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VITAMIN D STATUS IN WOMEN WITH UTERINE FIBROIDS (UF) OF THE UZBEK POPULATION.

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Abstract.
UF is the most common benign gynecological disease. Despite the high prevalence, the pathogenesis of the disease is not fully understood. To date, conservative treatment of fibroids is undergoing significant evolution, while surgical intervention remains in the background with the management of women with this pathology. We examined 152 women in the II clinic of the Tashkent Medical Academy. The saturation of the body with vitamin D (25 (OH) D) in both patients with UF and healthy ones was studied. In women of the main group, especially with severe symptoms, deficiency and severe deficiency of vitamin D prevail, and in patients with UF without clinical manifestations of the disease, 2/3 of women have deficiency, whereas in the control group almost half of the women showed normal levels of vitamin D. The study of this marker for the pathology of fibroids makes it possible to predict the development of the disease, the nature of the course and the risk of possible complications.
Keywords: uterine fibroids, vitamin D (prohormone D), risk factors, symptomatic fibroids.

I. Introduction

UF (D25 according to ICD-10) has always been the most common gynecological disease, which is second only to inflammatory diseases of the genitals and is diagnosed in 20-40% of women of reproductive age [1].Leiomyomas are benign clonal tumors in women that arise from the smooth muscle cells of the uterus (SMC) and contain an excess extracellular matrix. Although UF often has an asymptomatic course, the spectrum of its side effects on a woman's health and quality of life is large and not always detected. According to the native and foreign authors, UF is diagnosed in 30–35% of women of reproductive age, more often in late reproductive age, and in 1/3 of patients it becomes symptomatic [2].By the age of 50, fibroids affects more than 80% of women. According to the results of pathological studies, the incidence of UF reaches 84%, which is explained by the asymptomatic course of the disease.In connection with the rejuvenation of the disease, it is an urgent problem in many countries of the world.Symptomatic UF adversely affects the quality of life of women of reproductive age, worsening physical and mental well-being. Menorrhagia, iron deficiency anemia, infertility, chronic pelvic pain, psychological discomfort is just an incomplete list of these attributes of fibroids, which negatively affects the quality of life of women. According to Mohanambal M. et al. in their study with 362 women with fibroids, 58.8% complained of menorrhagia, 23% needed blood transfusion. UF can also lead to infertility, early termination and pregnancy complications [3].

According to world statistics, fibroids is,more often than other causes, a reason for hysterectomy .Symptomatic UF is often stopped by the radical surgical method, which significantly impairs the quality of life of these women in the postoperative period. Despite the fact that there are organ-preserving surgical

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methods, such as hysteroscopy and laparoscopic myomectomy, drug treatment of UF is associated with lower costs and incidence.

The authors described some common risk factors for the development of UF (age before menopause, black race, obesity), reproductive (infertility, previously menarche, the use of oral contraception up to 16 years, etc.) and environmental (diet, reduced insolation, leading to vitamin D deficiency, environmental toxins) factors that are the subject of ongoing research [4].According to many researchers, obesity is a significant potentiating endocrine factor of UF. Various studies have shown that BMI (body mass index) in women with UFis higher in 25-70% of cases. Despite the high prevalence of UF, pathogenesis, development, and risk factors are far from being fully understood.However, among women aged 15–54 years, fibroids account for 29% of gynecological hospitalizations.Dora Pavone et al. emphasize that fibroids account for 40–60% of all performed hysterectomies and 1/3 of them operated young women were aged 18–44 years.According to GeumSeonSohn et al, since UF is widespread in women of reproductive age and meanwhile, as women continue to postpone pregnancy, these patients need treatment methods that maintain fertility. It has beenrecently proven that UF is monoclonal in nature, that is to say, it develops from a single mutated cell or cell clone.The term “clonal expansion” has even been proposed to refer to this process. Recent studies have shown that myomatous cells can occur as a result of repeated mutations of various types, that means, the concept of UF is not uniform. The cytological characteristics of myomatous cells are also very diverse, if not contradictory.The main structural elements of the myomatous node are mature SMCs without signs of atypia. Some UF cells, unlike mature myometrial cells, generate properties characteristic to stem cells.Some authors in myomatous nodes observe an increase, while others, on the contrary, decrease the expression of both estrogen (ER) and progesterone receptors (PR) with a decrease in the expression of vitamin D receptors (VDR) [5].

A study by Gordon P. et al. (2013) demonstrated that uterine fibroids goes through its life cycle from the stage of growth initiation to involution of the neoplasm, which is a natural process for fibroids . The life of the myomatous node can be divided into four hypothetical phases. The growth of the neoplasm begins with a predominantly proliferative phase or occurs simultaneously with the synthesis of the extracellular matrix, which is excessive in comparison with the intensity of angiogenesis. A progressive excess of myocytes moves them away from the blood vessels and interstitial ischemia occurs. Under conditions of energy starvation, firstcellular degeneration and then the myocyte atrophy progress.As a result of degenerative collapse, the cell dies. In the life cycle described for UF myocyte, even cell death is fundamentally different from the known types of cell death - apoptosis and necrosis. Since this phenomenon was first described in the literature, the authors of the study proposed a new term - inanosis (inanosis, from the English inanition - depletion), and their arguments were confirmed by morphological studies. Thus, since the fibroid does not have a malignant potential, from a biological point of view it is doomed to death (involution). Obviously, it is this scenario that undergoes a large number of subclinical fibroids. Without factors stimulating vascular growth, the neoplasm witnesses natural involution.

