



## Comparative Study of Interleukin-6, Interleukin-1B Levels and Iron Profile Among Sudanese Rheumatoid Arthritis Patients with Iron Deficiency Anemia

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### Abstract

**Aims:** This study aimed to evaluate IL-6 and IL-1B levels and the iron profile (serum iron, ferritin, TIBC and TS%) in rheumatoid arthritis Sudanese patients.

**Study Design:** Case control. study.

**Place and Duration of Study:** This study was conducted at the Omdurman Islamic University, Sudan between 2018 and 2021.

**Methodology:** This study was conducted on 63 RA patients and 63 healthy individuals as control between 2018 and 2021. ELISA were used to measure the levels of IL-6 and IL-1B, while the iron profile were carried out using automated chemical analyzer, the Transferrin saturation percentage TS% was calculated using the formula: TS (%) = [serum iron (ug/dl)/serum transferrin (mg/dl)]<sup>17</sup>.

**Result:** IL-6 and IL-1B levels were increased in anemic RA patients. In all patients, 98.4% of IL-6 levels and 28.5% of IL-1B levels had risen. IDA was common with 77% of anemic RA patients, their serum iron, ferritin and TS% show significant decrease. There was significant negative correlation between serum iron, ferritin, TIBC, and TS% with IL-6 in RA patients. There was statistically significant positive correlation between serum iron and IL-1B in RA patients group.

**Conclusion:** The levels of IL-1 $\beta$ , IL-6 increased in RA patients and IDA showed 77% in case while there was association between IL-1 $\beta$ , IL-6 and serum iron in case. IDA is the most common and serious blood abnormality seen in RA. All of the above makes IL-1 $\beta$ , IL-6 and IDA with pivotal role in the pathophysiology of RA and this may affect the desirable option in the treatment of RA.

**Keywords:** Interleukin-6 (IL-6); Interleukin-1B (IL-1B); Rheumatoid Arthritis (RA); Enzyme-linked Immunosorbent Assay (ELISA); Transferrin Saturation Percentage (TS%); Total Iron Binding Capacity (TIBC); Iron Deficiency Anemia (IDA)

## Introduction

RA is a dangerous, progressive disorder that is characterized by a persistent inflammation of the synovial joints it typically causes functional disability, a lower life expectancy, and an increased death rate [1]. Patients with RA have higher levels of a number of proinflammatory cytokines in their synovial tissue or fluid, including IL-6 and interleukin (IL)-1 [2,3]. Increased levels of proinflammatory cytokines induce synovial tissue to proliferate, which in turn damages articular cartilage and destroys nearby bone [4,5]. Particularly the cytokine IL-6 has a variety of functions. Acute inflammatory reactions like fever or anemia are brought on when IL-6 is triggered. IL-6 encourages B cell proliferation, which contributes to the synthesis of rheumatoid factor [6]. In the serum and synovial membrane, elevated levels of IL-6 have recently been linked to RA [6,7]. This gave rise to the theory that IL-6 contributes to the pathogenesis of RA. The pro-inflammatory cytokines tumor necrosis factor TNF, interferon gamma (IFN), interleukin-1 (IL-1), and interleukin-6 are linked to the onset of rheumatoid anemia (IL-6). Particularly, interleukin-6 (IL-6) has significant impacts on the hormone hepcidin, which lowers iron absorption. Although rheumatoid anemia is typically the cause of anemia in a patient with rheumatoid arthritis, additional reasons occur depending on the disease's stage and the treatments utilized [8,9]. Many proinflammatory cytokines, including interferon, interleukin-1 (IL-1), and interleukin-6 (IL-6), as well as pro-inflammatory cytokines that have been shown to induce excessive hepcidin production, are synthesized in response to inflammation brought on by infection, autoimmune disease, and cancer [10]. cytokines that promote inflammation. The primary proinflammatory cytokine in rheumatoid arthritis is interleukin (IL)-1. The key discoveries in the synovial membrane include the inflow and/or local activation of mononuclear cells as well as the development of new blood vessels. Synovitis is a result of naive T cells differentiating into Th17 cells. Through antigen presentation, autoantibody synthesis, and cytokine generation, B cells assist the pathogenic process. Synoviocytes and chondrocytes both release enzymes that break down cartilage. The production of cytokines, particularly interleukin-1 (IL-1) has a number of negative consequences on bone and cartilage. Proinflammatory cytokines have both local and systemic effects. For example, they can cause acute-phase proteins to be produced, chronic illness anemia, cardiovascular disease, osteoporosis and other conditions

[11-13]. Interleukin-1 (IL-1) increased the production of acute-phase proteins, chemokines, matrix metalloproteinase (MMP), synovial fibroblast cytokines, osteoclasts, endothelial cell adhesion molecules and monocyte cytokines [11-17]. Interleukin-6 (IL-6) is overexpressed at sites of inflammation and is thought to play a key role in chronic inflammation. Is a multi-target cytokine with rheumatoid arthritis-related activity that promotes acute-phase proteins and contributes to the disease's systemic symptoms by producing hepcidin (anemia) [16].

