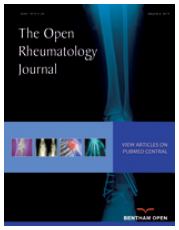

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CLINICAL TRIAL STUDY

Association of 25-Hydroxy Vitamin D with IL-17 Inflammatory Cytokines, and Osteoporosis in patients with Rheumatoid Arthritis in Kurdish nation / Iraq

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Abstract:

Introduction:

Rheumatoid arthritis (RA) is a long-term autoimmune disorder that primarily affects joints. Lower Vitamin D (Vit. D) levels correlate with more severe clinical manifestations in RA and other rheumatic diseases. IL-17A promotes inflammation by inducing various proinflammatory cytokines and chemokines. In this study, we evaluated the association between Vitamin. D and IL-17 in osteoporosis in Rheumatoid Arthritis in Kurdish nation / Iraq.

Objective:

Blood samples from rheumatoid arthritis (RA) patients were used to measure the levels of the inflammatory cytokine IL-17 and the Vit. D precursor 25(OH)D and bone loss in patients with RA in this study.

Methods:

In this study, 40 healthy controls were included in the research, which comprised 100 new cases of RA. ELISA was used to measure the level of serum 25(OH)D and IL-17. Moreover, DXA was used to assess average bone mineral density (BMD).

Results:

We discovered no difference between the two groups in terms of age or gender. This means that compared to the control group, the 25(OH)D serum levels in the RA group were lower (P 0.01; 16.85+8.7 nmol/l vs. 39.95 (-+9.8)). IL-17 serum levels were highly and negatively associated with 25(OH)D levels in arthritic patients. A comparison of 25(OH)D levels in patients with osteoporosis and osteopenia and those with BMD was also performed.

Conclusion:

Bone loss and IL-17 have been associated with reduced Vit. D levels in patients with rheumatoid arthritis; a lack of Vit. D may have a role in developing the disease, according to the data presented in this study.

Keywords: 25-hydroxyVitamin D, Rheumatoid, Arthritis, IL-17, Osteoporosis, Autoimmune disease, Inflammatory.

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1. INTRODUCTION

A chronic autoimmune illness affecting mainly the synovium, rheumatoid arthritis (RA) affects as much as one percent of the world's adult population [1]. If not treated early, it may cause joint injury and systemic complications that can lead to disability and early death if not managed [2]. There is a more significant impact on women than on males 3:1. The two types of autoantibodies associated with RA are rheumatoid factor (RF) and anti-citrullinated peptide (Anti-CCp) antibody [3]. The etiology and pathogenesis of RA have been connected despite its high prevalence. According to recent research, a deficiency of 25(OH)D has been linked to many health issues. Vit. D is produced in the skin from dermal 7-dehydrocholesterol is converted to 25(OH)D by solar light, although it may also be obtained *via* diet. In the liver, the Vitamin. D converted to 25- hydroxy Vitamin. D this which used to determine a person's vitamin D status 25(OH)D level

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[4]. In the kidneys and external tissues produce calcitriol, 1, 25(OH)2D3, which is the active form of Vitamin. D [5], it attaches to its receptor and begins to exert its biological effects. As the body's inflammation intensified, blood 25(OH)D levels fell [6]. Because of its ability to modulate immune cells, including macrophages and lymphocytes, 1,25(OH)2D3 exerts its immune regulatory functions. IL-17 and IL-23 production is reduced, while IL-4 and IL-10 expression is increased [7, 8]. Therefore 25(OH)D insufficiency may impair the immune system.

The role of IL-17 in promoting inflammation has been widely researched (particularly IL-17A and IL-17F) [9 - 11]. Cell adhesion molecules chemokines, matrix metalloprotease, and inducible nitric oxide synthase are all induced by proinflammatory cytokines [12]. In rheumatoid arthritis, IL-4 and IL-10, which lower inflammation, are effectively tolerated by the synovium of patients [13]. RA causes bone degradation and loss around joints. Osteoporosis in RA patients may be exacerbated by both chronic inflammation and glucocorticoids, which have been found to hasten bone loss. Healthy bone mineralization, development, and remodeling may be enabled by 25(OH)D, the ability to influence calcium and phosphorus metabolism in the body. Bone loss and osteoporosis (OP) are linked to low levels of 25(OH)D in RA [14, 15]; however, this has only been shown in a limited number of studies. Study participants with RA suffered from 25(OH)D levels below normal and elevated inflammatory cytokines and bone loss.

