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# STUDY OF ANEMIA IN RHEUMATOID ARTHRITIS

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**ABSTRACT**

**Introduction & Background:** Rheumatoid arthritis (RA) is a chronic inflammatory systemic disease of unknown etiology with a variety of extraarticular manifestations including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities including anaemia. Anemia in rheumatoid arthritis is common and multifactorial. We studied the prevalence, type of anemia and its correlation with disease activity in Indian patients in a tertiary care hospital.

**Aims:** To diagnose the type of anemia in patients with rheumatoid arthritis and to correlate it with disease activity of rheumatoid arthritis and medication.

**Settings and design:** It is a cross sectional analytical study carried out at department of pathology and department of medicine.

**Patient/ Material and Methods:** Fifty patients (45 female and 5 males) with recent onset (<5 years) RA were included in the study. The anemic patients were evaluated for the type of anemia. A serum ferritin level of ≤50 µg/l was taken as cut off for defining iron deficiency anemia. Disease activity assessment was done using DAS-28 score and functional disability assessment by using modified health assessment questionnaires (MHAQ) in all the patients.

**Statistical Analysis:** Data was analysed using SPSS (version 20). P value <0.05 was considered significant.

**Results:** Forty two patients (84%) out of fifty were found to be anemic with 19 patients (45.2%) having iron deficiency anemia and 23 (54.8%) having anemia of chronic disease. None of the patients had megaloblastic anemia. In anemic group DAS-28 score and MHAQ were found to be 4.95±1.21 and 1.07±0.58 respectively and in non-anemic group 3.41±0.60 and 0.40±0.36 respectively. The disease activity was higher in patients with iron deficiency anemia than those with anemia of chronic disease, but was not statistically significant.

**Conclusions:** Anemia is a common extraarticular manifestation in patients with RA and significantly correlates with higher disease activity. Anemia of chronic disease is the most common type of anemia in these patients. However, further studies including a larger number of patients with long term follow up are needed for conclusive results.



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## INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease of unknown etiology marked by a symmetric, peripheral polyarthritis. It is the most common form of chronic inflammatory arthritis and often results in joint damage and physical disability. RA is a systemic disease which may result in a variety of extra-articular manifestations, including fatigue, subcutaneous nodules, lung involvement, pericarditis, peripheral neuropathy, vasculitis, and hematologic abnormalities including anemia (Longo, 2012).

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As the disease progresses, patients with RA suffer significant disability and a marked reduction in their quality of life (Smolen, 2003). The disease activity is assessed with the help of DAS-28 score. The World Health Organization estimates that RA affects 23.7 million people worldwide with a prevalence of 0.5–1.0% of the adult population (Seldin, 1999). Anemia is the most common blood disorder affecting nearly one-fourth of the population of the world and two-third of patients with RA. The estimated lifetime prevalence of anemia in general population is 13.7%. The prevalence of anemia in the adult population in India is 47.5% (anemia defined as per WHO) with higher prevalence in females (50%) than in males (44.3%) (Nutritional anaemias, 1968 and Malhotra, 2004). The

commonest cause of anemia worldwide is iron deficiency. The different types of anemia which can occur in rheumatoid arthritis can be anemia of chronic disease (ACD), iron deficiency anemia (IDA) (Nutritional anaemias, 1968), aplastic anemia and anemia due to treatment with NSAIDS and DMARDs. The commonest form of anemia is ACD. It is not a very severe form of anemia but is refractory to most forms of treatment The severity of anemia parallels the degree of inflammation, correlating with the levels of erythrocyte sedimentation rate (ESR) and serum C-reactive protein (CRP). Also the platelet counts may be elevated in RA as an acute-phase reactant (Longo, 2012).

