Anaemia in patients with rheumatoid arthritis at the Kenyatta National Hospital, Nairobi, Kenya

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Abstract

Background: Anaemia is the commonest extra articular manifestation of Rheumatoid Arthritis (RA). Anaemia is an independent predictor of morbidity and mortality in the population. When RA is complicated by anaemia it is associated with a more severe disease and significant reduction in the quality of life in the affected patient.

Objectives: To determine the characteristics and the prevalence of anaemia in patients with RA at the Kenyatta National Hospital (KNH) and correlate the anaemia with the disease activity using the Modified Disease Activity Score 28 (MDAS28).

Design: A cross sectional descriptive study.

Methods: Patients presenting to the Rheumatology Outpatients Clinic (ROPC) in Kenyatta National Hospital were screened and those who met the American College of Rheumatology-European League Against Rheumatism (ACR-EULAR) diagnostic criteria for RA were consecutively recruited to the study. The study period was 6 months from September 2011 to March 2012. Consecutive sampling technique was applied until the desired sample size was achieved.

Results: Ninety seven patients were studied in a span of six months (September 2011 –March 2012). Females were 84 (86.6%) while males were 13 (13.4%) with a male to female (M: F) ratio of 1:6.8. The mean age of the study population was 50.7 years with age range of 18-88 years. Seventy nine percent of the patients had the clinical features of RA for more than one year while 69% had the diagnosis made in the last five years. Eighty percent of the patients were on methotrexate while 72% were on Non Steroidal Anti Inflammatory Drugs (NSAIDS). The mean haemoglobin was 12.4 g/dl with a range of 3-15.7g/dl. Thirty three percent of the patients had high disease activity while 57 (58.8%) had moderate disease score. The prevalence of anaemia in the study population was 33% with Anaemia of Chronic Disease (ACD) responsible for 75% of the cases of anaemia while Iron Deficiency Anaemia (IDA) was seen in 25% of the cases. Anaemia was commonly seen among the patients with high and moderate disease activity scores. None of the patients on remission and low disease scores had anaemia. Anaemia was also found to be independently related to the disease activity and the patient's gender with males being the most affected.

The use of Disease Modifying Anti Rheumatic Drugs (DMARDS) was found to confer protection to anaemia. The study did not demonstrate any significant association between the use of NSAIDs and use of steroids and IDA.

Conclusions: There is a high burden of anaemia in RA patients although it is lower compared to studies done elsewhere. Anaemia correlates very well with the disease activity. Anaemia of chronic disease is the commonest type. The use of DMARDs was associated with reduction of anaemia among the patients. Men form a small percentage of patients with RA locally but do present with severe anaemia.

Keywords: Anaemia, Rheumatoid arthritis, Kenyatta National Hospital

Introduction

Rheumatoid Arthritis (RA) is a chronic, symmetric, peripheral poly-arthritis of unknown aetiology which when untreated or if unresponsive to therapy, typically leads to deformity and destruction of joints through a persistent inflammatory synovitis. This leads to eventual erosion and destruction of cartilage and bone which form the joints[1].

As with other autoimmune rheumatic diseases, the diagnosis depends upon

the aggregation of characteristic symptoms, signs, laboratory data, and radiologic findings (The American College of Rheumatology and European League Against Rheumatism Criteria (*ACR –EULAR 2010 criteria*)[2] An estimated 1.5-2.0 million adults aged 18 and above (1% of the total world population) have RA[3]**.** The incidence of RA is typically two to three times higher in women than men. RA occurs in patients at any age, with a peak at 30 to 55 years[3-5].

