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Serum Interleukin-6 Levels in Rheumatoid Arthritis Patients with and without Anemia in Khartoum State, Sudan

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Abstract

Background

Rheumatoid arthritis (RA) is a widespread autoimmune disease that primarily affects the joints, causing pain and disability, which can significantly impact both individuals and communities. It develops due to immune system dysfunction, with IL-6 playing a key role in its progression. Many RA patients also experience anemia, most commonly due to chronic disease or iron deficiency, further complicating their condition.

Objective

This study aims to evaluate serum IL-6 levels, determine the prevalence of anemia and non-anemia in patients with rheumatoid arthritis (RA), and assess the relationship between blood parameters and disease activity among Sudanese patients with RA and iron deficiency anemia in Khartoum State.

Materials and Methods

This descriptive case-control study included 74 patients of both genders diagnosed with rheumatoid arthritis (RA), with and without anemia, and a disease duration of two years. The study was conducted in Khartoum State. Complete Blood Count (CBC) was performed using an Auto Hematology Analyzer. Serum IL-6 concentrations were measured in all patients and healthy individuals using

Chemiluminescent Immunoassay (CLIA). Data were collected through a simple questionnaire and self-administered interviews.

Results

Rheumatoid arthritis (RA) was more prevalent among females (46, 62.16%) than males (28, 37.83%), regardless of anemia status. Blood parameters varied significantly across different age groups. A strong link was found between IL-6 levels and WBC, RBC, and MCH values in RA patients with anemia, with Chi-square p-values of 0.001, 0.013, and 0.014, respectively. The odds ratios for WBC and RBC were 5.828 and 5.703, indicating a notable increase, especially among RA patients with anemia.

Conclusion

Our study highlights the association between IL-6, blood parameters, rheumatoid arthritis, and anemia, which may contribute to disease symptoms. Anemia is a significant complication of RA, linked to physical disability and increased mortality, with IL-6 playing a central role in its pathophysiology.

Keywords: Anemia, Rheumatoid arthritis, Interleukin-6, blood parameters, Sudanese patients

Introduction

Anemia is common in patients with rheumatoid arthritis (RA). Higher hemoglobin (Hb) levels may be associated with better clinical outcomes and patient-reported outcomes (1).Interleukin-6 (IL-6) is a glycoprotein with a molecular weight of 26 kDa and pleiotropic activity (2, 3), and is a soluble mediator with a pleiotropic effect on inflammation, immune response, and hematopoiesis (4), found to be elevated in serum as well as synovial fluid of patients with RA (2). IL-6 is a representative cytokine featuring pleiotropic activity and redundancy (5) involved in many biological functions that affect tissues beyond the immune system and the vasculature (3). IL-6 associated with the pathogenesis of rheumatoid arthritis and development of anemia in it (2, 5). High concentrations of IL-6 in both the synovial fluid and serum of patients with RA suggested a major role of this cytokine in the pathogenesis of RA (5). Persistent inflammation leads to erosive joint damage and functional impairment in the vast majority of patients (5, 6,7). Anemia of chronic disease (ACD), also known as anemia of chronic inflammation, is the major reason for developing anemia in RA patients and is common characteristic disorder that affects the health of rheumatoid patients (8,9). There are many types of anemia in RA such as iron deficiency anemia (IDA), anemia of chronic disease (ACD), the

combination of both IDA and ACD, and hemolytic anemia (10). The incidence of ACD increases with age, and in the elderly population it accounts for approximately one-third of all anemia cases (11). Recent studies suggest that ACD develops via multiple mechanisms including pathogenic iron homeostasis, impaired erythropoiesis, and the blunted erythropoietin response (12). Rheumatoid arthritis (RA) is a chronic autoimmune disorder (10, 13, and 14) characterized mainly by inflammation of the synovial tissues of the joints, but also potentially affects a variety of extra-articular organs (15). Patients with rheumatoid arthritis (RA) may have a wide range of hematologic abnormalities. Common manifestations among patients with active disease may be anemia (16). The objective of present study was to evaluate serum IL6 and to detect frequency of anemia/non-anemia and Rheumatoid arthritis (RA) patients and establish relationship between blood parameters and disease activity among Sudanese patients suffering from rheumatoid arthritis and deficiency anemia in Khartoum State.

