | 116.9 | 0.0 | 56.7 |
| 50-54 | 5330 | 5383 | 10713 | 0 | 1 | 1 | 0.0 | 55.7 | 28.0 |
| 55-59 | 3878 | 3940 | 7818 | 2 | 0 | 2 | 154.7 | 0.0 | 76.7 |
| 60-64 | 2014 | 2204 | 4218 | 1 | 4 | 5 | 149.0 | 544.5 | 355.6 |
| 64-69 | 956 | 1194 | 2150 | 1 | 2 | 3 | 313.8 | 502.5 | 418.6 |
| 70-74 | 810 | 868 | 1678 | 2 | 2 | 4 | 740.7 | 691.2 | 715.1 |
| 75-79 | 727 | 850 | 1577 | 1 | 2 | 3 | 412.7 | 705.9 | 570.7 |
| 80-84 | 290 | 487 | 777 | 0 | 4 | 4 | 0.0 | 2464.1 | 1544.4 |
| 85-89 | 201 | 336 | 537 | 0 | 0 | 0 | 0.0 | 0.0 | 0.0 |
| Above 90 | 91 | 181 | 272 | 0 | 1 | 1 | 0.0 | 1657.5 | 1102.9 |
| Totally 40+ | 25581 | 27569 | 53150 | 9 | 16 | 25 | 105.5 | 174.1 | 141.1 |

The assessment of the fracture registration system in Pap district performed at the first stage showed that at the start of the study all medical documentation was manual and was not digitalized later. In 40% of the cases there was no information about the mechanism of trauma and exact location of the fracture. It was impossible to identify IDC code of fractures or differentiate cases of low energetic fractures in the total pool of traumas registered in journals of traumatological units and clinic. At the same time within two years from 01.01.2011 to 31.12.2012 there were 366 registered cases of FPPF among people above 40 (average, 183 per a year) in Pap district. Annual incidence rate of FPPF for people above 40 was 541, 239, and 384 per 100 000 men, women, and both genders, respectively. Thus, incidence among men was 2 times higher, than among women, and that was absolutely not characteristic for osteoporosis [1]. At the pilot stage of the prospective study, using administrative resources, we involved maximum number of specialists with higher education in health care system of the district for the search and verification of all cases of FPPF among patients applying for medical help. Besides that, we could exclude high energetic fractures from the analysis, the cases resulting from traffic accidents, falling from height, which were extremely frequent in the district. As a result we revealed a number of hip

fractures, which was several times less than that in 2011and 2012 (Table 1).

**Table 2**

**Number and part of patients with femoral bone proximal part low energetic fractures revealed for a year of prospective study from various sources**

| Categories of patients | Number of patients | | |
|---|---|---|---|
| | total, *n* = 140 | men, *n* = 52 | women, *n* = 88 |
| Hospitalized to the traumatology unit | 47.34 % | 19.37 % | 28.32 % |
| Received out-patient therapy (at central traumatology station) | 36.26 % | 11.21 % | 25.28 % |
| Patients revealed by GP at home | 41.29 % | 20.39 % | 21.24 % |
| Cases revealed by GP nurses at home; cases registered by tabibs and elders | 15.11 % | 2.4 % | 13.15 % |
| Forensic expertise procedure | 1. 07 % | 0 | 1.1 % |

Note: GP-general practicioner

Estimated annual incidence of low energetic FPPF among the people of 40 years old and above in 2015 was equal to 105.5 in men, 174.1 in women, and 141.1 totally (per 100 000 of population). It should be noted that, fracture incidence rate among women was higher, than among men.

The basic prospective stage of data collection continued 12 months from the 1 April 2016 till the 31 March 2017. After the exclusion of severe cases of traffic accidents and falling from height above one's own height we detected 140 low energetic FPPF: 88 women and 52 men of 40 years old and elder. Among them only 47 cases were registered in traumatology clinic journals. Thus, only 34 % of the patients with FPPF were registered in Pap district (Table 2). Those patients had osteosynthesis, skeletal traction or immobilization of hip joint using plaster cast (derotation boot); just two of these patients had emergency surgery for endoprosthesis of hip joint. According to the data received from traumatologists of the central traumatology station in the district there were 36 more patients with FPPF (26% of the total number), who were followed by traumatologist.

General practitioners reported about 41 cases with FPPF (29% of the total number), when patients stayed at home almost without any medical help for the fracture and were not registered in the documents of the traumatology service. Other 15 cases never registered before (11%) were revealed by patronage GP nurses when they actively visited residents of the district and cooperated with tabibs and elders. All these cases were consequently clinically confirmed by traumatologists in compliance with the check-up protocol. One case of FPPF was registered postmortem in the forensic expertise of 73-years old woman (Table 2).

Totally, age and gender-specific structure of the groups of patients with FPPF, revealed from various medical sources, did not differ significantly. Among the patients of traumatology clinic, patients, who received medical help at the central traumatology station and those treated by GP, the proportion of women was equal to60%, 69%, and 51%, respectively, while the age median was equal to 75, 64, and 70 years old, respectively (Figure 1). Different from that, patients revealed by visiting at home and not registered by medical services were reliably elder (age range 80-94 years old, with median 89 years old), and there were more women (87%, compared to other groups $p < 0.05$) (Figure 2).

Summarized values of FPPF incidence among women and men dependent on age received from all sources are presented in Figure 2. The incidence of FPPF increased per 100 000 of population from 14.7 among 40-45-year old to 3514.4 among 85-89-year old women and from 31.6 to 2824.9 among men. FPPF incidence in women of all ages was a little bit higher, than in men, except the youngest participants of the study (40-44 года). Total incidence of FPPF among the patients above 50 was equal to 513.4, 315.1 and 418.4 per 100 000 women, men, and all patients, respectively.

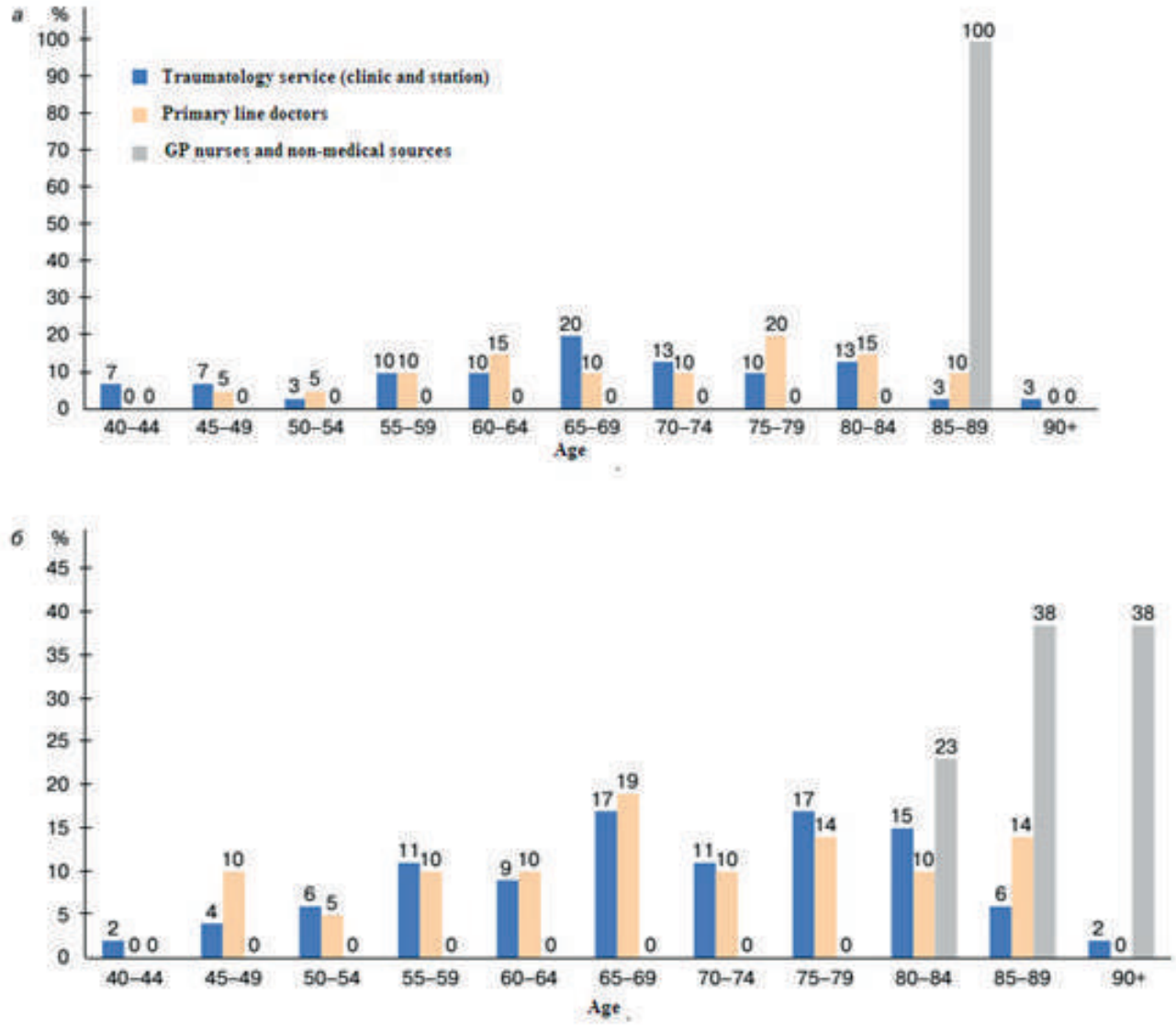


**Figure 1. Age-specific structure of groups of male (а) and female (б) patients with femoral bone proximal part fracture dependently on the source of information.**

Thus, the incidence rate of FPPF in 2016 in Pap district among the people of 40 years old and elder was 307 in women and 197 in men per 100 000 of population; ratio of women to men was 1.6 : 1. Supposing osteoporosis incidence rate in Pap district is close to that in the whole country we calculated standardized values of annual FPPF incidence (per 100 000 of population) among people of 40 years old and elder for the whole Uzbekistan. Taking into account even insignificant differences in demographic parameters of the region and the country as a whole, these values were 357.7 for women, 190.2 for men, and 294.6 for both. The same parameter for patients of 50 years old and elder was 567.1 for women, 355.3 for men, and 469.5 for both (per 100 000 of population).

According to WHO prognosis the proportion of population of Uzbekistan of 40 years old and elder by 2050 will increase 2.8 folds compared to 2015mostly due to the oldest people [3]. We estimated that, annually in Uzbekistan the number of women above 40 will increase more than three times from 16 091 cases in 2015 to 56 882 by 2050, while the number of FPPF among men will increase from 8969 in 2015 to 25 391 cases a year by 2050.

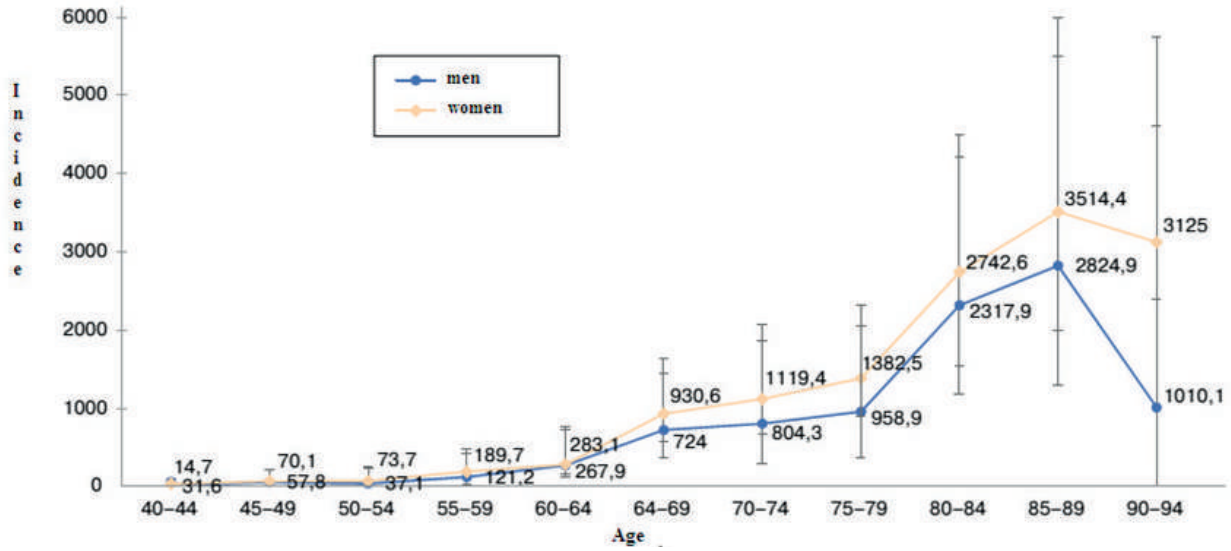


**Figure 2. Incidence rate of low energy fractures of proximal part of femoral bone among men and women in Pap district of the Republic of Uzbekistan (per 100 000), estimated on the basis of the results of the prospective stage of the study.**

Discussion

In the study we first estimated the incidence of low energy fractures of the proximal part of femoral bone in the Republic of Uzbekistan. It is planned to use these data for creation of authentic FRAX instrument for the calculation of 10-year probability of basic osteoporotic fractures and separately FPPF among the residents of the Republic of 40 years old and elder [14].

We took into account that, administrative, personnel, and technical resources of reliable data collection on patients with fractures should be created for the study. These reasons made us chose a small remote Pap district with a well organized central system of medical service for the study. Here we could get the data about the number of fractures and age and gender-specific incidence rate from various sources, and then extrapolate the results for the whole country.