There are limited local comprehensive studies on the prevalence of RA in Kenya. Owino *et al*[6] while studying the socio-demographic and clinical aspects in 180 patients seen in 2006 in KNH with rheumatologic complains found that 60 of the 180 patients studied met the ACR diagnostic criteria for RA; the male to female ratio of RA was 1:6.5. Patients with Rheumatoid Arthritis (RA) suffer from a variety of haematologic disorders, particularly anaemia, leukopenia, and thrombocytosis[7]. In patients with RA, the prevalence of anaemia ranges from 30 to 71% in various studies[8-14]. Anaemia in the older adults who are more likely to suffer from RA has been found to be associated with other markers of impaired physical function, including increased frailty, muscle weakness, and falls[14-16]. Anaemia is also associated with impaired cognitive performance, depressive symptoms, and reduced quality of life[17-19].

The commonest anaemia seen in RA is the classical model case of anaemia caused by chronic disease being mostly of the normocytic normo-chromic type; it is multi-factorial, reflected in the dimorphic appearance and wide red cell distribution width[20]. Iron Deficiency Anaemia (IDA) is the other important type of anaemia in RA and it manifests with a microcytic hypo- chromic picture.

Borah and colleagues[12] in a study in Northern India found a prevalence of 64% among patients who had been on follow up with RA for a period of more than 2 years and in this cohort 65% of the anaemia observed was ACD while IDA accounted for 33% of the anaemia observed. In 1997 Davis *et al*[13] studied 64 patients who were newly diagnosed to have RA attending an outpatient clinic in London and found an incidence of 61%, ACD accounted for 67% of the causes. Literature search does not yield any studies done in Africa on the prevalence of anaemia in this patient population. There is evidence that the patients who are anaemic have more severe RA, and also have more affected joints and higher levels of functional disability and pain. Anaemic patients, particularly those with Anaemia of Chronic Disease (ACD), have a significantly greater number of the American College of Rheumatism Criteria (ACR) for RA, significantly more erosive joint damage, and significantly increased concentrations of serum rheumatoid factor than patients without anaemia.

In our study we set out to establish the burden of anaemia among RA patients seen in Kenyatta National Hospital (KNH) Rheumatology Outpatients Clinic (ROPC) and determine how the severity of anaemia related to the disease activity. The study was designed to determine the prevalence of anaemia in this patient population, classify the anaemia types the patients had and correlate the same with the patients socio-demographic variables, disease activity using the modified disease activity score 28(MDAS28), patients level of education, duration of illness, the type of medication used and the duration of treatment.

Materials and Methods

The study design was a hospital based cross sectional descriptive study at the Rheumatology Outpatient Clinic, Kenyatta National Hospital. The study was commenced after obtaining all the necessary ethical approvals from the KNH research and ethics committee and from the Department of Clinical Medicine and Therapeutics, University of Nairobi. All patients above 18 years seen at KNH rheumatology clinic that met the ACR-EULAR criteria for diagnosis of rheumatoid arthritis were eligible. All patients gave an informed written consent. The study excluded patients with known hereditary forms of anaemia, patients with RA and mixed connective tissue diseases or SLE and also those with chronic liver and renal disease. The minimum sample size was calculated to be 96 patients.

Consecutive sampling method was applied. Anaemia in our study was defined as per the WHO parameters of haemoglobin of less than 13g/deciliter for males and 12g/deciliters for females. Anaemia of chronic disease was defined as normocytic normochromic anaemia with serum ferritin levels above 50g/l. Iron deficiency anaemia was defined as patients with hypochromic microcytic picture on PBF and MCV less than 76g/dl and serum ferritin levels below 50g/liter. Recruited patients were evaluated by medical history as per the study questionnaire. The disease activity was determined using a validated standardized tool the Modified Disease Activity score 28 (MDAS 28).

Physical examination was carried out looking for stigmata for diseases in the exclusion criteria and disease activity was determined using MDAS28 questionnaire.

Then blood was drawn for the appropriate laboratory tests. Data was collected and entered into a computer data base then cleaned and verified. Statistical analysis was done using SPSS version 17 software. Descriptive statistics –proportions were used for categorical variables. Measures of central tendencies were used for continuous variables. Correlation was done using the Spearman's -Rho correlation coefficients. Multivariate analysis was done using linear regression. Statistical significance was a P-value of ≤0.05.