Such a high prevalence of fibroids in the population makes the scientific world investigate subtle pathogenetic mechanisms in search of a universal response to all identified risk factors and the progression of this benign tumor.

In this regard, the last decade has been quite rich in response to new data, although in general today it can be said that not one of the theories of triggering the pathological process has been fully studied. Most often, aberrations affect chromosomes 6, 7, 12, and 14 (changes occur in the region of genes responsible for the processes of division, differentiation, and apoptosis - MED12, HMGA2, HMGA1, FH, BHD, TSC2, PCOLCE, ORC5L, LHFPL3). However, all these chromosomal aberrations occur a second time under the influence of numerous epigenetic factors [6].

To date, conservative treatment of UF has been very limited, with surgery being the main medical treatment for a century with frequent relapses of tumors. Currently, the management of women with UF is undergoing significant evolution, while the quality of life of the patient is the most important aspect that must be taken into account. Accordingly, surgical methods and aggressive treatment remain in the background in the management of women with this pathology. The reasons for the development and growth of UF are still not well understood, but most of the factors - growth promoters are associated with sex steroids, estrogen and progesterone, which have been studied for the most part. Considering the high prevalence of the disease in the population, at the present stage, the study of pathogenetic mechanisms is one of the urgent, but, unfortunately, incompletely studied issues in gynecology and is still the subject of discussion.

Currently, experts assess vitamin D deficiency as a new pandemic of the 21st century.
According to the results of 290 prospective cohort randomized trials, vitamin D levels affect 172 basic physiological indicators of human health associated with the risk of various diseases.

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It has been proven that for a good quality of life, the optimal level of 25 (OH) D in blood serum should be 40-60 ng / ml, while vitamin D deficiency (<30 ng / ml) is observed in every fourth person on the globe. In recent years, more than 5 thousand epidemiological studies have been conducted in studying the status of vitamin D.

Scientists have shown a clear relationship between a reduced level of vitamin D in blood plasma and an increased risk of developing UF, as well as its protective role in the development of this disease. In view of the enormous importance of fibrogenesis in the pathophysiology of UF, the search for an effective antifibrotic drug as a means of additional pathogenetic therapy continues. Several studies show that vitamin D deficiency is a risk factor for the development of UF [7].

In recent years, there has been an intensification of scientific research regarding the mechanisms and potential prospects for the use of vitamin D in UF. M. Sabry et al. in a one-stage study involving 204 women demonstrated the relationship between a reduced plasma vitamin D level and an increased risk of developing UF. A correlation between the plasma concentration of vitamin D and the tumor volume ($r = –0.31$; $p = 0.002$) was recorded. Baird et al. found that in women with normal plasma vitamin D levels, the risk of developing this tumor is reduced (OR = 0.68). Other retrospective studies have convincingly confirmed the opposite phenomenon: a significant increase in the risk of developing UF in women with verified vitamin D deficiency. Several gene expression products are involved in vitamin D metabolism. In this connection, case-control studies by L. Wise and a group of researchers are of great interest [8]. Scientists have analyzed the relationship between the presence of UF and the polymorphism of these genes. It was found that the presence of SNP ("single nucleotide polymorphism" - a variant of the DNA sequence) in the DHCR7 and ASIP genes wasassociated with anincreased risk of developing UF. The protective role of vitamin D against this disease has been demonstrated in several experimental *in vitro* studies. M. Blauer et al. found that the effect of calcitriol 1.25 [OH] 2D3 (active form of vitamin D) at a concentration of 0.1 nmol /L was associated with inhibition of proliferation by 12% during incubation with both normal HUtSMC(Human Uterine Smooth Muscle Cells) and tumor. The effect showed a clear dependence on the concentration of the substance: with its increase to 100 nmol / L, mitotic activity decreased by 62% in both types of cells. S. Halder et al. stimulated immortalized humanUF cells with TGF-β3 in the presence or absence of 1,25-dihydroxyvitamin D3. The authors found that vitamin D3 significantly offset the TGF-induced overexpression of fibronectin and type III collagen, and also interfered with the activation of the Smad cascade; according to the authors, this indicates the existence of a clear antifibrotic and antiproliferativeeffects of vitamin D in relation to UF. Subsequently, the same scientists conducted another laboratory work to clarify the role of vitamin D in UFoncobiology.