## Material and Methods

This case control study was conducted in Khartoum State, between 2018 and 2021 samples collected from Military Hospital, Khartoum, Sudan and Modern Medical Center, Khartoum, Sudan. A total of 126 volunteers were enrolled in this study; 63 were Sudanese patients diagnosed with anemic RA as a patient's group; the mean of their age was  $(46.04 \pm 10.07)$ . This study was approved by Omdurman Islamic University ethical committee. Patients were included after written informed consent. 5 ml of venous blood were collected from all participants, and then measure CBC using Sysmex Kx-21. The iron profile (serum ferritin, serum iron and total iron binding capacity) was carried out using automated chemical analyzer Roche/Hitachi cobas c311 and e411 (Roche Diagnostics GmbH, Mannheim, Germany). Transferrin saturation (TS) will calculated with the formula:  $TS (\%) = [\text{serum iron (ug/dl)} / 71] / \text{serum transferrin (mg/dl)}$  with these methods [17].

ELISA (CDRG state fax 4200. Germany) were used to measure the levels of IL-6 and IL-1B.

Principle: Standards or samples are added to the appropriate Micro ELISA strip-plate wells and combined to the specific antibody. Then a Horseradish Peroxidase (HRP)-conjugated antibody specific for Interleukin-1 (IL-1B) and Interleukin-6 (IL-6) is added to each Micro ELISA strip-plate well and incubated. Free components are washed away. The TMB substrate solution is added to each well. Only those wells that contain Interleukin-1 (IL-1B), Interleukin-6 (IL-6) and HRP conjugated Interleukin-1 (IL-1B) and Interleukin-6 (IL-6) antibody will appear blue in color and then turn yellow after the addition of the stop solution. The optical density (OD) is measure spectrophotometrically at a wavelength of 450 nm. The optical density value, extinction, is proportional to

the concentration of IL-6, IL1B and the calculate the concentration of Interleukin-1 (IL-1B) and Interleukin-6 (IL-6) in the samples by comparing the optical density of the samples to the standard curve.

Data were collected by direct questioner and analyzed by using statistical package for social sciences (SPSS) version 23. T. test and ANOVA test were used for comparison of means between different study groups, while correlation between quantitative variables was assessed with Pearson’s correlation. P. value considered significance if less than 0.05.

**Results**

126 individuals were included in this study, 63 of them were patients with rheumatoid arthritis as case group and 63 were healthy as control. This study revealed there was significant increase in IL-6 in RA patients (96.2306 ± 88.92) compared to control (2.8057 ± 1.88) with P. value 0.00 and also significant increase in IL1B in RA patients (12.9985 ± 17.61) compared to control (5.4421 ± 3.82) with P. value 0.01.

	Study population	Mean ± STD	p. value
IL6	Case	96.2306 ± 88.92	0.00
	Control	2.8057 ± 1.88	
IL1B	Case	12.9985 ± 17.61	0.01
	Control	5.4421 ± 3.82	

**Table 1:** Mean of IL6 and IL1B in rheumatoid arthritis patients compared to control.

There was significant difference in serum iron, ferritin, TS% between patients and control while the TIBC show insignificant difference with in case and control).

There was significant negative correlation between serum iron, ferritin, TIBC, and TS% with IL6 in RA patients. There was statistically significant (0.007) positive correlation between serum iron and I.

	Study population	Mean	Std. Deviation	p. value
Serum iron	Case	5.6603	3.13567	0.00
	Control	16.0921	5.79366	
Ferritin	Case	14.4587	19.78686	0.00
	Control	28.2492	19.39203	
TIBC	Case	50.6825	12.43404	0.9
	Control	50.8413	5.43479	
TS%	Case	12.9825	11.29851	0.00
	Control	31.8338	10.58306	

**Table 2:** Mean of iron status among patients with rheumatoid arthritis correlated to control.

L-1B in RA patients group.

		Serum iron	Ferritin	TIBC	TS%
IL6	P	0.989	0.480	0.869	0.408
	R	-.002	-0.091	-0.021	-.106
IL1B	P	0.954	0.530	0.646	0.243
	R	0.007	0.081	0.059	0.149

