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# Vitamin D Status In Women With Uterine Fibroid Of The Uzbek Population

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***ABSTRACT***

*Uterine fibroids are 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 patients with uterine fibroids and healthy women was studied. In women of the main group, especially with severe symptoms, deficiency and severe deficiency of vitamin D prevail, and in patients with myoma 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.*

***KEY WORDS:*** *uterine fibroids, vitamin D, risk factors, symptomatic fibroids.*

## INTRODUCTION

Uterine fibroids (D25 according to ICD-10) was, is and remains 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 [1,12,13,27]. Leiomyomas are benign clonal tumors in women that arise from the smooth muscle cells of the uterus and contain an excess extracellular matrix [50].

Although often uterine fibroids has an asymptomatic course, the spectrum of its side effects on the health and quality of life of a woman is large and not always detected. According to domestic and foreign authors, uterine fibroids are diagnosed in 30–35% of women of reproductive age, more often in late reproductive age, and in 1/3 of patients it becomes symptomatic [1.37.41]. By the age of 50, uterine fibroids affect more than 80% of women [35.37]. According to the results of pathoanatomical studies, the frequency of uterine fibroids 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 [6]. Symptomatic uterine fibroids adversely affects the quality of life of women of reproductive age, worsening physical and mental well-being [52]. Menorrhagia, iron deficiency anemia, infertility, chronic pelvic pain, psychological discomfort are just an incomplete list of these attributes of fibroids, which negatively affects the quality of life of women [12,13,27,35,40,50]. According to Mohanambal M. et al. in their study with 362 women with uterine myoma, 58.8% complained of menorrhagia, 23% needed blood transfusion [40]. Myoma can also lead to infertility, early termination and pregnancy complications [35.50].

According to world statistics, uterine fibroids are noticeably more likely than other causes to cause hysterectomy [13]. Symptomatic uterine fibroids are often stopped by a radical surgical method, which significantly impairs the quality of life of these women in the postoperative period [35]. Despite the fact that there are organ-preserving surgical methods, such as hysteroscopy and laparoscopic myomectomy, drug therapy of uterine fibroids is associated with lower costs and incidence [27].

The authors described some common risk factors for the development of uterine fibroids (age before menopause, black race, obesity), reproductive (infertility, earlier 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 [28,31]. According to many researchers, obesity is a significant potentiating endocrine factor in uterine fibroids. Various studies have shown that BMI in women with uterine myoma is higher in 25-70% of cases [2].

Despite the high prevalence of uterine fibroids, pathogenesis, development, and risk factors are far from 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 [28]. According to Geum Seon Sohn et al. consider, since uterine fibroids is widespread in women of reproductive age, and meanwhile, as women continue to postpone pregnancy, these patients need treatment methods that maintain fertility [31].

Recently, it has been proven that uterine fibroids are monoclonal in nature, that is, they develop from one mutated cell or cell clone. To refer to this process, the term "clonal expansion" has even been proposed. Recent studies have shown that myomatous cells can occur as a result of repeated mutations of various types, that is, the concept of uterine fibroids is not uniform. The cytological characteristics of myomatous cells themselves are also very diverse, if not contradictory. The main structural elements of the myomatous node are mature smooth muscle cells of the uterus without signs of atypia. Part of the cells of the uterine myoma, unlike mature myometrial cells, exhibit properties characteristic of 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) [15].

A study by Gordon P. et al. (2013) demonstrated that uterine fibroids go through their life cycle from the stage of growth initiation to involution of the neoplasm, which is a natural process for fibroids [32]. 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 - interstitial ischemia occurs. Under conditions of energy starvation, cellular degeneration progresses, and then myocyte atrophy. As a result of degenerative collapse, the cell dies. In the life cycle described for uterine fibroids, 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 undergoes natural involution [12].

Such a high prevalence of uterine fibroids in the population forces the scientific world to explore 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 turned out to be rather rich in 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 [14].

To date, conservative treatment of uterine fibroids 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 uterine myoma 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 with the management of women with this pathology [23].

The reasons for the development and growth of uterine fibroids 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. Given 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. 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 [7]. In recent years, more than 5 thousand epidemiological studies have been conducted to study the status of vitamin D [9].