## MATERIALS & METHODS

Fifty patients (45 female and 5 males) with recent onset (<5 years) RA diagnosed as per 2010 American College of Rheumatology/European League against Rheumatism Classification Criteria with age more than 18 years were included in the study (13). Patients with known comorbid conditions like tuberculosis, diabetes mellitus, pregnancy, arthropathies other than RA, patients on hematinics or with chronic bleeding (piles, menorrhagia, oesophageal varices) were excluded from the study. Complete blood counts, serum iron profile, serum ferritin, serum vitamin B12 and folate levels were performed. Anemia was defined as hemoglobin <12 g/dl in females and <13 g/dl in males. The anemic patients were evaluated for the type of anemia and serum ferritin ≤50 µg/l was taken as cut off for defining iron deficiency anemia. Disease activity assessment was done using DAS-28 score and functional disability assessment by using modified health assessment questionnaires (MHAQ) in all the patients (Steenland, 2001 and Kumar, 2002).

**Table/ Figure 1. Comparison of various parameters in anemic and non anemic RA patients**

| Parameter | Group | Number of patients | Mean | Standard deviation | p- value |
|---|---|---|---|---|---|
| TJC | Anemic | 42 | 5.43 | 4.27 | 0.025 |
| | Non anemic | 8 | 1.88 | 1.13 | |
| SJC | Anemic | 42 | 3.81 | 4.46 | 0.043 |
| | Non anemic | 8 | 0.5 | 0.54 | |
| ESR | Anemic | 42 | 39.76 | 21.998 | 0.146 |
| | Non anemic | 8 | 27.25 | 21.48 | |
| HAQ Score | Anemic | 42 | 1.07 | 0.58 | 0.003 |
| | Non anemic | 8 | 0.4 | 0.36 | |
| DAS-28 Score | Anemic | 42 | 4.95 | 1.21 | 0.001 |
| | Non anemic | 8 | 3.41 | 0.6 | |
| VAS | Anemic | 42 | 55 | 19.57 | <0.0001 |
| | Non anemic | 8 | 22.5 | 11.65 | |

**Table/ Figure 2. Comparison of various parameters between patients with IDA and patients with ACD.**

| Parameter | Group | Number of patients | Mean | Standard deviation | p- value |
|---|---|---|---|---|---|
| TJC | ACD | 23 | 4.26 | 2.47 | 0.05 |
| | IDA | 19 | 6.84 | 5.5 | |
| SJC | ACD | 23 | 2.65 | 2.52 | 0.064 |
| | IDA | 19 | 5.21 | 5.82 | |
| ESR | ACD | 23 | 31.52 | 22.06 | 0.006 |
| | IDA | 19 | 49.74 | 17.76 | |
| HAQ Score | ACD | 23 | 0.84 | 0.45 | 0.003 |
| | IDA | 19 | 1.35 | 0.6 | |
| DAS-28 Score | ACD | 23 | 4.5 | 1.01 | 0.007 |
| | IDA | 19 | 5.49 | 1.23 | |
| VAS | ACD | 23 | 48.26 | 17.23 | 0.012 |
| | IDA | 19 | 63.16 | 19.52 | |
| Serum ferritin | ACD | 23 | 90.57 | 22.78 | <0.0001 |
| | IDA | 19 | 32.05 | 10.4 | |

According to various studies 30-60 % of RA patients residing in developed countries have of IDA (Majithia, 2007; Efthimiou, 2010; Macfarlane, 2011 and Vreugdenhil, 1990). The anemia of chronic disease, IDA and others can be differentiated with the help of RBC indices, serum ferritin, serum tranferrin receptors and marrow staining for iron. Bone marrow staining is the definitive diagnostic method to differentiate ACD and IDA but is an invasive process. RBC indices show an overlap between ACD and IDA, so we need a noninvasive method to differentiate them. IDA is associated with serum ferritin less than 20µg/dl; a level greater than 100 µg/dl excludes IDA.As serum ferritin is an acute phase reactant protein it can be raised in inflammatory conditions creating an error in diagnosis. The presence of low serum ferritin (< 50 µg/l) along with high serum transferrin levels (50 g/l) and decreased mean corpuscular volume (MCV) of erythrocytes (80 fl) results in 100% sensitivity and specificity for the detection of iron deficiency and if serum ferritin is >50 µg/l and IDA is excluded then it is considered as ACD (10-12).