It was found that, firstly, in most tumor samples, the VDR content was reduced compared to cells of a healthy myometrium. Secondly, the authors noted that exposure to 1.25 [OH] 2D3 was accompanied by a decrease in the expression of fibrogenic factors and various proteoglycans (such as fibromodulin, biglycan and versican) in cells. In addition, incubation of cells with 1.25 [OH] 2D3 led to a clear upregulation of VDR. Thus, the authors confirmed the previously established antifibrotic properties of vitamin D. In the same year, this research team published the results of another scientific work, which showed that vitamin D reduces the expression of type 2 and 9 matrix metalloproteinases (MMP-2 and tissue MMP-9) depending on the dose, and, conversely, , increases the expression of an inhibitor of matrix metalloproteinases (TIMP), which together leads to a decrease in the intensity of fibrosis. The mentioned enzymes play a key role in maintaining the balance of remodeling of the extracellular matrix of fibroids, and therefore the effect of vitamin D on them is of great pharmacological and clinical importance. C. Sharan et al. demonstrated that the effect of vitamin D leads to a decrease in the growth of fibroid cells by 47.0 ± 0.03 and by 38.0 ± 0.02% at a concentration of 1.0 and 0.1 μmol / L, respectively, compared with the control samples after 120 h incubation. In addition, the authors found that vitamin D inhibited the activation of a number of regulatory kinases, promoted downregulation of the expression of certain proapoptotic proteins (such as BCL-2, BCL-w, CDK1 and PCNA), and also reduced the expression and activity of catechol-O-methyltransferase (COMT). Moreover, the preliminary suppression of expression of this enzyme completely eliminated the described pharmacodynamic effects of vitamin D, which indicates the great importance of COMT in their implementation. The work of Al-Hendy et al. was devoted to studying the effect of 1.25 [OH] 2D3 on the expression of sex hormone receptors in human myometrium and UF cells. The authors found a decrease in VDR expression in tumor cells, which correlates with upregulation of estrogen receptors-α (ER-α), as well as progesterone receptors (PR-A and PR-B). Exogenous 1.25 [OH] 2D3 exposure led to a significant decrease in the expression of the mentioned receptors in UF cells [9]. Incubation with vitamin D was also associated with a decrease in the production of SRC (steroid-receptor co-activator) co-activator, the function of which, in full accordance with the name, is to co-stimulate nuclear receptors and transcription of targeted genes. The authors concluded that 1.25 [OH] 2D3 has pronounced antiestrogen / antiprogestin properties, which is an additional molecular biological justification

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for the use of this drug in the treatment of patients with UF. The same scientists recently published the results of another important study, during which it was found that vitamin D3 inhibits some of the most important signaling cascades underlying the tumorigenesis of UF, WNT/β-catenin pathway and the mTOR pathway.

The protective effect of vitamin D3 on uterine leiomyoma has also been demonstrated in a number of *in vivo* studies. In experimental animal studies *in vivo*, Ayman Al-Hendy et al. evaluated the effective and safe potential treatment of fibroids with vitamin D in an Eker rat model. Scientists injected 1.25 [OH] 2D3 at a dose of 0.5 μg / kg / day subcutaneously to Eker rats in which myomatous nodes were verified. The treatment lasted for 3 weeks, a comparison was made with a control group of animals that were given a placebo. After completion of therapy, the animals were euthanized and tumor size was estimated.

The authors recorded a statistically significant volume reduction of myomatous nodes (approximately 75.0 ± 3.85%) in animals of the main group. In addition to this, it was found that vitamin D therapy was associated with suppression of genes involved in cell proliferation (PCNA, CCND1, Myc, Cdk1, Cdk2 and Cdk4), inhibiting programmed cell death (Bcl2, Bcl-x), as well as encoding ER and PR. Immunohistochemical analysis showed a decrease in the expression of MKI67 (one of the proliferation markers) and, conversely, an increase in the expression of caspase-3 (an enzyme involved in the implementation of apoptosis) in UF cells obtained from mice treated with vitamin D3. According to the authors, the results of the study indicate the great potential of 1.25 [OH] 2D3 as an antitumor drug in the treatment of UF. Subsequently, the same scientists studied the effects of paricalcitol (300 ng / kg / day), one of the analogues of 1.25 [OH] 2D3, which is characterized by a less pronounced tendency to hypercalcemia. The drug was administered to female nude mice for 4 weeks; a comparison was made with placebo and vitamin D3 (500 ng / kg / day). The authors found that both drugs helped to reduce the size of myomatous nodes with a minimal advantage of paricalcitol.

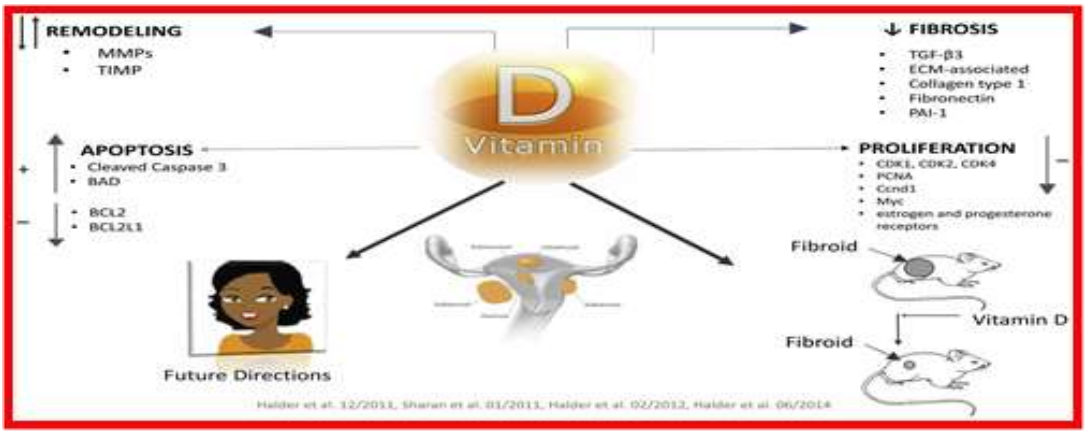

Fig. 1.The mechanism of action of vitamin D on the development of UF [10].

