Since 1983
EPITHEORESE KLINIKES FARMAKOLOGIAS KAI FARMAKOKINETIKES | 42(Sup1): 9-15 (2024)

Received: 19 July 2024 | **Accepted**: 13 December 2024 | **Published**: 27 December 2024

Open Access | RESEARCH

Role of several cytokines and vitamin D deficiency in the progression of rheumatoid arthritis in Iraqi patients

Rawaa AlChalabi[1], Rawaa Sadeq Jaafer[2], Rana I. Mahmood[3,*], Aya M. Al-Rahim[1], Dania Omer[1]

[1]Department of Molecular and Medical Biotechnology, College of Biotechnology, Al-Nahrain University, Jadriya, Baghdad, Iraq
[2]Rheumatology Center, Al-Yarmouk Teaching Hospital, Baghdad, Iraq
[3]Department of Biomedical Engineering, College of Engineering, Al-Nahrain University, Jadriya, Baghdad, Iraq

***Corresponding author:** Rana I. Mahmood, Department of Biomedical Engineering, College of Engineering, Al-Nahrain University, Jadriya, Baghdad, Iraq; Tel.: +964-7901531242; e-mail: rana.i.mahmood@nahrainuniv.edu.iq

ABSTRACT

Background: Rheumatoid arthritis (RA) is an inflammatory, systemic autoimmune disease that affects the synovial joints and connective tissues. It is thought that the etiopathogenesis of RA may be associated with the levels of pro- and anti-inflammatory cytokines as well as a vitamin D deficiency. *Aim:* This study sought to investigate the effects of vitamin D and of the serum levels of interleukin (IL)-17, IL-37, IL-8, and IL-10 on the progression of RA in Iraqi patients. *Methodology:* Blood was taken from 120 participants: 62 newly-diagnosed cases of RA and 58 healthy individuals. In order to compare the serum levels of cytokines in RA patients and in healthy individuals, an enzyme-linked immunosorbent test was used. We also assessed the serum levels of vitamin D by using the Cobas e 411 analyzer (Roche). *Results:* Our findings demonstrated that RA patients had greater serum levels of IL-8, IL-17, and IL-37 and lower levels of IL-10 compared to those of the control group. On the other hand, the serum vitamin D levels in RA patients were considerably lower than those of the healthy individuals. *Conclusion:* This study reveals a low level of vitamin D in the serum of Iraqi RA patients, which may be directly related to the enhancement of the stimulation of many inflammatory cytokines, thereby increasing the severity of the disease.

KEYWORDS

rheumatoid arthritis, vitamin D, cytokines, interleukins, Iraq

How to cite: AlChalabi R., Jaafer R. S., Mahmood R. I., Al-Rahim A. M., Omer D.: Role of several cytokines and vitamin D deficiency in the progression of rheumatoid arthritis in Iraqi patients. *Epitheorese Klin. Farmakol. Farmakokinet.* 42(Sup1): 9-15 (2024).
DOI: 10.61873/UTDA8218

Publisher note: PHARMAKON-Press stays neutral with regard to jurisdictional claims in published maps and institutional affiliations.

1. INTRODUCTION

Rheumatoid Arthritis (RA) is an autoimmune disease that results in inflammation, hardness, and swelling of the joints, as well as damage in the synovial membrane for both joints and bones, which ultimately leads to serious disability and premature death [1]. RA affects 0.5% to 1% of the human population, with an average age of onset between 40 and 50 years [2]. RA involves chronic synovial inflammation resulting in the destruction of joints and the erosion of the bones. The typical clinical signs of RA include morning stiffness, symmetric joint swellings, asthenia, and pain. These signs are regarded to be key for the diagnosis of the disease. RA progression consists of three main steps that start with autoimmunity development, local in-

flammation, and the induction of bone destruction [3-5]. Autoimmunity development amongst susceptible individuals can be impacted by different hereditary and environmental factors [6].

