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THE ROLE OF VITAMIN D IN RHEUMATOID ARTHRITIS AND ITS CORRELATION WITH DISEASE ACTIVITY

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Introduction

Vitamin D has immunomodulatory and anti-inflammatory effects, and its deficiency can cause a number of autoimmune diseases, including rheumatoid arthritis (RA). The relationship between vitamin D levels and RA severity is of interest to many researchers, as decreased vitamin D intake is associated with increased susceptibility to the development of rheumatoid arthritis (RA), and vitamin D deficiency is associated with disease activity in patients with RA.

Objective: To determine the association between serum vitamin D status and the course of rheumatoid arthritis.

Materials and methods: This case-control study was conducted at the Tashkent Medical Academy Clinic from October 2024 to January 2025. The study group included 60 patients with a confirmed diagnosis of RA who met the 1987 American modified criteria. An additional 60 age- and gender-matched participants without RA were included in the study as controls. The diagnosis of RA was established based on clinical symptoms, radiographic features, and an anticitrullinated protein level greater than 15 U/mL. All participants underwent a complete blood count and biochemical analysis, including determination of rheumatoid factor (RF) and C-reactive protein (CRP) levels. Serum 25(OH)D levels were measured. Vitamin D deficiency and insufficiency were determined according to the classification of the International Institute of Medicine and the Endocrinology Committee for Clinical Practice Guidelines. The data were entered into Statistica 6.0 (StatSoftInc., USA) for subsequent statistical analysis.

Results: The average age of participants with RA was 45 ± 10 years, compared with 47 ± 10 years in the control group. Participants with RA had significantly lower mean vitamin D levels than those in the control group (28.87 ± 5.12 vs. 34.12 ± 6.83; p value: <0.0001). The mean vitamin D level in patients with positive rheumatoid factor (RF)- was significantly lower compared to patients with RF-negative RA (25.11 ± 6.17 vs. 33.23 ± 5.03; p value: <0.0001). In the RA group, 44 (73.3%) participants were RF-positive. Among RF-positive patients, there were more participants with hypovitaminosis D compared to RF-negative ones (85.0% vs. 43.3%; p value: 0.00001).

Conclusion: Vitamin D deficiency is highly prevalent in patients with RA and is associated with disease severity. Therefore, vitamin D deficiency can be considered as a factor contributing to the worsening of rheumatoid arthritis. Thus, the study confirmed the importance of a comprehensive approach in the treatment of RA, including the use of vitamin D, to reduce the risk of osteoporosis and improve the clinical condition of patients.

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Введение: Витамин D обладает иммуномодулирующим и противовоспалительным действием, а его дефицит может вызывать ряд аутоиммунных заболеваний, включая ревматоидный артрит (РА). Связь между уровнем витамина D и тяжестью РА представляет интерес для многих исследователей так как снижение потребления витамина D связано с повышенной восприимчивостью к развитию ревматоидного артрита (РА), а дефицит витамина D связан с активностью заболевания у пациентов с РА.

Цель: Определить связь между статусом витамина D в сыворотке крови и течением заболевания ревматоидного артрита.

Материалы и методы: Это исследование «случай-контроль», проводившееся в клинике Ташкентской медицинской академии с октября 2024 года по январь 2025 года. В исследовательскую группу были включены 60 пациентов с подтвержденным диагнозом РА соответствовавших Американским модифицированным критериям 1987 г. Еще 60 участников без РА, сопоставимых по возрасту и полу, были включены в исследование в качестве контрольной группы. Диагноз РА устанавливался на основании клинических симптомов, рентгенологических особенностей и уровня антицитруллинированного белка более 15 ед/мл. Всем участникам было проведено общий и биохимический анализ крови, определяли уровень ревматоидного фактора (РФ) и С-реактивного белка (СРБ). Измеряли уровень 25(OH)D в сыворотке крови. Дефицит и недостаточность витамина D устанавливали согласно классификации Международного Института медицины и Комитета эндокринологов по созданию протоколов по клинической практике. Полученные данные были внесены в компьютерную программу Statistica 6.0 (StatSoftInc., США) для последующей статистической обработки.