Materials and Methods

Study Design: The source of the data was the laboratory findings for patients who attended private authorized clinical laboratories in Khartoum city of Sudan, period. The study included 74 patients from both gender defined as three groups. (group 1: 45 RT, group 2:10 Anemia and group 3:19 NA).

Study population: The present study is a case control hospital-based study conducted at Khartoum State. seventy-four Rheumatoid arthritis(RA) patients and with anemia aged 35 to 74 years old were examined at the common diseases clinics in Khartoum State (University of Al-Neelein faculty of Medical Science Laboratory, Al-Rayan Special Laboratory and Al-Widad Hospital). A total of 74 specimens from both genderes defined as three groups, and were selected from Patient's Clinics. A control group has been obtained from MAGLUMItm 800 and selected for the study. Informed consent has been obtained from guardians of all study participants. Study participants are individual with RT and anemia symptoms enrolled and investigated by the clinician at the study sites.

Data collection and sampling: The samples were collected in plane tube from the studied participants. The Personal data; Demographic details and clinical data information such as gender, age at onset of disease, and duration of disease used in diagnosis of RA/Anemia were collected and recorded from study participants using questionnaire. Both symptomatic Rheumatoid arthritis patients and Anemia associated with IL6 have been identified by clinician from two hospitals, Serum concentrations of IL-6 were measured in all RA/anemia patients and healthy individuals were examined via MAGLUMI- auto Chemiluminescence Immunoassay (CLIA) system according to the manufacturer's instructions (Eiffestrasse 80, 20537 Hamburg, Germany). Different blood parameters

have been evaluated. Serum concentrations of IL-6, was measured in all patients and healthy individual using CLIA. Patients with anemia were diagnosed according to the WHO criteria. Patients with hemoglobin value <12g/dL in women and<13g/dL in men were considered anemic.

Using vacutainer Needle holder 3 and 5 ml of whole blood has been taken in to EDTA and plain tube respectively, and used in to measure different hematological parameters (CBC, ferritin, IL-6). And it was leave the plain tubes in 30 minutes at room temperature to be collected. Then samples were centrifugation for 10 minutes at 3500 rpm. The serum separated by using automatic pipette and removed very careful to another plain tube and freeze to -40c to be reserve for IL-6 assay. After collection of 45 serums from patients who known as rheumatoid arthritis, also another 10 serum collected from anemic patients and 19 for non-anemic as control. All the samples were run in snibe Maglumi 800 after the control and calibration done.

Study population criteria: Sudanese patients known diagnosed to have RA with or without anemia. Serum concentrations of IL-6 were measured in all RA patients and healthy individuals using Chemilumscence immunoassay (CLIA) according to the manufacturer's instructions. The quantitative measurement of human ferritin concentration was estimated by CLIA according to the specifications provided by the manufacturer with regard to the corresponding concentration values in ng/ml. In IDA classification, a cutoff value of ferritin level, was taken as 10 ng/ml and 20 ng/ml in females and males, respectively, and any lower levels were considered as IDA. demonstrate the changes in serum level of IL-6, ferritin level, in different groups of patients with RA and to find out the potential correlation between serum level of IL-6 and ferritin level and the relationship between serum level of IL-6 Methods. The study included 74 patients from both genderes divided into three groups (group 1: 45 RA; group 2:10 Anemia and group 3: 19 non anemic).

Ethical Approval: This study will be approved from Al-Neelein University Institutional review board; The Informed Consent will be taken from every participant in this study before the sample is taken.

Statistical analysis: All the statistical analyses data were performed and analyzed using Statistical Package for the Social Sciences (SPSS) analysis software (version. 21.0; IBM Co., Armonk, NY, USA). The Chi-square (χ 2) test was performed to analyze significant differences between the Rheumatoid arthritis (RA) and anemia associated with the Interleukin-6 (IL-6). The results of demographic characteristics were presented as descriptive statistics in terms of relative frequency. P value < 0.05 was considered to be significant and were expressed as mean ± and standard deviation.

