Vitamin D status in rheumatoid arthritis patients

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Recently, in the scientific world, interest in vitamin D has increased significantly, which has a healthful effect on the human body. To date, more than 30 000 scientific studies have been conducted on the study of the properties of vitamin D. It is known that rheumatoid arthritis patients (RA) often have a wide range of concomitant diseases and metabolic disorders. Current studies indicate that most RA patients have deficiency and insufficiency of vitamin D. At the same time, there is evidence that the degree of the RA activity may have a definite influence on the ability of the body to intake vitamin D. The article presents modern literary data of the vitamin D role in homeostasis, the relationship between vitamin D and the autoimmune process in RA, and the results of own studies and analysis of the prevalence of deficiency and insufficiency of vitamin D in RA patients.

The objective: to assess the vitamin D status in RA patients and to study the prevalence of deficiency and insufficiency of vitamin D in RA patients.

Materials and methods. We enrolled 30 RA patients, the age of 28–46 years old, 24 female and 6 male, who signed an informed consent to participate in the study. The control group was 20 people (13 female and 7 male) aged 24–44 years, without autoimmune pathology, inflammatory conditions and diseases, and signed an informed consent to participate in the study. At the time of the survey RA patients and the control group did not receive any vitamin D medications.

For all patients and the control group carried out the thorough physical and laboratory examination. For evaluate vitamin D status, the M.F. Holick et al. (2011) classification was used, according to which the level of blood serum 25(OH)D is 75–375 nmol/L is considered as normal, the level of 50–75 nmol/L – as an insufficiency of vitamin D and the level below 50 nmol/L – as vitamin D deficiency. The statistical analysis was conducted on the personal computer by the Microsoft Excel and Statistica 10.0 programs. The average values (M), the standard deviation (s) and the reliability of statistical indicators (p). A p value of <0.05 was considered statistically significant.

Results. 22 (73.33%) RA patients showed a decrease 25(OH)D level in serum. Vitamin D insufficiency was in 8 (26.67%) patients, 25(OH)D level in blood serum was 42.63±2.13 nmol/L. Vitamin D deficiencies in 17 (56.67%) RA patients, 25(OH)D level was 35.29±8.99 nmol/L. The normal values of vitamin D were in 8 (26.67%) RA patients, 25(OH)D level was 83.5±8.45 nmol/L. In 18 (90.00%) persons of control group the 25(OH)D level was normal – 105.67±7.62 nmol/L. In 2 (10.00%) persons of control group the 25(OH)D was 69.05±3.47 nmol/L, which corresponds to vitamin D insufficiency. There was no vitamin D deficiency in the control group.

The increased C-reactive protein (C-rP) was in 15 (50.00%) RA patients. The middle C-rP was 300.15 nmol/L (Min 62.9 nmol/L; Max 633.5 nmol/L). We conducted the analysis of comparing the levels of 25(OH) D with the degree of RA disease activity by DAS28-CRP. In RA patients with III degree of activity the average level of 25(OH)D was 45.00±24.16 nmol/L and was significantly lower than in RA patients with I degree of activity, whose the average level of 25(OH)D was 55.73±20.06 nmol/L (p<0.05). The average level of 25(OH)D in serum in RA patients with II degree of activity was 59.50±29.12 nmol/L.

The level of serum ionized calcium in both studied groups were within the normal range and evaluate 2.38±0.27 mmol/L in RA patients and 2.43±0.18 mmol/L in the control group. Conclusions. The lowered levels of vitamin D in RA patients are found to be significantly more frequent than in the control group which equal in sex and age (p<0.001). The vitamin D insufficiency was found in 26.67% RA patients and in 10.00% control group (p<0.05). The vitamin D deficiency has been reported in 36.67% RA patients and has not been observed in the control group. There is a correlation between vitamin D deficiency and RA activity. There was a negative correlation between the vitamin D level and the degree of RA activity by the DAS28-CRP (r=-0.87; p<0.05). The vitamin D deficiency should be considered as a predictor of RA activity, which allows recommending the vitamin D medications as an additional therapy in RA patients.

Key words: rheumatoid arthritis, vitamin D, vitamin D deficiency, vitamin D insufficiency.