The stage of primary documentation checking revealed important details characterizing the existing system of traumatism registration in the district. Documents (reception/discharge journals, clinical registrars, and traumatology stations documents) were mostly filled by nurses and junior medical personnel. Some documents were incomplete, and the mechanism of trauma was not indicated. So, we identified about 10% of registers of "fractures of lower limb" or "fracture of upper limb" without exact location of trauma. Nevertheless, these documents had registration of unusual great number of hip fractures and more than double prevailing of that kind of trauma among men compared to women, which we related to a series of specific characteristics in the region. These included peculiarities of geographical location of Pap district: necessity of using mountain roads and pass, extremely low quality of the roads, and popularity of bicycles among men of all ages, and the fact, that the best paid local job for men was taxi driver, conditioning persistent trials of drivers to overcome the mountain pass twice a day working for 16-17 hours a day. Our hypothesis was confirmed by the results of the World Health Organization studies, which revealed that in 2012 traumatization rate due to traffic accidents was included in the dozen of the basic causes of death or invalidation in Uzbekistan, and its burden increased (DALY) by 20% from 1990 to 2010 [6]. Besides that, it should be noted, that construction works are usually done in the region without any insurance for the cost economy on equipment and tools which could prevent falling.

Thus, the results of official medical statistics could not be used for analysis, but were used for the understanding of fracture registration and osteoporosis therapy bias in Uzbekistan as a whole [14]. On the basis of the result of that stage we made a conclusion, that the accurate number of fractures among old people in the district could be revealed only in prospective study and more careful interaction with the population.

With the assistance of the extremely important administrative resource the pilot 4-month stage of the study allowed us to involve maximal number of heal care specialists including primary line doctors. At the same time mechanisms of fracture revealing were systematized and modernized in Pap district. The capability of exclusion of highly traumatic fractures from one side, and involvement

of GP in the detection of FPPF not registered by traumatology service from the other determined decrease in FPPF incidence rate as a whole, but that caused the change in the structure of the values. FPPF incidence among women increased, while the rise of FPPF incidence with aging became more obvious. At the same time astonishing fact confirming the existing problems in the organization of traumatological service in villages of Uzbekistan was that, we revealed relatively young patients with FPPF (10 subjects from 40 to 69 years old), the only doctor following whom was general practitioner. We do not exclude that some portion of the patients with FPPF could not apply for medical help at all, particularly in remote villages, so they could be left unregistered in our study.

That is why final estimation of FPPF incidence rate was based on the results of one-year prospective stage of the study involving GP nurses and volunteers. That enabled the registration of fractures never registered before. It was noted, that GP nurses, who were the messengers between specialists and society, became a key figure in the detection of earlier unknown cases of FPPF in the patients with the most severe conditions. Patients revealed with the help of nurses (15 patients, 11% of the total number of fractures per a year) (Table 2) did not receive not only traumatological, but even any primary medical help. Majority of those patients were old women. Extrapolating of these result for the whole country it can be concluded that the portion of unregistered patients with FPPF staying at home and fixed in bed in Uzbekistan can reach 11% and be the highest among the countries covered by EVA project.

Contribution of the primary medical service specialists to the detection of FPPF patients was considered to be quite significant. GP, particularly, revealed 41 patients with FPPF within a year equal to 29% of the total number of fractures (Table 2); there were no data of these patients in the registrars of traumatology services. Consequently, total summary FPPF incidence rate in the district equal to 307 among women and 197 among men per 100 000 a year turned out to be 40% higher, than one supposed without contribution of GP and nurses (114 and 185 per 100 000 a year for men and women, respectively). Detection of such a significant pool of patients with severe fractures who did not receive any special traumatologist's medical help certainly possesses not only medical, but also significant social aspect.

Thus, Uzbekistan joins other countries (Russia, Belarus, Georgia, Kazakhstan, and Kirgizstan), where the greater part of FPPF remains uncovered by medical statistics [7-10]. All these points made us propose the result of the most complete prospective stage of the 2016 study for the future creation of FRAX model in Uzbekistan and prognosis of the number of osteoporotic fractures in the country.

Obtained results let us make a statement, that FPPF incidence rate in Uzbekistan id the highest among the countries participating in EVA project and, consequently, categorize Uzbekistan as a country with a high osteoporotic fracture risk [11].

Besides that, it should be noted, that according to the prognoses the number of FPPF in Uzbekistan will increase more than three times by 2050, and that is the highest growth among the countries covered by EVA project. That could be explained by one more characteristic feature of Uzbekistan. According to UN demographic prognosis population of Uzbekistan above 70 years old within the period from 2015 till 2050 can increase from 890 thousand to 3434 thousand (3.9 folds) [2, 3]. For comparison the part of Russian people, citizens of Georgia and Armenia above 70 years old will increase approximately 1.5, 1.4 and 1.9 folds by 2050, respectively [8-11].

Epidemiologic results of the study could be used not only for creation of a specific FRAX tool for Uzbekistan, but also serve the basis for the design of National population osteoporosis prevention programs.

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## РОЛЬ ОФЭКТ/КТ В ДИАГНОСТИКЕ ГИПЕРПАРАТИРЕОИДИЗМА.

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**Цель исследования:** В этом исследование мы стремились проанализировать преимущество ОФЭКТ/КТ против планарной сцинтиграфии у пациентов с аденомой паращитовидной железы и её гиперплазии.

**Материалы и методы:** 10 пациенты с первичным гиперпаратиреозом и 15 пациенты с вторичным гиперпаратиреозом были обследованы через 20 и 120 минут после внутривенного введения технеция-99-метоксиизобутилисонитрила (технетрил). Всем пациентам была проведена операция после исследования, выявлено 12 аденом паращитовидной железы и 13 гиперплазия. Гистопатологические данные были сопоставлены с результатами исследования.

**Результаты и обсуждение:** ОФЭКТ/КТ смог обнаружить аденомы паращитовидных желез даже с наибольшим поперечным диаметром 0,6 см. Планарная сцинтиграфия не смогла обнаружить аденомы паращитовидной железы с поперечным диаметром от 1,0 до 1,2 см. 8 из 13 (61%) гиперплазированные паращитовидные желез были диагностированы с использованием планарной сцинтиграфии и 10 из 13 (76%) гиперплазированные паращитовидные железы были обнаружены с помощью ОФЭКТ/КТ исследований.

**Ключевые слова:** аденома паращитовидной железы, гиперплазия паращитовидных желёз, планарная сцинтиграфия, ОФЭКТ/КТ**.**

## БФЭКТ/КТ НИНГ ГИПЕРПАРАТИРЕОИДИЗМ ТАШХИСОТИДАГИ ЎРНИ

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**Тадқиқот мақсади:** Ушбу тадқиқотда биз БФЭКТ/КТ ва планар сцинтиграфиянинг қалқонсимон без аденомаси ва унгинг гиперплазияси билан оғриган беморларда ташлхислаш мохиятини ўрганишга харакат қилдик.

**Материал ва услублар:** 10 бемор бирламчи гиперпаратиреоз билан ва 15 бемор иккиламчи гиперпаратиреозом билан томир ичига технеций-99-метоксиизобутилисонитрил (технетрил) юборилгандан сунг 20 ва 120 дақиқада текширилди. Текширувдан сўнг беморларга жаррохлик амалиёти ўтказилди. Жаррохлик амалиётидан сўнг 12 қалқонолди бези аденомаси ва 13 гиперплазияси аниқланди. Гистопатологик хулосалар текширув натижалари билан солиштирилди.

**Натижалар ва муҳокама:** БФЭКТ/КТ кўндаланг ўлчами 0,6 см бўлган қалқонолди бези аденомаларини аниқлашга ёрдам берди. Планар сцинтиграфия эса кўндаланг ўлчами 1,0 - 1,2 см бўлган қалқонолди бези аденомаларини аниқлай олмади. 13 қалқонлди бези гиперплазиясидан 8 тасини (61%) планар сцинтиграфия аниқлаб берди ва 10 тасини (76%) БФЭКТ/КТ текшируви аниқлашда ёрдам берди.

**Калит сўзлар:** қалқонолди бези аденомаси, қалқонолди бези гиперплазияси, БФЭКТ/КТ, планар сцинтиграфия**.**

**Introduction**

**Objective**: In this study, we aimed to analyze the relationship between the diagnostic ability of single photon emission computed tomography/computed tomography (SPECT/CT) images in localization of parathyroid lesions and the size of adenomas or hyperplastic glands.

**Material and methods:** 10 patients with primary hyperparathyroidism (PHPT) and 15 patients with secondary hyperparathyroidism (SHPT) were imaged 20 and 120 minutes after the intravenous injection of technetium99m-methoxyisobutylisonitrile (Tc99-technetrile). All patients underwent surgery and 12 parathyroid adenomas and 13 hyperplastic glands were detected. Pathologic findings were correlated with imaging results.

**Results**: The SPECT/CT images were able to detect all parathyroid adenomas even with the greatest axial diameter of 0.6 cm. Planar scintigraphy could not detect parathyroid adenomas with an axial diameter of 1.0 to 1.2 cm. 8 out of 13 (61%) hyperplastic parathyroid glands were diagnosed, using planar imaging and 10 out of 13 (76%) hyperplastic parathyroid glands were localized, using SPECT/CT images. Also, 10 out of 12 (83%) parathyroid ademomas were diagnosed using planar imaging, but could not detect 2 out of 12 (16%) adenomas.

**Conclusion: onclusion**: SPECT/CT imaging is a more useful tool for localization of parathyroid lesions, particularly parathyroid adenomas, in comparison with planar and imaging.
**Key words:** adenomas of parathyroid glands, hyperplasia parathyroid glands, planar scintigraphy

**Introduction:** Technetium-99m methoxyisobutylisonitrile (Tc99-technetrile) parathyroid cintigraphy is a useful tool for localization of lesions in hyperparathyroidism. However, few reports have reviewed the diagnostic ability of single photon emission computed tomography/computed tomography (SPECT/CT) imaging in hyperparathyroidism using fusion images. In the present study, we aimed to evaluate the correlation between the diagnostic ability of fused SPECT/CT images in localization of parathyroid lesions and the size of adenomas or hyperplastic glands.

**Methods:** 25 patients with hyperparathyroidism underwent Tc99-technetrile using SPECT/CT imaging between April 2018 and March 2020. 10 patients were diagnosed with primary hyperparathyroidism and 15 patients diagnosed with secondary hyperparathyroidism with chronic renal failure. All patients underwent surgery. 12 lesions were identified as parathyroid adenomas, while 13 lesions were identified to be parathyroid hyperplasia. Parathyroid hormone and calcium levels remained within the normal range in 20 patients after the surgery, although parathyroid hormone level increased after the surgery in 5 patient with primary and secondary hyperparathyroidism. The SPECT/CT equipment used in this study was AnysScan 16 (Mediso, Hungary), which combines 16-slice multidetector CT and SPECT. 650MBq of Tc99m-technitrile was injected intravenously in all patients. Early and delayed neck and upper thorax planar images were acquired 20 and 120 minutes after the injection, respectively. SPECT/CT acquisition was performed immediately after obtaining the delayed planar images. Overall, 90 projections (128×128 matrix) were acquired (30 seconds each), with a total duration of 20 minutes for the whole SPECT/CT procedure. CT was performed immediately after SPECT imaging. The main CT parameters were 130 kV, 25 mAs, and a 1.25 mm slice thickness; no intravenous contrast medium was used. SPECT/CT data were analyzed on a Mediso workstation, which provided transaxial, coronal, and sagittal slices of SPECT, CT, and fused SPECT-CT data. The size of the lesions was obtained from the pathology reports.

**Results:** 12 parathyroid adenomas and 10 hyperplastic glands were correctly localized, using the SPECT/CT fusion images. In contrast, 3 hyperplastic parathyroid glands could not be detected by fusion images. 8 out of 10 parathyroid adenomas were localized on Tc99m-technitrile planar scintigraphy images, where as 10 parathyroid adenomas were localized on the SPECT/CT images. All parathyroid adenomas with the largest axial diameter of 0.6 cm or more were localized on the SPECT/CT images. In contrast, parathyroid adenomas with the greatest axial diameter of 1.0 to 1.2 cm were not localized on planar Tc99m-technitrile scintigraphy images (Figure 1).

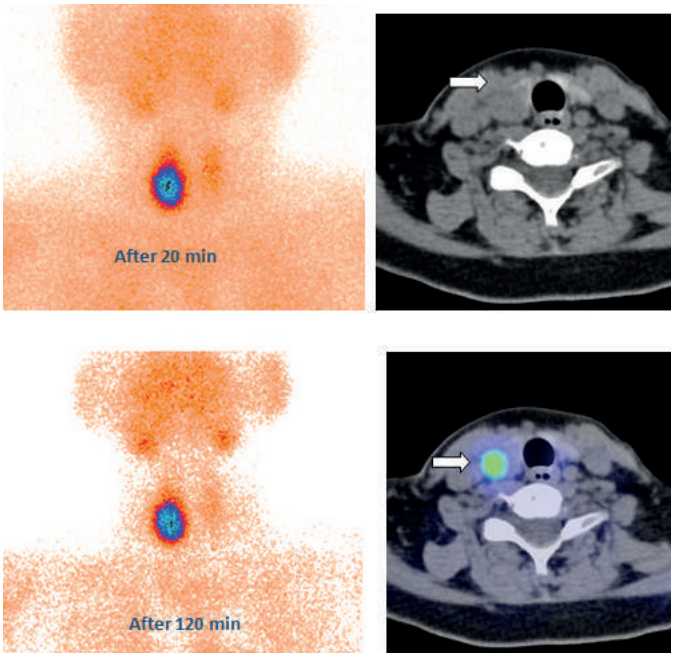


**Figure 1.** 1A. Initial and delayed phases of planar Tc99m-technetrile scintigraphy showed increased activity in the right lobe (arrow). Technetrile could not be used to differentiate between a parathyroid lesion and a thyroid lesion. 1B. Axial non-contrast enhanced CT of the neck. 1A lesion

was detected posterior to the right lobe of the thyroid (arrow). 1C. Fusion axial image of SPECT/CT. The radiotracer accumulated in the lesion posterior to the right lobe of the thyroid (arrow). Adenoma of the right lower parathyroid gland was removed during surgery

The mean size of the detected and undetected parathyroid adenomas in planar scintigraphy was 1.3±0.5 and 1.0±0.1 cm, respectively (P=0.7). The mean size of detected adenomas was 1.0±0.3 cm, based on the SPECT/CT images, and no adenoma remained undetected, using SPECT/CT images. 8 out of 13 (61%) hyperplastic parathyroid glands were localized, using planar Tc99-technetrile scintigraphy images, while 11 out of 13 (84%) hyperplastic parathyroid glands were localized, using the SPECT/CT images. 11 hyperplastic parathyroid glands with the greatest axial diameter of > 0.5 cm were correctly localized, using the SPECT/CT images. The mean size of 11 hyperplastic parathyroid glands detected on SPECT/CT images was 0.7±0.2 cm (range 0.5□0.9cm). 8 scintigraphically undetected hyperplastic parathyroid glands had the mean greatest axial diameter of 0.9±0.3 cm (range: 0.8-1.2 cm); there was not a statistically significant difference between the two groups (P=1.0). Although this negative result may reflect the small sample size in our study, it seems that other factors may play a role in the detection of hyperplastic glands, using scintigraphy (Table 1). Figure 1 shows a patient with PHPT due to left inferior parathyroid adenoma, which is not localized by planar scintigraphy, while detected by SPECT/CT imaging. Figure 2 shows a patient with SHPT due to right inferior hyperplastic parathyroid gland, which is not localized using planar scintigraphy, while detected by SPECT/CT imaging.