## RESULTS

Forty two patients (84%) out of fifty were found to be anemic with 19 patients (45.2%) having iron deficiency anemia and 23 (54.8%) having anemia of chronic disease. None of the patients had megaloblastic anemia. Comparisions of various parameters were done between anemic and nonanemic groups, which showed significantly higher prevalence of tender, swollen joint counts and erythrocyte sedimentation rate.

**Table/ Figure 3. Comparison of various studies with present study**

| Authors | Disease variable | Anemic group | Nonanemic group | P value |
|---|---|---|---|---|
| Tazi, *et al* | HAQ score | 1.44 ± 0.81 | 0.95 ± 0.77 | <0.001 |
| | DAS 28 score | 5.45 ± 1.55 | 4.7 ± 1.69 | <0.001 |
| | TJC | 5.37±6.32 | 2.23±4.27 | <0.001 |
| Agarwal *et al* | SJC | 8.81±8.08 | 3.82±5.77 | <0.001 |
| | DAS 28 score | 5.19±1.50 | 3.82±1.36 | <0.001 |
| | TJC | 17.4±5.45 | 8.27±5.87 | 0.0002 |
| Borah *et al* | SJC | 9.75±3.78 | 4.09±2.66 | 0.0001 |
| | HAQ score | 6.85±0.64 | 4.76±1.29 | 0.0001 |
| | DAS 28 score | 1.41±0.44 | 0.7±0.25 | 0.001 |
| | TJC | 31.42 ± 10.07 | 18.52 ± 11.28 | 0.001 |
| Ganna *et al* | SJC | 28.67 ± 9.01 | 16.53 ± 8.27 | 0.002 |
| | HAQ score | 1.98 ± 0.551 | .4 ± 0.6 | 0.02 |
| | DAS 28 score | 5.2 ± 1.3 | 2.8 ± 1.1 | 0.001 |
| | TJC | 5.43±4.27 | 1.88±1.13 | 0.025 |
| | SJC | 3.81±4.46 | 0.50±0.54 | 0.043 |
| Present study | HAQ score | 1.07±0.58 | 0.40±0.36 | 0.003 |
| | DAS 28 score | 4.95±1.21 | 3.41±0.60 | 0.001 |

In anemic group DAS-28 score and MHAQ were found to be 4.95±1.21 & 1.07±0.58 respectively and in non-anemic group 3.41±0.60 & 0.40±0.36 respectively which was highly significant (Table/Figure.1). All these parameters were further compared between the patients having IDA and ACD. The HAQ score and VAS was significantly higher in patients with IDA than in patients with ACD. (HAQ and VAS p-value 0.003 and <0.012 respectively). Also there was a significant difference in serum ferritin levels in between the patients with IDA and those with ACD (p= <0.001) (Table/Figure. 2).