Cytokines are low molecular weight glycoproteins that have a major influence on RA haemopoiesis, and immunological responses [7,8]. Due to the activation of invincible cells and synovial fibroblasts, RA patients have significantly higher serum levels of several proinflammatory cytokines than healthy individuals [9,10]. Many different cell types, such as macrophages, monocytes, and endothelial cells release chemokines, interleukins (IL), interferons (IFN), tumor necrosis factor-alpha (TNF-α), and other growth factors, while *their* production levels are organized at the transcriptional and post-transcriptional levels [11,12]. A chemokine called IL-8 is first made as a precursor peptide by different cells, and is subsequently cleaved in order to yield multiple active isoforms. Numerous transcription factors, including the hypoxia inducible factor 1, activator protein 1, and the nuclear factor kappa B, are activated by IL-8 signalling [13,14]. IL-8 not only accelerates the staffing and deposition of different immune cells in joints, but also expedites neo-angiogenesis. The elevated IL-8 concentrations in synovial fluids have been associated with the infirmity progression [15,16].

On the other hand, IL-17 is linked to both RA and the destruction of other cytokines that have proinflammatory action, such as TNF-α, IL-6, IL-1β, and IL-8, as well as the recruitment of immune cells to the synovium. T helper 17 (Th17) cell counts are higher in the blood of RA patients, and they have also been associated with higher IL-17 levels in the synovial fluid [15,17,18].

IL-10 is a pleiotropic cytokine, essential for controlling inflammation and preserving cell homeostasis [19]. IL-10 can be used in order to treat RA on account of its immunoregulatory and anti-inflammatory properties. IL-10 inhibits the generation of proinflammatory mediators in addition to suppressing T cell responses to certain antigens; it primarily functions by impeding the ability of macrophages to co-stimulate [20,21].

Finally, IL-37 is a precursor protein that belongs to the family of anti-inflammatory cytokines. The bone marrow, the thymus, the lymph nodes, monocytes, and B lymphocytes have all been linked to the functions of IL-37 [22,23]. Serum levels of IL-37 have been found to be abnormal in a number of inflammatory disorders. IL-37 can dramatically lower the Th17 cell expression of IL-17, IL-1, and IL-6, as well as prevented joint inflammation [24-26]. There is an increase in both the production and the expression of IL-37 after stimulation by cytokines that have proinflammatory effects, like IL-18, IL-1, IFN-γ, and TNF-α, as well as different toll-like receptor ligands. In addition, IL-37 levels have been found to be lower in patients who are responding to disease-modifying anti-rheumatic medications [27].

As with different autoimmune defects, there is serious concern about the involvement of vitamin D insufficiency in the RA aetiology [28]. It is also believed that environmental factors can trigger RA [29], in patients who possess an underlying genetic susceptibility [30], thereby resulting in the dysfunction of adaptive and innate immunity, and toppling the balance of autoimmunity over tolerance [31]. Although smoking is already known to be a significant environmental risk factor for RA, another possible factor is vitamin D. Numerous studies have reported the existence of an inverse connection between the RA disease severity and the vitamin D serum levels [32]. Additional studies have been carried out in order to obtain a clearer picture pertaining to vitamin D levels (that are indeed seen to be considerably lower in RA patients) and have found these to be associated with the progression of RA [33]. This study has aimed to investigate the serum levels of vitamin D, IL-8, IL-10, IL-17, and IL-37 in Iraqi RA patients.

2. METHODOLOGY

2.1. Participants and sample collection

A total of 120 human blood specimens were obtained for the undertaking of this study: 62 of them derived from patients with newly-diagnosed RA who were referred by the Rheumatology Department of the Al-Yarmouk Teaching Hospital in Baghdad (Iraq) and 58 of them were obtained from healthy individuals. Three mL of blood were drawn from each participant by using a venepuncture technique through disposable plastic syringes, were placed in a gel tube, and were allowed to clot at room temperature before being centrifuged for 15 min at 5,000 rpm in order to obtain the serum; the latter was subsequently stored at -20ºC.