Feofilova M.A. et al. presented the data in which, as the basic processes of myomatous transformation, vitamin D deficiency increases the risk of developing UF 2.0 times. According to the research of A.Z. Khashukoeva et al. the lowest plasma concentrations of 25 (OH) D3 were determined in patients with polycystic ovary syndrome and a combination of UF and adenomyosis, reaching 10.5 ± 2.7 and 13.1 ± 3.1 ng / ml, respectively . In the large-scale VITAL study (a factorial randomized, double-blind, placebo-controlled study of 2 × 2 benefits and risks) the role of vitamin D and omega-3 for primary prevention of cancer or CVD in the population is potentially assessed. According to a review by Dora Pavone et al. Vitamin D is a potent antitumor agent that inhibits the proliferation of leiomyoma cells in vitro and reduces the size of uterine leiomyoma in animal models in vivo. Compared to unchanged myometrium, in UF the reduced levels of the vitamin D receptor (VDR) are expressed; therefore, serum vitamin D deficiency and / or decreased VDR expression may be a key trigger for the development of UF. Wise L.A. et al. identified single nucleotide polymorphisms in genes involved in the metabolism of vitamin D, which are largely associated with the development of UF. Al-Hendy et al. proved in their studies that vitamin D can be a powerful antiestrogen agent that reduces the expression of sex steroid receptors, assuming that vitamin D can be used in conservative therapy in women with UF. Studies have shown that there is no associative relationship between the development of UF and other vitamins, such as vitamin C, E and folate, phytoestrogen (soy). Michal Ciebiera et al. conducted a retrospective cohort study, in which it was found that vitamin D deficiency and an excess of transforming growth factor β3 (TGF-β3) in blood serum, overweight and a burdened family history of women increase the risk of UF development [11].

Bratka et al. in his review suggested that vitamin D or its hypocalcemic analogue paracalcitriol can be a new therapeutic approach as an effective, safe, non-surgical treatment option for UF. His epidemiological data and animal studies in vitro and in vivo show the role of vitamin D in the biology of UF. The authors cite data from three studies showing a correlation between low levels of vitamin D and the incidence of UF. The authors describe their research in vitro studies that demonstrate that the vitamin D acts as a growth inhibitor and promotes apoptosis of leiomyoma cells. Mohamed Ali et al. in their studies showed that VDR milkness in normal SMC induces the expression of Wnt4 / b-catenin and causes fibrosis, increased cell proliferation, and extracellular matrix production. A prospective study by Lauren A. et al. including 2232 women with UF and 2432 healthy premenopausal women showed that three of the 12 polymorphisms of the genes involved in vitamin D metabolism were significantly associated with UF: rs4944957 and rs12800438 near DHCR7 and rs6058017 in ASIP. These data support the hypothesis that vitamin D deficiency is associated with the etiology of fibroids. According to the authors, in order to directly test the hypothesis, it is necessary to conduct prospective studies involving direct measurement of vitamin D levels before diagnosis UF. Bioactive Vitamin D is an antiproliferative prohormone that blocks the cell cycle in G1 / S and mitogenic signaling of estrogen, EGF and IGF-1, and activates TGFY, a fibrosis modulator and VDR-mediated apoptosis. Feng L. et al. in their work determined the expression of VDR genes in 5 women with UF using the Affymetrix U133 chip. The data showed different levels of expression depending on the location and suggest the role of vitamin D signaling in the biology of fibroids. Ana Corachan et al. in her experimental prospective study compared the effects of vitamin D on leiomyoma (HULP) and myometrial cell samples taken from women with hysterectomy by inhibiting the Wnt / b-catenin pathway, inducing apoptosis, and arresting cell growth. The results showed that vitamin D has an antiproliferative effect on HULP cells by stopping the cell growth and inhibiting the Wnt / b-catenin pathway, but not by regulating apoptosis, suggesting that vitamin D is an effective therapy for stabilizing the size of leiomyoma and preventing its growth. According to other researchers, vitamin D subsidy in women with uterine myoma can lead to a significant decrease ($p < 0.001$) in tumor size after a 10-week course of therapy.

Thus, the results of experimental studies in vitro and in vivo along with retrospective clinical studies, indicate the existence of a clear protective effect of vitamin D on UF growth, which is based on inhibition of cell proliferation, stimulation of apoptosis, regulation of extracellular matrix remodeling, and decrease in the expression of genitalreceptors hormones and other pharmacodynamic effects. In this regard, vitamin D should be considered not only as apromising adjuvant for pharmacotherapy in patients with UF, which, of course, requires more detailed study in theframework of prospective clinical studies, but also as a substrate for the development of new, more effective antitumor drugs .

Although the results are convincing, at current levels of data it is not enough to establish vitamin D as a drug therapy for the treatment of UF on humans. The next logical step would be to demonstrate an inhibitory effect on humans, which would require a randomized controlled trial, which is unfortunately not available by now. UF remains insufficiently studied.

Vitamin D and its regulation

Currently, vitamin D is assigned to the group of secosteroid prohormones; there is the effect of vitamin D deficiency on immune system disorders, the development of autoimmune reactions, diabetes mellitus, infections and oncological diseases, in particular breast cancer, prostate gland, co-rectal cancer. The two main forms of vitamin D are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D metabolism goes through the classic and alternative paths. Vitamin D2 is synthesized from ergosterol under ultraviolet radiation in plants, yeast, fungi and enters the body along with these products. Vitamin D3 is synthesized in several stages.