Полученные результаты: Средний возраст участников с РА составлял 45 ± 10 лет, тогда как в контрольной группе — 47 ± 10. У участников с РА средний уровень витамина D был значительно ниже, чем в контрольной группе (28,87 ± 5,12 против 34,12 ± 6,83; значение p: <0,0001). Средний уровень витамина D у пациентов с положительным ревматоидным фактором (РФ)- был значительно ниже по сравнению с пациентами с (РФ)-отрицательным РА (25,11 ± 6,17 против 33,23 ± 5,03; значение p: <0,0001). В группе РА 44 (73,3%) участник имел РФ-положительный результат. Среди РФ-положительных пациентов было больше участников с гиповитаминозом D по сравнению с РФ-отрицательными (85,0% против 43,3%; значение p: 0,00001).

Заключение: У пациентов с РА отмечается высокая распространенность дефицита витамина D, и существует связь с тяжестью заболевания. Исходя из этого дефицит витамина D можно рассматривать как один из факторов, способствующих ухудшению течения ревматоидного артрита. Таким образом, проведенное исследование подтвердило важность комплексного подхода в лечении РА, включая использование витамина D, для снижения риска остеопороза и улучшения клинического состояния пациентов.

Kirish: D vitamini tanqisligi 1 tip qandli diabet, tarqoq skleroz va revmatoid artrit (RA) kabi autoimmun kasalliklarning patogenezida ishtirok etadi. D vitaminini iste’mol qilishning kamayishi revmatoid artrit (RA) rivojlanishiga sezuvchanlikning oshishi bilan bog'liq va D vitamini etishmovchiligi RA bilan og‘rigan bemorlarda kasallik faolligi bilan bog‘liq.

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Maqsad: Qon zardobidagi D vitamini holati va revmatoid artritning kechishi o‘rtasidagi bog‘liqlikni aniqlash.

Materiallar va usullar: Bu Toshkent Tibbiyot Akademiyasi klinikasida 2024-yil oktabrdan 2025-yil yanvarigacha o‘tkazilgan holat-nazorat tadqiqotidir. Tadqiqot guruhiga 1987-yilda o'zgartirilgan Amerika mezonlariga javob beradigan RA tashxisi qo'yilgan tasdiqlangan 60 bemor kiritilgan. Tadqiqotga RAsiz qo'shimcha 60 nafar yosh va jinsga mos keladigan ishtirokchilar nazorat guruhi sifatida kiritildi. RA tashxisi klinik alomatlar, rentgenologik xususiyatlar va 15 U/ml dan yuqori antitsitrullinlangan oqsil darajasi asosida qo'yildi. Barcha ishtirokchilar to'liq qon tahlili va biokimyoviy tahlildan o'tkazildi, jumladan, revmatoid omil (RF) va C-reaktiv oqsil (CRP) darajasini aniqlash. Zardobdagi 25(OH)D darajasi o'lchandi. D vitamini yetishmovchiligi va yetishmovchiligi Xalqaro tibbiyot instituti va Klinik amaliyot bo'yicha endokrinologiya qo'mitasining tasnifiga muvofiq aniqlandi. Ma'lumotlar keyingi statistik tahlil uchun Statistica 6.0 (StatSoftInc., AQSh) ga kiritildi.

Natijalar: RA bilan og'rigan ishtirokchilarning o'rtacha yoshi 45 ± 10 yoshni tashkil etdi, bu nazorat guruhidagi 47 ± 10 yoshga nisbatan. RA bilan og'rigan ishtirokchilarda D vitaminining o'rtacha darajasi nazorat guruhidagilarga qaraganda ancha past edi (28,87 ± 5,12 va 34,12 ± 6,83; p qiymati: <0,0001). Musbat revmatoid omil (RF) bilan og'rigan bemorlarda D vitaminining o'rtacha darajasi RF-manfiy RA bilan og'rigan bemorlarga nisbatan ancha past edi (25,11 ± 6,17 va 33,23 ± 5,03; p qiymati: <0,0001). RA guruhida 44 (73,3%) ishtirokchi RF-musbat edi. RF-musbat bemorlar orasida RF-manfiy bo'lganlarga qaraganda D gipovitaminozi bilan og'rigan ishtirokchilar ko'proq edi (85,0% va 43,3%; p qiymati: 0,00001).

Xulosa: D vitamini yetishmovchiligi RA bilan og'rigan bemorlarda juda keng tarqalgan va kasallikning og'irligi bilan bog'liq. Shuning uchun, D vitamini yetishmovchiligini revmatoid artritning yomonlashishiga olib keladigan omil sifatida ko'rib chiqish mumkin. Shunday qilib, tadqiqot RA ni davolashda osteoporoz xavfini kamaytirish va bemorlarning klinik holatini yaxshilash uchun D vitamini qo'llashni o'z ichiga olgan kompleks yondashuvning muhimligini tasdiqladi.