The most active vitamin D molecular species are ergocalciferol (vitamin D₂) and cholecalciferol (vitamin D₃). For the first time, vitamin D deficiency described in the writings by Soranus of Ephesus (98–138 AD) and the ancient physician of Galen (131–211 AD). In 1918, the doctor Edward Mellanby in experiments on dogs showed that cod fat acts as a means anti-rachitic due to the presence in it of a certain vitamin [25]. In 1924, A. Hess and M. Weinstock during the action of ultraviolet rays whis wavelength 280–310 nm on vegetable oils received the first vitamin D₁-ergosterol. In 1928, Adolf Windaus received the Nobel Prize in Chemistry for the discovery of 7-dehydrocholesterol, a precursor of vitamin D, and in 1937 he isolated from the surface layers of the pig skin 7-dehydrocholesterol, which at ultraviolet radiation became an active vitamin D₃ [30].

Almost 80 years were needed to re-open vitamin D in the human body, as a hormone. In 1998, Hector F. DeLuca et al. (University of Wisconsin-Madison) described the presence of specific vitamin D receptors not only in target-tissues (intestines, bones, kidneys), but also in other tissues of the body. The identification of vitamin D receptors in cancer cells indicated wider functions of vitamin D than regulation of calcium metabolism and osteogenesis. There were found that vitamin D simulates secretion of insulin, thyroid hormones, parathormone during different researches. Thus, adequate vitamin D3 photosynthesis in the skin started to regarded as an important anti-carcinogenic factor, and as an additional factor in the fight against obesity and glucose tolerance.

Sources and metabolism of vitamin D

It is known, that vitamin D (in particular, its two most significant forms) has endogenous and exogenous origin in the human body. The main source of vitamin D is cholecalciferol...
proved that the active form of vitamin D₃ (ergocalciferol) is
in the body is food. Thus, in 1931, A. Scheunert experimentally
proved that the active form of vitamin D₃ (ergocalciferol) is
formed as a result of irradiation in the ultraviolet spectrum of
yeast and edible fungi [27].

Endogenous vitamin D₃ synthesis occurs in the skin under
the action of ultraviolet radiation (wavelength 290–320 nm)
in the composition of the sunlight. The epidermis and derma
contain the natural provitamin D (7-dehydrocholesterol),
which, under the influence of ultraviolet radiation, is
converted into provitamin D₃. Further, during the day, the skin
temperature contributes to the transformation of provitamin
D₃ into vitamin D₃. Vitamin D₃ in turn, binds to the circulating
carrier protein (vitamin D-binding protein) and enters the
bloodstream. In the liver, by hydroxylation in the 25th position,
vitamin D is converted into 25-oxyholecalciferol (25-ΟΗ-D₃).
Subsequently, in a complex of vitamin D-binding protein, it
is transported to the kidneys, where, with the participation
of parathormone, the final phase of activation of vitamin
calcitriol-1.25-dihydroxycholecalciferol (1.25(OH)D₃)
occurs. Today, 1.25(OH)₂D₃ is considered a potent kidney
hormone of the vitamin D group. It interacts with many target organs throughout the body by binding to
the nuclear receptor of vitamin D [2]. The amount of
vitamin D, which synthesized by sunlight, depends not only
on the wavelength, but also on the pigmentation of the skin
and the level of contamination the atmosphere. Also, the
bioavailability of vitamin D depends on age and it decreases
with age [15]. It has been established that in people 65 years
old and older observed a fourfold decrease in ability formation
of vitamin D₃ in the skin. In the winter, vitamin D deficiency
occurs more often than in the summer [18].

Absorption of vitamin D occurs predominantly in the
proximal small intestine in the presence of bile acids. After
absorption, cholecalciferol is present in the chylomicrons in
free form and partly in the form of ether. In the blood, most
of it is in a bound state with gamma-globulins and albumins.
Deposition of vitamin D is largely in the adipose tissue, as
well as in the skin, muscle and liver. The main processes of
biotransformation occur in the skin, liver, kidneys [4].

The functions of vitamin D in the human body
As previously established, the action of 1.25(OH)D on the
intestine, bone, and kidneys is to increase the permeability
of the intestinal epithelium for calcium and phosphorus. This
is increasing the absorption of calcium, as well as the
mobilization of calcium from bones, establishing an adequate
concentration of calcium and phosphorus in extracellular fluid
to ensure normal bone mineralization. Vitamin D also affects
the differentiation of cells and prevents their proliferation.
It was found that 1α-hydroxylation of 25(OH)D occurs
not only in the kidneys, but also in many other tissues. The
extra-kidney-synthesized 1.25(OH)D acts as an autocrine
agent with cell-specific functions, such as inhibition of cell
proliferation, cell differentiation stimulation and immune
regulation. Most biological actions of 1.25(OH)D are due
to interaction with nuclear receptors of vitamin D, which
are located on cellular and nuclear membranes. The expression
of these receptors is found in a variety of tissues and cells,
in particular in epidermal, hematopoietic, and many cancer cells.

