

**Types of Anaemia and its Correlation with Disease Activity in Patients with Rheumatoid Arthritis among Kurdish Population of Iraq**

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**Abstract:**

**Background:** Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease characterized by articular and extra-articular manifestation as weight loss, fatigue, malaise, and anemia.

**Objectives:** The aim of this study was to find the prevalence of different types of anemia and its correlation with the disease activity among patients with RA in Sulaymaniyah province and to determine the associated risk factors.

**Patients and Methods:** A cross sectional study carried out in Sulaymaniyah general medical Hospital for periods from October-2014 to the end of June-2015. A convenient sample of 100 rheumatoid arthritis patients were selected from patients seen in the rheumatology clinic. One hundred healthy voluntary controls of same age groups were selected and same parameters for diagnosis of anemia are used in both groups.

**Results:** The prevalence of all types of anemias among the rheumatoid Arthritis (RA) patients was 40% which more than that found in control group. The common types of anemia was anemia of chronic disease (28%), iron deficiency (10%), thalassemia minor (1%), and megaloblastic anemia 1%. We found a significant correlation of RA with each low hemoglobin, low hematocrit, high leucocyte count and high ESR. Anemia among RA patients in our study was significantly more prevalent among low socioeconomic status patients. The majority of RA patients had moderately or high active disease, which revealed no association between disease activity and anemia ( $p$  value=0.3).

**Conclusion:** the prevalence and types of anemias among RA patients in Sulaymaniyah was comparable to that found in other studies and it was two times common than the normal healthy peoples. In our study we concluded that little evidence found between disease activity and anemia.

**Keywords:** Rheumatoid Arthritis, Anemia, Sulaymaniyah, Kurdistan Region, Iraq

**Introduction:**

Rheumatoid arthritis (RA) is chronic systemic auto-immune inflammatory disease characterized by articular and extra-articular manifestation, such as weight loss, fatigue, malaise and anemia<sup>(1)</sup>.

RA is associated with a high risk for morbidity and premature death secondary to the earlier development of cardiovascular, lung diseases and malignancy<sup>(2)</sup>.

Extra-articular manifestations of RA occur in about 40% of patients, either in the beginning or during the course of their disease <sup>(3)</sup>.

Patients with RA, who have high titers of rheumatoid factor, are most likely to have extra-articular manifestations of their disease <sup>(4)</sup>. Patients with RA may present with hematological abnormalities either at the time of diagnosis, or during the course of their illness. Hematological manifestations in RA can be broadly categorized into areas of anemia, thrombocytosis, neutropenia, thrombocytopenia, eosinophilia, and hematological malignancies <sup>(5)</sup>. Anemia is, by far, one of the most common extra-articular manifestations of RA. The cause of anemia in RA is multifactorial including disease activity, drug-induced, nutritional, gastrointestinal bleeding, bone marrow suppression, and ineffective erythropoiesis <sup>(6)</sup>. Anemia of chronic disease (ACD) usually normochromic normocytic type observed in RA, where it usually correlates with the disease activity. Eosinophilia in RA reflects active disease or hypersensitivity to drugs <sup>(7)</sup>. Thrombocytosis is a frequent finding in active RA and is correlated

with the number of active inflamed joints <sup>(8)</sup>. Lymphadenopathy is sometimes observed in active RA, usually presenting on biopsy as benign follicular hyperplasia <sup>(9)</sup>. The types of anemia in RA may include anemia of chronic disease, iron-deficiency anemia, vitamin deficiency anemia, aplastic anemia, or hemolytic anemia <sup>(10)</sup>.

The first principle of treating RA associated anemia is to reduce inflammation as much as possible using non-steroidal anti-inflammatory drugs (NSAIDs), disease modifying anti rheumatoid drugs (DMARDs). Erythropoietin stimulating agents (ESA) therapy has been shown to be effective in treating RA induced ACD. However, RA patients tend to have a blunted response to ESA therapy, and higher than normal ESA doses are often required. In these patients, ACD shows improvement when inflammation has decreased. When iron deficiency occurs concomitantly with ACD, iron repletion may be needed, either alone or as adjunct therapy with ESAs. ESA therapy in combination with iron supplementation corrects anemia in most patients with RA, and may improve RA outcomes and quality of life <sup>(11)</sup>. The

aims of this study were to find the prevalence, types of anemia among patients with RA in Sulaymaniyah and to determine the associated risk factors.