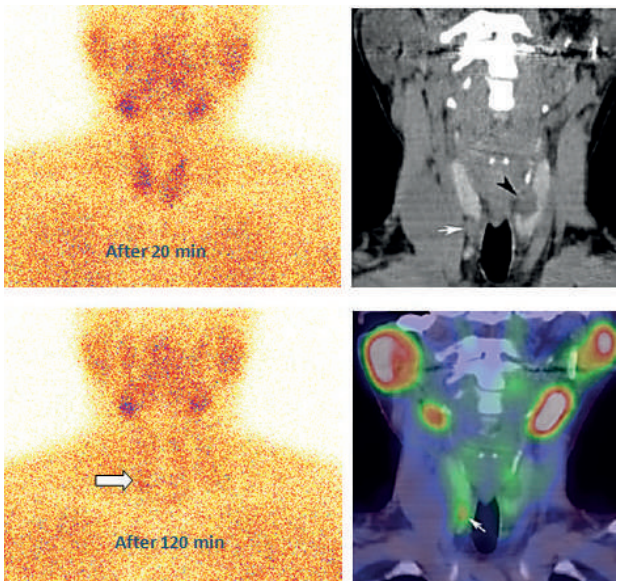


**Figure 2.** A. Initial and delayed phases of Tc99m-technerile planar scintigraphy showed abnormal uptake. B. Coronal non-contrast enhanced CT of the neck. A lesion was detected in the inferior right portion of the thyroid lobe (arrow). A cystic mass was detected in the left lobe of the thyroid (arrowhead). C. A coronal fused image (SPECT/CT). The fusion image demonstrated a faint abnormal uptake of Tc99m-technetrile in the inferior right portion of the thyroid lobe (arrow). Right inferior hyperplastic parathyroid gland was removed during surgery.

**Table 1. Characteristics of the patients and detections of lesion Tc99m planar and SPECT/CT image.**

| Patient | Age | Sex | Pathology | Localization of the lesions | Size of lesions (cm) | Planar | SPECT/CT |
|---|---|---|---|---|---|---|---|
| 1 | 50 | F | A | RIPG | 1.5 x 3.5 | yes | yes |
| 2 | 45 | F | A | RIPG | 1.2 x 3.5 | no | yes |
| 3 | 43 | F | A | LIPG | 1.6 x 2.8 | yes | yes |
| 4 | 55 | F | H | RSPG | 1.0 x 2.0 | no | no |
| 5 | 35 | F | H | LIPG | 1.5 x 1.8 | yes | yes |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| **6** | 40 | M | A | LSPG | 1.4 x 1.6 | yes | yes |
| **7** | 43 | F | H | RIPG | 1.0 x 1.8 | no | no |
| **8** | 52 | F | A | LIPG | 1.2 x 3.6 | no | yes |
| **9** | 30 | M | A | LSPG | 1.6 x 2.5 | yes | yes |
| **10** | 25 | F | H | RIPG | 1.5 x 1.8 | yes | yes |
| **11** | 20 | F | A | RSPG | 1.0 x 2.8 | no | yes |
| **12** | 40 | F | A | LIPG | 1.2 x 3.2 | no | yes |
| **13** | 23 | F | A | LSPG | 1.5 x 3.0 | yes | yes |
| **14** | 60 | M | A | RIPG | 1.6 x 2.8 | yes | yes |
| **15** | 55 | F | H | RSPG | 1.4 x 1.8 | yes | yes |
| **16** | 38 | F | H | RIPG | 1.5 x 1.6 | yes | yes |
| **17** | 30 | F | A | LIPG | 1.5 x 3.0 | yes | yes |
| **18** | 27 | F | A | RSPG | 1.6 x 3.2 | yes | yes |
| **19** | 44 | F | H | RIPG | 1.0 x 1.8 | no | no |
| **20** | 46 | M | H | LIPG | 1.4 x 1.5 | no | yes |
| **21** | 40 | F | H | LSPG | 1.5 x 1.5 | yes | yes |
| **22** | 32 | F | H | RIPG | 1.4 x 1.5 | yes | yes |
| **23** | 26 | M | H | LIPG | 1.1 x 1.5 | no | yes |
| **24** | 48 | M | H | RIPG | 1.4 x 1.4 | yes | yes |
| **25** | 41 | M | H | LIPG | 1.5 x 1.6 | yes | yes |

A – Adenoma. H – Hyperplasia. M – Male. F – Female. LSPG – Left superior parathyroid gland. RSPG – Right superior parathyroid gland. LIPG – Left inferior parathyroid gland. RIPG – Right inferior parathyroid gland.

**Discussion:** The main advantage of SPECT/CT systems is their application for the acquisition of high-precision fusion images, using both CT and SPECT imaging. Fusion images can be used for making a differential diagnosis between benign and malignant diseases in different body organs, determining the stage of the lesion, confirming a metastasis or its recurrence and selecting a treatment strategy. SPECT/CT imaging can be also used to clarify the existence of an abnormal uptake, based on the diminution of scattered radiation (1, 2). Although planar Tc99m-technetrile has been used in localization of parathyroid adenomas or hyperplasia, it is not always easy to detect these lesions in the delayed phase. In this regard, Shafiei et al. investigated the diagnostic ability of 99m Tc-sestamibi parathyroid SPECT/CT imaging in 48 patients with PHPT. The sensitivity and specificity of SPECT/CT for localization of parathyroid adenomas were 78% and 97%, respectively. These results indicate that SPECT/CT is a useful tool for localizing parathyroid adenomas (3). Ciappuccini et al. analyzed 94 patients with PHPT. In their study, dual-phase 99m Tc-sestamibi scintigraphy with SPECT/CT enabled the diagnosis of parathyroid adenomas in 56 out of 94 patients (63%) with PHPT (4). Furthermore, Papathyanassion et al. and Li et al. reported that 99m Tc-MIBI SPECT/CT is useful in detecting an ectopic parathyroid gland in patients with HPT (5, 6). Meanwhile, Torregrosa et al. performed 99m Tc-MIBI scintigraphy in patients with PHPT (n=16) and SHPT (n=22) and found 93% and 54% sensitivities for lesion localization in cases with PHPT and SHPT, respectively. They found that 99m Tc-MIBI planar scintigraphy can be used as the imaging technique of choice for preoperative localization of an abnormal parathyroid gland in patients with PHPT, but only as a complementary imaging technique in patients with SHPT (7). In addition, Caldarella et al. reviewed 24 studies on 471 patients with SHPT, using 99m Tc-MIBI planar images. The sensitivity and specificity of 99m Tc-MIBI planar scintigraphy in detecting hyperplastic glands in SHPT patients were 58% and 93%, respectively. Considering the inadequate diagnostic accuracy of this technique, it should not be considered a first-line diagnostic imaging method for preoperative localization in patients with SHPT (8). In the present study, the detection rate of hyperplastic parathyroid glands, using Tc99m-technetrile planar imaging, was poor. The degree of 99m Tc-MIBI uptake in parathyroid gland is influenced by the content of mitochondria-rich oxyphil cells. It is thought that Tc99m-tecnetrile easily accumulates

in parathyroid adenomas, which contain many oxyphil cells (9, 10). In our study, the detection rate of hyperplastic gland, using Tc99m-technetrile planar imaging was poor. Although Tc99m-technetrile planar scintigraphy was not successful in the localization of hyperplastic glands, in patient No. 5, fusion images were effective in the localization of hyperplastic gland with a faint abnormal uptake of Tc99m-tecnetrile in the right lower parathyroid (Figure 2). No previous studies have evaluated the correlation between the diagnostic ability of fusion images and the size of parathyroid lesions or hyperplastic glands, based on pathological evaluations. In the current study, size of lesions in pathological evaluations was used for making comparisons. It showed that fusion images could detect parathyroid adenomas with the greatest axial diameter of > 0.7 cm, while planar Tc99m-tecnetrile scintigraphy imaging were unable to detect parathyroid adenomas with the largest axial diameter of 1.01.2 cm.

**Conclusion:** SPECT/CT fusion imaging is a more useful tool for the localization of parathyroid lesions in hyperparathyroidism, especially parathyroid adenomas, in comparison with planar Tc99m-tecnetrile parathyroid scintigraphy.

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## CLINICAL CASE: AUTOIMMUNE POLYGLANDULAR SYNDROME WITH HEART DAMAGE

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There is a clinical case report of the young patient with autoimmune polyendocrine syndrome type II has been observed in this article that was presented with diabetes type I, dysfunction of thyroid gland and primary insufficiency of the adrenal cortex.

**Key words:** autoimmune polyendocrine syndrome type II, diabetes type I, chronic autoimmune thyroiditis, primary chronic adrenal insufficiency, vitiligo

## КЛИНИЧЕСКИЙ СЛУЧАЙ: АУТОИММУННЫЙ ПОЛИГЛАНДУЛЯРНЫЙ СИНДРОМ С ПОРАЖЕНИЕМ СЕРДЦА

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Аутоиммунный полигландулярный синдром проявляется одновременной недостаточностью нескольких эндокринных желез и часто протекает с аутоиммунным поражением неэндокринных органов. При аутоиммунном синдроме 2 типа также было зарегестрировано идиопатическое нарушение проводимости сердца. В данной статье описана поздняя диагностика редко встречающейся в практике тяжелой эндокринной патологии – аутоиммунной полигландулярной недостаточности и аномалии развития – синдрома Вольфа-Паркинсона-Уайта, на примере одного пациента.

По причине постепенного развития на протяжение многих лет каждого из этих синдромов, несмотря на достаточное количество симптомов, поздняя диагностика приводит не только к тяжелому течению заболевания, но и к развитию осложнений. Своевременная, правильная диагностика аутоиммунного полигландулярного синдрома требует от специалистов профессионализма и мультидисциплинарного подхода.

**Ключевые слова:** аутоиммунный полигландулярный синдром 2 типа, диабет 1 типа, хронический аутоиммунный тиреоидит, первичная хроническая надпочечниковая недостаточность, витилиго.

## КЛИНИК ВАЗИЯТ: ЮРАК ПАТОЛОГИЯСИ БИЛАН АУТОИММУННЫЙ ПОЛИГЛАНДУЛЯР СИНДРОМ

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Аутоиммун полигландуляр синдром бир неча эндокрин безларининг етишмовчилиги билан намоён булади ва купинча ноэндокрин аъзолардаги аутоиммун касалликлар билан биргалигда кечади. Аутоиммун полигландуляр синдром 2-турида юрак утказувчанлигининг идеопатик бузилишлари хам кайд этилган. Ушбу маколада амалиётда кам учрайдиган огир эндокрин патология

Аутоиммун полигландуляр етишмовчилик ва ривожланиш анамалияси булган Вольф-Паркинсон-Уайт синдромининг бир беморда кечиктириб аникланиши еритилган.

Хар иккала синдром хам йилар давомида аста-секинлик билан ривожланиб бораётканлиги сабабли, етарлича симптомлар мавжуд булишига карамай уз вактида ташхисланмаган хамда касалликнинг кечишини огирлаштирибгина колмай, асоратлар ривожланишига хам сабаб булган.

Аутоиммун полигландуляр синдромни уз вактида тугри ташхислаш мутахассислардан про-

фессионализм ва мультидисциплинар ендашувни талаб килади.

**Калит сўзлари:** аутоиммун полигландуляр синдром, 1- тур диабет, сурункали аутоиммун тиреоидит, бирламчи сурункали буйрак усти бези етишмовчилиги, витилиго.

Syndromes of the polyglandular insufficiency is characterized with sequential and simultaneous decrease of the functions of several endocrine glands based on general cause associate with autoimmune process in the certain organs and tissues.

Classification depends on combination of single glands insufficiency that unite in 1 out of 4 types. Based on given syndromes that autoimmune reaction has a link with autoantibodies to endocrine tissues and lead to inflammation, lymphocytic infiltration and partial and full destruction of the glandular tissue. Several endocrine glands are involved in the given process, although a clinical manifestation of this pathology does not always occur simultaneously. Sometimes dysfunction of immune system can result in autoimmune reactions in non-endocrine organs. Diagnosis requires to determine the level of hormones and autoantibodies to the effected endocrine glands. Clinical polymorphism, prolonged latent period among the first appearances of the syndrome manifestation demand advanced immune methods and monitoring of the residual functions of the target organs with aim of timely beginning therapy and prevention of crisis situations. A treatment links with replacement of insufficient hormones and sometimes, associates with immunosuppressors.