2. MATERIALS AND METHODS

2.1. Patients and Controls

This study was a Case-control and cross-sectional study in Rizgary's teaching hospital's Rheumatology Department, recruited 100 newly diagnosed RA Patients according to the 2010 ACR/Eular classification criteria for RA [16], along with 40 healthy control who were similar in terms of age and gender to the patient group, participants who had no history of RA and no clinical signs indicating immunological diseases or chronic infections. These individuals were not included because they had additional conditions such as kidney, thyroid, parathyroid gland dysfunction, or other concurrent autoimmune or viral hepatitis diseases. No one in the group of RA patients or the group of healthy controls had ever taken Vit.D before. University of Hawler College of Medicine, Erbil, Iraq's Institutional Ethics and Research Advisory Committee (IERAC) authorized the research with code 20201013-5-8. A written permission was obtained from each participant before participating in the study.

2.2. Measurement of 25(OH)D and IL-7

A sterile vacutainer was used to collect blood samples by venipuncture. Individuals were tested for liver and kidney function and a full blood count. ELFA (enzyme-linked fluorescence assay) assessments of total serum 25 OH Vit D levels were then performed on VIDAS (BIOMERIEUX) An inadequate level of vitamin D is defined as being less than 50 nmol /L (or < 20 ng/ml); an insufficient level is defined as being between 50 and 75 nmol /L (or >20ng/ml and <30 ng/ml),>75nmol/L (>30 ng/ml) normal, and a hazardous level is defined as being more than 100 nmol/L.(16) By following the manufacturer's procedure, plasma was utilized to measure the concentration of IL-17 (KOMA BIOTECH INC.) IL-17 levels were detected using human ELISA kits, which had a sensitivity of 5.5 pg/ml for IL-17 detection .

2.3. Measurement of Bone Mineral Density (BMD)

To diagnose osteoporosis, the researchers used BMD data from young age adults [17]. According to the World Health Organization's classification, BMD was used to determine if a patient had osteopenia, osteoporosis, or none of these conditions [18]. BMD was measured using a Lunar Prodigy DXA scanner at L2-L4 in the spine and the greater trochanter, Ward triangle, and lumbar spine (GE Healthcare). BMD was calculated using the formula bone area (cm2)/bone mineral content (g) as a percentage of total bone area.

3. RESULTS

This study included 100 patients with RA and 40 healthy individuals as a control group, both groups were close to each other in terms of age and BMI. Patients had a mean BMI of 23.4, while the BMI of controls was 23.1; Table **1** shows no statistically significant differences in sociodemographic factors such as age and BMI between patients and control groups).

Table 1. Sociodemographic features of RA patients and the control group.

Variables(Mean ± SD)	Control	RA Patients	P-Value
Age	46.6 (±10.4)	47.4 (±10.2)	0.102
Height (cm)	162.8 (±5.4)	160.9 (±5.1)	0.052
Weight (Kg)	57.15 (±4.12)	58.5 (±4.5)	0.103
BMI	23.1 (±1.35)	23.4 (±1.21)	0.202
Vit D3 Level (ng/ml)	39.95 (±9.8)	16.85 (±8.7)	0.001
IL-17 (≥ 1-4 pg/ml)	0.9 (±0.81)	5.3(±3.52)	0.001
ESR (mm)	5.2 (±1.7)	6.4 (±2.6)	0.803
CRP (IU/ml)	3.1 (±1.1)	4.8 (±1.6)	0.410
RF (IU/ml)	3.2 (±2.7)	(26.7±19.8)	0.000
Anti-CCP (U/ml)	12.6 (±18.2)	44.8 (±13.5)	0.000

Vit. D levels differed significantly (p 0.001) between the RA patients (means 16.85 ng/ml) and the controls (means 39.95 ng/ml), Also, as expected, a significant relationship was observed between RF in the two groups and also Anti-CCP (Table **1**). Also, there is a significant difference between proinflammatory IL-17 in RA patients and healthy controls (P.Value<0.05).