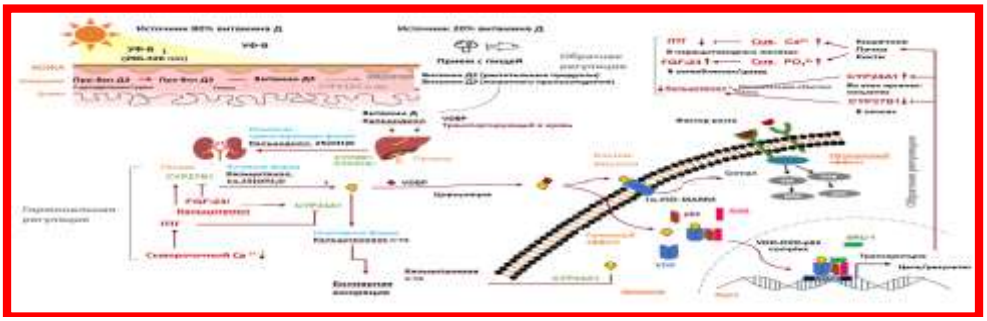

Fig. 2.The pattern of metabolism and regulation of vitamin D.

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An alternative way of metabolism of vitamin D occurs through an enzyme that cleaves the side chain of cytochrome P450 - CYP11A1, in which hydroxymethabolites of vitamin D are formed. One of them is 20 (OH) D, which has an anti-proliferative, anti-inflammatory effect, and also contributes to the differentiation of cells, alike calcitriol. In addition, these metabolites enhance the protective mechanisms from UV-induced damage of skin DNA and oxidative stress, which has antitumor properties on cell lines. 20 (OH) D and 20, 23 (OH) D metabolites are also effective as partial VDR agonists. The same metabolites can bind to the α and γ isoforms of the irethrin-bound orphan receptor (RORα and RORγ), which refers to the family of ligand-dependent transcription factors. In this case, 20 (OH) D and 20, 23 (OH) D, when interacting with ROR receptors, have an inhibitory effect on the transcription of the Bmall and G6Pase genes.

In a review of the literature, M.A. Bukhalko et al. there is information on the role of VDR polymorphism in human pathology and the numerous pleiotropic effects of prohormone D on the human body. According to a review by Mailyan EA, the available data indicate that circulating levels of 25 (OH) D, which reflect the body's saturation of vitamin D, are 23-80% dependent on genetic factors.

It is important to note that laboratory determination of the serum level of prohormone 25 (OH) D is considered to be the most acceptable, reliable and clinically significant for assessing the vitamin D saturation of the human body. The half-life of 25 (OH) D is quite long and is about 15 days, which makes it also preferable for assessing vitamin D status [12].

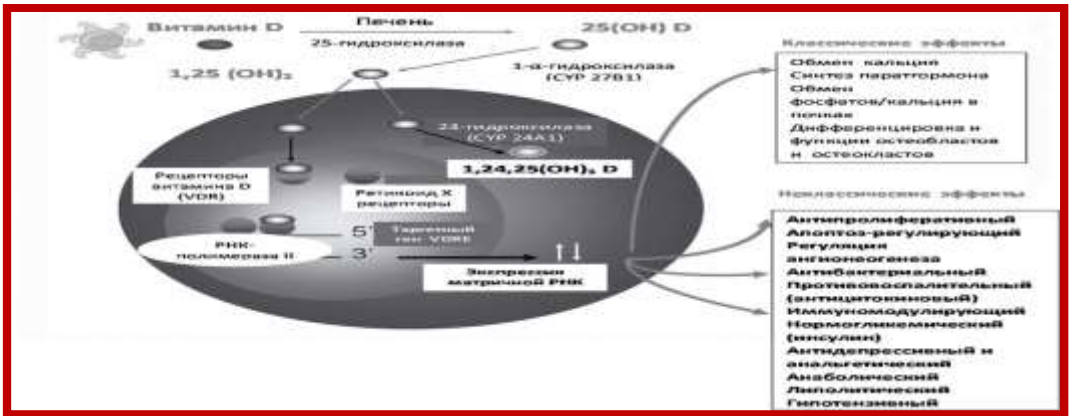

Fig. 3."Classical" and "non-classical" effects of vitamin (hormone) D.

The Russian Association of Endocrinologists recommends (2015) to determine vitamin D deficiency by the following criteria:

№	Criteria	Values	
		ng / ml	nmol / l
1	Norm	>30 ng / ml	> 75 nmol / l
2	Insufficiency	20–30 ng / ml	50 - 75 nmol l
3	Deficiency	<20 ng / ml	< 50 nmol / l
4	Severe deficiency	<10 ng / ml	< 25 nmol / l
5	Hypervitaminosis D	>150 ng / ml	> 375 nmol / l

Table 1. Criteria for the availability of vitamin D by blood content (Russian Association of Endocrinologists. Clinical recommendations.2015 [13].

Thus, research in the field of UF pathogenesis in combination with the achievements of modern technology and pharmacology made it possible to introduce in clinical practice the medical, non-surgical, and minimally invasive surgical techniques, being a real alternative to radical surgery, which was recently considered as a gold standard in the treatment of this pathology.