Polyglandular syndrome includes a broad spectrum of the autoimmune disorders. George J. Kahaly sorts out two main types of the autoimmune polyglandular syndrome (APS). There are juvenile ( first type) and APS of the adults ( second type). The min role in the nature of APS plays: lymphocytes infiltration of the effected gland, circulation of the organ specific antibodies in the serum, immune defects in the cells and association with (HLA) DR/DQ genes[11]. APS II occurs most frequently. The main components are primary adrenal insufficiency (Addison's disease), autoimmune diseases of thyroid gland and / of I type diabetes. Autoimmune diseases of thyroid gland demonstrated with chronic autoimmune thyroiditis of the Hashimato and Graves' disease. However other components of the APS II can occur such as primary hypogonadism, myasthenia, celiac disease, pernicious anemia, alopecia, vitiligo, serositis APS II type is polygenic disease and it is based on genetic predisposition to autoimmune tissue damage as a result of specific genes of the system HLA (DR3, DR4, B8, DQA1 and others). Classical APS II characterized by the presence of primary chronic adrenal insufficiency and autoimmune thyroid glands damage - Graves' disease or hypothyroidism as a result of autoimmune thyroiditis. This combination is known as Schmidt syndrome, association of primary chronic adrenal insufficiency with thyroid glands damage and I type diabetes – Carnenter's syndrome. Foreign researchers (Betterle) modified the given classification by adding APS III and IV types that pathogenesis similar to APS II but is characterized with association of the autoimmune damage differing from APS II .

**Autoimmune polyglandular syndromes**

A Type 1

1. Chronic mucocutaneous candidiasis
2. Hypoparateriosis
3. Chronic adrenal insufficiency

A Type 2

1. Chronic adrenal insufficiency
2. Insulin-dependent diabetes mellitus
3. thyroid glands damage

Wolff Parkinson White syndrome is the most frequent premature ventricular excitation ( it is observed in 0,1-0,3% of people out of general population) that occurs when an additional bunch of Kent presents and the many have no any symptoms of the heart disease. Despite of a great progress in the studying of disease, molecular and genetic basics that responsible for syndromes of many patients has left unknown. On march 2020, it is known that just several genes damage leads to the Wolff Parkinson White syndrome.

CTLA-4 and PD-1 is expressed on the T-cells when they activate and considered to be membrane immunoglobulins. PD -1 is marker of activated T-cells. Inhibitory receptors CTLA-4 and PD-1 (modulator of immune synapse) play a key role in regulation of immune reactions. They suppress excessive development of immune respond and prevent autoimmune reactions. CTLA-4 and PD-1 weaken the function of the effector ( reactive ) T-cells.

CD28 –membrane protein that expressed on the T-cells and it participates in stimulation of the T – cells. Connection of T-lymphocytes receptors with antigen MHC in the absence of stimulating signal from CD 28 lead to disability of lymphocyte to provide normal immune respond and lymphocytic tolerance.

T-lymphocytic receptor (*TCR) is a sup*erficial protein complex of T-lymphocyte that responsible for detection of progressive antigens connect with major histocompatibility complex on the surface of antigen-presenting cells. Interaction of *TCR with molecules of the major histocompatibility complex and antigens that link with* them leads to activation of T- lymphocytes and considered to be a key point in launching of immune responds.

In molecular mechanism of suppression of the T-lymphocytes activity, we can see that CTLA-4 inhibits competitively CD 28 that leads to a decrease of рГКГ/ТКР and production of PD-1

However under influence of different exogenous and/ or endogenous factors can appear mutation of the different genes, one of them is deletion of gen that means destruction – chromosomal rearrangement with loss of chromosomal locus. In experimental deletion in a mice with PD-1 deficiency was observed that in the long run this leads to autoimmune dilatation cardiomyopathy or to autoimmune myocarditis[12]. These days, there is no description of the cases with gene damage that define protein PD-1 in the scientific literature.

**The aim of work:** to demonstrate the importance of timely diagnosis and treatment of APS II in clinical practice.

**Methods of research:** In our clinical practice we came up with rare and atypical variant of manifestation and course of APS II and clinical observation of the young men with APS II comprising type 1 diabetes, thyroid glands damage and primary adrenal insufficiency is presented to your attention

| **Characteristics** | **Type 1** | **Type 2** |
|---|---|---|
| Inheritance | autosomal recessive | Polygenetic |
| | Connect with environment | |
| Genetic association or connection with | Equal distribution | some HLA |
| Sex | Young age | |
| Age | | |
| **Endocrine disorders** | | |
| **Addison disease** | | |
| hypoparathyroidism | 60-72% | 70% |
| Autoimmune thyroid glands damage | Odinary (79-96%) | rare |
| | Less frequently (около 5%) | |
| Diabetes mellitus of the first type | 14% | Often (about 70%) |
| Primary hypogonadism | Out of them 60% females; 14% males | > 50% |
| | | About 5% |
| | - | - |
| Hypophysitis | | Occur |
| **Dermatological** | | |
| Chronic mucoviscidosis | | - |
| | In the beginning frequently (about 100%) | Occur |
| Skin candidiasis | General (about 50%) | About 5% |
| Alopecia | About 13% | Occur |
| | - | Occur |
| Vitiligo | - | - |
| Dermatitis herpetiformis | | |
| **Gastrointestinal** | | |
| Celiac disease | No (only steatorium ) | Presented in 2-3% |
| Autoimmune hepatitis | About 12% | - |

| | | |
|---|---|---|
| **Hematological**<br>Pernicious anemia<br>Erythrocyte hypoplasia<br>Idiopathic thrombocytopenic purpura | <br>About 13%<br><br>Occur<br><br><br>Do not occur | <br>As frequently as APS<br>-<br><br><br>Occur |
| **Ectodermal**<br>Enamel hypoplasia<br>Dystrophy of nails<br>Calcification of the tympanic membrane | <br>+<br>+<br><br>+ | <br>-<br>-<br><br>- |
| **Neurological**<br>Myasthenia gravis<br>Stifman syndrome<br>Parkinson's disease | <br>-<br>-<br>- | <br>+<br>+<br>+ |
| Others<br>Asplenia<br>Keratopathy<br>Progressive myopathy<br>Deficit IgA<br>Serositis<br>Idiopatic heart block | <br>+<br>+<br>+<br>-<br>-<br>-<br><br>- | <br>-<br>-<br>-<br>+<br>+<br>+<br><br>+ |

**Results of the research and their discussions:** In 2019, patient X., at the age of 32 years old came to the Samarkand endocrinological dispensary with complains: dry mouth, elevation of the glucose level in the blood, increase of depigmentation of the skin, weakness, loss of appetite, elevation of the blood preassure, tachycardia, infertility.

According to patient's words, he has been ailing since 17 years old. He was in Russia in order to treat vitiligo during the period 2012-2014. At that time he suffered from a dislocation of the left shoulder because of doing sports, treatment of which led to the development of the allergic reaction to non- steroid anti-inflammatory drugs and penicillin. He several times suffered from anaphylactic shock with swelling of the face and larynx. He took glucocorticosteroids. Since 2016 he has had 1 type diabetes. Initially he took biguanides 500 mg/day. At present day he took long-acting human insulin analog at the dose 16 unit per day. In 2017 he treated in cardiology dispensary with diagnosis of Wolff Parkinson White syndrome because of palpitation. There were no children during one-year period after wedding party. Thus an analysis was taken and azospermia was found.

**Anamnesis vitae:** He was a first child in his family and was born on time, his height was 52 cm and body weight 3200 kg, the newborn period was free of deviation. He grew and developed well and started walking in one year and 2 month, development of the speech was in one year. He was ill with chickenpox when he was a child. Vitiligo was detected in 12 years old. In 2017, he began to be examined because of infertility and sequentially were detected azospermia, autoimmune thyroiditis and 1 type diabetes. In 2017 Wolff Parkinson White syndrome were diagnosed. In 2017 he two times suffered from anaphylactic shock. The mother had this pregnancy first time and pregnancy was difficult with toxicosis during the whole period of the pregnancy. The mother in the early period of the pregnancy was ill with acute respiratory infections and influenza, then she took glucose and vitamin C. Any chronic diseases were absent in the anamnesis of the parent's boy. They have one more healthy child. Marriage is not related. Bad habits were absent.

During the examination a general condition was satisfactory. Skin was dark with large areas of depigmentation. Visible mucous membranes were pale and dry. The lymph nodes were acceptable for palpation and were not enlarged. Thyroid gland was located in a typical place, on palpation compacted, was not enlarged. The surface was rough and painful. Hemodynamics was stable: Arterial pressure 130/90 mm Hg.

During the examination in Samarkand regional endocrinology dispensary were found:

**In biochemical blood analysis:** protein -78 g/l, cholesterol – 3,0 mmol/l, albumin - 38,4 g/l, urea – 6,1 mmol/l, bilirubin – 11,9 mmol/l, glucose – 8,0 mmol/l

**On glycemic profile** in $3^{00}$ -7,9 mmol/l, in $7^{00}$ -8,0 mmol/l, in $10^{00}$-11,2 mmol/l, in $17^{00}$-8,4 mmol/l.

**In general urine analysis glucose** -1 %, proteins -0,033 g/l, epithelium 1-2 in sight, leucocytes 10-11 in sight, salt (+).

**In the analysis (profile) of thyroid hormones** – TTH -2,45 ng\ml, T4 free – 15,8 pmol/l, anti TPO – 32 MU/ml

Elevation of the glycemic index up to 11,2 mmol/l with gradual decrease during first days up to 8,0 mmol/l were noted at patients.

**In the instrumental methods of examination:** On ultrasound was detected pyelonephritis, chronic prostatitis. On ultrasound – thyroid gland was compacted with heterogeneous structure

**On ECG** – sinus tachycardia, WPW syndrome, dystrophic changes in the myocardium, signs of hypertrophy of the both ventricles.

**On Echocardiography** – chambers of the heart was not dilated, walls hypertrophy was not found, moderate systolic dysfunction of the left ventricul, fraction of ejection 47%, heart rate 89 beats per minutes, a zone of the local fibrose of the front-septal segment of basal and partially middle region of the left ventrical, contractility of the given section was decreased, diffuse hypokinesia of the interventricular septum.

**In the department condition of the general endocrinology was fulfiled:** long-acting human insulin analog 16 units in $22^{00}$, short-acting insulin 6 units before main meals, aktovegin 400 mg + solution of natrii chloride 0,9 % – 200,0 intravenous drip. On the background of therapy his condition was stabilized, patient was studied according diabetes program, he was discharged under the observation of local therapist and endocrinologist. A following recommendations regarding pharmacotherapy were given to the patient: long-acting human insulin analog 16 units in $22^{00}$, with recount on bread units according to main meals.

**Patient was made diagnosis:** Main – autoimmune polyglandular syndrome II type:1 type diabetis, autoimmune thyroiditis, common form of vitiligo . Complication – diabetic nephropathy with proteinuria, ХБП-С 2.

**Concomitant:** WPW, rhythm disturbance by the type of transient paroxysmal tachycardia, myocardial dystrophy

**Conclusion:** On the example of one patient, we concluded that timely diagnostics of the APS components enable to prevent the development of severe complications of the given syndrome, to alleviate patient's suffering and prevent the deterioration of their quality of life.

Patients with APS II must be studied and warned about symptoms of diseases associated with high risk because during patient's life one type of APS can turn to another one, as new components were added [10]. We recommend to include category of individuals work of whom connect with high attention, especially during evening and night hours, risk factors of the development of autoimmune diseases and to expand monitoring during the medical examinations with inclusion of hormonal blood test.

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## ДИАБЕТОЛОГИЯДА ШАХСГА ЙЎНАЛТИРИЛГАН ЁНДАШУВ: ГЕНОМ ТЕХНОЛОГИЯЛАРИ АҲАМИЯТИ

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**Хулоса**
Мақолада шахсга йўналтирилган тиббиёт асоси сифатида қандли диабетнинг генетик маркёрлари бўйича адабиётлар шарҳи келтирилган
**Калит сўзлар:** қандли диабет, генетик маркёрлар, шахсийлаштирилган тиббиёт

## ПЕРСОНАЛИЗИРОВАННЫЙ ПОДХОД В ДИАБЕТОЛОГИИ: РОЛЬ ГЕНОМНЫХ ТЕХНОЛОГИЙ

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**Резюме**
В статье приведен обзор литературных данных по генетическим маркёрам сахарного диабета, как об основе персонифицированной медицины.
**Ключевые слова:** сахарный диабет, генетические маркёры, персонифицированная медицина.

## PERSONALIZED APPROACH IN DIABETOLOGY: THE ROLE OF GENOMIC TECHNOLOGIES

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**Summary**
The article presents literature review of the data of genetic markers of diabetes mellitus as a basis of personified medicine.
**Key words:** diabetes mellitus, genetic markers, personified medicine

Patient-centered approach has been applied in the therapy of DM type 2 since 2012 according to recommendations of American Diabetes Association (ADA) and European Association of Studying Diabetes (EASD) [36]. That approach suggests treatment of DM type 2 patients taking into account patient's age, duration of the disease, estimated life expectancy, severe associate diseases, diagnosed vascular complications, patient's will to cooperate, and available resources. Personalized approach in the therapy and prophylaxis is topical for the modern health care system. American scientist Leroy Hood formulated the direction of the future medicine in his concept based on four principles:

1. Predictive, providing prognosis of the disease on the basis of individual genomic characteristics (creation of probable health prognosis based on genetic tests);
2. Preventive, being proactive and providing prevention of disease development by means of prophylaxis;
3. Personalized, based on individual approach to every patient, which , among other things, suggests creation of a unique genetic passport for the therapy and patient's health status control;

4. Participatory (participation, partnership), based on a close cooperation of various profile doctors and patients, and converting a patient from a subject of therapy to an object of therapeutic process [6].