Results

Out of 74 patients enrolled in our study, 45(60.8%) were found to be RA. The age of the study participants ranged between 35 to 74 years old with a mean age of 2.4 years, which were grouped into four age groups (35-44), (45-54), (55-64) and (65-74) with the following percentages 35.13%, 16.2%, 25.7 and 23.0% respectively. The present study showed 29(64.4%) in the females and 16(35.5%) in the males within RA patients/n=45. And showed 6(60%) in males, 4(40%) in females within anemic patients as shown in (Fig. 1), (Table 2). Frequency percentage of both gender within RA anemia, anemic and non-anemic patients was found 46(62.2%) in females, and 28(37.83%) in males, (Figure.2). There were significant changes in the WBCS and HGB of blood parameters between the age groups which found 0.03(data is not shown). The association of IL-6 variant with RA risk was expressed as odds ratio (OR) and 95% confidence interval (95% CI). There was a significant p-value of IL6 with WBCS, RBCS and MCH with Chi square p-value = 0.001,0.013 and 0.014, respectively. The statistic odd ratio was found 5.828 and 5.703 for WBCs and RBCs. departure of frequencies of serum IL-6 within blood parameters was tested by Chi-square test, and P value <0.05 (Table 3). There was no statistically significant difference between RA and Anemia patients with blood parameter in HGB, MCV, MCHC and PLT. (Table 3). The result reflects that, 10(13.5%%) out of 74 patients are anemic and 19(25.7%) are non-anemic. The RBCs level ranged from 4g/dl to 5.8g/dl in anemic. Rheumatoid arthritis patient with mean ± SD of 1.24±0.570 and with p-value= 0.04. For non-anemic patients, the RBCs level range from 12 g/dl to17 g/dl with a mean ± SD of 0.86±0.693 with p-value 0.05, this difference was found to be highly statistically significant with (p value=0.05). (Table 4).

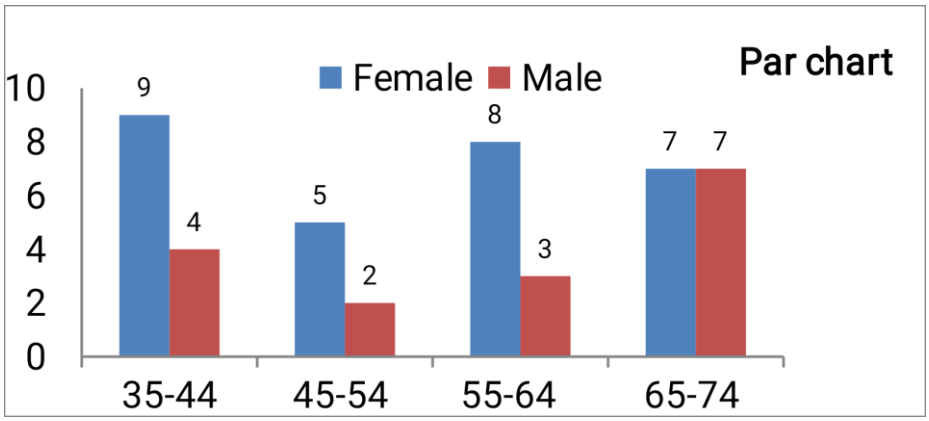


Figure (1): Frequency of the age group between males and females

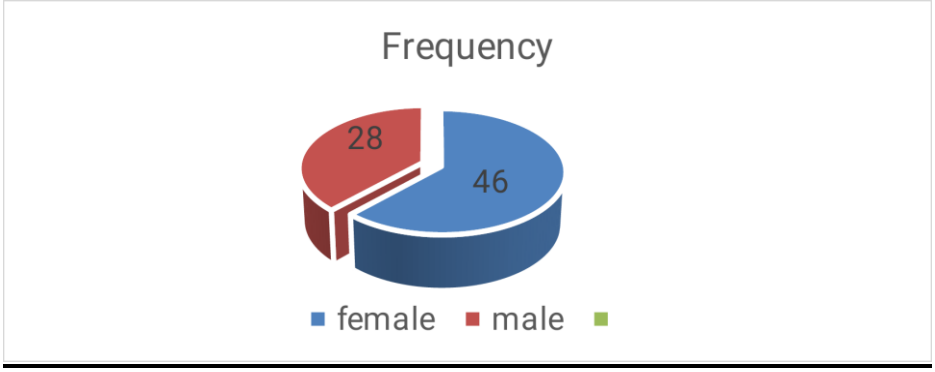


Figure (2): Frequency of the gender among study participants

Table (1): Percentage of Age and Gender of Rheumatoid arthritis and Anemia in each age group among study participants