Scientists have shown a clear relationship between a reduced level of vitamin D in blood plasma and an increased risk of developing uterine fibroids, as well as its protective role in the development of this disease. In view of the enormous importance of fibrogenesis in the pathophysiology of uterine fibroids, 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 uterine fibroids [24,28,40,43,47].

In recent years, there has been an intensification of scientific research regarding the mechanisms and potential prospects for the use of vitamin D in uterine fibroids. M. Sabry et al. in a one-stage study involving 204 women, they demonstrated the relationship between a reduced plasma vitamin D level and an increased risk of uterine fibroids. A correlation was recorded between the plasma concentration of vitamin D and the tumor volume ($r = –0.31$; $p = 0.002$) [47]. D. Baird et al. found that in women with normal plasma vitamin D levels, the risk of developing this tumor is reduced (OR = 0.68) [24]. Other retrospective studies have convincingly confirmed the opposite phenomenon: a significant increase in the risk of developing uterine fibroids in women with verified vitamin D deficiency.

The metabolism of vitamin D involves the expression products of several genes. In this connection, case-control studies by L. Wise and a group of researchers are of great interest [54,55]. Scientists have analyzed the relationship between the presence of uterine fibroids 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 was associated with an increased risk of uterine fibroids. The protective role of vitamin D against this disease has been demonstrated in several experimental in vitro studies. M. Blauer et al. found that exposure to calcitriol 1.25 [OH] 2D3 (the 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 smooth muscle cells of the uterus and tumor cells. 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 [25]. S. Halder et al. stimulated immortal cells of human uterine fibroids with TGF-β3 in the presence or absence of 1,25-dihydroxyvitamin D3. The authors found that vitamin D3 significantly offset 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 antiproliferative effects of vitamin D in relation to uterine fibroids [51]. Subsequently, the same scientists conducted another laboratory work to clarify the role of vitamin D in the oncobiology of uterine fibroids. 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 matrix types 2 and 9 metalloproteinases (MMP-2 and tissue MMP -9) depending on the dose, and also, on the contrary, 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 exposure to vitamin D leads to a decrease in fibroid growth of myoma cells by $47.0 \pm 0.03$ and by $38.0 \pm 0.02$% at a concentration of 1.0 and 0.1 μmol / L, respectively, compared with control samples after 120 h incubation. In addition, the authors found that vitamin D inhibited the activation of a number of regulatory kinases, helped downregulate 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 [49]. 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 myometrial and uterine fibroids. 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 uterine fibroid cells [21]. 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 for the use of this drug in the treatment of patients with uterine myoma. 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 uterine fibroids, the 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 [22]. 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 volumetric reduction of myomatous nodes (approximately 75.0 ± 3.85%) in animals of the main group. In addition, 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 myoma 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 uterine fibroids. 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.

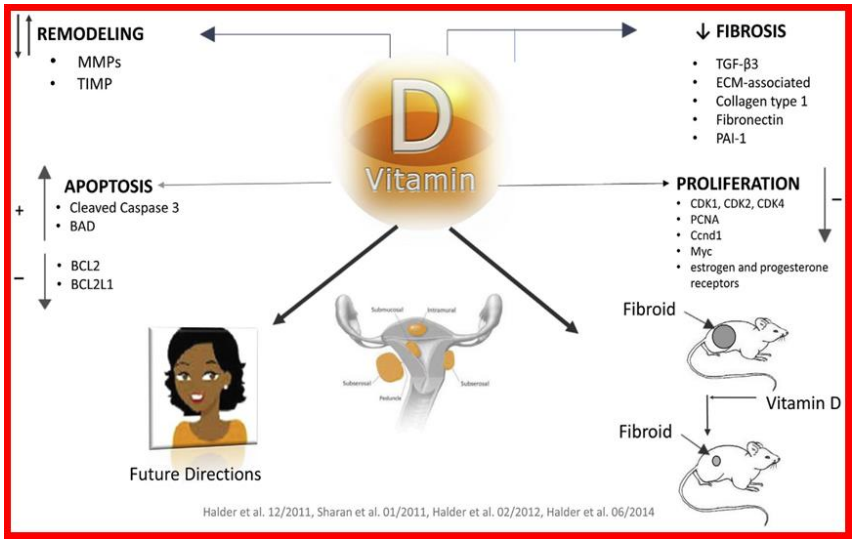



**Fig. 1. The mechanism of action of vitamin D on the development of uterine fibroids [50].**

Feofilova M.A. et al. data are presented that, as the basic processes of myomatous transformation, vitamin D deficiency increases the risk of developing uterine fibroids by 2.0 times [17]. According to research 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 uterine fibroids and adenomyosis, reaching 10.5 ± 2.7 and 13.1 ± 3.1 ng / ml, respectively [18]. In a large-scale study, VITAL (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 evaluated [20].