It is known, that genetic predisposition, risk factors, and their interrelation play a certain role in the development of DM type 2 [44]. Diabetes mellitus type 2 risk factors are subdivided to modified and non-modified ones. Modified risk factors include overweight, obesity, insufficient physical activity, prediabetes, arterial hypertension, dislipidemia, PCOS, and cardiovascular diseases. Non-modified risk factors are age, family history of DM, gestational DM or birth of a big baby in the history. Crucial step in the creation of the branch of personalized medicine was human genome decoding [5]. Nowadays scientists search for genetic markers, which can cause development of diabetes itself and its complications.

Contribution of genetic factors to the development of DM is undeniable. It is confirmed by a high level of CM type 2 concordance in monozygotic twins and family inheritance [511]. At the same time DM is a multifactor disease. According to diverse studies results a certain gene can serve to be an independent risk factor or be associated with one or several risk factors. The "first wave" in the detection of candidate genes associated with the development of DM was attributed to genes responsible for rare forms of DM (MODY, mitochondrial and neonatal DM) [4]. It was also shown that, some of these genes were associated with DM type 2 [29].

Preliminary studies were aiming detection of polymorphic markers in candidate genes, products of which (proteins) are involved to the pathogenesis of DM type 2 [7]. That was the way genes, associated with insulin resistance, obesity, β-cells dysfunction, and decrease in incretin response were identified. In 1997 C.J.Yen et al described relation of polymorphic marker rs18012824 of PPARG2 gene to the increased risk of DM type 2 development [57]. That gene codes PPARG2 receptor, which belongs to the super family of nuclear receptors from the group of transcription factors. Its activation and binding to X retinoid receptor form geyterodimer interrelating with specific DNA sequences, which code proteins participating in lipid and glucose metabolism. PPARG2 activation leads to differentiation of adipocytes, promoting acceleration of adipogenesis, and participates in the regulation of fatty acids exchange [20]. It was shown that, homozygous Pro12Pro differ by expressed resistance to insulin, obesity, and have 20% higher risk of DM type 2 development compared to carriers of AlA12Ala (OR~1.14) [14].

In 1998 association of KCNJ11 gene with DM type 2 was revealed. It is interesting that, earlier there were data about participation of that gene in the pathogenesis of neonatal DM [29]. That gene codes Kir6.2 protein, one of two subunits of ATP-dependent potassium channel. This channel effects secretion of insulin by β-cells by means of alteration in membrane potential. Increase in glucose level in blood leads to increase of ATP and decrease of the channel permeability; membrane potential diminishes, and Ca2+ ions flow into cell increases, which in its turn, causes increased secretion of granules with insulin. Mutation in KCNJ11 gene in replacement of Glutamate by Lysine in 23 codon (Gly23Lys) leading to alterations in Kir6.2 protein structure and channel dysfunction - channel is not closed with ATP, glucose; membrane stays polarized and insulin secretion does not occur. Results of researches showed that, polymorphic marker rs5219 (Gly23Lys) of the gene was associated to DM type 2 (OR~1.15) [54]. Another subunit of potassium ions transportation channel, represented by sulfonyl urea receptor (SUR1), codes ABCC8 gene. Polymorphic marker rs757110 of this gene is associated with DM type 2 (OR~1.15),and neonatal DM [29]. In 2000 adiponectin gene (ADIPOQ) was described. Adiponectin is a protein secreted by adipocytes; it affects tissue sensitivity to insulin. Association with DM type 2 was determined in French [55], Swedish [34], Japanese [32] and Latin populations, though it was not revealed in Indians of Pima tribe and African Americans [31].

In 2003 TCF7L2 gene was found, which codes β-catenin nuclear receptor, canonic activator of Wnt signal pathway. Proteins of Wnt signal pathway play a key role in normal embryogenesis, division and differentiation of cells [46]. It was shown that, TCF7L2 nuclear receptor interaction with proteins of Wnt signal pathway regulate proglucagon secretion, which in its turn, defines glucose-dependent insulin secretion and also effects maturation of β-cells of pancreas from lipopotent stem cells [6]. Initially revealed in Island interaction of the gene with the development of DM type 2 was later confirmed in other populations in America and Europe, while presence of predisposing variants of TCF7L2 gene polymorphism increased risk of DM type 2 development by 50% (OR~1.5) [30, 24]. Molecular mechanism of TCF7L2 gene participation in the pathogenesis of DM type 2 was that presence of T risk allele, TCF7L2 gene polymorphic marker rs7903146 decreased glucose-dependent

insulin secretion and also revealed alteration in proinsulin conversion to insulin [39, 49]. Recent researches showed that, carriers of T risk allele of TCF7L2 gene polymorphic markers rs7903146 without DM type 2 had higher HbA1c, decrease of the first stage in insulin secretion and concentration of gastrointestinal peptide in the process of oral glucose tolerant test compared to C allele carriers, confirming disorder in incretin response to glucose stimulation [39, 23]. Z.S. Akbarov et al showed that, presence of minor allele of rs7903146 polymorphism of TCF7L2 gene can be considered to be factor of diabetes mellitus type 2 development in Uzbek nation [2].

Significant break in the study of genetic predisposition to DM and its complications was made due to complete genomic studies and active implementation of Genome-Wide Association Studies – GWAS [6]. The first GWAS- test on DM type 2 was performed in France and included 661 patients and 614 people in the control group. The study revealed a link between several single-nucleotide polymorphic markers and DM type 2, by these means identifying the genes associated with the disease: SLC30A8, HHEX, LOC387761, EXT2. Besides that, association of DM with TCF7L2 gene identified earlier was confirmed [51]. After some time associations of DM type 2 with SLC30A8, HHEX genes were confirmed and a new gene CDKAL1 was identified [52]. Diabetes Genetics Replication and Meta-analysis (DIAGRAM) consortium contributed to the identification of five new loci: JAZF1, CDC123/CAMK1D, TSPAN/LGR5, THADA, ADAMSTS9 [35]. The role of many other isolated genes was also established in the pathogenesis of the disease. Particularly, TCF7L2 and HHEX genes are transcription factors regulating activity of other genes [38]. In earlier clinical studies it was showed that baby's low body mass at birth was a risk factor of DM type 2 development. Results of Helsinki Birth Cohort Study suggested the presence of association of HHEX-IDE, CDKN2A/2B and JAZF1 genes with baby's low weight at birth [45].

Undoubtedly, there is question about possibility of application of the results obtained in GWAS for the estimation of DM type 2 development risk and its prevention. Bright example of the possible application of genetic testing for prognosis of DM type development is result of Diabetes Prevention Program (DPP). It was reliably proven that, people possessing allele variant TT of TCF7L2 gene polymorphic marker rs7903146 had higher risk of transfer from glucose tolerance disorder stage to DM type 2, than carriers of allele variant CC (HR-1.55 95% CI 1.20–2.01, P<0.001). Effect of genotype influence was more expressed in the group receiving placebo, than in groups with modification of lifestyle or receiving metformin. TT genotype was associated with decrease in insulin secretion, but not with the values of insulin resistance. Similar results were obtained for rs12255372 marker of TCF7L2 gene [25].

Importance of the study of individual genetic predisposition to the development of DM type 2 is confirmed by the results of two large complementary studies. The first study showed existence of obvious dependence of DM type 2 development risk on the fasting glucose level. From 1st January 1997 till 31st November 2000 a cohort of 46 578 patients, who had plasma fasting glucose below 5.55 mmol/L was formed. That group of people was followed up to 30th April, 2007. All cases of death and DM development were registered. After the end of observation all 46 578 included in the observation were divided to four categories dependently on their primary plasma fasting glucose (PFG), and particularly <4.7 mmol/L, 4.7–4.94mmol/L, 5–5.2 mmol/L, and 5.3–5.5 mmol/L. For the time of observation there were 1854 cases of first time revealed DM type 2. Mean time of disease development was 54.6 months from the start of observation. Later using Cox regression analysis DM development risk was estimated in the studied groups taking into account age, gender, body mass index (BMI), arterial pressure, blood lipids, smocking, and cardiovascular pathologies. It was determined that, independently of aforesaid common known clinical risk factors, PFG served to be an independent risk factor of DM type 2 development, and every next higher level of PFG increased diabetes risk by 6% ( HR 1.06 (95% CI, 05–1.07, P<0.0001)). It was determined that, in the group of patients with PFG<4.7 mmol/L DM type development risk was equal to 3.1/1000 (95% CI 2.6–3.1), while among the patients with PFG 5.3–5.5 mmol/L the risk was equal to 9.9/1000 (95% CI, 9.3–10.0), in other words, between the mentioned groups relative risk increased almost 3 folds, and all these occurred with PFG alterations in the normal range [42].

Second large research studied the influence of individual genotype on fasting glucose level in healthy children and adolescents. Clinical-genetic investigation revealed the presence of reliable association between polymorphism of ADCY5 (rs11708067), CRY2 (rs11605924), GLIS3 (rs7034200), PROX1 (rs340874), SLC2A2 (rs1920090), G6PC2 (rs560887), MTNR1B (rs10830963), SLC30A8 (rs1326624), GCK (rs4607517) genes and fasting glucose level. Totally there were 16 SNP isolated.

In comparison of children and adolescents with low and high genetic risk the difference in PFG was 0.25mmol/L (95% CI, 0.15–0.35). Analysis of weighted risks showed increase in fasting glucose level by 0.026 mmol/L (0.021–0.031) for each negative allele of the indicated genes. The influence of these markers on fasting glucose did not depend on age. Meta-analysis of six studies performed in Europe with participation of 6000 boys and girls aged 9–16 years old showed that, new loci associated with adult PFG in GWAS were also associated with PFG in healthy children and adolescents. Taking into account the results of that study demonstrating interrelation of DM development risk with PFG, the influence f these loci on the DM type 2 development risk becomes obvious. Children and adolescents possessing alleles of G6PC2, MTNR1B, GCK, and GLIS3 genes, associated with PFG increase also had decrease in β-cells function assessed with the help of HOMA-model [17].

Researches dedicated to the probability of DM type development prognosis based on the estimation of genetic risk have been performed for almost 10 years. Some of these researches, like Framingham Offspring Study, Malmö Preventive Project, and Botnia Study [41, 40] did not demonstrate any advantage in prognosis of disease development with estimation of genetic risk, though the analysis included from 11 to 20locuses associated with DM type 2. At the same time there a guess that estimation of genetic risk of disease development, genetic testing can be more useful in young people prior to development of phenotypic features being risk factors of DM type 2. Repeated analysis of Framingham Offspring Study recently performed by de Miguel-Yanes with colleagues showed that estimation of genetic risk of DM development was more significant for people under 50, and contribution of 40 loci associated with DM was assessed [21].

Till the modern time there more than 100 loci identified with predisposition to DM type 2, and most of them with the help of GWAS [56, 48, 26, 47]. It should be noted that, majority of perspective studies in the area of personalized medicine will be based on the data of postgenomic technologies such as proteomics, transcriptomics, metabolomics. A separate branch in individual genomic studies is epigenomics letting us study DNA methylation on cytosine under the influence of DNA-methyl transferase [5]. There is hypomethylation of DNA in oncogenes of some tumors together with hypermethylation of suppressor genes [15]. Changes in methylation of DNA were observed also in case of DM type 2, cardiovascular and autoimmune diseases [22, 19]. Application of genomic technologies can lead to increase of prognosis cost, but it does not commensurate with expenses linked with severe complication of diabetes, such as blindness, renal failure, amputations, and cardiovascular catastrophes.

Assessment of the values of certain polymorphic marker in the disease development requires detection of dominance of negative (causing pathology) genotype over protective one, in other words the genotype the presence of which is the reason of certain pathology absence. Recently there appeared works demonstrating that application of ACE inhibitors in non-diabetic patients caused decrease in DM type 2 development risk [11]. D.F.Geng et al performed a meta-analysis, which showed that, therapy with ACE – I decreases the risk of diabetes mellitus type 2 development. The meta-analysis included 9 randomized controlled studies in 92404 patients 72128 of them originally had no diabetes mellitus. ACE-I therapy reliably decreased the risk of diabetes mellitus development by 20% compared to the control independently of AP decrease. With ACVE-I therapy the risk of diabetes mellitus development reliably decreased compared to beta-blockers/diuretics application by 22%, to placebo application by 21%, and Calcium antagonists by 15%. Risk decrease was noted in patients with arterial hypertension, coronary heart disease, and cardiac failure. In patients with glucose tolerance disorders Ramipril reliably decreased DM morbidity rate. Results of meta-analysis confirm efficacy of ACE-I in the prevention of diabetes mellitus [66]. It is known that ACE-I inhibit the action of angiotensin-converting enzyme (ACE), which is one of the most important components of rennin-angiotensin system (RAS) converting angiotensin I to angiotensin II and being vasoconstrictor. Amount of ACE in blood is expressed by ACE gene located in the 16 introne of 17 chromosome (17q 23). That gene is characterized by insertion-deletion (I/D) polymorphism. ACE gene polymorphism marker is considered to be a fragment with 300 nucleotide pairs (np)length, which is absent or additional in that gene. Insertion (I) has 490 np, deletion (D) 190np. On the basis of I and D alleles distribution we can distinguish three genetic variants of polymorphism: homozygous II, DD, and heterozygous ID. I/D polymorphism is not structural, but seemingly it effects expression degree of the gene. That is confirmed by several studies where it was shown that, healthy people with DD genotype had maximal blood ACE, people with II genotype had two times less blood ACE, and heterozygous ones had intermediate blood level of the enzyme. Besides that, there are differences in ACE activity in various

genotypes of that gene. ACE activity is highest in people homozygous in D allele (DD genotype), the lowest in those, who are homozygous in I allele (II genotype), and it is intermediate in heterozygous subjects (ID genotype) [5]. In some populations ACE gene demonstrated its importance in the development of DM type 2 [43, 18, 12, 13]; at the same time in other populations that kind of association was not revealed [16]. G.E. Roitberg et al revealed expressed prevailing of IR syndrome with a complete set of components in DD genotypic group, confirming significant strong association between ACE gene polymorphism and IR syndrome development [10]. Back in 2002 M.I. Balabolkin et al reported that in groups of patients where ACE therapy was effective prevailing genotypes were ID and DD, while in the group of patients, where ACE therapy was not so effective there was high prevalence of II genotype [5]. G.J. Abdullayeva reported that, Uzbek men suffering EH had higher prevalence of I/D genotype different from healthy subjects of that category [1].

