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25-Oh Vitamin D3/D2 Levels in Osteoarthritis and Rheumatoid Arthritis Patients

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Abstract

Background and Objectives: Vitamin D exerts many other extraskeletal effects than the pivotal role in mineral metabolism, thus, deficiency of vitamin D has been shown not only in degenerative bone disease but also in many autoimmune diseases. We aimed to investigate the serum levels of 25-OH Vitamin D3/D2 in a Bulgarian cohort of patients with Osteoarthritis (OA) and Rheumatoid Arthritis (RA) and to establish correlations with some demographic and clinical, laboratory and instrumental findings.

Materials and Methods: 25-OH vitamin D3/D2 levels were assessed in serum samples of thirty-five patients as follows: fifteen OA patients, twenty with RA, and 16 healthy controls, by automated ELISA.

Results: We found that the levels of 25-OH Vit.D3/D2 in OA patients (13.51 ± 7.89 ng/ml) differed significantly (p=0.002) from the RA patients (21.27 ± 6.77 ng/ml) and healthy controls (22.86 ± 7.91 ng/ml). The mean levels of 25-OH Vit.D3/D2 in OA patients were interpreted as insufficient, close to the defined deficiency (<12 ng/ml), whereas the mean levels in RA patients and healthy controls were evaluated as sufficient. Lower average levels of 25-OH Vit.D3/D2 were documented in women than in men in both OA and RA patients, and the lowest mean level of 25-OH vitamin D3/D2 in OA patients was observed among patients between 41-60 years (p=0.002). RA patients on disease modifying anti-rheumatic drugs exerted higher levels of 25-OH Vit.D3/D2 compared to the patients without therapy (p=0.068).

Conclusion: We could suggest that vitamin D supplementation in OA patients would be of benefit for them.

Keywords: 25-OH vitamin D; Vitamin D2; Vitamin D3; Osteoarthritis; Rheumatoid arthritis

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Introduction

The biological functions of vitamin D are mainly involved in the maintaining of calcium-phosphorus homeostasis and bone metabolism [1]. Shortly, vitamin D3 (cholecalciferol) is normally produced in the skin under the influence of UV-B rays from the sun. Then, it is metabolized in the liver into 25-OH vitamin D3. In contrast, vitamin D2 (ergocalciferol) is mostly obtained from dietary sources and supplements. In the liver, it is also converted to its corresponding 25-OH derivate [2,3].

Now, it is known that vitamin D exerts many other extraskeletal effects than the pivotal role in mineral metabolism, i.e., modulation of many other systems in the human body, including the immune system [2]. It was shown that cells in the bone marrow, brain, colon, breast, and immune system express the Vitamin D Receptor (VDR) [3]. VDR is constitutively express on activated T- and B-lymphocytes, monocytes, antigen-presenting cells and other immune cells [4]. Furthermore, the enzyme responsible for the synthesis of the active metabolite of vitamin D, 25(OH) D-1α-hydroxylase, is also abundant in immune cells, especially macrophages and dendritic cells. Via the VDR, Vitamin D may exert a variety of cytokine-modulating effect and influences the function of the immune cells [5,6]. Studies in mouse and human cell models demonstrate that vitamin D could inhibit antigen presentation, T-cell proliferation, Th1 and Th17 cells responses and function [7]. Moreover, vitamin D is able to slow differentiation of B-cells in plasmatic cells and to suppress the

production of immunoglobulins, which is of particular importance in autoimmunity [7,8].

Deficiency of vitamin D has shown to be associated with many autoimmune diseases, i.e., Rheumatoid Arthritis (RA), systemic sclerosis, systemic lupus erythematosus, multiple sclerosis, type1 diabetes mellitus, etc. [3,9]. These associations depended on the serum levels of vitamin D, vitamin D supplementation, sun/UV exposure, VDR polymorphisms, etc., in both experimental autoimmune models and epidemiological studies in humans [2]. However, no causal relationship between vitamin D and autoimmune diseases was provided.