Rheumatoid arthritis(RA) N=45		Anemia N=10		Non-Anemic N=19		Total Age group N=74
(M) (%)	(F) (%)	(M) (%)	(F) (%)	(M) (%)	(F) (%)	Age group /frequency
4 (8.80%)	9 (20.00 %)	3 (30%)	2 (20%)	3(15.8%)	5(26.31%)	35-44age =26 (35.13%)
2 (4.44%)	5 (11.11%)	1 (10 %)	0 (0. %)	1(5.3%)	3(15.8%)	45-54age=12 (16.2%)
3(6.66%)	8 (17.77%)	2 (20%)	1 (10 %)	1(5.3%)	4(20.05%)	55-64age=19 (25.7%)
7 (15.5%)	7 (15.5%)	0 (0.0%)	1 (10%)	1(5.3%)	1(5.3%)	65-74age=17 (23.0)
T=16 (35.5%)	T= 29 (64.4%)	T=6 (60.0%)	T=4 (40.0%)	T=6 (31.6%)	T=13(68.42%)	Total /74/74 (100%)

Abbreviations: N=number, F%= female percentage, M%= male percentage and T= total.

Table (3): Significant P-value <0.05 association between Serum level of interleukin 6 of Rheumatoid arthritis and Anaemia' patients within blood parameters among study participants using Chi square's exact test and Odd Ratio,

Serum level of IL6 of Rh/ Anaemia		frequencies	OR	COR		P-value
				L	H	
WBCs**IL6***	Normal=4-11	N:16(29.0%) H:39(70.9%)	1.137	0.496	5.828	0.001
RBCs**IL6***	Normal=4.2-5.2	N:4 (7.27%)	2.115	0.74	5.703	0.013
HGB*IL6	Normal=12.5-17	N: 43(87.2%)	0.421	0.161	2.955	0.324
	Hypo=<12	H:12 (21.8%)				
MCV*IL6	Normal=76-96	N: 20(36.4%)	1.000	0.326	3.069	0.114
	Micro=<76	M:35 (63.6%)				
MCH*IL6	Normal=26-32	N: 22(40%)	1.429	0.291	2.985	0.014
	Hypo=<26	H: 33(60%)				
MCHC*IL6	Normal=32-37	N: 29(52.7%)	1.374	0.31	3.106	0.522
	Hypo=<32	H: 26(47.3%)				
PLT**IL6***	*150-450*	N: 55(100%)	-	-	-	-
		H: 55(100%)				

Table 4: Demographic, hematological, and blood parameters comparison between rheumatoid arthritis /anemic and non-anemic patients, regard with p-value <0.005

Comparison between	**Total RA patients**		**Total anemic RA**	**Total Non-Anemic**	
Groups	**RA patients**	**P≤**	**anemic RA**	**Non-anemic**	**P≤**
Parameters	**N=45**		**N=10**	**N =19**	
Gender F/M	29/16		4/6	13/6	
Females%	64.4%	NS	40%	68.42	NS
Males%	35.5%		60%	31.57%	
Age(years)		NS	2.00 ± 1.155	2.03 ± 1.085	NS
WBCs(10∧3/µ)L	1.38±0.936	0.03	1.42±0.19	1.28±0.960	NS
RBCs (10∧6/L)	1.24±0.570	0.04	1.24±0.567	0.86±0.693	0.05
HGB (g/dl)	0.27±0.447	NS	0.22±0.417	0.17±0.384	NS
MCV (fl)	0.56 ± 0.503	NS	0.64±0.485	0.62±0.494	0.002
MCH (pg)	0.53 ± 0.505	NS	0.60 ± 0.494	0.69 ± 0.471	NS
MCHC(g/L)	0.42±0.499	NS	0.47±0.504	0.48±0.509	NS
PLT	00±00	NS		0.14 ± 0.35	0.009
IL-6 (pg/mL)	0.76 ± 0.981	NS	0.62 ± 0.933	0.55 ± 0.910	NS