It is known, that gene of endothelial NO-synthetase (eNOS) participates in NO synthesis, and, consequently, in the regulation of vascular tension, blood flow rate, and arterial pressure. NO is also important in the pathogenesis of IHD, as it suppresses proliferation of smooth muscle cells; it has protective effect in relation to platelet aggregation and inhibits leukocytes adhesion to endothelium. According to classic endothelial dysfunction theory suppression or decrease of eNOS activity leads to NO deficit, where response to lesion plays a key role in the initiation of atherogenesis and development of atherothrombosis [33]. Gene of eNOS is located in the 7 chromosome; in its exones and introns there are several polymorphic areas, among which the most well studied is polymorphic marker in the intron of the 4 gene of eNOS (4a/4b-polymorphism) [8]. I.A. Karimova studied 4a/4b polymorphism of eNOS gene in male Uzbek patients with essential hypertension. She reported significant accumulation of 4b allele and 4b/4b- genotype 4a/4b-polymorphic marker of eNOS gene in patients with essential hypertension and healthy Uzbek men [9].

CRP gene (C-reactive protein, pentraxin-related) codes C-reactive protein and located on chromosome 1 (1q21-q23). C-reactive protein is a basic protein of inflammatory acute phase present in plasma. AIRGENE study assessed the impact of 7 SNP on the concentration of C-reactive protein. It was found that, minor allele 3872T of C3872T polymorphism was strongly associated with decrease in C-reactive protein level by these means diminishing the risk of lethal outcome of cardiovascular diseases [37]. On the basis of GOLDN study CRP gene polymorphism association with basic plasma CRP was studied in a group of 1123 Caucasian Americans with metabolic syndrome. The correlation of polymorphism with response to 3-week fenofibrates therapy was also studied. C3872T polymorphism has no influence on therapeutic effect, but a strong C>T ($P<0.001$) association with basic CRP was revealed [50]. In Mexicans CRP gene showed a strong association with the development of DM type 2 [27].

Thus, on the basis of the literature review, it can be concluded that, clarification of polymorphic markers importance in DM type 2 can promote creation of genetic passport of a patient, and consequently, development of personalized medicine. Studies of 4a/4b polymorphism of eNOS gene and -757T/C polymorphisms of CRP gene in Uzbek population did not reveal their value in the development of DM type 2, different from rs4341 I/D polymorphism of ACE gene, DD genotype of which was considered to be genetic risk factor of DM type 2 development in Uzbek people [53], and that can be taken into account in the prognosis of DM type 2 in that category of subjects living in Uzbekistan territory.

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# PROGNOSTIC SIGNIFICANCE OF RISK FACTORS IN THE DEVELOPMENT OF THYROTOXICOSIS

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**Summary**
**Thyrotoxicosis development risk factors and their prognostic significance during conservative treatment of Graves' disease**

**Ubaydullaeva N.B., Allayarova G.I., Almuradov F.F.**

The most significant risk factors for the development of thyrotoxicosis recurrence in conservative treatment with a high indicator of relative risk and etiological proportion were: age over 30 years (RR = 6,24; EF = 83,97%), patient compliance (RR = 5,71; EF = 82,49%) and thyroid volume ≥30 cm3 (RR = 5.33; EF = 81.24%). It was also found that age over 30 years (AUC - 0.85), patient compliance (AUC - 0.83) and thyroid volume ≥30 см3 (AUC - 0.82) have excellent prognostic strength.

**Резюме**
**Факторы риска развития тиреотоксикоза и их прогностическая значимость при консервативном лечении болезни Грейвса**

Убайдуллаева Н.Б., Аллаярова Г.И., Алмурадов Ф.Ф.

Наиболее значимыми факторами риска развития рецидива тиреотоксикоза при консервативном лечении с высоким показателем относительного риска и этиологической доли оказались: возраст старше 30 лет (RR=6,24; EF=83,97%), комплаентность больного (RR=5,71; EF=82,49%) и объем ЩЖ ≥30 см3 (RR=5,33; EF=81,24%). Также установлено, что возраст старше 30 лет (величина AUC – 0,85), комплаентность больного (величина AUC – 0,83) и объем ЩЖ ≥30 см3 (величина AUC – 0,82) обладают отличной прогностической силой.

**Хулоса**
**Грейвс касаллигини консерватив даволашдан сўнг тиреотоксикознинг қайталанишига сабаб бўлувчи хавф омилларини баҳолаш прогностик аҳамияти**

**Убайдуллаева Н.Б., Аллаярова Г.И., Алмурадов Ф.Ф.**

Консерватив даволашдан дан сўнг тиротоксикознинг қайталаниш хавфи юқори бўлган ва этиологик нисбати юқори бўлган хавф омиллари қуйидагилардан иборат: бемор ёши 30 ёшдан ортганлиги (RR=6,24; EF=83,97%), беморниг комплаентлиги (RR=5,71; EF=82,49%) ва қалқонсимон без ҳажми ≥30 см3 (RR=5,33; EF=81,24%). Бундан келиб чиқиб бемор ёши 30 ёшдан ортганлиги (AUC кўрсаткичи – 0.85), беморниг комплаентлиги (AUC кўрсаткичи – 0.83) ва қалқонсимон без ҳажми ≥30 см3 (AUC кўрсаткичи – 0.82), мукаммал предиктив кучга эга эканлиги аниқланди.

Thyrotoxicosis is a clinical syndrome caused by the negative effect of a persistent excess of thyroid hormones on the body. Graves' disease (GD), multinodular toxic goiter, and the hyperthyroid phase of chronic autoimmune thyroiditis are the most common causes of thyrotoxicosis, which requires differential diagnosis. Graves' disease is a systemic autoimmune disease that characterized by a persistent increase in the production of thyroid hormones (thyroid gland), which develops because of the production of antibodies to the thyroid stimulating hormone receptor (TSHR-Abs). The clinical picture might limit by manifestations of thyrotoxicosis syn-drome, or be combined with extra-thyroid

pathology, with skin and eye damage [2; 3; 6; 7].

The prevalence of the GD in the general population reaches 2-5% depending on the region, and the annual incidence is 5-7 people per 100,000 populations. GD is more common in women than in men (from 7: 1 to 10: 1), aged 30 to 50 years. The syndrome of persistent thyrotoxicosis in 75-80% of cases is associated with GD [1].

Despite certain successes, on achieved results in the diagnosis and development of complications, there were no clear prognostic criteria for euthyroid state achievement, which can lead to a thyrotoxicosis developing risk decrease, thus prompts researchers to search for ways to predict and prevent thyrotoxicosis.

The high social significance of GD is due to its mainly occurs in people of working age [5; 9; 10]. Due to mass prophylaxis in the regions of iodine deficiency, clinical course of the GD has also changed. Noted acceleration in the manifestation of GD in susceptible individuals, a higher decrease in the number of patients with thyrotoxicosis remission and its duration against the background of conservative therapy [9; 10]. A feature of thyrotoxicosis against the background of GD is a rapidly growing clinical picture and, mainly, the young age of patients. This determines the medical and social significance of this disease. With the ineffectiveness of drug therapy, or with a relapse of GD, indicated radical treatment – surgical or radionuclide.

The relevance of this study lies in the fact that the recently observed significant increase of GD in Uzbekistan is one of the main reasons for the disability increase, and the decrease in the quality of life of patients in this category. The implementation of this grant will contribute to improving GD diagnostics with the use of high-tech methods and pathogenetically sound comprehensive treatment of GD, which will lead to life expectancy increase, disability reduction, and quality of life improvement.

**Objective:** to identify GD recurrence risk factors in women who received conservative therapy.

Materials and methods.

To analyze the results of the questionnaire and assess the thyrotoxicosis recurrence risk factors was performed retrospective and prospective analysis of clinical and medical history indicators of 65 women at reproductive age who received conservative treatment.

The studied patient's average age was 32.8 ± 8.4 years. The control group included 35 healthy women aged 33.5 ± 7.6 years. Each woman filled out a pre-designed questionnaire beforehand.

Thyroid stimulating hormone (TSH), free triiodothyonine (FT3) and free thyroxine (FT4) and anti-thyroperoxidase antibodies (AbTPO) levels determined by the immunochemiluminescent method in the RSSPMC of Endocrinology of the Ministry of Health of the Republic of Uzbekistan.

Predictive efficacy (AUC classifier) was determined with the use of standard formula: AUC = (Se + Sp) / 2; where Se (sensitivity) and Sp (specificity).

Statistical analysis of the obtained data: statistical processing of the results carried out using the computer program Microsoft Excel using the methods of variation statistics and using Student's t-test. Differences between groups were considered statistically significant at $P < 0.05$.

**Results and discussion**

In accordance with the objectives, on the complex and comprehensive prospective basis and retrospective study of patients with GD, were determined prognostic factors for the outcome of the disease and evaluated their role in the thyrotoxicosis recurrence development.

To determine the most diagnostically significant risk factors, was carried out an integral assessment of the risk factors of thyrotoxicosis using the method of normalizing intensive indicators of E.N. Shigan [8], based on the Bayesian probabilistic method.

Data analysis showed that the risk range for the thyrotoxicosis recurrence development is in the range of 29.55-117.45.

This range accepted as 100%. After dividing the scale into three equal intervals and named intervals as following: weak (29.55-58.85 - favorable forecast, risk values within 30%); moderate - (58.85–88.15 - required careful monitoring, risk values within 30–59%); high - (88.15-117.45 - unfavorable prognosis, the probability of thyrotoxicosis relapse developing from 60% to 100%).

Subsequently, taking into account the data of the prognostic table by the value of the relative risk (OP - RR) (Table 1.), we determined the ranking position of each factor and calculated its etiological fraction (EF) [4].

An analysis of the data found that the most significant risk factors for the thyrotoxicosis recurrence development with a high relative risk and etiological fraction were (almost complete conditionality) age over 30 years (RR = 6.24; EF = 83.97%), patient compliance ( RR = 5.71; EF = 82.49%) and

thyroid volume (TG volume) ≥30 cm3 (RR = 5.33; EF = 81.24%).

**Table 1.**

The distribution of risk factors by degree of significance for the thyrotoxicosis recurrence development and the degree of condition of the disease in women, depending on the relative risk, etiological fraction and the corresponding risk factors

| Risk factors | RR | EF, % | Rank | Conditionality degree | RR | EF, % |
|---|---|---|---|---|---|---|
| Age over 30 | 6,24 | 83,97 | 1 | almost complete | 5,0 < - | 81 - 100 |
| Patient compliance | 5,71 | 82,49 | 2 | | | |
| TG volume ≥ 30 $cm^3$ | 5,33 | 81,24 | 3 | | | |
| Disease debut ≥ 2 years | 5,03 | 80,12 | 4 | Very high | 3,2 - ≤5,0 | 67 - 80 |
| Treatment duration ≥ 2 years | 4,42 | 77,38 | 5 | | | |
| TSH <0,17 mIU / L | 4,22 | 76,32 | 6 | | | |
| FT3 > 5,8 pmol / L | 3,51 | 71,51 | 7 | | | |
| FT4 > 23 pmol / L | 3,19 | 68,65 | 8 | | | |
| GD heredity | 3,11 | 67,85 | 9 | | | |
| Stress | 2,97 | 66,33 | 10 | high | 2 - ≤3,2 | 51 - 66 |
| AbTPO ≥12 IU/ml | 1,99 | 49,75 | 11 | Average | 1,5 - ≤2,0 | 33 - 50 |
| Labors ≥ 5 | 1,87 | 46,52 | 12 | | | |
| Endocrine ophthalmopathy | 1,83 | 45,36 | 13 | | | |

In to the very high disease conditionality category entered: disease debut ≥2 years (RR=5,03; % EF=80,12), treatment duration ≥2 years (RR=4,42; EF = 77,38%), TSH level < 0,17 mIU / L (RR = 4,22; EF = 76,32%), FT3 level > 5,8 pmol / L (RR = 3,51; EF = 71,51%), FT4 level > 23 pmol / L (RR = 3,19; EF = 68,65%) and GD heredity (RR = 3,11; EF=67,85%).

Stress factor (RR = 2,97; EF = 66,33%) has a high degree of conditionality for the recurrent thyrotoxicosis development.

The average degree gradation of the thyrotoxicosis recurrence development conditionality was: AbTPO level ≥ 12 IU/ml (RR=1,99; % EF=49,75), labors ≥ 5 (RR=1,87; EF = 46,52%) and endocrine ophthalmopathy (RR = 1,83; EF=45,36%).

By multi-factor analysis, we assessed the prognostic probability of each factor in the thyrotoxicosis recurrence development.

In order to evaluate the quality of a prognostic model of the thyrotoxicosis recurrence we calculated all risk factors parameters of the AUC (Table 2.).