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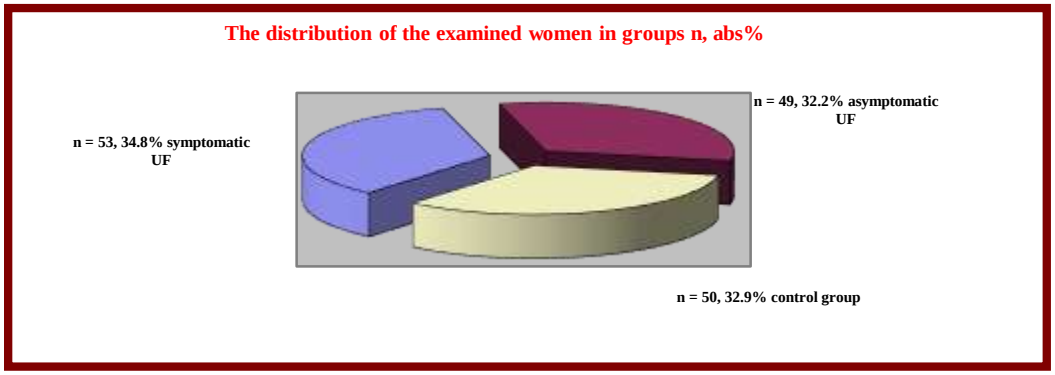
Assessment of Vitamin D Saturation in Women with UF

Purpose of the study. To identify the level of vitamin D availability and its relationship with the clinical course in women with uterine fibroids.

II. Materials and methods

The design of a cohort prospective controlled trial was used. In accordance with the goal, an integrated approach was used, providing clinical and medical-statistical research methods.

The study was based on a clinical and laboratory examination of 152 women of comparable age who entered the Women's Health Center and the Gynecology Department of the second clinic of the Tashkent Medical Academy of the Republic of Uzbekistan. The examined women were divided into 2 groups: the control group consisted of 50 healthy women and the main group of 102 women with UF. The main group of patients was divided into 2 subgroups - 53 women with symptomatic UF and 49 women with asymptomatic UF.



Inclusion criteria: patients with a diagnosis of uterine fibroids with symptomatic and asymptomatic course and age from 19 to 54 years, conditionally healthy women without UF of comparable age, informed consent of the patient to the examination.

Exclusion criteria: the age of women under 19 and older than 54 years; pregnant women; patients registered in the dispensary; alcohol abuse taking drugs; refusal to participate in the proposed survey.

Clinical evaluation of the results of the study. The diagnosis of uterine fibroids was established on the basis of: gynecological history, clinical manifestations, laboratory and instrumental studies. For all women with UF, during the observation, risk factors were identified on a modified scale recommended by the guidelines, a general clinical examination, including a general blood test, a general urine test, a blood group and rhesus, a blood count, a biochemical blood test, an ultrasound of the uterus and appendages (determining the volume of the uterus by Brunn (1981) and myomatous node) with duplex scanning of the uterine artery, morphological studies of uterine aspirates. The marker of body saturation with vitamin D - 25 (OH) D was determined in the peripheral venous blood from the cubital vein of the examined women on the 5th - 7th day of the menstrual cycle. The plasma concentration of the main metabolite of vitamin D - 25 (OH) D was determined in the laboratory "DIYOR MEDICAL CENTER" on the basis of a contract, by ELISA (Enzyme-linked immunosorbent assay) of quantitative determination - chemiluminescent analysis on microparticles (CMIA).

Mathematical processing and statistical analysis of the results were carried out using the program "Statistika 6.0". Non parametric methods were implemented. The average, relative values were calculated. Differences in indicators, as well as correlations between them, were considered essential at a significance level of $p < 0.05$.

III. Results and discussion

The age of the examined women in the main group was 19-55 years old, the average age in the first subgroup was 44.35 ± 0.83 ($n = 53$) and in the second subgroup 42.6 ± 0.7 years ($n = 49$). Whereas in the control group ($n = 50$), the average age was 40.12 ± 0.7 years ($p < 0.01$).

The diagnosis of uterine fibroids for all women of the main group was confirmed by ultrasound. The Ultrasound revealed the number and localization of myomatous nodes of women with UF. In women with symptomatic UF ($n = 53$), 1/3 (32.1%) of women had multiple UF (more than 2 myomatous nodes) and 2/3