According to a review by Dora Pavone et al. Vitamin D is a powerful antitumor agent that inhibits the proliferation of leiomyoma cells in vitro and reduces the size of uterine leiomyoma in animal models in vivo [28]. Compared to unchanged myometrium, uterine fibroids express reduced levels of vitamin D receptor (VDR); therefore, serum vitamin D deficiency and / or decreased VDR expression may be a key trigger for the development of uterine fibroids [26]. Wise L.A. et al. single nucleotide polymorphisms in the genes involved in the metabolism of vitamin D were identified, which are largely associated with the development of uterine fibroids [53,54]. 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, suggesting that vitamin D can be used in conservative therapy in women with uterine myoma [21]. Studies have shown that there is no associative relationship between the development of uterine fibroids and other vitamins, such as vitamin C, E and folate [44], phytoestrogen (soy) [42, 54]. 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 uterine fibroids [39].

In his review, Bratka et al. suggested that vitamin D or its hypocalcemic analogue paracalcitriol may be a new therapeutic approach as an effective, safe, non-surgical option for treating uterine fibroids. His epidemiological data and animal studies in vitro and in vivo show the role of vitamin D in the biology of uterine fibroids [26]. The authors cite data from three studies showing a correlation between low levels of vitamin D and the incidence of uterine fibroids. The authors describe in vitro studies that demonstrate that vitamin D acts as a growth inhibitor and promotes apoptosis of leiomyoma cells.

Mohamed Ali et al. in their studies, it was shown that silencing of VDR in normal smooth muscle cells of the uterus induces the expression of Wnt4 / b-catenin and causes fibrosis, increased cell proliferation, and extracellular matrix production [40]. A prospective study by Lauren A. et al. including 2232 women with uterine myoma and 2432 healthy premenopausal women showed that three of the 12 polymorphisms of the genes involved in vitamin D metabolism were significantly associated with uterine myoma: rs4944957 and rs12800438 near DHCR7 and rs6058017 in ASIP [36]. 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, including direct measurement of vitamin D levels before the diagnosis of uterine fibroids.

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, they determined the expression of VDR genes in 5 women with uterine myoma using the Affymetrix U133 microcircuit. The data showed different levels of expression depending on location and suggest the role of vitamin D signaling in the biology of fibroids [30].

Ana Corachan et al. in her pilot prospective study, she 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 cell growth and inhibiting the Wnt / b-catenin pathway, but not by regulating apoptosis, suggesting that vitamin D is an effective therapy to stabilize the size of leiomyoma and prevent its growth [19]. According to other researchers, vitamin D supplementation in women with uterine myoma can lead to a significant decrease ($p < 0.001$) in tumor size after a 10-week course of therapy [38].

Thus, the results of in vitro and in vivo experimental studies, as well as retrospective clinical studies, indicate the existence of a clear protective effect of vitamin D on the growth of uterine fibroids, which is based on inhibition of cell proliferation, stimulation of apoptosis, regulation of extracellular matrix remodeling, and decrease in receptor expression sex hormones and other pharmacodynamic effects. In this regard, vitamin D should be considered not only as a promising adjuvant for pharmacotherapy in patients with uterine myoma, which, of course, requires more detailed study in the framework of prospective clinical studies, but also as a substrate for the development of new, even more effective antitumor drugs [4 ].

Although the results are conclusive, at current levels of data it is not enough to establish vitamin D as a drug therapy for the treatment of uterine fibroids in humans [35]. The next logical step would be

to demonstrate an inhibitory effect in humans, which would require a randomized controlled trial, unfortunately, which by now is not available. uterine fibroids remains poorly understood.