**Table 2.**

Risk factors associated with the development of recurrent thyrotoxicosis and their prognostic significance

| Prognostic factor | AUC |
|---|---|
| Age over 30 | 0,85 |
| Patient compliance | 0,83 |
| TG volume ≥ 30 $cm^3$ | 0,82 |
| Disease debut ≥ 2 years | 0,75 |
| Treatment duration ≥ 2 years | 0,79 |
| TSH < 0,17 mIU / L | 0,75 |
| FT3 > 5,8 pmol / L | 0,74 |
| FT4 > 23 pmol / L | 0,72 |

| | |
|---|---|
| GD heredity | 0,72 |
| Stress | 0,70 |
| AbTPO ≥ 12 IU/ml | 0,67 |
| Labors ≥ 5 | 0,64 |
| Endocrine ophthalmopathy | 0,62 |
| Total indicator | 0,73 |

Moreover, the aggregate prognostic value of risk factors is defined as "good" (AUC value – 0,73).

Then we evaluated the diagnostic efficacy of each factor.

As a result of the analysis, it is established that the age over 30 (AUC - 0,85), patient compliance ( AUC - 0,83) and TG volume ≥ 30 cm3 ( AUC - 0,82) have excellent predictive force. To the category «good» predictive importance enters such factors: treatment duration ≥ 2 years (AUC - 0,79), disease debut ≥ 2 years (AUC - 0,75), TSH level < 0,17 mIU / L (AUC - 0,75), FT3 level > 5,8 pmol / L (AUC - 0,74), FT4 > 23 pmol / L (AUC - 0,74), GD heredity (AUC - 0,72) and stress (AUC - 0,72).

The main problem of conservative treatment of diffuse toxic goiter is the high recurrence rate after discontinuation of treatment and the objective difficulties in predicting them. In the United States, remission rates after 1-2 years of thionamide therapy range from 13 to 80%. There is information on the relapses occurrence after treatment with thyroostatics in 53-54% of patients (period of observation after the end of treatment - 1 year). In five years of observation, 60-67% of cases are reported of thyrotoxicosis recurrence. The lowest recurrence rates for long-term observation are 35%. According to some data, one year after reaching euthyroidism by thyroostatics, 40-50% of patients develop long-term disease remission, which on 30-40% of patients persists for 10 years or more.

Currently, there are three main methods of treatment of diffuse toxic goiter. This is a conservative treatment, surgery, and treatment with radioactive iodine. Since none of these methods is not pathogenic, the attitudes towards them endocrinologists in different countries are not the same. This is largely because none of the treatments does not guarantee a potentially ideal outcome - saving euthyroid status.

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Thus, the most statistically significant factors of thyrotoxicosis relapse in women with GD were determined with conservative treatment. Among the factors associated with the development of a thyrotoxicosis relapse, the most prognostically significant, having almost complete, very high and high conditionality, age over 30 years, patient compliance, thyroid volume ≥ 30 cm3, also disease onset ≥ 2 years, treatment duration ≥2 years, TSH level <0.17 mIU / L.

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**Хулоса**

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УДК:577.164.16:616.462

# PHYSIOLOGY OF VITAMIN B12 AND ITS STATUS IN TYPE 2 DIABETES

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**Резюме**
**Физиология витамина B12 и его статус при диабете 2 типа**

**Ф.А.Хайдарова, А.В.Алиева, К.Ш.Кенджаева**

В статье приведен краткий обзор литературы по физиологической роли витамина B12 и его обмене в норме, а также его статус при терапии метформином пациентов с диабетом 2 типа.
**Ключевые слова:** витамин B12, диабет 2 типа, метформин

**Хулоса**
**Витамин B12 физиологияси ва 2-тур диабетда унинг статуси**

**Ф.А.Хайдарова, А.В.Алиева, К.Ш.Кенджаева**

Маколада нормада витамин B12 физиологик роли ва унинг алмашинуви, хамда 2-тур диабет метформин кабул киладиган беморларда унинг статуси буйича киска адабиёт шахри келтирилган.
**Калит сузлар:** витамин B12, 2-тур диабет, метформин

**Summary**
**Physiology of vitamin B12 and its status in type 2 diabetes**

**F.A.Khaydarova, A.V.Alieva and K.Sh.Kenjaeva**

In this article, brief review of physiological role and normal metabolism of vitamin B12, and its status in patients with type 2 diabetes taking Metformin is provided.
**Key words:** vitamin B12, type 2 diabetes, Metformin

Vitamin B12, or Cobalamin, or external Castle's factor, is a water-soluble vitamin essential for DNA synthesis, hematopoiesis, and the normal functioning of the nervous system.

**Physiology of Vitamin B12 Metabolism**

The only source of Vitamin B12 is a food of animal origin, and the amount of the vitamin consumed daily is about 5-15 (sometimes up to 50) μg [34]. Under the action of gastric pepsin, vitamin B12 is released from binding to animal proteins and combines with the R-protein of saliva, which protects vitamin B12 from destruction in the acidic environment of the stomach.

In the alkaline environment of the duodenum, pancreatic proteases break down the bond of vitamin B12 with the R-protein, after which the cobalamin binds to the intrinsic Castle's factor, released by the parietal cells of the fundus of the stomach in response to food intake. In this complex, which provides resistance to the action of proteolytic enzymes and protects against absorption of vitamin B12 by intestinal bacteria, cobalamin reaches the distal ileum, where it is absorbed. In the cytoplasm of enterocytes, the connection between Castle's external and internal factors is lost, the latter is destroyed, and the cobalamin enters the portal system binded with the transport protein transcobalamin II, and partially with alpha and beta globulins. In this form, vitamin B12 enters the liver, where up to 90% is deposited [17], and into the bone marrow, where it is included in the hematopoiesis process. About 0.1% of liver cobalamin is excreted daily with bile, but of this amount, ¾ is reabsorbed in the ileum and only ¼ is excreted with the feces. Excess vitamin B12 is excreted in the urine.

The total content of vitamin B12 in the body is 2-5 mg, while about 2-5 micrograms per day is

consumed. Therefore, even if the intake with food is decreased, the liver depot of vitamin B12 is sufficient to provide the enzymatic reactions in which it is involved for 3-5 years.

**A bit of biochemistry.**

The vitamin B12 molecule consists of a cobalt atom surrounded by a tetrahydropyrrole ring, each element of which has a radical group: i.e. cyanocobalamin, hydroxycobalamin, methylcobalamine and deoxyadenosylcobalamin, or cobalamide. The first two compounds are stable, the latter are coenzymes of the two most important enzyme reactions:

1. In the isomerization reaction under the action of the methylmalonyl-CoA mutase enzyme, methylmalonic acid (an exchange product of fatty acids with an odd number of carbon atoms, as well as of some amino acids) turns into the succinic acid, which subsequently enters the Krebs' cycle.

2. The second enzyme, whose coenzyme is methylcobalamine, is 5-methyltetrahydrofolate (MTHF)-homocysteine-methyltransferase. With its participation a methyl group is attached to homocysteine and methionine is formed, which is subsequently used for the synthesis of adrenaline, creatine, carnitine, choline and phosphatidylcholine. And due to the transfer of the methyl group from MTHF to cobalamin, free folic acid is retained in the cell in an amount necessary for adequate synthesis of nucleic acids.

Thus, a lack of vitamin B12 will be biochemically accompanied by an increase in the level of methylmalonic acid and homocysteine, and a decrease in the level of methionine and folic acid [14].

**From physiology to pathophysiology**

Folic acid deficiency with a lack of vitamin B12 leads to a slowdown in cell division (due to a decrease in the synthesis of purine nucleotides and DNA), which disrupts the blood cells formation process with the development of megaloblastic anemia. The number of red blood cells decreases 3-4 times, but their size increases; erythrocytes also have a shorter lifespan and are more likely to undergo hemolysis. In addition to megalocytes, ovalocytes, hypersegmented leukocytes appear in the blood, and pancytopenia is observed [1].

An increase in toxic methylmalonate leads to the incorporation of fatty acids with an odd number of carbon atoms into the myelin sheath of neurons and leads to their fatty degeneration. A decrease in the level of methionine leads to a decrease in the synthesis of acetylcholine, as well as lecithin and sphingomyelin. An increase in homocysteine and homocysteine acid levels leads to the appearance of reactive oxygen species in the cytoplasm of neurons, which accelerates their apoptosis. As a result of the above processes, spotted demyelination of the gray matter of the brain, spinal cord and peripheral nerves develops, which is clinically manifested by funicular myelosis, distal paresthesias, increased tendon reflexes, and the appearance of ataxia [2].

It is believed that disorientation in space, hallucinations and memory impairment in vitamin B12 deficiency develops as a result of anemia and is not associated with the damage to the central nervous system.

Violation of cellular repair in vitamin B12 deficiency is clinically manifested by atrophic Hunter's glossitis ("varnished" tongue), stomatitis, malabsorption due to atrophy of the villi and inflammation of the intestinal mucosa [4].

Vitamin B12 deficiency can be caused by disorders at any stage of its absorption and metabolism, such as inadequate food intake, especially among alcohol abusers and vegetarians, malabsorption in chronic atrophic gastritis, mainly in the elderly, pernicious anemia, celiac disease, chronic pancreatitis and taking drugs such as metformin and proton pump inhibitors (PPIs).

In the standards for the treatment of type 2 diabetes mellitus, with a very rare exception, the first step in therapy is the administration of metformin, the drug continues to be administered while other groups of glucose-lowering drugs are added if the monotherapy is ineffective. Metformin is stopped if the GFR is below 30 ml/min/1.73 $m^2$ or is not prescribed de novo if the GFR is below 45 ml/min/1.73 $m^2$. From the standpoint of glucose-lowering therapy and cardiovascular and oncological safety, the use of metformin is fully justified and verified by many years of clinical practice. However, it is known that the long-term use of metformin is accompanied by the vitamin B12 deficiency [5; 24; 25] with the prevalence varying from 5.8 to 52%. Such a variety in the prevalence may be explained by the use of different criteria for vitamin B12 deficiency in various studies [8; 10; 15; 16; 21; 33].

The risk of vitamin B12 deficiency associated with metformin intake increases significantly with age [19; 32], increasing the dose of metformin and the duration of its use [26]. Chinese authors showed that increasing the dose of metformin for every 1 g/day increased the risk of vitamin B12 deficiency by 2.9 times (95% CI, 2.15-3.87) [18]. Similar results were obtained by Beulens JW and

co-authors [7]. Moreover, malabsorption of vitamin B12 begins after 4-6 months of metformin use, and clinically significant signs of this vitamin deficiency appear after 5-10 years (due to the liver depot of vitamin B12) [9].

The proposed mechanism for explaining metformin-induced vitamin B12 deficiency in patients with type 2 diabetes is the follows:

• impaired motility of the small intestine, which stimulates the excessive growth of conditionally pathogenic bacterial flora and subsequently leads to vitamin B12 deficiency;

• competitive suppression or inactivation of vitamin B12 absorption;

• a change in the level of Castle's internal factor (IFC) and interaction with the enterocytes cubulin receptors;

• suppression of calcium-dependent absorption of the vitamin B12-IFC complex in the terminal ileum. This overwhelming effect is offset by the use of calcium supplements;

• increased deposition in red blood cells and liver [36].

Hematologic and neuro-cognitive impairments with vitamin B12 deficiency [17] worsen the clinical manifestations of diabetic polyneuropathy and encephalopathy. A number of authors consider vitamin B12 deficiency in patients with diabetes as a risk factor for the development of diabetic neuropathy [6; 35; 18; 23].

In addition, there is an increased risk of cardiovascular complications associated with an increase in homocysteine levels on the background of a decrease of vitamin B12 level [10].

Despite the high prevalence and potential severity of B12 deficient conditions, there are still no common international recommendations regarding the methods of diagnosis and treatment, as well as screening for vitamin B12 deficiency in patients with diabetes. A number of researchers consider it clinically justified to assess vitamin B12 levels before starting metformin therapy and subsequently annually in elderly patients taking metformin for a long time (≥3-4 years), in high doses (≥2 g/day), and also in patients with clinical deterioration of distal diabetic polyneuropathy in the presence or absence of hematological disorders [11; 22; 34]

The approach to screening for vitamin B12 deficiency in patients with diabetes is the same as in the general population. At the initial stage, the serum level of vitamin B12 is determined. A concentration of <200 pg / ml is usually diagnostic for vitamin B12 deficiency; a level of >400 pg/ml confirms the absence of vitamin B12 deficiency. Measuring of serum level of homocysteine and methylmalonic acid (MMA) is a more sensitive and specific screening approach, especially for patients with type 2 diabetes with borderline values of vitamin B12 ranging from 200 to 400 pg/dl and having mild hematological symptoms. The normal levels of homocysteine and MMA in the blood serum are 5-15 μmol/L and <0.28 μmol/L, respectively [12; 13; 34].

Treatment for vitamin B12 deficiency does not depend on its etiology. All vitamin B12 deficient patients should receive oral or parenteral replacement therapy. Both routes of administration lead to comparable desired hematological and neurological improvements, regardless of the etiology of the deficiency. Andres E. et al. consider that intramuscular administration or oral administration of vitamin B12 at a dose of 1000 μg/day for a week, then 1 time per week for 4 weeks is enough to correct vitamin B12 deficiency in adult patients with type 2 diabetes [3].

Mahajan R. et al. in their study concluded that doses of vitamin B12 of 1000 μg annually would be sufficient to replenish vitamin B12 in its clinically manifested deficiency, especially in adult patients with type 2 diabetes who have been taking metformin for a long time [20; 27-31].

Thus, clinical and biochemical deficiency of vitamin B12 is widespread among patients with type 2 diabetes. However, there are no clear recommendations for screening for vitamin B12 deficiency, the multiplicity and dose of its supplementation in this category of patients. In patients with symptoms of polyneuropathy on the background of glycemia close to the target values, the active search for vitamin B12 deficiency is necessary.