As shown in Table **2**, the decrease in Vit. D level has a significant relationship (P.Value<0.05) with the increase in IL-17 level in the patient group. Therefore, it can be concluded that the decrease in Vit. D level increases the level of IL-17.

Table 2. RA patients' IL-17 proinflammatory cytokine levels were compared to their Vitamin. D levels.

Level of Cytokines	Normal Vitamin. D	Low Vitamin. D	P-Value
IL-17 (pg/ml, mean±SD)	1.87±1.3	4.97±1.87	0.001

The incidence of osteoporosis was significantly higher in the RA group compared with the normal control group, as shown in Table **3**.

Table 3. Comparison of BMD values between RA patients and healthy control population.

BMD (g/cm2)	RA (No,%)	Control (No,%)	P-Value
Normal BMD	18 (18%) 1.32 g/cm2	15 (37.5%) 3.29 g/cm2	0.015*
Osteopenia	51 (51%) 1.02 g/cm2	11 (27.5%) 2.54g/cm2	
Osteoporosis	31 (31%) 0.04g/cm2	14 (35%) 0.10 g/cm2	
Total	100	40	

*There is an 8.3142 Chi-square statistic. The significance level is set at 0.05. The p.Value for this study is 0.015653. At a p.value of 0.05, this finding is very significant.

As can be seen in Table **3**, 82% of patients with RA showed osteoporosis and osteopenia. And only 18% showed normal BMD. These results showed a significant correlation compared to the healthy group.

In this study, the relationship between the level of vitamins. D and IL-17 were also compared with the BMD level of the RA patients. According to the results (Table **4**), the decrease in the level of Vitamin. D and the increase in the level of IL-17 have a significant relationship with bone degeneration.

4. DISCUSSION

Case-control and cross-sectional research approaches were used by the investigators in this study. RA patients Vitamin. D levels were shown to be lower than those of healthy controls, as in several recent European studies [19, 20]. Three additional studies [21 - 23] found no differences in Vitamin. D levels between RA patients and healthy controls. No one knows why these gaps occur, although they may be due to differences in research populations, sample sizes, and possible confounders such as age, BMI, and seasonal fluctuations in blood Vitamin. D levels (which are lower in the winter).

Table 4. This table shows the association of osteopenia and osteoporosis with the level of Vitamin. D and the level of IL-17 in RA patients.

-	No.	Serum Level Of Vit-D (mean±SD)	Serum Level of IL-17 (mean±SD)	P-Value
Normal BMD	18	60.75±19.36	6.18±1.96	0.001*
Osteopenia	51	41.53±12.18	15.37±3.41	0.001*
Osteoporosis	31	37.65±15.13	19.65±4.55	0.001*

*The one-sample t-test of two-tailed P.Value is less than 0.0001.

There is an association between Vitamin. D blood levels and levels of proinflammatory cytokines in patients with Rheumatoid Arthritis. The inflammatory cytokine IL-17 was inversely and substantially linked to Vitamin. D serum concentrations. Our results are supported by Cutolo *et al*. [23, 24], who found that Vitamin. D may reduce RA-related inflammation and immune dysregulation by inhibiting the Th17 response.

Our findings support Cranney A *et al*., who found that people with RA had a greater risk of osteoporosis than healthy controls [25]. Osteoporosis is common in RA patients. Inflammatory diseases, such as rheumatoid arthritis, alter bone biomechanics and alter bone components *via* increased production of proinflammatory cytokines or hormone-mediated processes [26 - 29]. Physical constraints, insufficient therapy, and the disease contributes to an increased risk of osteoporosis and bone loss in RA patients [30, 31].