2.2. Ethical approval and the consent of the study participants

The Iraqi Ministry of Health's Ethics Committee has approved the study's protocol (397; 23-Oct-2022). Every study participant provided his/her consent, and under the guidance of the consultant and following permission for the collection of samples from both patients and healthy individuals, the personal data of each participant were recorded through a questionnaire.

2.3. Measurement of the serum levels of cytokines

An ELISA kit that was procured from Abcam (USA) was employed in order to measure the serum levels of IL-8, IL-10, IL-17, and IL-37 (ab214030, ab185986, ab100556, and ab213798, respectively).

2.4. Measurement of the serum levels of vitamin D

The measurement of the serum levels of vitamin D was undertaken by using a Cobas e 411 analyzer from Roche (Germany). One mL of the serum from each of the study's participants was transferred into a tube and was then loaded on the analyzer.

2.5. Statistical analysis

Statistical analysis was conducted by using the SPSS software (version 27). Continuous variables were summarized as mean ± standard deviation. The *t*-test was used in order to assess whether there is a significant difference between the two groups.

3. RESULTS

The 120 participants belonged to two groups: the first group comprised 62 RA patients, of which 52 were women (83.9%) and 10 were men (16.1%), while the second group was made up of 58 healthy individuals, of which 38 were women (65.5%) and 20 were men (34.5%). RA was more common and severe in women than in men. The age of the study participants ranged from 39 to 85 years, with a mean of 48.65 (±1.43) and 43.39 (±1.67) for RA patients and healthy individuals, respectively. The age group of 40-50 years included the majority of the participants in the study.

A critical role is played by cytokine level with regard to the development of various chronic inflammatory disorders, such as RA [34]. As shown in Table 1, a significant difference was seen in terms of the serum levels of IL-8, IL-10, IL-17, and IL-37 amongst the RA patient group *versus* the healthy individual (control) group (p=0.0034, p=0.0354, p=0.0050, and p=0.0267, respectively): all cytokine levels were found to be significantly higher in the serum of RA patients, with the exception of IL-10 that was found to be significantly lower.

Table 2 reveals the observed significant decrease in vitamin D serum levels identified in the serum of RA patients when compared to those in the serum of healthy individuals (p=0.0352).

4. DISCUSSION

It has been shown that cytokines are capable of modifying the cellular microenvironment and lead to autoimmune development and inflammatory defects, including RA [35,36]. IL-8 has the ability to trigger the activation of neutrophils that promote degranulation, generating respiratory bursts as well as releasing lysosomal enzymes; activities that are related to the aetiology of various inflammatory disorders [13]. The IL-8 malfunction can cause pain in RA due to cartilage degradation [37]. In patients with radiographic injury, the IL-10 concentration is found decreased as well, and is

Table 1. Serum cytokine levels in rheumatoid arthritis (RA) patients and healthy individuals. Statistical analysis: *, p<0.05; **, p<0.01.

	Cytokine levels (pg/mL) (mean ± standard deviation)			
Group	**IL-8**	**IL-10**	**IL-17**	**IL-37**
RA patients	137.53 ± 12.69 (**)	27.45 ± 1.13 (*)	96.24 ± 4.91(**)	69.85 ± 17.37 (*)
Healthy individuals	35.71 ± 3.52	56.62 ± 6.84	21.43 ± 2.64	19.26 ± 0.87

Table 2. Serum vitamin D levels in rheumatoid arthritis (RA) patients and healthy individuals. Statistical analysis: *, p<0.05.

	Vitamin D levels (ng/mL)	
Group	(mean ± standard deviation)	(Min, max values recorded)
RA patients	8.3 ± 1.14 (*)	6.18, 19.74
Healthy individuals	39.97 ± 6.4	25.43, 51.20

associated with the disease progression in RA [38].

Our study's findings demonstrate increased serum IL-8 and IL-17 levels in RA, thereby signifying the possible effect of those cytokines in the RA pathology. Moreover, our findings suggest that the increased levels of the inflammatory IL-8 and IL-17 cytokines may be related to the pathogenesis, severity, and prospect of RA.