**Table 3:** Correlation between serum iron, Ferritin, TIBC, TS% and IL6, IL1B.

## Discussion

It is thought that IL-1 and IL-6 play a role in the pathogenesis of rheumatoid arthritis (RA). The pleiotropic cytokine interleukin 6 (IL-6) plays a crucial part in the pathogenesis of rheumatoid arthritis (RA). While interleukin-1beta (IL-1), a significant mediator of inflammation, has an impact on cell division and proliferation. Both the local events and the systemic acute phase response rely heavily on cytokines. It has been demonstrated that interleukin-1 (IL-1) is the main cytokine mediating the destruction of joints during inflammation and that it is a powerful inducer of the production of IL-6 [18]. Synovitis is a result of naive T cells differentiating into Th17 cells. Through antigen presentation, autoantibody synthesis, and cytokine generation, B cells assist the pathogenic process. Synoviocytes and chondrocytes both release enzymes that break down cartilage. The production of cytokines, particularly interleukin-1 (IL-1), has a number of negative consequences on bone and cartilage. Proinflammatory cytokines have both local and systemic effects. For example, they can cause acute-phase proteins to be produced, chronic illness anemia, cardiovascular disease, osteoporosis, and other conditions [11-13]. Through B-cell maturation and TH-17 differentiation, IL-6 may help to initiate and maintain the autoimmune process. IL-6 can encourage synovitis and the degeneration of joints. Many of the RA systemic symptoms may also be caused by IL-6, which produces hepcidin and causes the acute-phase reaction C-reactive protein (CRP) and anemia [19]. This study revealed there was significant increase in Proinflammatory cytokines IL-6 and IL-1B in RA patients compared to control. This agree with the study done by [20,21].

More over the increase in IL-6 in RA patients was agree with the study done by [22-24].

Also the increase in IL1-B in RA patients was agree with the study done by [21,25-29]. On other hand the study done by [30] disagree with this study it showed markedly reduced of IL-1B in RA patients. The iron profile in this study showed significantly decreased in serum iron, serum ferritin and TS % in RA patients. This agree with the study done by [22-31]. A serum ferritin and serum iron were also significantly reduced in the study done by [32,33]. while the decrease in serum iron and TS% was shown in the study done by [22-32]. Also serum ferritin and TS % in RA patients this agree with [44]. lastly TS% was significant decrease

in the study done by [34]. The a serum ferritin and TS% do not correlation with the high levels of IL-6, IL-1B While the serum iron correlate with high level of IL1B, IL-6 in RA Sudanese patients, this agree with the study done by [22,35,36]. Patients with rheumatoid arthritis frequently have anemia. Shortening of the erythrocyte lifetime, insufficient bone marrow erythropoiesis in response to the anemia, and abnormalities in iron metabolism are some of the factors that contribute to rheumatoid anemia [37,38]. The interleukin-1 (IL-1) and interleukin-6 pro-inflammatory cytokines have an impact on the onset of rheumatoid anemia (IL-6). Particularly, interleukin-6 (IL-6) has significant effects on the hormone hepcidin, which lowers iron levels. Depending on the stage of the disease and the medications used, there are several reasons of anemia in rheumatoid arthritis patients, even though rheumatoid anemia is typically the case. he most frequent of them is iron deficiency anemia caused by improper absorption or, more frequently, iron loss. Patients with rheumatoid arthritis whose anemia is brought on by drugs like methotrexate, through a variety of factors [8,9]. The decline in erythropoiesis is caused by the direct inhibitory effects of the connection between IL-1B and serum iron on the bone marrow's generation of red blood cells. Erythropoietin synthesis and iron regulation are also hampered. Additionally, the erythrocyte half-life is decreased by the increased erythrophagocytosis [39]. The suppression of iron release from the macrophageal system and the hypoferrremia of ACD were thought to be caused by IL-1, interferon gamma, and tumor necrosis factor alpha [40]. In RA, cytokines such TNF-alpha, interferon gamma, IL-1, IL-6, and IL-10 are released. As a result, iron is deposited in macrophages and macrophages are activated [41,42]. Hepcidin also stimulates this mechanism. The production of ferritin is induced by TNF alpha, interleukin-1, interleukin-6 and interleukin-10, which promotes the retention of iron in macrophages [43]. Anemia and lower blood iron levels are the results of the aforementioned processes.

## Conclusion

77% of Rheumatoid arthritis patients was IDA, there was high levels of IL1B, IL6 and there was strong correlation between IL1B, IL-6 and serum iron.

IL-6 is proinflammatory, induces acute-phase proteins (including CRP) and contributes to the systemic manifestations of

RA, while the IL-1 $\beta$  appear to correlate with systemic inflammation, and systemic features of RA. IDA is the most common and serious blood abnormality seen in rheumatoid arthritis. All of the above makes IL-1 $\beta$ , IL-6 and IDA with pivotal role in the pathophysiology of RA, and this may be affect the desirable option in the treatment of RA.

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### Competing Interests

The authors declare no competing interests.

### Authors' Contributions

Rouaa Babikir Ahmed: data curation; investigation; methodology; validation; writing – original draft; writing – review and editing. Khalid Mohamed Khalid Elhussain, Babiker Ahmed Mohammed, Doaa Abdullah Gasim, Elyasaa Ahmed Gubartalla Ali, Manal Mohammed Khalid Elhussien, Nora Nahal Bouderbera, Mohammed Babiker Omer, Rufaida Abdalla Ahmed, Khalid Babikir Ahmed: conceptualization; formal analysis; project administration; supervision; visualization.

### Consent and Ethical Approval

The authors considered all related ethical rules and consent.

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