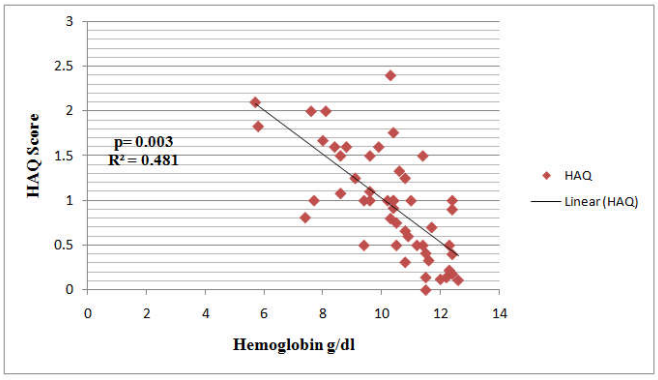


**Table /Figure 4. Correlation between anemia and HAQ**

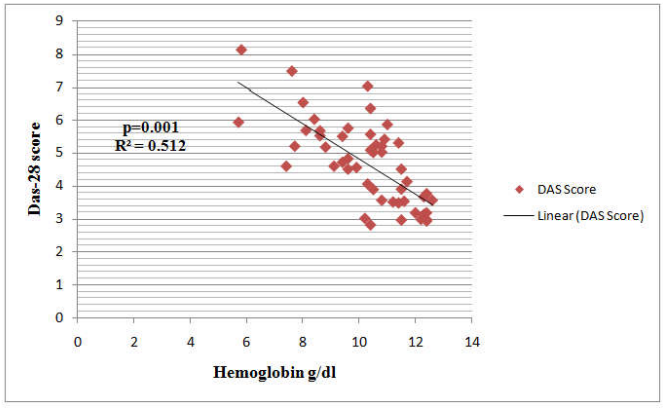


**Table /Figure 5. Correlation between anemia and DAS-28 score**

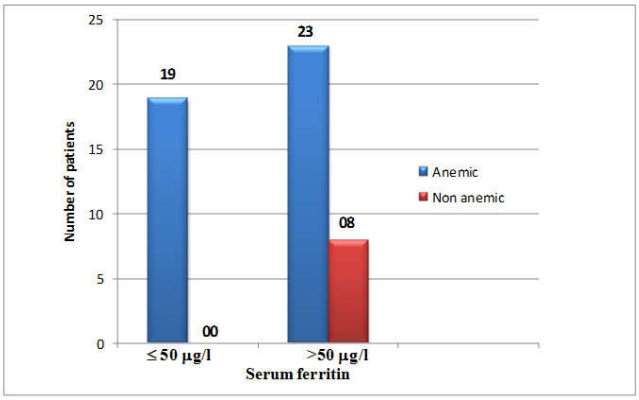


**Table /Figure 6. Serum ferritin in anemic and non anemic patient**

## DISCUSSION

In this study prevalence and type of anemia in patients with rheumatoid arthritis and it's correlation with disease activity were assessed. The mean age of the study population was 42.48 ±12.07 years and the median value was 42 years. This is similar to a study by Agarwal *et al* (Agrawal, 2006) where the mean age was 43.9±11.83 years. Median duration of disease was 3 years. On clinical examination, tender joint counts ranged from 0 to 24, with a median of 4. Swollen joint counts ranged from 0 to 20, with a median of 2. All patients in this study had active disease. Functional disability in rheumatoid arthritis (RA) reflects the cumulative effects of the disease over time. Various factors are responsible for functional disability, such as pain, swollen joints, tender joints and joint deformities. In this study, functional disability was assessed by HAQ score using the Indian version of the health assessment questionnaire. HAQ score is an important indicator of disability in RA. It ranged from 0 to 2.4, with a mean of 0.961±0.6 (median=1.0). This result is similar to the study conducted by Aletaha *et al*. (D2) in which 1342 patients with early RA were assessed for response to treatment after one year and the baseline mean HAQ score. Among 50 patients, mild, moderate and severe functional disability (HAQ: 0-<1, 1-<2, 2-3) was present in 24, 22 and 4 patients, respectively (Table/Figure.4). Disease activity was quantified using DAS28 scores. Scores ranged from 2.8 to 8.14, with a mean of

4.70±1.27. Out of 50 patients, 9 patients (18%) were in the low disease activity category (DAS28: 2.6-<3.2), 21 patients (42%) were in the moderate disease activity category (DAS28: 3.2 – 5.1) and 20 patients (40%) were in severe disease activity category (DAS: >5.1). None of the patients were in remission phase (DAS28: <2.6) (Fig. 2) Most of the patients had high disease activity reflecting the fact that this study included newly diagnosed patients with RA and few of them (3 patients) were not taking treatment in the recent past. In a study by Tazi *et al* (Tazi, 2015) in1129 patients of rheumatoid arthritis, the mean DAS 28 score was 4.94 ± 1.68, which is similar to the value of the present study. In this study, anaemia was defined as a haemoglobin level < 13 g/dl in men and < 12 g/dl in women. 42 patients (84%) were found to be anemic. This was higher than the figures reported in other studies (33%-71%) (Agrawal, 2006 and Wolfe, 2006) as WHO criteria were used for defining anemia in our present study whereas Hb< 11 g/dl in women and <12g/dl in men was used in most of the other studies. ESR was elevated in 47 patients (94%) with a mean of 39.76±22 mm in 1 st hour in anemic patients and 27.25±21.48 in nonanemic patients.