On the other hand, IL-37 has been assessed by several research works that have focused on inflammatory and autoimmune disorders throughout the preceding decade [24]. IL-37 can modulate cell multiplication, differentiation, and the suppression of innate and acquired immunity [39]. Moreover, IL-37 can curb the generation of proinflammatory cytokines; a fact that has sparked interest in its possible effects on RA; a disorder where proinflammatory cytokines are of considerable significance [38]. In this study, the serum levels of IL-37 have been found to be considerably increased in RA patients when compared with those of healthy individuals. Age-related increases in the serum levels of IL-37 have also been observed, with patients over 60 years demonstrating the greatest values (p=0.037) [39]. Elevated levels of IL-37 have also been shown in Chinese RA patients, where the levels of IL-37 have been associated with proinflammatory cytokines and the Disease Activity Score-28. Finally, IL-37 levels are known to rise in newly diagnosed RA patients, while IL-37 levels are known to dramatically decreased in treated patients; together with our findings, the aforementioned studies suggest that IL-37 might play a key role in RA aetiology [40].

The term "autoimmune disorders" refers to conditions where the immune system cannot differentiate between the self and non-self tissue [41]. People who suffer from conditions like RA have T cells that attack their self-tissues and produce inflammation in the tissues around them. Although the reasons for the ineffective immune defence are unknown, it is clear that several risk factors have a significant impact. Autoimmune disorders are affected by environmental and hereditary factors [42]. Vitamin D affects various autoimmune diseases, while its deficiency might be one of the environmental factors that is often involved in controlling self-tolerance [43].

Decreased serum levels of vitamin D_3 have been associated with the disruption of autophagy, increased IFN-α circulation levels, an increase in the numbers of CD4+/CD8+ T cells, and an increase in proinflammatory cytokines [44]. It has been reported that vitamin D levels impact physiological systems that go well beyond its known activities in bone and calcium homeostasis [45]. The immunomodulatory effects of vitamin D's active form, 1,25-dihydroxyvitamin D_3 (1,25-$(OH)_2D_3$), are well-known among those influences [46,47].

The RA patients in our study exhibited lower serum levels of vitamin D than the healthy individuals. A negative relation between the severity of RA disease and serum 25-OH-D levels has been revealed by many studies [9,48]. An estimated 43% to 80% of RA patients is believed to suffer from vitamin D deficiency or insufficiency [49,50]. Our research has also confirmed that plenty of RA patients had a deficiency of vitamin D, even though they had been administered vitamin D supplements. In our study, all patients visited the Rheumatology Department of the Al-Yarmouk Teaching Hospital located in Baghdad (Iraq) where, on average, sunlight remains for a duration of about 12 to 14 h every day. This is indeed an interesting finding of our study, which is backed by other research works that have demonstrated that there is a very strong connection between the patients' RA activity and the low serum levels of vitamin D [51,52]. Nevertheless, there are certain limitations in our study. Firstly, all the patients were drawn from a single hospital; therefore, they might not accurately reflect the RA population of Iraq as a whole. Another limitation is that certain drugs (such as rifampicin) used by the RA patients can cause a reduction in the serum vitamin D levels. Lastly, thyroid disorders (which are frequently encountered in RA patients) are very likely to cause hypovitaminosis D.

5. CONCLUSION

Our study has revealed that Iraqi RA patients carry greater serum levels of IL-8, IL-17, and IL-37 and lower levels of IL-10 compared to healthy individuals. Moreover, the serum vitamin D levels in Iraqi RA patients were found to be considerably lower than those of the healthy individuals assessed. The identified low level of vitamin D in the serum of Iraqi RA patients may be directly related to the enhancement of the stimulation of many inflammatory cytokines, thereby increasing the severity of the disease.

ACKNOWLEDGMENTS

The authors are grateful to the College of Biotechnology of the Al-Nahrain University and to the Department of Rheumatology of the Al-Yarmouk Teaching Hospital for providing the laboratories and for recommending samples for this study, respectively.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

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