Results

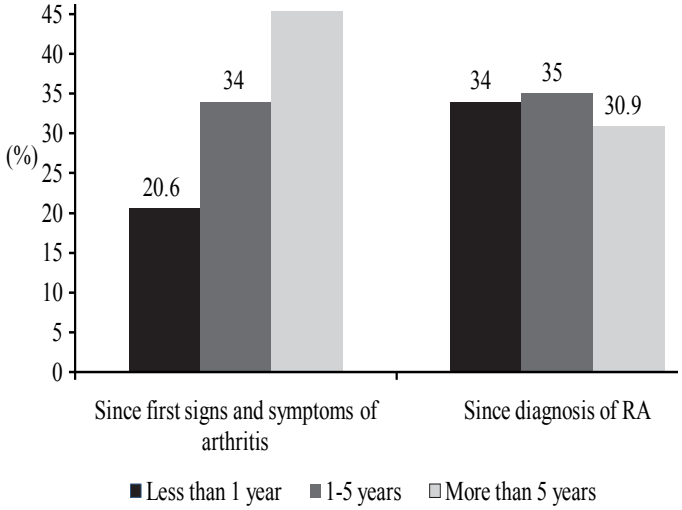
In a period of 6 months (September 2011 – February 2012) 108 patients with RA were identified, of these 103 met the EULAR-ACR criteria for RA and were recruited to the study. Three patients had RA with mixed connective tissue disease/ SLE and were duly omitted. One patient was recruited but declined to give consent to have blood tests done. Two patients did not have their ESR done hence were excluded from the final analysis. Hence results from 97 patients were analysed. A summary of the demographic characteristics of interest in the study population are shown in Table 1.

Table 1: Characteristics of the study population

Variable	Frequency (%) (SD)
Age	
Mean (SD)	50.7 (17.8)
Min-Max	18-88
Age groups	
<30	13 (13.4)
30-49	28 (28.9)
50-69	40 (41.2)
≥70	16 (16.5)
Gender	
Male	13 (13.4)
Female	84 (86.6)

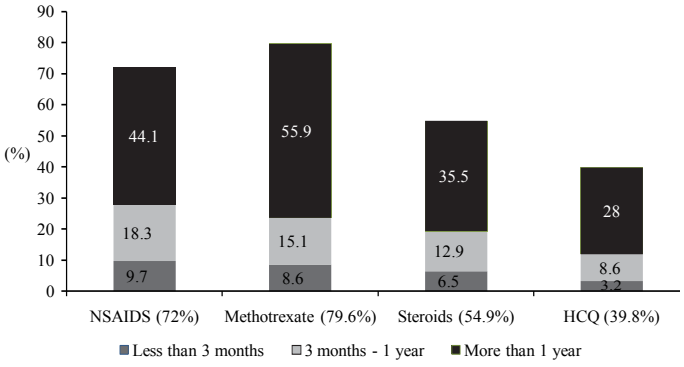
The mean age of the entire patient population was 50.7 years with a range of 18 - 88 years. The peak age group was 50-69 years who constituted 40% of the study population. Majority of the patients (86.6%) were females. There was an almost equal mix of the patient population from rural and urban setting. Nairobi and its environs contributed 49.5% of the total population while Central Kenya contributed 32% of the patients reflecting the traditional catchment area of Kenyatta National Hospital. From the patients' history and evaluation around 79% of the patients had the symptoms of RA for a period of longer than 1 year before a diagnosis was made, whilst 69% of the patients had been diagnosed with RA in the last 5 years. Figure 1 is a summary of patients history and duration of RA