## VITAMIN D AND ITS REGULATION

Currently, vitamin D is assigned to the group of sexo-steroidal prohormones, 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 along the classic and alternative paths. Vitamin D2 is synthesized from ergosterol under ultraviolet radiation in plants, yeast, fungi and enters the body with these products. Vitamin D3 is synthesized in several stages.

An alternative way of vitamin D metabolism is through an enzyme that cleaves the side chain of cytochrome P450 - CYP11A1, in which the 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 differentiation of cells, like calcitriol. In addition, these metabolites enhance the protective mechanisms against UV-induced DNA damage to the skin and oxidative stress, have anti-tumor properties on cell lines. 20 (OH) D and 20, 23 (OH) D metabolites also act as partial VDR agonists. The same metabolites can bind to the α and γ isoforms of the irethrin-coupled 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 [10].

In a review of the literature, M.A. Bukhalko et al. information is presented on the role of VDR polymorphism in human pathology and the numerous pleiotropic effects of prohormone D on the human body [3]. 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 [8].

It is important to note that laboratory determination of the serum level of prohormone 25 (OH) D is 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 also makes it preferable for assessing vitamin D status [11].

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

**Table 1. Criteria for the availability of vitamin D by blood content (Russian Association of Endocrinologists. Clinical recommendations. 2015 [14]).**

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

Thus, studies in the field of the pathogenesis of uterine fibroids in combination with the achievements of modern technology and pharmacology made it possible to introduce in clinical practice medical, non-surgical, and minimally invasive surgical techniques, which are a real alternative to radical surgery, which was recently considered the gold standard in the treatment of this pathology [16].

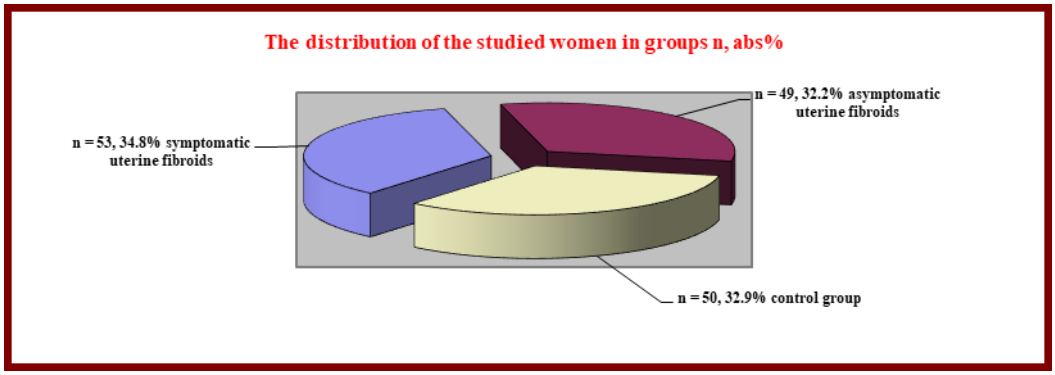
The aim of the study is to identify the level of vitamin D availability and its relationship with the clinical course in women with uterine fibroids.

## MATERIALS AND METHODS

The design of a cohort prospective controlled trial was used. In accordance with the goal, an integrated approach was used, providing for 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 uterine myoma. The main group of patients was divided into 2 subgroups - 53 women with symptomatic uterine myoma and 49 women with asymptomatic uterine myoma.




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 uterine fibroids 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 uterine fibroids 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 coagulogram, a biochemical blood test, an ultrasound of the uterus and appendages (determination of the volume of the uterus according to Brunn (1981) and myomatous node) with duplex scanning of the uterine artery, morphological studies of aspirates from the uterus. 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 quantitative determination - chemiluminescent analysis on microparticles (CMIA).