There was no significant difference between the two groups. Serum ferritin was done in all patients. A value of ≤50 µg/dl of serum ferritin was present in 19 patients with mean of 32.05±10.40 µg/dl, all of these had low serum iron levels (mean±S.D=29.45±9.41), increased total iron binding capacity (mean±S.D=443±37.42), unbound iron binding capacity (mean±S.D= 413.63±41.15) and decreased transferrin saturation (mean±S.D= 11.16±4.33). Thirty one patients had serum ferritin levels more than 50µg/dl. Among these 23 patients were anemic and 8 were nonanemic (Table/Figure. 6). Anemic patients with serum ferritin >50 were categorized as having anemia of chronic disease (n=23). These patients had low to normal serum iron levels (mean ±S.D=64.17±16.95), TIBC (mean±S.D=273.57±54.10 µg/dl) and UIBC (mean±S.D=204.87±51.13µg/dl) towards lower level of normal limits and normal to increased transferrin saturation (mean±S.D=28.18 ±4.70 %). Iron profile of non anemic patients was within normal limits. Thus, on the basis of serum ferritin and iron profile the anemic patients were divided into those with ACD and those with IDA. Twenty three patients (54.8%) had ACD and 19 patients (45.2%) had IDA. ACD was the commonest type of anemia in patients with RA. However, the prevalence of IDA was higher than that reported in other studies as WHO criteria were used in the present study. Our results are comparable to a study by Agarwal *et al*. in which 51.6% patients had ACD and 48.8% had IDA (Agrawal, 2006).

A higher degree of functional disability and disease activity, measured by HAQ and DAS 28 score were noted in anemic patients (1.06 versus 0.40, p=0.003 and 4.95 versus 3.41, p=0.001 respectively). Anemic patients also had significantly higher number of tender joints (p=0.025) and swollen joints (p=0.043) which reflects that severity of anemia is related with disease activity and inflammation. (Table/figure. 4 and 5) This was similar to the results of previous studies. (Table/figure. 3) In anemic patients there were significantly higher HAQ and DAS 28 scores in patients with IDA than in those with ACD. Serum ferritin is a reliable marker of iron stores in iron deficiency anemia. But as it is an acute phase reactant it does not correlate well with iron stores in patients with RA. In the present study, serum ferritin level of ≤50 µg/l was used to categorise patients having IDA.As RA is an inflammatory disease a higher cut off value for serum ferritin is required to define IDA in patients with than those having uncomplicated IDA. Various studies have reported the cut of values of serum ferritin in between 30 and 70 µg/l to define iron deficiency anemia in patients with RA (Bultink, 2001). Serum transferrin receptor (sTfR) levels and its ratio to serum ferritin (sTFR-ferritin index <1) has been shown to be of value in distinguishing IDA from ACD (Bultink, 2001). However a single sTfR value is of limited value in determining the level of iron storage in an individual with RA. Also this test is expensive and not widely available in a developing country like India. At present no single test is available to distinguish ACD from IDA in patients with RA. Thus, anemia screening should be a part of routine management of rheumatoid arthritis in order to reduce disease associated morbidity and to establish appropriate treatment for these patients.

**Conclusion**

It is concluded that anemia is a common extra-articular manifestation in patients with rheumatoid arthritis with a prevalence of 84% and it was significantly correlated with higher disease activity. Anemia of chronic disease is the most common type of anemia in patients with rheumatoid arthritis. It is difficult to differentiate iron deficiency anemia and anemia of chronic disease on the basis of serum ferritin alone in patients with RA, as it is an acute phase reactant it can be raised in some of the patients even in the presence of iron deficient state. Some of the patients can also have concomitant ACD and IDA. It is also concluded that better hemoglobin levels are associated with lesser disability and better quality of life. Hence screening and treating for anemia is important in management of patients with rheumatoid arthritis. However, further studies including a larger number of patients with long term follow up are needed for conclusive results.

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