Figure 1: Summary of patient's history



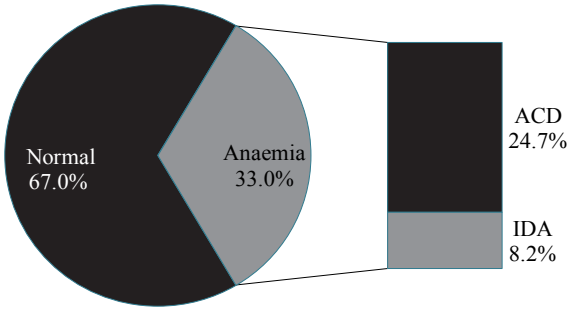
The commonest drug used by the patients was methotrexate seen in 80% of the study population while 72% of the patients were regularly on NSAID. It is worth noting that 100% of the patients who were on methotrexate were on supplementation on a daily basis as depicted in Figure 2.

Figure 2: Medication use and time scale



The mean haemoglobin was 12.4g/dl with a range of 3.0-15.7g/dl. The mean haemoglobin for females was 12.5g/dl with a median (IQR) 12.9g/dl (11.9-13.7) While the mean haemoglobin for males was 11.8 g/dl with a median of 12.7g/dl and IQR-(11.3-13.5). The mean serum ferritin was 73.3mg/l with a range of (6.9-1977mg/l). The prevalence of anaemia was 33% (95% CI 23.6-42.4%) in the study population. 24.7% (95% CI 16.1-33.3%) of the patients had Anaemia of Chronic Disease (ACD) while 8.3% (95% CI 2.8-13.8%) had Iron Deficient Anaemia (IDA) as depicted in Figure 3.

Figure 3: Prevalence of anaemia in RA patients



The modified disease activity score 28 showed that most patients had moderate to high disease activity with 58.8% of the patients having moderate disease activity while high disease activity was seen in 33% of the patients. Only 4% of the patients were on remission and another 4% had low disease activity. The relationship between the presence of anaemia and the MDAS28 in the study population is summarized in Table 2.

Table 2 : Comparison of MDAS 28 among the patients and anaemia

Variable	No. with anaemia (%)	No. with normal Hb (%)	P value
DAS28			
Low (<2.6)	0 (0.0)	4 (6.2)	
Remission (2.7-3.2)	0 (0.0)	4 (6.2)	<0.001
Moderate (3.3-5.1)	10 (31.3)	47 (72.3)	
High disease activity (>5.1)	22 (68.8)	10 (15.2)	

There was a trend of increased chance of being anaemic as the disease activity score increased from remission to high disease activity. Being male was significantly associated with being anaemic with a P-value of 0.008. There was no significant association of anaemia with the patient's age, the level of education or the time since the diagnosis of RA. Findings are summarized in Table 3**.**

Table 3 : Association of anemia with disease duration

Variable	Anaemia		OR (95% CI)	P value
	Yes	No		
Duration since diagnosis of RA				
Less than 1 year	9 (30.0)	23 (35.9)	1.0	
1-5 years	13 (43.3)	20 (31.3)	2.3 (0.6-9.1)	0.236
More than 5 years	8 (26.7)	21 (32.8)	2.4 (0.5-12.3)	0.306

Association of anaemia with treatment: The study results demonstrated that the use of DMARD was associated with reduced likelihood of patients being anaemic. The introduction of any DMARD medication was protective of anaemia (P value of 0.012). The use of methotrexate alone or in combination was significantly associated with reduced possibility of patients getting anaemia p value (0.044). The findings can be attributed to the control of the disease which the DMARDs confer to the patients leading to reduction of the chronic inflammation (Table 4).