### Materials and methods

A cross sectional study carried out in Sulaymaniyah General Hospital in Sulaymaniyah governorate for period from 1<sup>st</sup> of October, 2014 to the end of June, 2015. It included 100 patients with RA who attended to Rheumatology Consultation clinic or admitted to

Rheumatology ward of Sulaymaniyah General Hospital.

**Inclusion criteria:** All patients who met the 2010 ACR-EULAR classification criteria for Rheumatoid Arthritis were included <sup>(12)</sup> (table1), a score of  $\geq 6/10$  is needed for diagnosis of patient as having RA.

Table 1 : criteria for diagnosis of RA

<b>A.Joint involvement</b>	<b>SCORE</b>
1 large joint	0
2- 10 larg joint	1
1-3 small joints(with or without large joint)	2
4-10 small joints(with or without large joint)	3
>10 joints(at least 1 small joint)	5
<b>A.Serology(at least 1 test result is needed for classification)</b>	
Negative RF and Anti ccp	0
Low positive RF and Anti ccp	2
High positive RF and Anti ccp	3
<b>C.Acute phase reactants</b>	
Normal CRP and ESR	0
Abnormal CRP and ESR	1
<b>D.Duration of symptoms</b>	
Less than 6 weeks	0
6 weeks or more	1

N.B : A score of  $\geq 6/10$  is needed for diagnosis of patient as having RA

**Exclusion criteria:** Any cause of anemia not related to RA which includes patients with active GIT bleedings, bleeding tendencies, menorrhagia, malignancies, renal failure, diabetic patients, chronic infections were excluded in our study. The data were collected through direct interview and using prepared questionnaire. The known cases of RA were diagnosed by consultant Rheumatologist. Full medical history and clinical examination were done for all patients. A total of 100 healthy controls were selected and required information was collected from them. The questionnaire included: socio-demographic characteristics as Age, gender, residence and socioeconomic status. RA characteristics: disease activity assessed by DAS-28, rheumatoid factor (RF) and duration of RA, treatment modalities of RA, family history of RA and anemia, Laboratory tests done as complete blood count, blood smear, reticulocyte count, coombs test and ESR done by autoanalyzer, serum iron and TIBC done by C111Cobas Roche Company, serum ferritin, serum B12, and folate by E411 Cobas Roche Company, Hb-electrophoresis done for selected cases

by HPLC (high performance liquid chromatography, D10) The World Health Organization (WHO) criteria were used to define anemia as hemoglobin threshold of <120 g/L for women and <130 g/L for men <sup>(13)</sup>. The disease activity evaluated according to DAS-28 in which values less than 2.6 corresponds for clinical remission, values ranging (2.6-3.2) are regarded as low disease activity, values ranging(3.2-5.1) are regarded as moderate disease activity and more than 5.1 regarded as high disease activity. All patients gave their oral consent before beginning of the study and agreement was taken from official review ethical committee of Sulaymaniyah General Hospital.

**Statistical analysis:** Statistical Package for Social Sciences (SPSS) version 20 was used. Descriptive statistics presented as (mean  $\pm$  standard deviation) and frequencies as percentages. Chi-square used for categorical variables and Fishers exact test was used when expected variables were less than 20%. Independence t-test was used to compare between two means. In all statistical analysis, level of significance (p value) set at  $\leq 0.05$ .

**Results:**

A total of 100 patients with RA were included in present study with mean age  $50\pm 13$  years, 52% of them were  $\geq 50$  years. Female were more than males with male to female ratio of 1:9.01.

More than half of RA patients were living in urban areas. The socioeconomic status was presented as following; 21 patients were good, 44 were fair and 35 RA patients had low socioeconomic status as shown in (table 2).

**Table 2: Sociodemographic characteristics of RA patients.**

Variable	No.	%
<b>Age mean<math>\pm</math>SD (50<math>\pm</math>13 years)</b>		
20-29 years	8	8.0
30-39 years	12	12.0
40-49 years	28	28.0
$\geq 50$ years	52	52.0
<b>Gender</b>		
Male	9	9.0
Female	91	91.0
<b>Residence</b>		
Urban	52	52.0
Rural	48	48.0
<b>Socioeconomic status</b>		
Good	21	21.0
Fair	44	44.0
Low	35	35.0

Mean RA disease duration was  $11\pm 9$  years, 65% of RA patients had disease duration  $\leq 10$  years. The Rheumatoid factor (RF) was positive for 91% of RA patients and negative for 9% of them.