Discussion

Rheumatoid arthritis (RA) is characterized by inflammation of the synovial membrane and proliferation of the synovial lining, which results in erosion of cartilage and bone. This study to detect frequency of anemia in patients of Rheumatoid arthritis (RA) and to establish relationship between blood parameters level and disease activity in RA among Sudanese. The sex difference in this study showed that in the total number of Seventy-four patients with all three groups, the present study revealed that females were the predominant Forty-six with a ratio 62.2% were high effect more than the males were just predominantly Twenty-Two with ratio 37.8%. This agree with other studies in Sudan where found 72(90%) with female and 8(10%) with male [14]. Another study indicated a high prevalence of RA and anemia cases were collected from females, whereas 96(91.4%) with female and 9(8.57%) with male [21, 16]. The reason of high ratio is greater than previous studies in other countries due to the occupation, with regards to men engaged in managerial and technical occupations and in professions have a lower than expected prevalence of RA. Also, females were three times more likely to develop RA than males. Also this study showed a highly statistical significant p-value between female and male among RA patients and non- anemic (p-value= 0.002). This in contract to

other study which recorded no significant difference was found for the percentage of females between RA patients and controls (75.12% vs. 67.83%, P>0.05) (5).The most frequent age group among study participants was 35-44 years =26 (35.13%) followed by 55-64year=19 (25.7%) This has been shows in previous study in Sudan by safa et.al which recorded 20-60 years old diagnosed with RA with consideration of the disease duration (14). The present study showed that there were no significant differences in RA and anemia patients between blood parameters, except in the WBCS, RBCS and MCH with odd ratio 5.828 and 5.703 and Chi square p-value = 0.001,0.013 and 0.014, respectively. This is in contract to other study in al- Iraq who recorded high significantly in all blood parameters among participants except in the WBCs, MCH and MCH among ICD patients and MCH among RA patients (10). In this study, 45/74 (60.8%) participant cases were found to be rheumatoid Arthurs. Anemia of chronic disease ICD (10/74 ,13.5%) was the commonest type of anemia observed in this study, 19/74, 25.7% were found to be non- anemic. this study finds a higher occurrence of RA. Similar results were obtained in a study done in 2018 in which ACD was seen in 55.00% and 67.80% in anemic RA cases (28). In the study by Adriana Sabauet et al, 70.4% patients were anemic in which IDA was present in 47.36% patients and the rest of 52.63% patients had ACD (29). Helen A. at el (papadaki HA) had observed 57.5% RA patient anemic out of which 37.5% patients had ACD (30). In previous other cross-sectional studies, ACD has been reported to be present in 30% to 70% of patients with RA (31,32) as confirmed by the data from Wolfe. These findings support the notion that ACD is the most frequent cause of anemia in RA. Data analysis in this study showed that there were significant differences in hematological parameters among RA patients and between anemic/non-anemic patients ($p<0.05$), whereas recorded p-value 0.03 and 0.04 for WBCs and RBCs among RA patients respectively and 0.05, 0.002 and 0.009 for RBCs, MCV and PLT among anemic/non-anemic patients, respectively. This is in agreement with other public paper which recorded 0.01, 0.001 and 0.01 for WBCs, RBCs and HGB among RA patients, respectively. and 0.005,0.005, 0.006 and 0.02 for RBCs, HGB, MCV and IL6 among anemic and non-anemic patients, respectively (10).The mean ± values in the present study was varied. Recorded mean ± 1.38±0.936 and 1.24±0.570 of WBCs and RBCs among RA patients respectively with high p-value 0.03. and 1.24±0.567, 0.64±0.485 of RBCs and MCV with anemic. And 0.86±0.693, 0.62±0.494 and 0.14±0.35 of RBCs, MCV and PLT with high p-value 0.009 among non-anemic patients, respectively. This reported in other studies, whereas recorded mean ± SD 8.7g/dl±1.5 with Hb level ranged from 7g/dl to 11g/dl in anemic rheumatoid arthritis patient with mean ± SD of 8.7g/dl±1.5 and mean ± SD of14.1g/dl ± 1.3with Hb level range from 12 g/dl to17 g/dl for non-anemic patients with highly statistically significant with p value=0.000 (13, 33). The present study reveals that there is no statistically significant difference in the serum of

IL6 with mean value 0.76±0.981 pg/m, 0.62±0.933 pg/ml and 0.55±0.910 pg/ml Among RA, ICD patients and non-anemic. This is not agreement with other studies which recorded a high significantly p-value=0.0001 in the RA patients and 0.02 between ICD patients and non-anemic (10).

Conclusion

In conclusion, we suggest that RA patients undergo a routine analysis of their hemoglobin levels, and when decreased hemoglobin level is suspected, adequate investigation should be performed. our study highlighted it has been found that IL-6 plays a key role in the development of this disease. IL-6 and ferritin level estimation may be workable tests to differentiate the patients with anemia in RA. The results indicated a significant relationship between RA and Anemia. However, patients with RA showed higher serum level of IL-6.

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