Nuclear receptors of vitamin D are also present on many
cells of the immune system, including antigen presenting
cells (monocytes / macrophages, dendritic cells). In a number
of modern studies were found that 1.25(OH)D actively
participates in the regulation of immunogenesis and cellular
proliferation [19]. In particular, it inhibits antigen-induced
proliferation of T-cells, production of cytokines, suppresses the
development of helper T-cells of type 1 (Th-1), vitamin D can thereby
stimulate the development of Th-2-cells, which can be used in
the treatment of autoimmune diseases [24]. Also, 1.25(OH)D
and its analogs suppress differentiation and maturation of
dendritic cells, transforming them into antigen presenting cells
that play a key role in inducing a T-mediated immune response.

Assessment of vitamin D status
The extra-kidney activity of 1.25(OH)D depends on the
serum level 25(OH)D). The serum level of 25(OH)D does not
directly reflect the supply of vitamin in the tissues of the body,
but it can show the total amount of vitamin D, which produced
in the skin and consumed with food and supplements [11, 16].
It is generally accepted to use the classification M.F. Holick
et al. (2011) for the assessment of vitamin D status.

In accordance with this classification:

- the 25(OH)D blood serum level 75–375 nmol/L is
considered as normal;
- the level 50–75 nmol/L is insufficient vitamin D;
- the level below 50 nmol/L is vitamin D deficiency.

Research of vitamin D in RA patients
RA patients often have a wide range of concomitant
diseases and metabolic disorders [3, 10]. Current studies
indicate that vitamin D deficiency and insufficiency are
observed in most RA patients. At the same time, there is
evidence that the degree of activity of the RA may have a
certain effect on the ability of the body to uptake vitamin D
[6, 7].

The researches conducted by guidance of prof. V.V. Povo-
rozyuk in 2016, showed a negative correlation between the
level of 25(OH)D in serum and clinical and biochemical pa-
rameters of RA activity [6, 7]. The interes of treseachers in
insufficiency and deficiency of vitamin D is also due to the
impact on the course and prognosis of the disease and on the
quality of life of RA patients.

Regarding RA epidemiology, the rates of morbidity in
the world are relatively stable and vary in the range from
0.5% to 1.0% [16], in particular, there is evidence of a higher
prevalence of RA among the inhabitants of the northern
countries compared to the southern ones, which may be with
vitamin D by influence of ultraviolet radiation. For example,
in Finland it makes up 0.8%, in Italy 0.3% [14].

Costenbader K.H., Feskanich D. et al. (2008) have shown
that a well-balanced diet does not always ensure adequate
vitamin D intake, as it is contained in a limited amount of
foods, in particular in the form of D₃ – of plant origin, D₃ –
of animal origin [13]. Vitamin D deficiency is contributing to
insufficent food intake, limitation of sunlight, and violation of
vitamin D digestibility due to disease [29]. An additional dose
of vitamin D and sufficient insolation helps to reduce the signs
of inflammation somewhat, prolong remission, and reduce the
risk of disability in RA patients. The role of vitamin D in the
development of autoimmune pathological response differs from
its role in the normal function of the immune system. It has
been established that vitamin D activates T-lymphocytes, but
excessive activation of T-cells in RA patients does not occur
because the disease regulates the release of proinflammatory
cytokines, reducing their formation [24, 19].
The study, which conducted within the framework of the Iowa Women’s Health Study (IWHS) and published in 2003, in the Journal of Rheumatology, examined the consumption of vitamin D in food and dietary supplements by the questionnaires before the start of RA. An attempt was made to link the consumption of vitamin D and the incidence of RA in older women. The results of the study support the view that vitamin D plays an important role in preventing RA. The study included about 41,000 women aged 55–89 who had no history of RA. During the 11 years of observation, which included routine measurements of level 25(OH)D, 152 new cases of RA were confirmed. The consumption of vitamin D and calcium was assessed using questionnaires. The findings of researchers indicated a negative correlation between higher intake of vitamin D and the risk of developing RA, particularly in patients taking vitamin D supplements, and there was no association between calcium intake and the risk of developing RA. There was also an increased risk of RA among older women with lower 25(OH)D levels, but researchers note that the findings are preliminary. Separate new studies suggest that there is not enough data to confirm the low levels of vitamin D in serum as a risk factor for RA development [26].