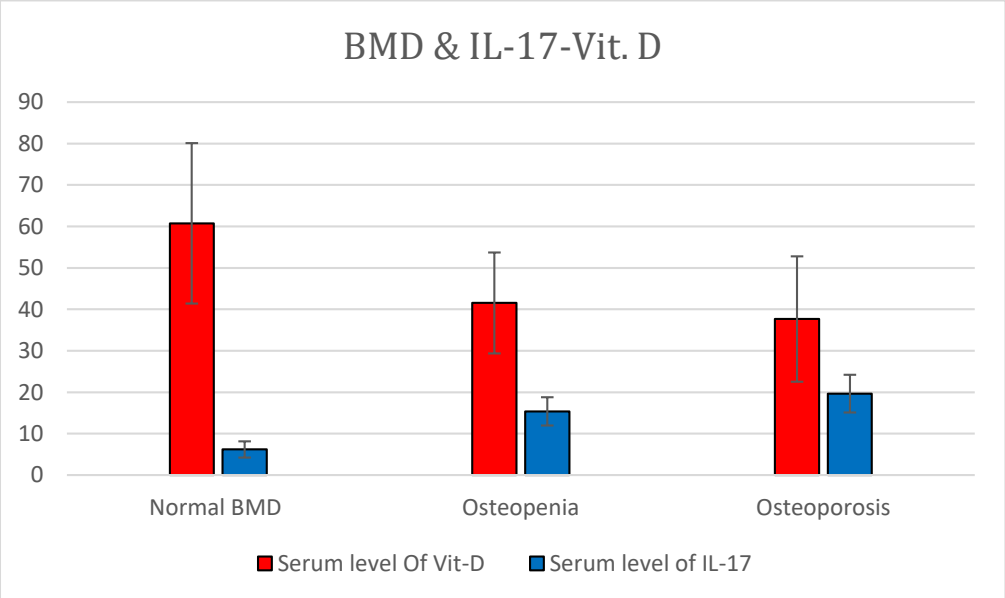

Chart (1). Vitamin. D and IL-17 levels in three groups of normal BMD, osteopenia and osteoporosis: It is noticeable that the level of IL-17 increases with the decrease of Vitamin. D level.

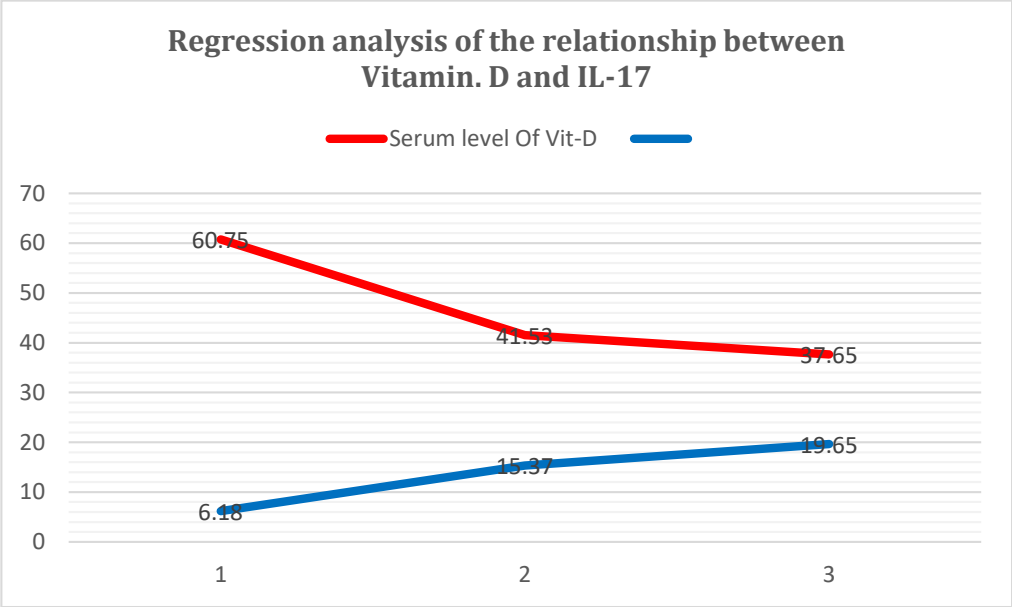

Chart (2). Regression analysis of the relationship between Vitamin. D and interleukin levels in RA patients: It is noticeable that the level of IL-17 increases with the decrease of Vitamin. D level.