The treatment types used by RA patients were distributed as followings; prednisolone (16.8%), Folic acid (16.8%), Methotrexate (16.5%), Calcium & Vitamin D (14.2%), combination

therapy (12.5%), hydroxychloroquine (10.8%), Alendronate (2.6%), Leflunomide (2.3%), Etanercept (3.1%), Rituximab (1.3%), Adalimumab (0.4%), and Azathioprine (0.4%). Mean DAS-28 of RA patients was  $5\pm 1.2$ , while 57% of RA patients had high disease activity.

Mean Hb of RA patients was  $12.3\pm 1.4$  mg/dl, 40% of them had low Hb level. Mean PCV of RA patients was  $40.1\pm 30.8$  %, 33% of them had low PCV level. Mean WBC of RA patients was  $8.4\pm 2.9 \times 10^9$ , 20% of them had high WBC count as shown in table 3.

**Table 3: hematological parameter of patient with RA**

Variable	No.	%
<b>Hb mean<math>\pm</math>SD (12.3<math>\pm</math>1.4 mg/dl)</b>		
Normal	60	60.0
Low	40	40.0
Total	100	100.0
<b>PCV mean<math>\pm</math>SD (40.1<math>\pm</math>30.8 %)</b>		
Normal	67	67.0
Low	33	33.0
Total	100	100.0
<b>WBC mean<math>\pm</math>SD (8.4<math>\pm</math>2.9 <math>\times 10^9</math>)</b>		
Normal	80	80.0
High	20	20.0
Total	100	100.0
<b>Platelets mean<math>\pm</math>SD (259.9<math>\pm</math>65.9<math>\times 10^9</math>)</b>		
Normal	100	100
Reticulocytes level	100	100

Anemia was found in 40 patients (40%) with RA patient and 70.0% of anemic patients had anemia of chronic diseases (ACD), 25% had iron

deficiency anemia IDA, 2.5% megaloblastic anemia and 2.5% had Thalassemia minor (Fig 1).

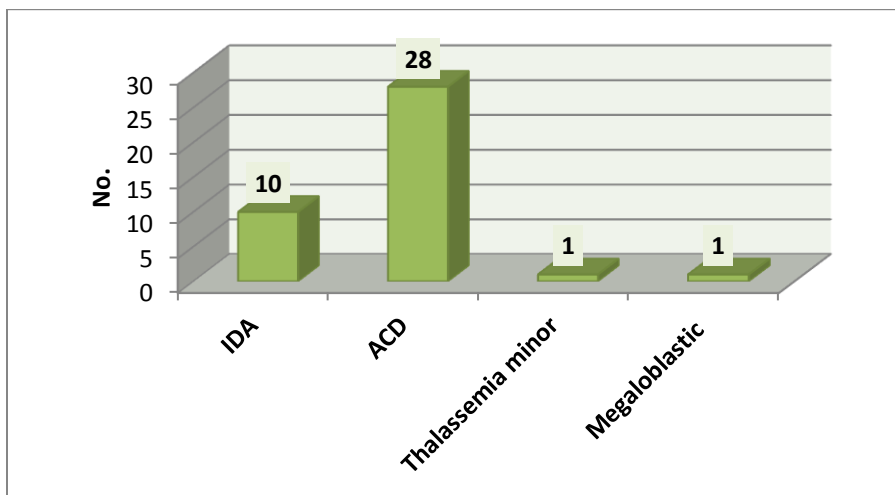


Figure 1: Types of anemia among RA patients.

Mean serum iron of anemic RA patients was  $98.4 \pm 35.9$   $\mu\text{g/dl}$ , with 72.5% had low iron level. Mean TIBC level of anemic RA patients was  $385.9 \pm 67.9$   $\mu\text{g/dl}$ , with 47.5% had low TIBC level and 20% had high TIBC level. Mean serum ferritin of anemic RA patients was  $73.3 \pm 56.1$   $\text{ng/ml}$ , with 22.5% had low ferritin level while 25% had high ferritin level. Only one patient had low B12 level. Hb-electrophoresis was positive only for one patient. All of RA patients had normal folate level and negative

Coombs test. Mean ESR of RA patients was  $46.3 \pm 19.3$   $\text{mm/hr}$ , all of RA patients had high ESR.