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Туракулов Ялкин Халматович (1916-2005г.). Советский, узбекский ученый-биохимик и эндокринолог. Доктор биологических наук. Заслуженный деятель науки. Профессор. Академик АН УзССР, Лауреат Ленинской премии. Участник Великой Отечественной войны.

Ялкин Холматовича Туракулова с полным основанием можно отнести к жизни тех замечательных людей, которые способствовали прогрессу человеческого общества. Его открытия и творения, создавшие ему мировое признание, связаны с той областью медицины, которая основана на работе внутреннего механизма человеческого организма, регулируемого щитовидной железой и обеспечивающего рост, формирование организма, развитие мозга и стимулирующего обмен веществ и влияющие на все процессы, происходящие в клетках и тканях. Он впервые обратил внимание на то, что вся эта работа связана с химическими и биологическими явлениями и развитие новой науки в Узбекистане, называемой биохимией, целиком относится к его заслугам. Благодаря его работам в Центральной Азии были ликвидированы такие заболевания как малярия, зоб и многие желудочно-кишечные заболевания, которые во многих частях мира до сих пор являются бичом здоровья населения. Он внес великий вклад в здоровье нации.

Его звали Ялкин, означающее «пламенный», но это был псевдоним, его настоящее имя было Абдулазиз, так его звали родственники, но псевдоним более подходил к его личности, характеру и образу. В его душе горел неугасимый огонь творчества и созидания, который не угасал до его последнего дыхания. Это сделало его жизнь яркой и пламенной, творческой и созидательной. Он был представителем и частью того великого поколения узбекских ученых и деятелей культуры, которое было обязано своим рождением и формированием Советскому государству. В СССР в двадцатые и тридцатые годы была создана самая передовая система образования, которая позволила за десять лет ликвидировать безграмотность в республиках Центральной Азии. Законодательно было утверждено обязательное среднее образование. Были созданы многочисленные училища, школы ликбеза, интернаты и детские дома, куда подбирали бездомных сирот, обучали их и превращали в пролетарскую интеллигенцию.

Неграмотность является величайшей трагедией азиатских и африканских народов. Не может быть независимым и свободным народ, не умеющий читать и писать, не может быть обеспеченным народ, не научившийся владеть техникой и современными средствами коммуникаций. Неграмотность тормозит менталитет нации и развитие её самосознания. Грамотность является основным показателем качества жизни народа. Ликвидация неграмотности в Узбекистане создала в республике неисчерпаемый потенциал материального и духовного развития.

Я. Туракулов был одним из самых ярких плодов этой системы. Его индивидуальный талант, личные человеческие качества нашли в ней благодатную почву и раскрылись во всей своей мощи. Естественности и возвышенности. Он был и останется одной из самых ярких звезд нашего духовного наследия.

Он родился 10 ноября в 1917 года в просвещенной и высокообразованной семье в городе Мерке, расположенном на полпути от Ташкента до Бишкека. Начальное образование он получил в Ташкенте в Трудовой опытно-показательной школе им. Карла Либкнехта, открытой в 1918г.

под попечительством супруги В. Ленина Н.К. Крупской. Во главе её стоял выдающийся русский педагог В. Ф. Лубенцов. В школе труд сочетался с учебой, вместе с изучением правописания и математики ученики занимались выведением кроликов, выращиванием пшеницы, выведением тутового шелкопряда. В школе он познакомился с книгами на русском и узбекском языках, которые раскрыли ему волшебный мир науки и культуры. Они сыграли главную роль в формировании характера юного Ялкина. Его впечатлительная натура жадно впитывала книги, которые были совсем далеки от его возраста.

Свое образование Я. Туракулов продолжил в Намангане в школе второй ступени (после пятого класса). В 1931г. 14 летний Ялкин был принят на подготовительное отделение Ташкентского медицинского института, а в следующем году он становится студентом института. Учение давалось тяжело, тяжелы были и материальные условия жизни того периода. В 1936г. из 65 поступивших вместе с ним закончили институт только пятеро. Среди них был и Я. Туракулов. Молодежь росла быстро, ей предоставили все возможности для овладения науками. Его оставили на кафедре биохимии, на которой он начал преподавание курса химии, органической химии и биохимии. В 1939г. его судьба круто меняется. 22-летнего Я. Туракулова назначают директором, созданного в том же году Ташкентского фармацевтического института. Но проработал он в этой должности недолго. Грянула война – великая, отечественная и Я. Туракулов ушел на фронт воевать. 24-летнего майора медицинской службы Я. Туракулова назначают командиром медико-санитарного батальона первой гвардейской воздушно-десантной дивизии. О победах все знали из газет, а как она добывалась знают только военврачи, которые ежедневно видели сотни искалеченных молодых людей, некоторые умирали у них на руках, некоторым ампутировали руки, ноги, некоторых увозили в тыл без двух ног или лишившимися зрения. Многих возвращали к жизни на операционном столе. Самыми любимыми словами юного комбата становятся:” Будет жить”. Он боролся за жизнь тяжело раненых в операционной, размещенной в обыкновенной армейской палатке, метаясь между операционной и противошоковой палаткой, где проводились реанимационные мероприятия по выведению из шокового состояния тяжело раненых. За боевые заслуги Я. Туракулов был награжден орденами Красной Звезды, Отечественной войны и медалями


Работать приходилось под гром артиллерийской канонады и пулеметным обстрелом вражеской авиации. При этом был достигнут высокий процент возвращения в строй раненых (72.3%) и больных (90.6%). Это было большим достижением гвардии майора Ялкина Туракулова. 9 мая, день победы был для него праздником особенным, самым любимым. Он гордился, что в этой победе есть и частица его жизни, его боевой славы. Осенью 1943г., когда танки повернули на запад, и вся армия пошла в наступление, двинулся за ней и медико-санитарный батальон майора Я. Туракулова. Не суждено было ему с родной дивизией дойти до Берлина. Его машина подорвалась на мине, он был тяжело ранен и отправлен в госпиталь. Лечился он в Харькове и Пензе и видимо один бог знает, как выживали подорвавшиеся на мине. Вернулся в Ташкент лишь в апреле 1944г. Никто из родственников и друзей не знал о его прибытии. Он вышел на перрон ташкентского вокзала на костылях и с армейским вещмешком за плечами. Так пешком он дошел до ближайшего из родственников.

После продолжительного лечения он вновь был назначен на должность директора фармацевтического института. Круг первый замкнулся со счастливым окончанием. Начинался новый этап жизни, который по извилистыми и подчас трудными тропами вел к всемирной славе.

В конце 1945г. решением правительства Узбекистана 50 молодых ученых были командированы в Москву для подготовки докторских диссертаций. Надо было укреплять созданную в 1943г. Академию наук молодыми талантливыми кадрами. Все из них оправдали надежды и впоследствии стали ведущими учеными, академиками и составили основу будущего могучего потенциала узбекской науки, которой предстояло возродить великие традиции

академии Мамуна и гениальных предков – Авиценны, Беруни, Фараби, аль-Хоразми. Это был цвет растущей научной молодежи. Они стали гордостью нации, их работы нашли мировое признание.

Я. Туракулов был самым молодым из них, но за его плечами был фронт, где один день считается за год мирной жизни. Он был назначен старостой группы. В Москве его определили в Институт биологической и медицинской химии Академии медицинских наук(АМН) СССР в лаборатории углеводов под руководством выдающегося ученого с мировым именем академика Я. О. Парнаса, ставшего для него одновременно духовным отцом, научным руководителем и наставником. Школа Я. Парнаса определила всю дальнейшую научную деятельность Я. Туракулова. Он избрал биохимию и эндокринологии.

Он не смог завершить свою докторскую диссертацию. В 1947г. его отзывают в Ташкент и назначают ректором Ташкентского медицинского института(ТашМИ). В тот год ему исполнилось едва тридцать лет, но правительство не ошиблось, доверив ему столь высокую должность. Это была эпоха молодых талантов, которым открывались огромные возможности для роста и развития. Став руководителем ТашМИ, он внес в работу коллектива дух творчества, он требовал совершенствования педагогической методики и внедрения новых передовых методов лечения. Он много получил за годы пребывания в Москве и стремился передать своему коллективу тот огромный заряд творческой энергии, который отличал институт, в котором он готовил докторскую диссертацию. Он создал новый коллектив на основе беззаветной преданности своему благородному делу. Он был личностью неординарной, обаятельной и руководил он неординарно, не было в нем высокомерия или мании величия. Он был простым, скромным, стеснительным, открытым и доступным. Досуг его был посвящен семье, шахматам и чтению классической литературы.

В 1955г. его назначают ректором Андижанского медицинского института, но в январе 1957г. в связи с созданием в Ташкенте Института ядерной физики ему поручают организацию лаборатории радиационной биофизики, которая стала одним из первых мировых центров в этой области. Он был настолько талантлив, что ему поручали самые разнообразные организации, зная, что он сумеет организовать коллективы и придать им правильное направление в работе. Ему удавалось вдохновлять коллективы, вселять в них тот творческий дух, в котором рождаются открытия и таланты. В этом же году ему новое поручение – создать

Институт краевой медицины, который занимался бы исследованием и лечением болезней имеющих локальную этимологию. Его назначают директором института. Учитывая огромную научную и практическую значимость института в 1963г. его передают в ведение АМН СССР. Он становится научным учреждением всесоюзного масштаба. Здесь кипела научная мысль, молодые таланты, которых тщательно подбирал директор, устраивали семинары, научные дискуссии, совершенствуя свое профессиональное мастерство, повышая свой научный уровень. Директор всячески поддерживал этот творческий дух коллектива. По его инициативе в Институте сложились новые направления научных исследований биохимия и биофизика. За период с 1957 по 1963гг в институте было защищено 80 кандидатских и 19 докторских диссертаций. Результаты всех работ внедрялись в практику, а новые доктора наук начинали возглавлять новые открывающиеся для них лаборатории, где продолжали свои исследованию. Некоторых сразу же поле защиты направляли на руководящие работы в другие научные учреждения. В каждом из них была заложена частица его новых идей. По его инициативе в институте были открыты отделы базедовой болезни (зоб) и сахарного диабета. Тысячи людей избавились от этих тяжелых недугов благодаря новым прогрессивным методам лечения.

В 1959г. он защитил докторскую диссертацию, в которой раскрыл биохимические тайны болезней щитовидной железы, предвосхитив теоретически многие достижения современных нанотехнологий.

Советское государство высоко оценило значимость его работ. В 1964г. он был удостоен Ленинской премии за научные достижения, высшей в то время награды страны. В 1966г. он был избран академиком АН УзССР. В 1961г. он был избран председателем Узбекского биохимического общества. Последовали зарубежные поездки – конгрессы, конференции, семинары в Дании, Франции, Японии, Москве. Его доклады и сообщения принимались восторженно и вызывали самые высокие оценки. Научные труды Я. Туракулова были переведены на английский язык и изданы в зарубежных странах. Слава несла его на своих крыльях. Он был счастлив и чувство счастливой судьбы не покидало его. Он был счастлив в научной, преподавательской, общественной и семейной жизни. Им было опубликовано более 200 научных статей, монографии и учебников

С 1963 по 1966гг он был вице-президентом АН УзССР и возглавлял Отделение химико-технологических и биологических наук. Одновременно он являлся председателем редакционно-издательского совета АН и помог многим ученым опубликовать свои труды в издательстве Фан. Велики его заслуги в пропаганде научных знаний в широких народных массах. Он был одним из тех просветителей, которые оказывают огромное влияние на развитие духовной культуры. Я. Туракулов организовал четыре научно-исследовательских института, руководил двумя университетами и двумя учебными институтами и подготовил более 100 кандидатов и докторов наук. Последним его детищем стала лаборатория нейроэндокринологии в Институте эндокринологии, который был организован под его руководством в марте 1979г.

Я.Х.Туракулов автор более 600 научных статей в области биохимии, молекулярной биологии, эндокринологии, генетики, энзимологии, им написано более 120 научно-популярных и публицистических работ. Под его редакцией вышло около 50 трудов, монографий, учебников, в том числе, монография «Тиреоидные гормоны» (1972) совместно с московскими учеными (изд-во «Наука»), переизданная на английском языке в США и Израиле, монография Я.Х.Туракулова «Щитовидная железа» (изд-во «Наука»), Москва. Издание учебников «Биохимия», «Молекулярная биология» на русском и узбекском языках, и, совместно с коллегами, - учебника для старших классов «Общая биология», переведенного на все языки народов Средней Азии.

Я.Х.Туракулов был постоянным участником Всемирных конгрессов по биохимии и эндокринологии, выступал с докладами в Копенгагене (1960), Токио (1961 и 1967), Нью-Йорке (1964), Праге (1967), Швейцарии (1970), Швеции (1973), Гамбурге (1976), Канаде (1979) и ряде конференций Федерации Европейских биохимических обществ (ФЕБО).

С 1966 года – член Президиума и вице-президент Узбекистанского общества дружбы и культурных связей с зарубежными странами. В 1975 году был избран Председателем городского общества любителей книги. В течение многих лет был главным редактором научно-популярного журнала «Фан ва турмуш» («Наука и жизнь»), членом редколлегий научных журналов ряда стран.

Я.Х.Туракулов был многократно награжден Грамотами Верховного Совета Республики Узбекистан, он - лауреат Госпремии имени Бируни, награжден орденами «Эль-юрт хурмати», «Буюк хизматлари учун», «Жасорат». «Шухрат», а также высшей наградой АН - Медалью Аль Хорезми, и многими другими.

Он ушел из жизни 1 марта 2005г. в возрасте 88 лет, прожив прекрасную, плодотворную и великую жизнь, оставаясь любимым и почитаемым своим народом.

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# O‘RTA OSIYO ENDOKRINOLOGIK

# ЦЕНТРАЛЬНО АЗИАТСКИЙ ЭНДОКРИНОЛОГИЧЕСКИЙ

# CENTRAL ASIAN ENDOCRINOLOGICAL

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