In recent years, low levels of vitamin D were associated with the risk of RA development [10]. Since the VDRs were found in macrophages, chondrocytes, and synoviocytes in the synovial membrane as well as in bone erosion sites in RA patients, the deficiency of vitamin D was associated with IL-17-mediated joint inflammation and angiogenesis in RA pathogenesis [11].

Serum vitamin D levels have been also associated with degenerative joint diseases, such as Osteoarthritis (OA). It was observed that vitamin D has an effect on articular cartilage remodeling towards regeneration [12]. However, the exact mechanism is not fully understood. Recent studies suggest the role of vitamin D in the increased risk of development and progression of OA, but the results of other studies have been conflicted [12]. It is thought that vitamin D controls matrix metalloproteinase and prostaglandin E2 secretion via VDR on chondrocytes, as well as maintains the production of proteoglycans. Playing a major role in the metabolism of the subchondral bone, vitamin D may inhibit bone remodeling [13].

On this background, we aimed to investigate the serum levels of 25-OH Vitamin D3/D2 in a Bulgarian cohort of patients with OA and RA and to establish correlations with some demographic and clinical, laboratory and instrumental findings.

Material and Methods

Subjects of the study

Thirty-five patients were recruited in our study as follows: fifteen OA patients (29.4%) at mean age 65.9 ± 14.5 years, twenty with RA (39.2%) at mean age 48.5 ± 15.7 years, and 16 (31.4%) healthy controls at mean age 35.4 ± 9.2 years. Females were 41 (80.4%) and males-10 (19.6%) of the patients.

The diagnoses of RA and OA patients were made according to the American College of Rheumatology (ACR) diagnostic criteria for RA and OA. Selection of patients and healthy controls for the study was performed in the Clinic of Rheumatology, University Hospital St. Ivan Rilski, Sofia, according to the relevant inclusion and exclusion criteria. No one of the study subjects had been supplemented with vitamin D during and six months prior to the study. The study was performed between August-September 2016 to avoid bias regarding the seasonal variations in vitamin D levels.

All study subjects were informed about the purpose of the study and gave written consent for participation approved by the Ethical Committee of the Medical University of Sofia.

Serum samples collection

Five Milliliters (ml) of peripheral venous blood from totally fifty-one subjects were collected in sterile tubes (Vacutainer BD-Plymouth, UK, 5 mL) from all study subjects. Serum samples were tested immediately after transportation to the laboratory.

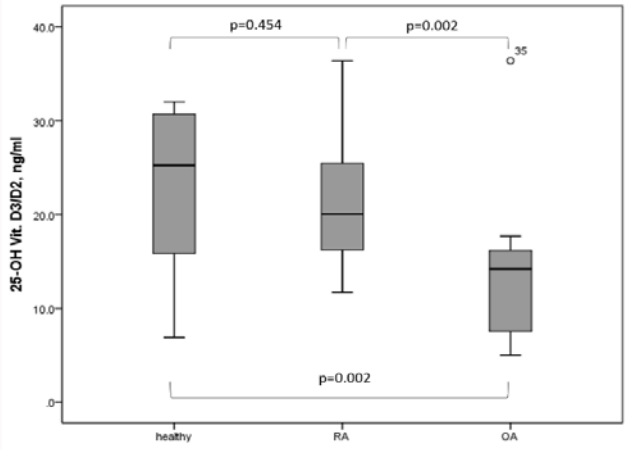


Figure 1: 25-OH Vit. D3/D2 levels in different study groups.

Immunological testing for vitamin D

25-OH Vitamin D3/D2 levels were assessed by an automated ELISA maker and reader for the quantitative determination of the total 25-OH vitamin D3 (cholecalciferol) and 25-OH vitamin D2 (ergocalciferol) concentrations in serum samples (25-OH Vitamin D3/D2, Alegria, Orgentec Diagnostika, Germany). The test uses an antibody that binds equally well and with high affinity both forms of vitamin D. The range of detection of the test is 5 ng/ml - 120 ng/ml, whereas the interpretations of the results are the following: <12 ng/ml (Deficiency); 12 ng/ml - 20 ng/ml (Insufficiency); >20 ng/ml - 150 ng/ml (Sufficiency).