No significant differences were observed between anemic and non-anemic RA patients regarding DAS-28 and rheumatoid factor (RF) ( $p > 0.05$ ). No significant differences were observed between anemic and non-anemic RA patients regarding family history of RA and anemia ( $p > 0.05$ ) as shown in (table 4)



**Table 4: Distribution of RA characteristics according to anemia.**

Variable	Anemic		Non anemic		$\chi^2$	P
	No.	%	No.	%		
<b>DAS28</b>					3.0*	0.3
Remission	0	-	1	100.0		
Low activity	3	50.0	3	50.0		
Moderate activity	11	30.6	25	69.4		
High activity	26	45.6	31	54.4		
<b>RF</b>					3.4*	0.06
Sero +ve	39	42.8	52	57.2		
Sero -ve	1	11.1	8	88.9		
<b>Family history of RA</b>					2.3	0.1
Positive	15	51.7	14	48.3		
Negative	25	35.2	46	64.8		
<b>Family history of anemia</b>					0.9*	0.3
Positive	2	66.7	1	33.3		
Negative	38	39.2	59	60.8		

\*Fishers exact test.

### Discussion:

Rheumatoid arthritis (RA) is an autoimmune disorder of unknown etiology characterized by symmetric, erosive synovitis and, in some cases, extra articular involvement. Extra-articular manifestations can be detected in almost any organ system, causing considerable disease related morbidity and interference with quality of life. Anemia is a frequently occurring extra-articular manifestation of RA, being mostly of the

normochromic and normocytic type. Anemia is multifactorial, reflected in dimorphic appearance and wide red cell distribution width. Anemia of chronic disease (ACD) and iron deficiency anemia (IDA) are the most important types of anemia in RA patients<sup>(14)</sup>.

In this study, prevalence of anemia among studied RA patients was (40%). The result was close to that of Wilson A et al<sup>(15)</sup> who reported the anemia to be

ranged of 33-66% among RA patients, but was higher than that reported by Muia GM, et al in which he reported prevalence of 33%<sup>(16)</sup>. On other hand, other studies found higher prevalence which reached up to 70.6%<sup>(17)</sup>.

Prevalence ratio of developing anemia among RA patients was 2:1 as compared to healthy controls. This prevalence ratio is close to that reported by Han C, et al study who reported a prevalence ratio of anemia among RA patients as 2.2.:1<sup>(18)</sup>

In this study we have found no significant association between disease activity and anemia ( $p$  value=0.3), while in other epidemiological study it was reported that lower hemoglobin levels was associated with increased disease activity as measured by the number of tender and swollen joints, ESR, CRP level, and assessments of pain and fatigue (DAS-28 score)<sup>(19)</sup>. Han C et al reported that anemia independently contributes to physical disability in patients with RA<sup>(20)</sup>.

More than two thirds of detected anemic RA cases in present study were anemia of chronic diseases (ACD) and 25% of them were iron deficiency anemia (IDA). This result was close to many studies as Ravindran V, et al study<sup>(21)</sup> and

Swaak A study<sup>(22)</sup>, this explained on bases that inflammatory cytokines released during ACD can alter systemic iron metabolism by inducing excess synthesis of hepcidin, the iron regulatory hormone. Since hepcidin inhibits iron export from cells by blocking ferroportin activity, excess hepcidin is the root cause of the hypoferremia and iron-restricted erythropoiesis seen in ACD<sup>(23), (24)</sup>.

In this study we found that mean age of RA patients was 50±13 years with predominance of female gender. This is consistent with results of Muia et al study<sup>(16)</sup>. RA was significantly associated with rural living and low socioeconomic status ( $P\leq 0.05$ ). This is similar to results of Putrick P, et al study<sup>(25)</sup>. High levels ESR and WBC were significantly associated with RA patients ( $P\leq 0.05$ ). This finding was close to that of Shenair D, et al study<sup>(26)</sup>. More than half of studied RA patients had high DAS28 activity. This finding is higher than that reported by Ganna S study<sup>(24)</sup> which reported that 30% of RA patients had high DAS-28 activity.

Anemia among RA patients in our study was significantly more prevalent among low socioeconomic status patients ( $P=0.05$ ). This finding was close to that of Gordon MM, et al study<sup>(27)</sup>.

Bengtsson et al reported the association between high socioeconomic and educational status and a lower risk for the development of RA in a population representative of the Swedish population, suggesting that environmental factors or lifestyle might influence disease evolution<sup>(28)</sup>. Pedersen et al reported that the educational level was inversely associated to the risk of developing RA in the Danish population and the risk was twice as lower for those individuals with a higher number of years of formal schooling<sup>(29)</sup>.