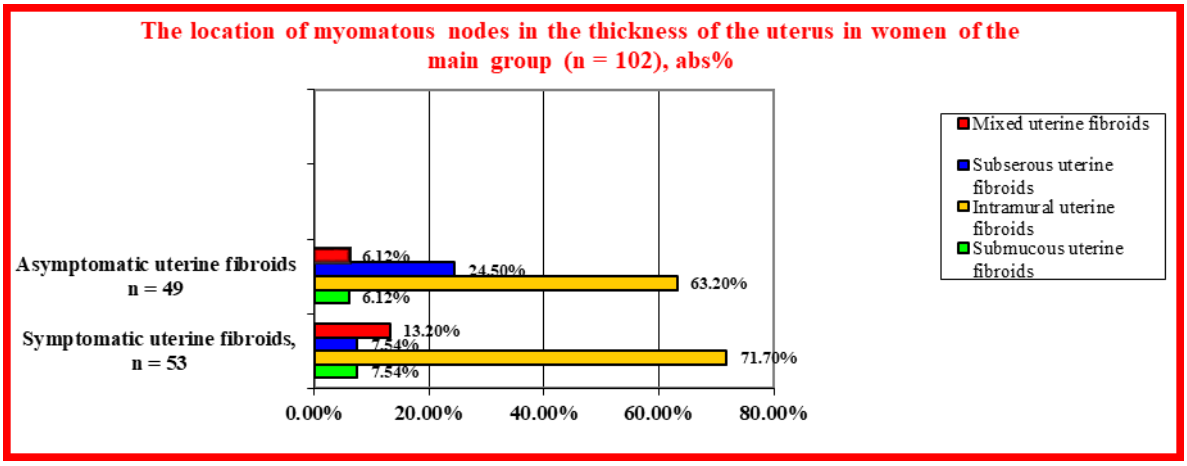
Mathematical processing and statistical analysis of the results were carried out using the program "Statistika 6.0". Non parametric methods were used. The average, relative values were calculated. Differences in indicators, as well as correlations between them, were considered significant at a significance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

## RESULTS AND DISCUSSION

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

All women of the main group were diagnosed with uterine fibroids by ultrasound (ultrasound). Ultrasound of women with uterine myoma revealed the number and localization of myomatous nodes. In women with symptomatic uterine fibroids ($n = 53$), 1/3 (32.1%) of women had multiple uterine fibroids (more than 2 myomatous nodes) and 2/3 (67.9%) had a solid tumor, whereas in the studied with asymptomatic uterine fibroids, multinodular uterine fibroids were found to be 2 times less compared with symptomatic uterine fibroids (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 in equal proportions and subserous (7, 15% and 24.5%) - 3 times more often detected in women with asymptomatic uterine myoma. Mixed myomatous nodes in women with symptomatic uterine fibroids

were 2 times more likely than in women with asymptomatic uterine fibroids (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 uterine myoma was 237.54 mm3, asymptomatic uterine myoma was 103.45 mm3 and in the control group was 52.1 mm3.

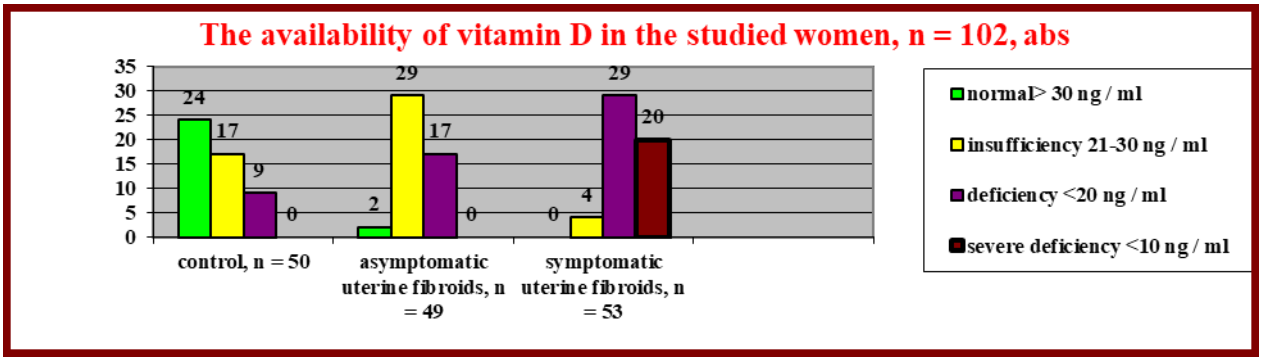
According to the analysis of risk factors for the development of uterine fibroids in the studied women of the main group in the subgroup of symptomatic uterine fibroids (n = 53), 1.9% of women calculated high risk (31 points), 84.9% - medium risk and 11, 3% is low risk, while in the subgroup of asymptomatic 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 of uterine fibroids in 34% and 24.5%, infertility in 3.7% and 2.4%, curettage of the uterine cavity 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 uterine fibroids).