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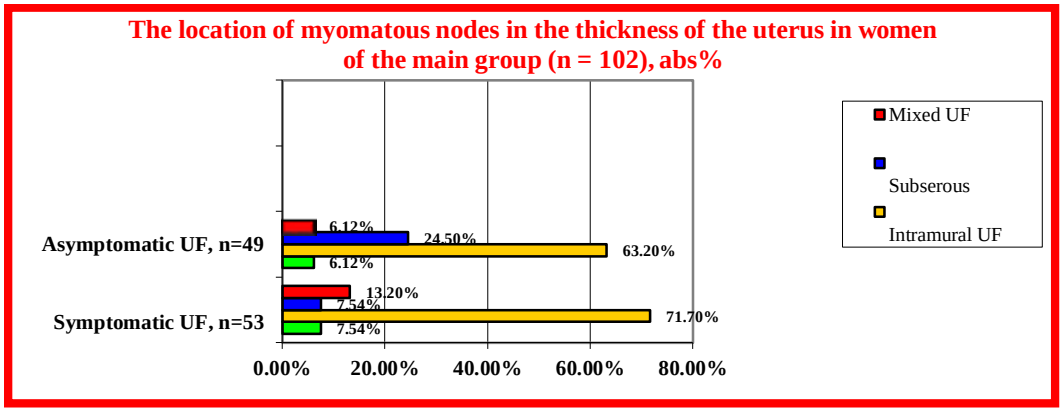
(67.9%) had a solid tumor, while in those with asymptomatic UF the multinodular UF was found to be 2 times less compared with symptomatic UF (14.3% and 85.7%, respectively). According to the localization of the myomatous node in the thickness of the uterus in both groups of the main group : the intramural node prevailed (71.7% and 63.2%, respectively, of the groups), submucous (7.15% and 6.12%) nodes were in equal proportions and subserous (7, 15% and 24.5%) were 3 times more often detected in women with asymptomatic UF. Mixed myomatous nodes in women with symptomatic UF were twice as often as in women with asymptomatic UF (13.2% and 6.12%, respectively).



The median uterine volume in an ultrasound study calculated using the Brunn formula (1981) in the subgroup with symptomatic UF made up 237.54 mm3, asymptomatic UF - 103.45 mm3 and in the control group - 52.1 mm3. According to the analysis of risk factors for the development of UF in the studied women of the main group in the subgroup of symptomatic UF (n = 53), 1.9% of women calculated a high risk (31 points), 84.9% - medium risk and 11.3% - low risk, while in the subgroup of asymptomatic fibroids (n = 49), the amount of high risk was not detected, the average risk was found in more than half of the studied women of the main group (52.2%), and low - in 47.8% ($p < 0.001$). Among the identified risk factors, such factors as excess BMI prevailed (29.7 + 11.83 and 28.1 + 0.08 kg / m2, respectively, in the subgroups and in the control group 23.3 + 0.01 kg / m2, p <0 01), a burdened obstetric and gynecological history (hereditary burden on UF in 34% and 24.5%, infertility in 3.7% and 2.4%, curettage of the uterus in more than 2/3 and 1/3 of women, manual examination of the uterine cavity in 22.6% and 18.3%, respectively, of the subgroups of the main group), reduced insolation (less than an hour / day in 71.2% of the studied women had symptomatic and 67.3% of asymptomatic UF).

Women with symptomatic UF of the main group (n = 53) turned up with a different clinic: the bleeding symptom and anemia were more prevalent in 83.01% (n = 44), of which hemotransfusion was made in 16.9% due to severe anemia; symptom of rapid growth - 9.43% (n = 5), infertility symptom in 5.6% (n = 3) and pelvic pain symptom (n = 2) 3.77%.

Vitamin D status of examined women

It is important to note that according to researchers, the determination by laboratory methods of the initial serum level of prohormone 25 (OH) D is the most acceptable, reliable and clinically significant for assessing the saturation of vitamin D of the human body [14]. An analysis of the initial blood vitamin D content showed that the values in the group of women with UF ranged from 4 to 36 ng / ml and averaged 16.7 + 1.8 ng / ml, which turned out to be significantly lower than in healthy women ($p <0.001$). When assessing the blood content of vitamin D in the structure of the main group, women with symptomatic UF averaged 11.84 + 0.46 ng / ml and asymptomatic - 21.54 + 0.04, whereas in the control group - 29.83 +1.13 ng / ml ($p <0.001$).

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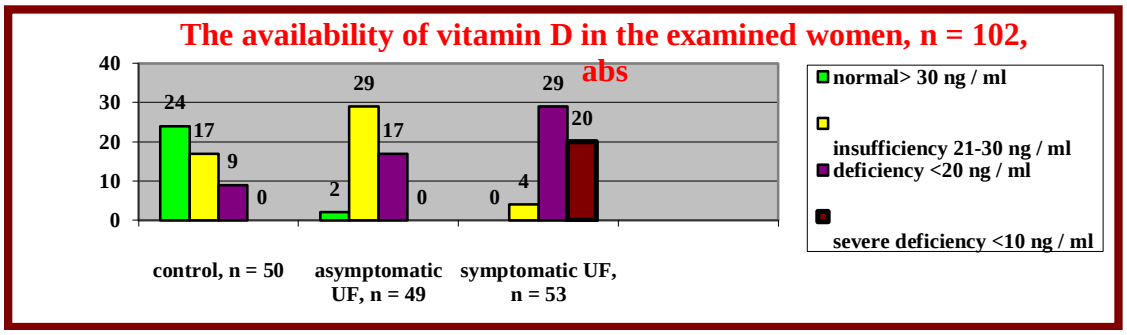

The distribution of women by the degree of provision with vitamin D, based on its content in the blood (Table 2), showed a significant difference between the subgroups of the main group and the healthy ones.