Platelets level among RA patients was normal, although, mean platelets among anemic patients was significantly higher than that of non-anemic ( $P=0.03$ ). This is consistent with results of Safak S, et al study<sup>(30)</sup>. ESR level was significantly increased among anemic RA patients in our study ( $P<0.001$ ). This is similar to results of Ganna S study<sup>(24)</sup>. Recent studies have revealed a key role of cytokines and other mediators of inflammation in the development not only of the articular syndrome, but also a whole range of systemic manifestations of the disease<sup>(31)</sup>. Wilson A, et al in their systematic review, suggested that patients with RA who have anemia are likely to

have more severe joint disease and if the anemia is successfully treated, the joint disease will likely respond to treatment as well<sup>(15)</sup>.

### **Conclusion:**

The prevalence of anemia among RA patients in Sulaymaniyah was comparable to that found in other studies and it was two times common than the normal healthy peoples. Anemia of chronic diseases was the most common type of anemia among RA patients. The majority of RA patients had moderately or high active disease, which revealed no association between disease activity and anemia.

### **Acknowledgment:**

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### **Authorship contribution:**

**HAG** who designed the project of the study, **RRM** supervisor of the research article, **SFA** primary investigator, **NK and AFA** shared in rewriting and editing of the all parts of the manuscript.

**Conflict of interest:**

All authors declare that there is no any conflict of interest in publishing this article.

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## أنواع فقر الدم وارتباطها مع نشاط المرض في المرضى الذين يعانون من التهاب المفاصل الرثوي بين السكان الأكراد في العراق

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### الملخص:

**الخلفية:** التهاب المفاصل الروماتويدي هو من أمراض المناعة الذاتية والتهاب مزمن يتميز بأعراضه المفصلية وخارج المفصلية ك فقدان الوزن، والتعب، والشعور بالضيق، وفقر الدم. **الأهداف:** الهدف من هذه الدراسة تتمثل في العثور على انتشار أنواع مختلفة من فقر الدم وعلاقته مع نشاط المرض بين المرضى الذين يعانون من التهاب المفاصل الروماتويدي في محافظة السليمانية وتحديد عوامل الخطر المرتبطة بها.

**المرضى والطرق:** تم اختيار دراسة مقطعية أجريت في مستشفى عام السليمانية للفترة من أكتوبر 2014 إلى نهاية يونيو-2015. عينة ملائمة من 100 مريض يعانون من التهاب المفاصل الروماتويدي من المرضى الذين تم فحصهم في عيادة الروماتيزم. وقد تم اختيار مائة من الضوابط الطوعية الصحية من الفئات العمرية نفسها، استخدمت نفس المعايير لتشخيص فقر الدم في كلا المجموعتين.

**النتائج:** كان معدل انتشار جميع أنواع فقر الدم بين المرضى المصابين بالتهاب المفاصل الروماتيزمي (40%) أكثر من تلك الموجودة في المجموعة الضابطة. وكانت الأنواع الشائعة من فقر الدم الناتج عن الأمراض المزمنة (28%)، ونقص الحديد (10%)، الثلاسيميا الصغرى (1%)، وفقر الدم الوبيل (1%). لقد وجدنا ارتباط كبير بين الروماتيزم الرثوي مع كل من الهيموغلوبين المنخفض، وانخفاض الهيماتوكريت، وارتفاع عدد كريات بيضاء وارتفاع راسب الدم. كان فقر الدم بين مرضى التهاب المفاصل الروماتويدي في دراستنا بشكل ملحوظ أكثر انتشارا بين مرضى انخفاض الوضع الاجتماعي والاقتصادي. وكانت الغالبية العظمى من مرضى التهاب المفاصل الروماتويدي لديهم متوسط الى شديد النشاط، والتي كشفت عن عدم وجود علاقة بين نشاط المرض وفقر الدم ( $p = 0.3$ ). **الخلاصة:** مدى انتشار وأنواع فقر الدم بين مرضى التهاب المفاصل الروماتويدي في السليمانية كان مماثلة لتلك الموجودة في دراسات أخرى، وكان مرتين أكثر من الناس الاصحاء. في دراستنا خلصنا إلى أن القليل من الأدلة وجدت بين نشاط المرض وفقر الدم.

**كلمات البحث:** التهاب المفاصل الروماتويدي، فقر الدم، السليمانية