The immunological testing for Vitamin D was performed at the Laboratory of Clinical Immunology, University Hospital "St. Ivan Rilski", Sofia, according to the manufacturer`s instructions.

Statistical methods

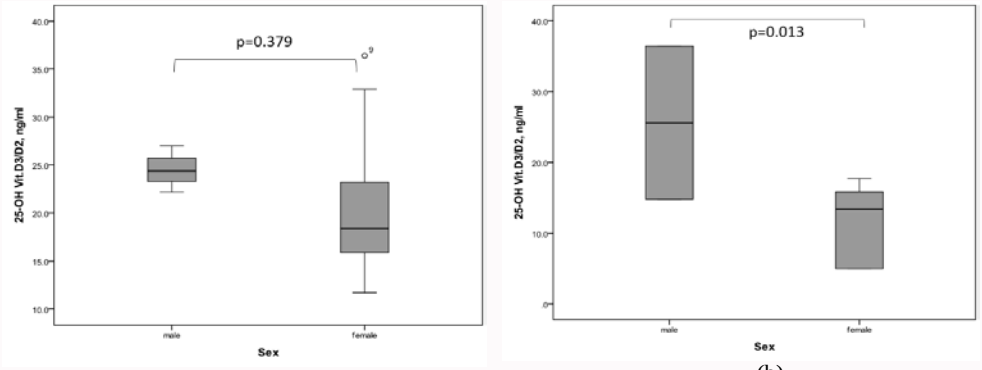
The raw data were analyzed by the software package for statistical analysis (SPSS®, IBM 2009), v. 19 and the results were accepted for significant if the p-value was less than 0.05.

Results

We found that the levels of 25-OH Vit.D3/D2 in OA patients (13.51 ng/ml ± 7.89 ng/ml) differed significantly (p=0.002) from the RA patients (21.27 ng/ml ± 6.77 ng/ml) and healthy controls (22.86 ng/ml ± 7.91 ng/ml) (Figure 1). The differences in the average levels of 25-OH Vit.D3/D2 between RA patients and healthy controls were non-significant (p=0.454). According to the reference range, the mean levels of 25-OH Vit.D3/D2 in OA patients were interpreted as insufficient, close to the defined deficiency (<12 ng/ml), whereas the mean levels in RA patients and healthy controls were evaluated as sufficient (Figure 1).

From the RA patients, one (5%) possessed vitamin D deficiency, nine (45%) insufficiency and ten (50%) sufficiency, whereas from the OA patients the distribution was: five (33.3%), nine (60%) and one (6.7%), respectively. Regarding healthy controls, one (6.3%) was with deficiency, five (31.3%) with insufficiency and ten (62.5%) with sufficiency.

When we divided the RA and OA according to their sex affiliations, we found lower average levels of 25-OH Vit.D3/D2 in



(a) (b)

Figure 2: 25-OH Vit. D3/D2 levels depending on sex in: (a) RA patients; (b) OA patients.

Table 1: 25-OH vitamin D3/D2 levels in the different study subjects depending on the age. The results are presented as mean ± SD (range).

	OA patients	RA patients	Healthy controls
Under 20 years	-	36.40	-
21-40 years	36.50	18.90 ± 6.60 (11.70-36.40)	23.77 ± 8.09 (6.90-32.00)
41-60 years	9.20 ± 4.02 (5.00-13.40)	21.50 ± 6.03 (13.90-32.90)	20.13 ± 7.71 (14.40-31.50)
61-80 years	13.05 ± 5.11 (5.00-17.70)	20.50 ± 5.68 (13.80-27.00)	-
Above 80 years	15.80	-	-
Significance, p	0.002	0.112	0.444

women than in men in both groups (20.69 ± 7.17 *vs.* 24.53 ± 2.40 ng/ml, p=0.379; 11.65 ± 5.00 *vs.* 25.60 ng/ml ± 15.27 ng/ml, p=0.013, respectively) (Figure 2A and B).