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune systemic inflammatory disease of connective tissue of unknown etiology, characterized by: inflammation predominantly of the peripheral joints; destruction of intra-articular cartilage; destructive, deforming, progressive, symmetrical polyarthritis with subsequent ankylosing of the affected joints; often extra-articular manifestations with damage to internal organs. RA is, first of all, a chronic inflammatory debilitating disease of the synovial joint lining [1]. The prevalence of RA is approximately 0.5-1% of the world population [2]. The pathogenesis of RA is an autoimmune inflammatory disease that includes pathological activation of osteoclasts, B and T cells, fibroblasts, chondrocytes, dendritic cells and proteolytic enzymes, which leads to damage to cartilage, bones and tendons [3]. Moreover, activation of the immune system leads to severe complications, causing systemic and extra-articular manifestations of RA [3].

Until recently, the dominant function of the active form of vitamin D (calcitriol) was believed to be its influence on calcium-phosphorus homeostasis. However, recent studies have demonstrated its pleiotropic effects on numerous physiological processes. In the vast majority of cases, calcitriol exerts its effects through vitamin D receptors (VDRs), which are found in over forty target tissues. Recent studies have shown that VDRs are located in primary lymphoid organs—the thymus and bone marrow—that is, at the sites of immune cell differentiation, as

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well as in mononuclear cells, dendritic cells, antigen-bearing and activated B cells, CD4+ T cells, and neutrophils. VDR activation in immune defense cells leads to gene transcription and initiates a cascade of antiproliferative and immunoregulatory processes. Given that vitamin D deficiency (VDD) is associated with exacerbation of the Th1-mediated immune response, it plays a role in the pathogenesis of RA. Immune cells express vitamin D receptors. Vitamin D is responsible for regulating innate and adaptive immune responses and strengthening the immune system; a decrease in its level leads to autoimmunity [4]. Several autoimmune diseases are associated with vitamin D, including insulin-dependent diabetes mellitus, multiple sclerosis, inflammatory bowel disease, systemic lupus erythematosus, and RA [5]. In this study, we will determine the association between vitamin D levels and RA.

Materials and methods.

This case-control study was conducted at the Tashkent Medical Academy Multidisciplinary Clinic from October 2024 to January 2025. The study group included 60 patients with a confirmed diagnosis of RA who met the 1987 American Modified RA Criteria. The diagnosis was established based on clinical symptoms, radiographic features, and an anticitrullinated protein level greater than 15 U/mL. An additional 60 participants without RA, matched for age and gender, were included in the study as a control group. The control group consisted of the patients' relatives or persons accompanying them to the hospital. Participants who reported taking vitamin D supplements were excluded from the study. Patients were included in the study through a consecutive convenience sample. The entire procedure was explained to each participant, and their consent was obtained. After registration, data were collected on variables such as gender, age, smoking history, rheumatoid factor (RF), and comorbidities such as diabetes, hypertension, and asthma. Patients with vitamin D levels less than 30 ng/ml were classified as having hypovitaminosis D [6]. Statistical analysis was performed using Statistica 6.0 (StatSoftInc., USA).

Results obtained

The mean age of the participants with RA was 43 ± 10 years, while that of the control group was 45 ± 10. All parameters, including gender distribution and comorbidities, were compared between the two groups, and no
significant differences were found (Table 1).

Table 1

Comparison of characteristics of participants in both groups

Characteristics	Research group (n=60)	Control group (n=60)	p
Age in years (mean ± standard deviation)	45 ± 10	47 ± 10	HC
Men (%)	22 (36.6%)	23 (38.3%)	HC
BMI over 30 kg/m2 (%)	11 (18.3%)	12 (20.0%)	HC
Diabetics (%)	15 (25.0%)	16 (26.6%)	HC
Hypertensive patients (%)	17 (28.3%)	15 (25.0%)	HC
Current smokers (%)	9 (15.0%)	10 (16.7%)	HC

Note: BMI - body mass index; kg/m2 - kilograms per square meter; NS - not significant

The mean vitamin D level in participants with RA was significantly lower compared with the control group (28.87 ± 5.12 vs. 34.12 ± 6.83; p value: <0.0001). There were more

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participants with hypovitaminosis D in RA than in the control group (76.6% vs. 45.0%; p value: <0.0001) (Table 2).