Table 4: Summary of the association of anaemia with treatment

Variable	Anaemia		OR (95% CI)	P value
	Yes	No		
NSAIDS				
Yes	22 (71.0)	45 (72.6)	0.9 (0.4-2.4)	0.870
No	9 (29.0)	17 (27.4)	1.0	
DMARDS				
Yes	27 (87.1)	59 (100.0)	-	0.012
No	4 (12.9)	0 (0.0)		
Methotrexate				
Yes	20 (74.1)	54 (91.5)	0.3 (0.1-0.9)	0.044
No	7 (25.9)	5 (8.5)	1.0	
Steroids				
Yes	19 (70.4)	32 (54.2)	2.0 (0.9-5.3)	0.158
No	8 (29.6)	27(45.8)	1.0	
HCQ				
Yes	11 (40.7)	26 (44.1)	0.9 (0.3-2.2)	0.772
No	16 (59.3)	33 (55.9)	1.0	
Sulphasalazine				
Yes	2 (7.4)	9 (15.3)	0.4 (0.1-2.2)	0.490
No	25 (92.6)	50 (84.7)	1.0	
Leflunamide				
Yes	2 (7.4)	4 (6.8)	1.1 (0.2-6.4)	1.000
No	25 (92.6)	55 (93.2)	1.0	

Multivariate analysis of factors associated with anaemia: The study demonstrated that gender and age were independently associated with anaemia after analysis.

Discussion

Anaemia in RA is associated with increased morbidity and mortality. Anaemic patients have also been shown to have poor quality of life. There is evidence that prompt diagnosis and institution of appropriate treatment leads to better health among the affected individuals. Literature search does not yield any studies done in Africa on anaemia among patients with RA hence the findings of the study will shed light on the burden and the findings can be used to improve patient on care. The total number of patients identified in a span of 6 months was 108 out of which 103 patients met the strict ACR-EULAR CRITERIA for RA[1]. This number is almost double (n=65) of what Owino *et al*[6] found in 2008 . This is an indication of the rise in the patient numbers in the recent past after enhanced patients awareness of RA and starting of specialized ROPC.

The study population was middle aged with a mean age of 50.7 years. The highest proportion of patients were above 50 years (56%). This mirrors favorably with worldwide epidemiologic data on RA which peaks from the 5th decade [4]. The M: F ratio of RA in the patient population was at 1:68, this was lower than the universally published ration of M:F of 1:3, however the study still demonstrated that RA burden like other connective tissue is still highest among the female

gender[4,5] .There was a delay before diagnosis of RA was made with 79% of patients reporting to have had signs and symptoms of the disease for a period of over one year while 69% had the proper diagnosis made in the last one year only. The reasons given for delayed diagnosis was management in other peripheral facilities and use of NSAIDs which patients reported to give them some relief. Literature search did not yield any other studies to compare the average span of time patients take before diagnosis and its effect on treatment outcomes.

Ninety two percent of the patients had been started on DMARDs with methotrexate being the drug of choice seen in 76% of the total population; 55.9% of them had been on methotrexate for a period of over one year. Agrawwal in India found only 49% of patients used methotrexate[22]. The popularity of methotrexate can be attributed to its simple dosing regimen of once a week, affordable cost, its proven benefits in reducing the chronic inflammation in RA. The two factors lead to improved compliance to the treatment.

The prevalence of anaemia in the study was 33% of the study population. This is lower compared to other studies done in a developing country specifically India. Borah *et al*[12] studied patients who had been diagnosed to have RA in the past 2 years in a rural Northern India and found a prevalence of 64%. while Agrawwal *et al*[22] still in Lucknow India found a prevalence of 70.6% when he did a 2 year prospective follow up of 214 patients with RA. Possible reasons for the differences can be due to the study design and difference in study populations being compared. The two studies from India looked at patients who had had RA in a span of less than 2 years while in our study 65% of the patients had RA for a period of more than one year meaning most had been started on appropriate treatment to control the disease. In addition, Agrawwal *et al*[22] did a two year prospective study. Another plausible reason for the difference in the findings may be attributed to the high prevalence of anaemia in India at almost 50% in the rural areas as compared to Kenya with a prevalence of around 38% according to the WHO global data base on anaemia burden[22].

