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The Immunological Role of the 1L-37/ IL-17 Axis in Patients with Rheumatoid Arthritis and Its Correlation with serum Vitamin D levels

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Abstract

This type of autoimmune disorder, which primarily causes joint disease, is known as rheumatoid arthritis (RA). In RA, significant joint damage leads to a gradual loss of cartilage, and as the disease progresses, bones may also be affected. Patients experience a wide range of symptoms, depending on the disease stage. Interleukin-17 and interleukin-37 play a vital role in the pathogenesis of rheumatoid arthritis, this study aimed to determine the levels of certain cytokines, such as interleukin-17 and interleukin-37, and to demonstrate the presence of low serum vitamin D levels in rheumatoid arthritis patients in Iraq. Samples were collected from an outpatient clinic at Baghdad Medical City Hospital and included 72 patients with rheumatoid arthritis (aged 23–65 years) in Baghdad between November 2025 and April 2026. The patients were distributed by sex: 59 females and 13 males. Control groups (35 individuals of varying ages) were also evaluated. The gender distribution in the sample was as follows: females (81.9%) and males (18.1%). Interleukin-17 (IL-17) levels were measured using ELISA in the blood of patients and control group members. Serum IL-17 and vitamin D levels were also measured. Results: The IL-17 level in patients was 16.53 ± 3.21 pg/mL, and in the control group, it was 9.31 ± 0.06 pg/mL. The difference between these two values was statistically significant ($P<0.001$). In contrast, the IL-37 level (14.20 ± 1.21 pg/ml for patients and 12.42 ± 2.13 pg/ml for control individuals) was statistically significantly higher ($P = 0.001$*), but the 25(OH)D level (15.79 ± 4.07 ng/ml) in our patients was much lower than the level obtained in the control group (36.94 ng/ml ± 7.98 ng/ml).

Keywords: Autoimmune disease, IL-17, Rheumatoid arthritis, vitamin D, IL-37.

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Introduction

Rheumatoid arthritis is defined as a chronic autoimmune disease that primarily affects the joints, characterized by symmetrical joint inflammation and progressive destruction of cartilage and bone. The severity of its symptoms varies among patients. Autologous hormones may play a role in this disease, as these hormones are associated with increased inflammation and cartilage damage in rheumatoid arthritis patients due to their role in promoting the production of cytokines and metalloproteinase enzymes [1]. A novel subset of helper T cells, known as Th17 cells, has been identified as producing interleukin-17 (IL-17). Interleukin-17 directly contributes to cartilage destruction by stimulating the production of matrix metalloproteinases (MMPs), which degrade collagen and cartilage-forming proteoglycans. Laboratory studies have shown that interleukin-23 stimulates osteoblasts and synovial fibroblasts to produce RANKL, the key molecule that activates osteoclasts [2]. Interleukin-37 (IL-37) is a pro-inflammatory cytokine. The function of interleukin-37 has been primarily associated with the bone marrow, thymus, lymph nodes, monocytes, and B lymphocytes [3]. Abnormal serum levels of interleukin-37 have been found in several inflammatory disorders. TNF-α, IL-1β, and IL-6 are among the most important cytokines that maintain synovial inflammation. Recent reviews indicate that IL-37 can reduce the production of these mediators by regulating intracellular and extracellular signaling. This effect helps to decrease the activation of synovial cells and macrophages, thereby limiting the persistence of the inflammatory cycle [4]. Vitamin D is also one of the most important steroid hormones, undergoing chemical transformations in both the liver and kidneys to reach its active form. It has recently been increasing interest in vitamin D deficiency as contributing to rheumatoid arthritis pathogenesis, The well-established immunomodulatory action of active vitamin D1,25-dihydroxyvitamin D3 (1,25(OH)D) may be enhanced by the fact that both calcium, phosphorus and thyroid hormones are required for production of active vitamin D and as most immune cells, including activated T cells dendritic and macrophages and expressing vitamin D receptors, are functionally activated by active vitamin D [5] .

Methodology

The samples for this study were taken from one out-patient clinic belong to (Baghdad Teaching hospital / Medical city), we recruited total rheumatoid arthritics patients (23 to 65 year olds) with both sex (59 Female ,13male), and recruited also Healthy subjects (of both sexes), all in ages comparable with control. Samples of venous blood (5 ml) were collected from each participant in the hypothyroidism, with healthy person's groups in the same time and delivered immediately to laboratories without delay.

Collecting a blood sample

Blood (5mL) was collected by venipuncture from hypothyroid patients using sterile 10 mL syringes blood was then put into a test tube containing coagulation inducer and gelatin medium this test tube was used for separation of serum

Serological tests

Serum 25-hydroxyvitamin D3 (25(OH)D3) concentrations were assessed in both the patient and control groups using a standard enzyme-linked immunosorbent assay (ELISA). A commercially available vitamin D kit (the ELISA kit from Bioactive Diagnostics, Germany) was used for this assessment.