Table 2

Comparison of vitamin D levels in the study and control groups

Characteristics	Research group (n=60)	Control group (n=60)	p
Average vitamin D level (ng/ml)	28.87 ± 5.15	34.12 ± 6.83	<0.0001
Hypovitaminosis D (%)	46 (76.6%)	27 (45.0%)	<0.0001

Note: ng/ml - nanograms per milliliter

In the RA group, 44 (73.3%) participants were RF-positive. The mean vitamin D level in seropositive RA participants was significantly lower compared to RF-negative RA patients (25.11 ± 6.17 vs. 33.23 ± 5.03; p value: <0.0001). There were more participants with hypovitaminosis D among RF-positive participants compared to RF-negative ones (85.0% vs. 43.3%; p value: 0.00001) (Table 3).

Table 3

Comparison of vitamin D levels in combination with rheumatoid factor

Характеристики	RA patients with positive RF (n= 44)	RA patients with negative RF (n= 16)	p
Average vitamin D level (ng/ml)	25.11 ± 6.17	33.23 ± 5.03	<0.0001
Hypovitaminosis D (%)	37 (84.0%)	7 (43,7%)	<0.0001

Note: ng/ml - nanograms per milliliter, RA - rheumatoid arthritis, RF - rheumatoid factor

Discussion

Our study results showed that patients with RA had lower levels of vitamin D status. Moreover, mean vitamin D levels were lower in RF-positive patients than in RF-negative RA participants. Similarly, hypovitaminosis was reported to be more common in RF-positive RA patients than in RF-negative RA patients.

Consistent with our study results, a cross-sectional study by Atwa et al. found that vitamin D deficiency was significantly more common in patients with RA [6]. Another retrospective study by Haque et al. suggested that 61% of RA patients had vitamin D deficiency [7]. A prospective study involving 29,368 healthy women was conducted to examine the relationship between vitamin D and RA activity. Vitamin D was added to their diets. The group reported only 152 cases of RA in these women over an 11-year follow-up period, suggesting a reduced risk of RA with increased intake of stable vitamin D [8]. The role of vitamin D in the pathogenesis of autoimmune diseases, including RA, has been repeatedly noted in the protocol [9]. RA is believed to be induced by the interaction of environmental elements in patients with genetic vulnerability [10-12], providing a cause for impairment of innate and adaptive immunity, disrupting the balance between autoimmunity and endurance [13]. Although smoking is considered one of the main environmental risk factors for the development of RA, vitamin D is also a potential risk factor [9]. On the other hand, since RA limits mobility, patients limit their outdoor activities [14]. This, in turn, limits sun exposure, which is a key step in the D stage. The subsequent deficiency in this level can also aggravate the disease.

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Overall, several studies have observed the impact of RA treatment regimens on the apparent inverse relationship between serum 25-hydroxyvitamin D3 (25-OHD3) and RA disease activity [15-17]. Treatment of RA is aimed at reducing disease activity, maximizing joint function, and, accordingly, controlling serum 25-OHD3 levels. Initiating treatment early in the disease course can offset the effects of vitamin D depletion, resulting in a reduction in disease activity. Since the 1990s, early and aggressive treatment of new RA has been widely used to increase the chances of achieving remission [18]. This approach is now fully agreed upon in clinical practice; however, its application in the context of low vitamin D levels and vitamin D replacement therapy for early treatment, as recently analyzed in RA patients, remains unclear.

Considering the above results, our study provides estimates of D in RA. However, there are several limitations. First, the study was conducted at a single institution, with limited and less diverse samples. Second, as this was a case-control study, it was not possible to establish a causal relationship between the two. Future multicenter prospective studies with a larger sample size and diversity are needed to confirm the results of our study. Furthermore, studies on vitamin D dosing are also needed to explore more effective treatments.

Conclusions

Data show a high prevalence of vitamin D deficiency in patients with RA and its association with disease severity. This may be a causal factor in its development or progression. Therefore, a high index of suspicion is required when evaluating at-risk patients, especially women, with complaints of vitamin D deficiency. Vitamin D supplementation may be necessary for RA prevention. In patients with RA, it is important to monitor vitamin D levels and take it as needed to prevent disease progression.

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