Women with symptomatic uterine fibroids of the main group (n = 53) were treated 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 IN WOMEN STUDIED

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 [11].

An analysis of the initial vitamin D blood content of the blood showed that the values in the group of women with uterine fibroids 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 content of vitamin D in the blood in the structure of the main group in women with symptomatic uterine myoma, on average, it was 11.84 + 0.46 ng / ml and in the asymptomatic one it was 21.54 + 0.04, whereas in the control group 29, 83 + 1.13 ng / ml (p <0.001).




The distribution of women according to 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.

**Table 2. Vitamin D levels in women in the study groups.**

| № | Groups | Symptomatic uterine fibroids, n = 53 | | Asymptomatic uterine fibroids, n = 49 | | Control group, n = 50 | |
|---|---|---|---|---|---|---|---|
| | Criteria | n, abs | (ng / ml) | n, abs | (ng / ml) | n, abs | (ng / ml) |
| 1 | Norm | 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 | Deficit | 29 (54,7%) | 14,02±0,2*** | 17 (34,7%) | 16,8±1,6‘‘ | 9 (18%) | 14,2±0,9 |
| 4 | Severe deficit | 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.

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; whereas the correlation between these indicators in the main group, especially in the subgroup of symptomatic uterine myoma, was a direct average positive (r = 0.482, p <0.001).

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

Discussion. The women studied were mostly of late reproductive age, which is consistent with the authors' data that uterine fibroids are more often diagnosed in this period [12,13,46].

According to WHO (2012), vitamin D intake from food and factors affecting its absorption metabolism, as well as obesity, affect the state of vitamin D levels. The researchers described the relationship of excess BMI with vitamin D deficiency [23, 48]. Our analysis to identify excess BMI is consistent with the data of foreign researchers [29]: in 47.2% of women with symptomatic uterine myoma, obesity I, II, III degree was calculated (28.3%, 11.3%, 7.5%, respectively) .

In the main group of women with asymptomatic uterine myoma, 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 uterine myoma, normal values in women were not revealed a deficit of 54.7% and a pronounced deficit of 37.7%, which is 2.88 times greater than in the group of asymptomatic uterine fibroids and 5.4 times compared with the control group. It is noteworthy 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.

When determining the level of provision of prohormone D in the studied women, its pronounced deficiency was detected in the subgroup of symptomatic uterine myoma (6.62 + 0.9 ng / ml) in 37.7% of women with an explicit clinic of menorrhagia (in 100% of women) and recurrent course diseases, and in the subgroup of asymptomatic uterine myoma in 1/3 of patients (36.7%) there is 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 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 uterine myoma and clinical manifestations of the disease, and the size of the uterus. Thus, studying the saturation of the body with vitamin D, we found that in women with uterine fibroids especially with severe symptoms, deficiency prevails (in ½ women) and severe deficiency (in 1/3 of women), and in patients with uterine fibroids without clinical manifestations of the disease 2/3 of women have deficiency, 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 uterine fibroids (<10 ng / ml) had bright clinical manifestations of the disease: menorrhagia leading to anemia in women of this category, rapid growth of the myomatous node against a background of critical vitamin D deficiency and accompanying with pelvic pain, infertility, according to the ultrasound picture, an increase in the volume of the uterus and pronounced scularization of the perifibroid plexus, frequent relapses of the disease against the background the inefficiency of conservative therapy worsens the quality of life of women. It was established that in women with symptomatic uterine myoma, the level of vitamin D was significantly lower in the group compared with the group of asymptomatic uterine myoma, which is consistent with other researchers [29].

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 uterine fibroids, compared with the control group.

It was revealed that in women with vitamin D deficiency and / or deficiency, the chances of developing uterine fibroids is a positive strong factor, which proves the lack of prohormone as a strong provoking factor for the development of the disease in these women. It was revealed that in women with excess body weight, the chances of developing fibroids (OR) are also 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.

## 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 necessitates the search and introduction into clinical practice of new drugs and treatment methods with pronounced antiproliferative activity. The results of our studies show that lower values of vitamin D in patients with uterine myoma 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 health, given the high prevalence of vitamin D deficiency in developing countries, the impact of lifestyle and geographical latitude on the status of vitamin D. Further studies are needed 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 research in this direction should be considered extremely promising.

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