The levels of 25-OH vitamin D3/D2 decreased in healthy persons with age (Table 1). We found the lowest mean level of 25-OH vitamin D3/D2 in OA patients between 41-60 years (p=0.002), and normal level in the 21-40-year-old group. In contrast, younger RA patients possessed normal mean levels of 25-OH vitamin D3/D2, whereas the patients among 41-80 years suffered from insufficiency, and among 21-40 years - from deficiency (Table 1).

We did not find significant differences in 25-OH Vit.D3/D2 levels in RA patients regarding disease duration, cigarettes smoking, morning stiffness, disease activity (assessed by DAS28, SDAI and CDAI), the presence and degree of the synovitis, laboratory (CRP, ESR, hemoglobin) and immunological (rheuma factor IgG, IgM, IgA; anti-CCP antibodies) findings and corticosteroid use.

However, patients on Disease Modifying Anti-Rheumatic Drugs (DMARDs) exerted higher levels of 25-OH

Vit.D3/D2 (26.02 ng/ml ± 7.69 ng/ml) compared to the patients without therapy (19.68 ng/ml ± 5.88 ng/ml) (p=0.068) (Figure 3).

Receiver Operating Characteristic (ROC) curve analysis revealed acceptable area under the curve (AUC=0.672 95%CI [0.509-0.835], p=0.050) for 25-OH Vit.D3/D2 in OA and RA patients diagnosis (Figure 4).

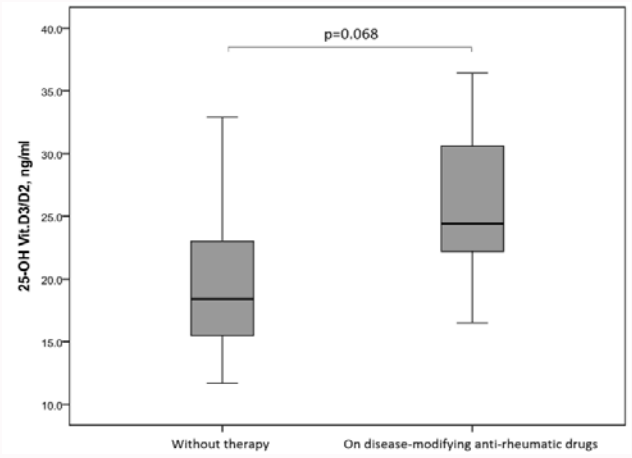


Figure 3: 25-OH Vit. D3/D2 levels in RA patients depending on the use of disease-modifying anti-rheumatic drugs.

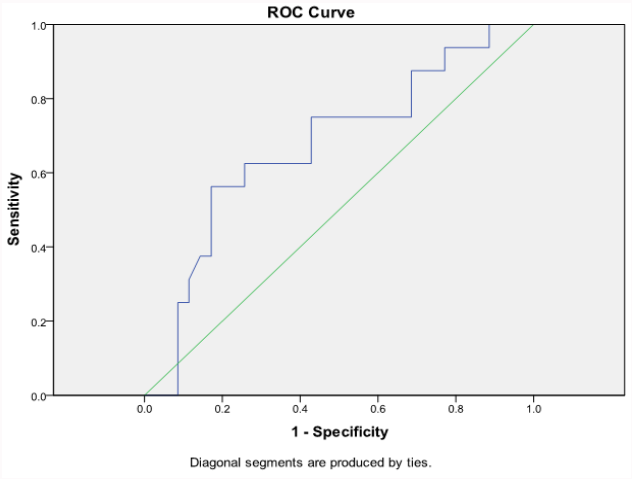


Figure 4: Receiver Operating Characteristic (ROC) curve analysis of 25-OH Vit. D3/D2 in patients with RA and OA.