Also, the researchers studied another factor: the effect of medication of RA on calcium metabolism. It is known that glucocorticoids, in particular, prednisolone, in long-term administration, have a negative effect on calcium metabolism, reduce the effect of vitamin D on absorption of Ca2+ in the intestinal cavity and cause secondary osteoporosis, steroid myopathy, pathological bone fractures. Therefore it is recommended the prophylaxis of osteoporosis, especially in patients with risk factors (genetic predisposition, elderly age, postmenopausal period, inadequate protein and calcium intake, excessive smoking and alcohol use, decreased physical activity).

Thus, in one of the studies conducted on the basis of the Institute of Biochemistry, Paladin National Academy of Sciences of Ukraine and published in 2016, in the European Review for Medical and Pharmacological Sciences, was evaluated the effectiveness of vitamin D, and its combined action with vitamin E in the correction of phagocytes functions disorders caused by chronic glucocorticoid use. The appointment of prednisolone was accompanied by a deficiency of vitamin D, and decomposition of the function of phagocytes associated with antimicrobial activity. The combined use of vitamin D3 with prednisolone and, to a greater extent, its association with α–tocopherol partially restores the function of phagocytes. Thus, vitamin D3 and α–tocopherol can prevent immunosuppressive effects of prednisolone by increasing the effectiveness of phagocytosis oxygen-dependent mechanisms and increasing the functional activity of phagocytic cells [28].

The objective: to assess the vitamin D status in RA patients and to study the prevalence of deficiency and insufficiency of vitamin D in RA patients.

MATERIALS AND METHODS
The study was conducted at the Family Medicine Department of Shupyk National Medical Academy of Postgraduate Education on the basis of the Municipal Institution of Kyiv Regional Council «Kyiv Regional Clinical Hospital» in 2017. The study included 30 RA patients aged 28–46 years old, 24 female and 6 male (80.0% and 20.0% respectively), who signed an informed consent to participate in the study. The control group was 20 people, 13 female and 7 male (65.0% and 35.0% respectively), aged 24–44 years old, without autoimmune pathology, inflammatory conditions and diseases, and signed an informed consent to participate in the study. At the time of the survey RA patients and the control group did not receive any vitamin D medications.

For all patients and the control group carried out thorough physical and laboratory examination. For evaluate vitamin D status, the M.F. Holick et al. (2011) classification was used, according to which the level of blood serum 25(OH) D is 75–375 nmol/L is considered as normal, the level of 50–75 nmol/L – as an insufficiency of vitamin D and the level below 50 nmol/L – as vitamin D deficiency. The statistical analysis was conducted on the personal computer by the Microsoft Excel and Statistica 10.0 programs. The average values (M), the standard deviation (s) and the reliability of statistical indicators (p). A p value of <0.05 was considered statistically significant.

RESULTS AND DISCUSSION
By results of our study, 22 (73.33%) RA patients showed a decrease 25(OH)D level in serum. Vitamin D insufficiency was in 8 (26.67%) patients, 25(OH)D level in blood serum was 42.63±2.13 nmol/L. Vitamin D deficiency in 17 (56.67%) RA patients, 25(OH)D level was 35.29±8.99 nmol/L. The normal values of vitamin D were in 8 (26.67%) RA patients, 25(OH)D level was 83.5±8.45 nmol/L. In 18 (90.00%) persons of control group the 25(OH)D was normal – 105.67±7.62 nmol/L. In 2 (10.00%) persons of control group the 25(OH)D was 69.05±3.47 nmol/L, which corresponds to vitamin D insufficiency. There was no vitamin D deficiency in the control group.

The increased C-reactive protein (С-RP) was in 15 (50.00%) RA patients. The middle С-RP was 300.15 nmol/L (Min 62.9 nmol/L; Max 653.5 nmol/L). We conducted the analysis of comparing the levels of 25(OH) D with the degree of RA disease activity by DAS28-CRP. In RA patients with III degree of activity the average level of 25(OH)D was 45.00±24.16 nmol/L and was significantly lower than in RA patients with I degree of activity, whose the average level of 25(OH)D was 55.73±20.06 nmol/L (p<0.05). The average level of 25(OH)D in serum in RA patients with II degree of activity was 59.50±29.12 nmol/L.