Measuring the level of cytokines IL-17 and 1L-37 in the serum of Patients.

The kit Peprotech (USA) used to measure the cytokine as per the manufacturer's directions.

All calculation and effects of different groups of study in (control & patients) group: Calculations for SPSS (standard statistical package version 24) and test for significance,Data presented as (means sd), statistical signifficance at $p< 0.05$ and hign statistical significance $p< 0.001$

Results and Discussion

In this study, patients with rheumatoid arthritis aged 23-65years were used to analyze samples [6], [7]. Whereas, the patients selected as sample set of this experiment mostly composed of female with 81.9% male while 18.1 % only for this case of male as shown in **figure 1**

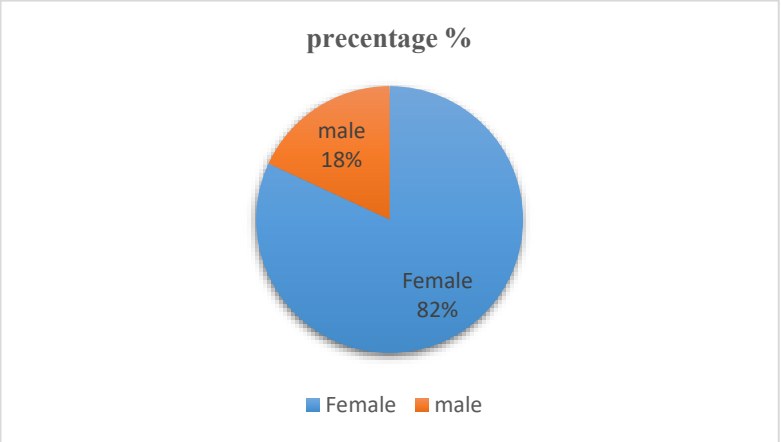


Figure 1. The percentage of female compared with male

The ratio of females to males to infection generally ranges from 2:1 to 3:1 This ratio may vary according to geographical regions, as some studies have recorded percentage range between 1.4:1 in Poland to 5.7:1 in France (1) [8]. AlChalabi et al. agreed, stating that the percentage of females was (83.9%) while the percentage of males was (16.1%). The function of estrogen is complex, two-fold in the regulation of the immune system, while its high levels during pregnancy provide an anti-inflammatory effect and temporarily alleviate rheumatoid symptoms, its decline during menopause or after childbirth is associated with an increased risk of developing and worsening the disease [9], [10]. Other studies have shown that females express lower levels of the AIRE protein after puberty compared to males [11], [12]. This protein plays a crucial role in maintaining immune tolerance within the thymus gland, which partially explains the higher susceptibility of females to autoimmune diseases [13].

Table1 shows that patients with Rheumatoid arthritis demonstrated significantly lower concentrations of serum 25-hydroxy vitamin D [25(OH)D] level (15.79±4.07 ng/mL) compared to normal control group (36.94±7.98 ng/mL) with statistical analysis $p < 0.001$ [14].

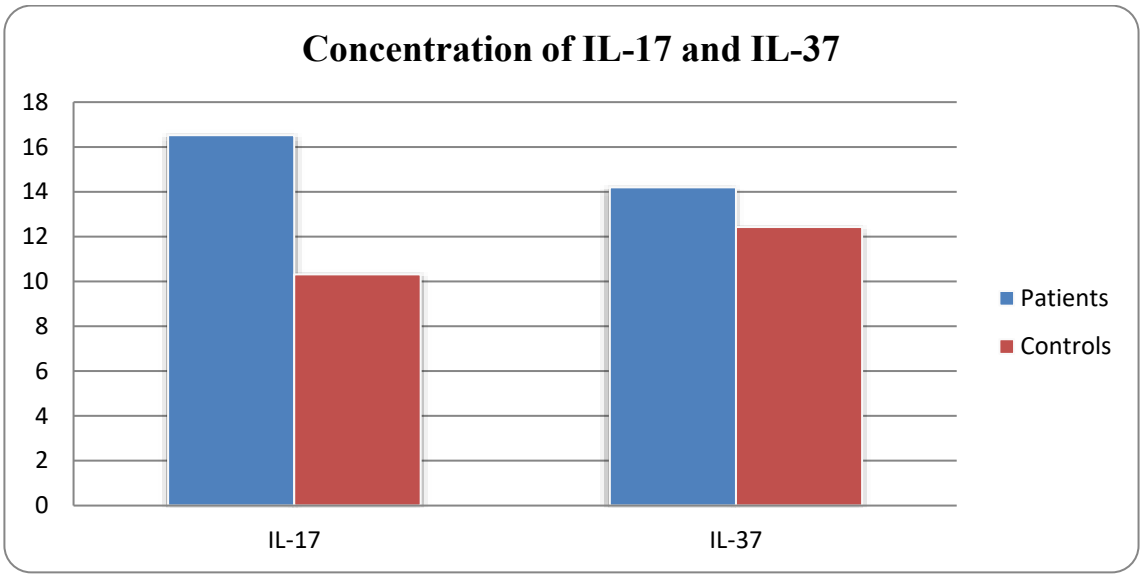
Table 1. concentration Vitamin-D in patients compared with healthy