№	Groups	Symptomatic UF, n=53		Asymptomatic UF, n=49		Control group, n=50	
	Crteria	n, abs	(ng / ml)	n, abs	(ng / ml)	n, abs	(ng/ml)
1	Normal	0	-	2 (4,08%)	34±1,2‘‘‘	24 (48%)	40,4±1,7
2	Insufficiency	4 (7,54%)	20,8±1,9***	29 (59,2%)	23,6±1,4‘‘‘	17 (34%)	24,4±1,7
3	Deficiency	29 (54,7%)	14,02±0,2***	17 (34,7%)	16,8±1,6‘‘‘	9 (18%)	14,2±0,9
4	Severe deficiency	20 (37,7%)	6,62±0,9***	0	-	0	-

Note: * p<0.001 in relation to the first subgroup; -‘P<0.001 with respect to the second subgroup.

Table 2. Vitamin D levels in women of examined groups.

Correlation analysis showed a direct weak positive relationship in the control group between the content of vitamin D in the blood and BMI (r = 0.345, p <0.001), that is, normal levels of BMI corresponded to normal values of vitamin D; while the correlation between these indicators in the main group, especially in the subgroup of symptomatic UF, was a direct average positive (r = 0.482, p <0.001).

The chances of developing (OR) UF in women with vitamin D deficiency and / or deficiency (OR = 16.13) and obesity (OR = 7.38) were more than one.

IV. Discussion

The examined women were mainly at a late reproductive age, which is consistent with the authors' data that UF is more often diagnosed in this period [15]. According to WHO (2012), the intake of the vitamin D with food and factors influencing the absorption of its metabolism, as well as obesity, affect the state of vitamin D levels. The researchers described the relationship of excess BMI with vitamin D deficiency [16]. Our analysis to identify excess BMI is consistent with the data of foreign researchers: in 47.2% of women with symptomatic UF, the obesity I, II, III degree was calculated (28.3%, 11.3%, 7.5%, respectively). In the main group of women with asymptomatic UF, normal values of vitamin D were only 4.08% of cases, insufficiency - in more than half (59.2%) and deficiency- in 1/3 of women; in the subgroup of symptomatic UF, normal values were not found, the deficit is 54.7% and the pronounced deficit is 37.7%, which is 2.88 times greater than in the asymptomatic UF group and 5.4 times compared with the control group. The noticeable is the fact that, despite the absence of the disease, 52% of healthy women had insufficient levels and deficiency of vitamin D in the blood, in a country with sufficient insolation. [17]

When determining the level of provision of prohormone D in the examined women, its pronounced deficiency was detected in the subgroup of symptomatic UF (6.62 + 0.9 ng / ml) in 37.7% of women with a clear clinic of menorrhagia (in 100% of women) and a recurrent course of the disease, and in the subgroup of asymptomatic UF, 1/3 of patients (36.7%) had a deficiency of vitamin D (16.7 + 1.6). Values of prohormone in the control group were significantly different (p <0.001). When comparing vitamin D indices between the subgroups of the main group, the statistical differences were significant, indicating the presence of a relationship between the level of vitamin D saturation of women with UF and clinical manifestations of the disease, the size of the uterus. Thus, studying the saturation of the body with vitamin D, we found that in women with UF, especially with severe symptoms, deficiency (in ½ women) and severe deficiency (in 1/3 of women) prevail, and in

patients with UFF without clinical manifestations of the disease in 2 / 3 women - its insufficiency, while in the control group almost half of the women showed normal levels of vitamin D. Analysis of the clinical picture showed that patients with severe vitamin D deficiency in the subgroup of symptomatic UF (<10 ng / ml) had vivid clinical manifestations of the disease: menorrhagia leading to anemia in women of this category, rapid growth of the myomatous node at a time of critical deficiency of the vitamin D accompanying with pelvic pain, infertility, according to the ultrasound picture, an increase in the volume of the uterus and a pronounced vascularization of the perifibroid plexus, frequent relapses of the disease while there is the ineffectiveness of the conservative therapy worsens the quality of life of women. It was established that in women with symptomatic UF, the level of vitamin D was significantly lower in the group compared with the group of asymptomatic UF, which is consistent with the data of other researchers [18].

The correlation showed a significant positive average relationship between the content of vitamin D in the blood and BMI, the most pronounced in the main group of symptomatic UF, compared with the control group.

It is revealed that in women with vitamin D deficiency and / or deficiency, the chances of developing UF are considered to be a positive strong factor, which proves the lack of prohormone factor as a strong provoking factor for the development of the disease in these women [19] . It is revealed that in women with excess body weight, the chances of developing fibroids (OR) are also considered as a positive strong promoter factor; this dictates that excess weight is a factor for the development of severe clinical symptoms of the disease in women with symptomatic uterine myoma.

V. Conclusion

Despite numerous studies, proposals and the introduction of new tools and methods for treating uterine fibroids, it remains the most common gynecological pathology. This the search and introduction of new drugs and treatment methods with pronounced antiproliferative activity into clinical practice. The results of our studies show that lower values of vitamin D in patients with UF can affect the nature of the course of the disease and the incidence of complications. This fact may find widespread use in the future in the field of healthcare, considering the high prevalence of vitamin D deficiency in developing countries, the impact of lifestyle and geographical latitude on vitamin D status. Further studies are required to detail the mechanisms of influence of vitamin D on the reproductive sphere. The study of the effect of vitamin or prohormone D on the pathology of fibroids is the basis of modern personalized medicine, since it makes it possible to predict the development of the disease, the nature of the course and the risk of possible complications. Further developments in this direction should be extremely considered perspective.

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