The results of our study were consistent with the research of Ranganathan *et al*., this team investigated the relationship between Vitamin. D, IL-17 and vascular function of people with rheumatoid arthritis. This group reported that deficiency of Vitamin. D was associated with increased levels of IL-17, this group concluded that: Maintaining normal serum Vitamin. D levels may protect against RA's IL-17-mediated inflammation and vascular dysfunction [32].

Vitamin D deficiency and interleukin-17 levels were both shown to be highly related to osteoporosis risk in RA patients, according to a cross-sectional study (IL-17). Because Vitamin. D and parathyroid hormones affect bone directly; this may be the case. Since all subjects investigated had normal parathyroid glands, Vitamin D impacted the RANK/RANL system regulation [33]. It has been found that Vitamin D inhibits the synthesis of OPG in osteoblasts (a critical regulator of bone turnover in healthy individuals) [34]. When osteoblasts stimulate the production of RANKL, it is responsible for bone resorption, calcium and phosphate excretion rise [35]. The link between Vitamin D and PTH (parathyroid hormone) is complex. Vitamin D activation is enhanced by PTH, although calcitriol suppresses PTH synthesis and release [36]. Additionally, Vitamin D has been shown to limit the growth of parathyroid cells [37]. Vitamin D deficiency may cause secondary hyperparathyroidism, a condition in which the PTH levels in the blood rise to maintain normal calcium levels in the body [38].

Saleh *et al*. also investigated the relationship between IL-17 and Vitamin. D in RA patients, this group reported that there is an inverse relationship between Vitamin. D and interleukin levels [39].

Regarding the sample size of the current study, although it is advisable in case-control studies to have at least the same number of participants as cases to avoid any false positive correction method in the analysis, but the number of samples in our study was 40 compared to 100 cases because of the following reasons: During the data collection period, 19 March 2020 - 20th November 2020, Rzgary teaching hospital was allocated for referring COVID_19 cases, therefore most of the patient wards had these patients that made difficulties for the researchers to find appropriate controls for all the 100 cases. Also, an equal or larger group of controls to increase power to be able to detect even a small odds ratio when exposure is relatively rare, in our study the exposure to vitamin D deficiency, for instance, was high in RA cases, the results which were parallel to several recent European studies [19, 20]. Finally, the mean and standard deviations were used to analyze variation between cases and control; the mean, as well known, is least affected by the fluctuation of sampling.

CONCLUSION

Vitamin D levels were shown to be lower in RA patients and to be related to higher levels of IL-17 and osteoporosis in RA patients. An inverse relationship between Vit. D and IL-17 levels in other autoimmune diseases have also been reported [40, 41], But so far, the exact mechanism of the relationship between the decrease in Vit. D levels and the increase in IL-17 levels in autoimmune diseases, especially rheumatoid arthritis, have not been determined. But based on the findings, it can be suggested using the allowed dose of Vit. D can reduce the effects of the disease, especially bone degeneration.

LIST OF ABBREVIATIONS

RA	=	Rheumatoid Arthritis
RF	=	Rheumatoid Factor
Anti-CCp	=	Anti-Citrullinated Peptide

BMI = Body Mass Index

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The University of Hawler College of Medicine, Erbil, Iraq's Institutional Ethics and Research Advisory Committee (IERAC) authorized the research with code 20201013-5-8.

HUMAN AND ANIMAL RIGHTS

No animals were used for studies that are the basis of this research. All the humans were used in accordance with the ethical standards of the committee responsible for human experimentation (institutional and national), and with the Helsinki Declaration of 1975, as revised in 2013 (http://ethics.iit.edu/ecodes/node/3931).

CONSENT FOR PUBLICATION

Written permission was obtained from each participant before participating in the study.

STANDARDS OF REPORTING

STROBE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data supporting the findings of the article is available within the article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest in the authorship or publication of this contribution.

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Declared none.

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