The study showed that 75% of the cases of anaemia were ACD while IDA accounted for 25%. The findings compare well with other studies done in other centers. Borah *et al*[12] study in India found a prevalence of 65% and 33% respectively for the two main forms of anaemia in RA. The high prevalence of ACD can be explained by inadequate control of the disease as it was found that ACD was the common form of anaemia in those patients with moderate and high disease activity. Delayed diagnosis is also a possible major contributing factor of the high ACD burden. The study did not demonstrate any significant association between IDA and use of NSAIDs and use of steroids (P value 0.870); however the patients who had been on NSAIDs for more than one year were likely to have anaemia (P value 0.033). Paradoxically the predominant anaemia was still ACD as opposed to IDA which would have been the expected finding at 74% and 26% for ACD and IDA respectively (n=19). This could possibly be explained by regular prescription of proton pump inhibitors among the patients on long term NSAID prescriptions and also the failure of clinicians to adequately adjust patients treatment once resolution of the severe presenting symptom of pain seen in RA has resolved .

Anaemia and disease activity score: There was a statistically significant relationship between the disease activity and occurrence of anaemia ($P < 0.001$). Multivariate analysis also found that the disease activity was independently associated with anaemia. Similar findings have been reported by others, Agrawwal *et al*[22] found anaemic patients had severe disease activity with a mean MDAS of 5.3 compared to non anaemic patients who had moderate disease activity (3.3-5.1) with mean disease activity of 3.83. Borah[12] demonstrated that there was an inverse correlation between haemoglobin level and the disease activity score.

The study also demonstrated that the MDAS28 scores were higher in patients with ACD with an average score of 5.6 which correlates with high disease activity score. The mean MDAS 28 in patients with IDA was 5.3. Aggrawal[22] found patients with ACD had average disease activity of 5.69 while those who had IDA had an average disease activity of 4.7. Anaemia tended to be commoner among males with 45% of them being anaemic ($P<0.008$); this finding in our study has not been reported in literature elsewhere. The finding could be by chance due to the small number of patients studied although multivariate analysis showed this variable to be independently associated with anaemia. Other possible explanations to this finding could be poor health seeking behaviour in males and delay in diagnosis of RA in males with 3 male patients having had arthritis symptoms for over 5 years before diagnosis.

The use of NSAIDS was not significantly associated with anaemia. Of the anaemic patients 22(71%) were on a NSAID vs. 72.6% of patients on NSAIDs who had normal haemoglobin n=45 (P 0.870). The initiation of any DMARD reduced the likelihood of anaemia (P value-0.012). Methotrexate alone reduced the chance of patients being anaemic (P value-0.044) . Sub group analysis of steroids and hydroxychloroquine did not show a significant association with anaemia. The introduction of DMARDS /methotrexate leads to control of the inflammatory process hence this protects the patients from being anaemic[23] .

Conclusions

There is still a high burden of anaemia in our RA patients although it is lower compared to other areas. Anaemia correlates with the disease activity and those patients with anaemia tend to have high disease activity scores and the commonest anaemia type in this group is ACD

which means the disease control is still not adequate. Introduction of DMARDs is associated with reduction of the incidence of anaemia hence they are protective from both the disease and its complications. Men form a small percentage of patients with RA and when they present they have more severe disease and severe anaemia.

Study limitations

Recall bias was a major challenge encountered. This may affect the reporting of onset of disease symptoms. Other causes of anaemia can be confounders. The study was cross sectional in nature and it involved a highly pre-selected patient population being seen in a referral tertiary institution hence the findings may not be reflective of the total population. Serum ferritin though is a proven marker to estimate the level of iron store its being an inflammatory marker may be elevated by other causes.

Recommedations

A bigger multicenter African study is recommended and this should include a larger male patient population to confirm the findings of a high prevalence of severe anaemia in this gender are recommended. ACD being the commonest form of anaemia means that we have to enhance care of patients and retard the chronic inflammation which is the hallmark of RA and through this the burden of anaemia will be reduced. Increased surveillance for anaemia and early introduction of DMARDs in patients with RA.

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