The level of serum ionized calcium in both studied groups were within the normal range and evaluate 2.38±0.27 nmol/L in RA patients and 2.43±0.18 nmol/L in the control group.

CONCLUSIONS
1. The lowered levels of vitamin D in RA patients are found to be significantly more frequent than in the control group which equal in sex and age (p<0.001).
2. The vitamin D insufficiency was found in 26.67% RA patients and in 10.00% control group (p<0.05).
3. The vitamin D deficiency has been reported in 56.67% RA patients and has not been observed in the control group.
4. There was a correlation between vitamin D deficiency and RA activity. There was a negative correlation between the vitamin D level and the degree of RA activity by the DAS28-CRP (r=-0.87; p<0.05).
5. The vitamin D deficiency should be considered as a predictor of RA activity, which allows recommending the vitamin D medications as an additional therapy in RA patients.

Prospects for further research. Today, the role of vitamin D in the development and progression of RA has not yet been fully studied, but there is a certain correlation between vitamin D deficiency and RA activity. It is worth considering cholecalciferol not only as a nutrient supplement for the prevention of rickets in children, but also as well as an important autocrine agent to maintain an adequate concentration in the serum of blood, it is necessary to pay attention.
Статус витамина D у пациентов с ревматоидным артритом

В последнее время в научном мире значительное внимание стали уделять роли витамина D, который оказывает оздоровительное воздействие на организм человека. На сегодня проведено более 30 тыс. научных исследований, посвященных изучению его влияния на организм человека. Известно, что у пациентов с ревматоидным артритом (РА) часто проявляется коррекция спектра сопутствующих заболеваний и метаболических нарушений. Современные исследования показывают, что у пациентов с РА наблюдается дефицит и недостаточность витамина D. В то же время существуют дан- ные, что уровень активности течения РА может влиять на связь РА с недостаточностью витамина D. В статте приведены современные литературные данные о важности витамина D, а также характеристика заболеваний и анализ распространенности дефицита и недостаточности витамина D у пациентов с РА.

Среди заболеваний, связанных с дефицитом витамина D, в первую очередь, следует назвать ревматоидный артрит (РА). Основная цель данной работы — оценить статус витамина D у пациентов с РА на основании проведенного исследования.

Цель исследования: оценить статус витамина D у пациентов с РА и определить зависимость дефицита и недостаточности витамина D у пациентов с РА.

Материалы и методы. Проведен набор и обследование 30 пациентов с РА в возрасте 28–46 лет, 24 женщины и 6 мужчин, которые предоставили письменное согласие на участие в исследовании. В качестве контрольной группы использовали 21 здоровый человек (15 женщин и 7 мужчин) в возрасте 24–44 лет без аутоиммунной патологии, воспалительных состояний и заболеваний. На момент обследования пациенты с РА и лица группы контроля не принимали никаких препаратов витамина D. Всем пациентам и лицам группы контроля проводили тщательное физическое и лабораторное обследование.

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Все пациенты с РА и лица группы контроля участвовали в исследовании. Оценка статуса витамина D у пациентов с РА и лиц группы контроля проводилась на персональном компьютере с помощью программы Microsoft Excel for Windows и Statistica 10.0. Оценивали основные статистические параметры: среднюю (М), стандартное отклонение (s) и достоверность статистических показателей (р), соответствующих количественных соотношений. Результаты.

У ревматоидный артрит, витамин D, дефицит витамина D.

В статусе витамина D у пациентов с РА значимо ниже, чем у лиц группы контроля. Средний уровень 25(ОН)D в сыворотке крови у пациентов с РА составлял 83,5±8,45 нмоль/л, у лиц группы контроля — 105,67±7,62 нмоль/л, что статистически значимо ниже, чем у пациентов с РА.

Результаты. У результатов исследования у 27 (90.00%) пациентов с РА было выявлено снижение уровня 25(ОН)D в сыворотке крови. У 8 (26.67%) пациентов уровень 25(ОН)D в сыворотке крови составлял 83,5±8,45 нмоль/л, что статистически значимо выше, чем у пациентов с РА.

Заключение. Сниженный уровень витамина D у пациентов с РА ассоциирован с повышенным риском развития и прогрессирования заболевания. Витамин D является важным регулятором метаболизма кальция и фосфора, что может способствовать улучшению состояния заболеваемости у пациентов с РА.

Ключевые слова: витамин D, дефицит витамина D, недостаточность витамина D.
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REFERENCES