Discussion

Hypovitaminosis D generally includes cases of deficiency and insufficiency of 25-OH Vit.D3/D2, commonly with serum levels below 20 ng/ml and is prevalent worldwide [14]. Low levels of vitamin D are usually associated with OA, particularly in the elderly patients. We have also found a significant drop of vitamin D serum levels from a sufficiency in 21-40 years range to a deficiency in 41-60 years range. However, in the 61-80 and over 80 years OA patients we observed a tendency for a slight increase. The similar tendency was shown also for RA patients and healthy persons. The explanation for these observations is grounded in the fact that the capacity of human skin to produce vitamin D decreases with age [1].

It was documented that 24% of advanced stage elderly OA patients in the United Kingdom were found deficient for vitamin D (mean level 16 ng/ml), and up to 26% in Ireland, whereas the insufficiency was observed in up to 70% of OA patients [1]. In our study, the percentages were similar - 33.3% for deficiency versus 60% for insufficiency, respectively. According to RA patients, only 5% of patients were assessed as deficient and up to 45% of them were with insufficient vitamin D levels. However, half of RA patients were found sufficient, whereas only one OA patient was with sufficient vitamin D level. Other authors reported a higher prevalence of deficiency over insufficiency among RA patients: 57.8% and 31.4%, respectively) [15].

In our study, patients with OA showed the lowest mean level of vitamin D (closer to deficiency) compared to RA and healthy controls, whose mean levels were evaluated as sufficient. Other studies also documented decreased serum levels of vitamin D in OA patients [12] and RA patients [16]. We found lower average levels of 25-OH Vit. D3/D2 in women than in men in both OA and RA patients. However, not all authors report for significant differences between male and female patients with RA [15]. We have to mention that levels of vitamin D are strongly dependent of geographical region (i.e. sun lighting), nutrition, etc. [17].

It has been shown that patients with knee OA have significantly decreased serum levels of vitamin D, which correlated with the medial meniscal deterioration. Additionally, low vitamin D levels have also been associated with radiographic hip OA [1]. However, we have to take into consideration that the observed vitamin D deficiency is more prevalent in elderly patients with advanced OA [12]. There are only a few studies devoted to the vitamin D effects on articular cartilage regeneration. It was shown that persons with sufficient levels of vitamin D had a lower risk of developing OA, as well as supplementation decreased articular cartilage degeneration which can be evaluated radio graphically [12]. Furthermore, there are some controversial results regarding the effect of vitamin D on OA progression and pain management. Thus, the issue of vitamin D supplementation in prevention and treatment of OA is up to date, but require future studies regarding regimen and doses [12].

Many studies reported a correlation between the deficiency of vitamin D and disease activity in RA [18-20]. It was shown a significant negative correlation between DAS28-ESR and vitamin D (r=−0.277, p=0.014), which increased to r=−0.352 (p=;0.002) after age and sex adjustment [15]. Some authors reported also negative correlations between vitamin D and CRP and ESR, but the relations were evaluated as very week (r= −0.115 and r= −0.18, respectively) [16]. However, we did not find such correlation with the disease activity or laboratory findings. Interestingly, RA patients on DMARDs exerted higher levels of 25-OH Vit.D3/D2 compared to the patients without therapy, although with borderline significance. An experimental model with mice with collagen-induced arthritis demonstrated that substitution treatment with vitamin D prevents the development and progression of this type of arthritis [21]. Such studies raise the possibility vitamin D to be used as a therapeutic agent in RA and other autoimmune diseases as well [2].

Conclusion

Taken together, our results showed significantly lower mean serum level of 25-OH vitamin D3/D2 in a degenerative rheumatic disease, such as OA, whereas the mean levels in RA patients and healthy controls were interpreted as sufficient. We could suggest that vitamin D supplementation in OA patients would be of benefit for them.

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