parameter	Group	Mean ± SD (ng/mL)	P-value
Vitamin-D	patients	**15.79 ± 4.07**	P < 0.001*
	healthy	**36.94 ± 7.98**	

Hypovitaminosis D3 has been linked to an illness causing elevated plasma concentration of interferon-alpha and enhanced peripheral CD4+ and CD8+ T cells as well as higher plasma concentrations of pro-inflammatory cytokines [15], [16]. Physiologic alterations of vitamin D levels have been reported, with immune-regulatory activities being one among many effect attributed to active form of vitamin D, 1,25-(OH)2D3 Our results are consistent with AL Chalabi's et al. finding of lower vitamin D levels (8.3 ± 1.14) compared to healthy individuals, while several studies have shown an inverse relationship between the severity of rheumatoid arthritis and 25-hydroxyvitamin D blood levels in constants Pre-inflammatory cytokines play a pivotal role in regulating the immune response and promoting inflammation in patients compared to healthy individuals [17]. The outcome in Table 2 (Figure 2) indicate that patients had significant higher mean concentrations (16.53 3.21) pg/ml for interleukin-17 (IL-17) than in normal persons (9.31 0.06) pg/ml. While it shows the patients had significantly higher concentrations (14.20 1.21) pg/ml for interleukin-37 (IL-37) than in normal individuals (12.42 2.13) pg/ml, was significant statistically with probability $P < 0.001$*.

Table 2. concentration of cytokine in patients with Hypothyroidisms and Control

parameter	Patients N=72	healthy N=35	P-value
IL-17	16.53 ± 3.21	9.31 ± 0.06	P < 0.001*
IL-37	14.20 ± 1.21	12.42 ± 2.13	



Cytokines have already been shown to influence the cellular environment and participate in the initiation of autoimmune and inflammatory diseases, such as rheumatoid arthritis. The sharp rise in IL-17 levels in the RA patients is concordant with AL Chalabi's et al and Al-Taie et al study in that they too noted significant increased level in RA patients.IL-17 stimulates synovial fibroblasts and macrophages to increase in production of inflammatory mediators and signaling molecules like IL-6, IL-8, and GM-CSF these mediators elevated the attraction of neutrophils and immune cells to the joint. In contrast, IL-17 exhibits a stronger effect when working with TNF-α, as their synergistic effect can increase the production of IL-6 and chemokines and enhance the activation of synovial membrane cells. This partially explains why elevated IL-17 levels do not necessarily indicate that inhibition alone will lead to significant improvement; the inflammatory network may persist via alternative pathways or other cytokines. The results obtained by Al-Tae et al. also match with ours, who found highly increased levels of serum IL-37 in RA patients in comparison with controls [18]. Our findings also align with those of Cao et al. who reviewed published research on the relationship between serum IL-37 levels and rheumatoid arthritis. The results consistently demonstrated significantly elevated IL-37 levels in patients with rheumatoid arthritis [19]. This study also established a correlation between IL-37 levels and disease activity. Also ours results agree with the results reported by Bani-Wais et al. it reported significantly increased IL-37 concentration in patients with rheumatoid arthritis compared to healthy individuals. Conversely, another study by Ding et al. revealed that the following mediators, The IL-23/IL-17/NF-κB pathway forms a central network linking the initiation of synovitis and its progression to bone and cartilage destruction [20]. Studies have shown that IL-37 levels may rise in response to inflammatory stimulation and cytokines, such as Toll receptor agonists (TLRs), - interleukin-1 beta (IL-1) - interleukin-18 (IL-18) -tumor necrosis factor-alpha (TNF-) IL-37 may contribute to a negative feedback mechanism that inhibits the release of excess cytokines that involve in inflammatory rheumatoid arthritis [21]. Furthermore, research in 2023 demonstrated that IL-37 reduces pyro ptosis in these cells by inhibiting the NF-κB pathway, thereby decreasing the release of joint-damaging substances [22].

Conclusions

Our study revealed that there were high serum levels of interleukin 17 and interleukin 37 in rheumatoid arthritis patient's compared to normal Iraqi controls, but vitamin D serum levels in the rheumatoid patients were low compared to the control ones which may lead to enhancement of expression of various cytokines resulting in more disease severity.

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