Research article

Prevalence of abnormal liver function tests in rheumatoid arthritis

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Abstract

Objective: To determine the prevalence of Abnormal Liver Function Tests (LFTs) in patients with rheumatoid arthritis at the rheumatology out-patient clinic, Kenyatta National Hospital (KNH).

Design: Cross-sectional descriptive study.

Setting: Rheumatology out-patient clinic at KNH.

Participants: One hundred and seven RA patients.

Results: The overall prevalence of abnormal LFTs in the study population was 57%. The most common abnormal LFTs were direct bilirubin and alkaline phosphatase (ALP), which were elevated in 34.6% and 15% of the study population, respectively. Abnormal direct bilirubin was associated with longer duration of disease; adjusted Odds Ratio (OR) 0.54 (0.34, 0.86) p-value 0.009 and higher disease activity, adjusted OR 2.79 (1.23, 6.25) p-value 0.014. Abnormal ALP was significantly associated with BMI, adjusted OR 0.205 (0.074, 0.57), p-value 0.002 as well as duration of disease, adjusted OR 1.14 (1.013, 1.29), p-value 0.031.

Conclusion: This study found the prevalence of liver dysfunction in patients with rheumatoid arthritis to be high, at 57%, and recommends regular monitoring of liver function tests in patients with rheumatoid arthritis.

Introduction

Rheumatoid Arthritis (RA) is a systemic, chronic, progressive inflammatory disease characterized by symmetric joint polyarthritis that progresses to severe joint destruction[1]. As a systemic illness, RA has many extra-articular manifestations and co-morbidities, many of which have been studied in our local setting, and have been found to correlate with disease activity[2-5]. The liver has however been overlooked as a target organ in patients with RA. Rheumatoid arthritis can affect the liver in many ways[6,7]; dysfunction is thought to arise from the disease itself, independent autoimmune disease, infections such as viral hepatitis or as a consequence of anti-inflammatory drugs such as Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) or Disease Modifying Anti-Rheumatic Drugs (DMARDs)[6]. The most common DMARDs used in treatment of RA in our setting are methotrexate and leflunomide, which can be hepatotoxic. The risk of hepatotoxicity while on treatment with DMARDs may be increased in the presence of hepatitis or alcohol intake.

LFTs may be abnormal in up to 50% of patients with RA and this has been shown to correlate with disease activity[7,8]. The 'rheumatoid liver' has long been a topic of interest and previous studies noted histological changes in the liver of RA patients who were not on treatment with DMARDs such as fatty change, cellular necrosis, chronic passive congestion and gross atrophy[9-12]. Studies have also investigated use of multiple DMARDs, which were thought to predispose patients with RA to a higher risk of developing hepatotoxicity[13,14].

With increasing awareness and knowledge of the RA, more patients are being diagnosed early and started on treatment, which may be life-long. Effective treatment modalities may have hepatotoxic effects. Abnormal LFTs are in themselves an independent predictor of mortality[15]. Due to high mortality from both RA as well as abnormal LFTs, such a subset of patients could therefore be at a higher risk. This is especially so because we currently have limited ways of managing liver injury in our setting. It is therefore important for us to monitor liver dysfunction in patients with RA.

Materials and Methods

This was a cross-sectional descriptive survey carried out among 107 RA patients at the outpatient rheumatology clinic of KNH. Using an estimate of 146 RA patients on follow up at KNH, a minimum sample size of 106 RA patients was calculated. Consecutive sampling was used to recruit participants. History and clinical examination were carried out, as per the data capture form. Blood samples were collected from patients for LFTs and Erythrocyte Sedimentation Rate (ESR).

LFTs analysis was carried out in the KNH renal laboratory using the Biolys Superior 50i, an automatic biochemistry analyzer. It was able to analyze the following parameters; Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Gamma Glutamyl Transferase (GGT), Alkaline Phosphatase (ALP), albumin, total protein, total and direct bilirubin using the manufacturer's protocol. The laboratory provided reference ranges for the tests. Determination of ESR was done at the Department of Haematology Laboratory, University of Nairobi, using the Wintrobe method. Both laboratories undergo internal and external quality control measures and are run by qualified laboratory technologists.

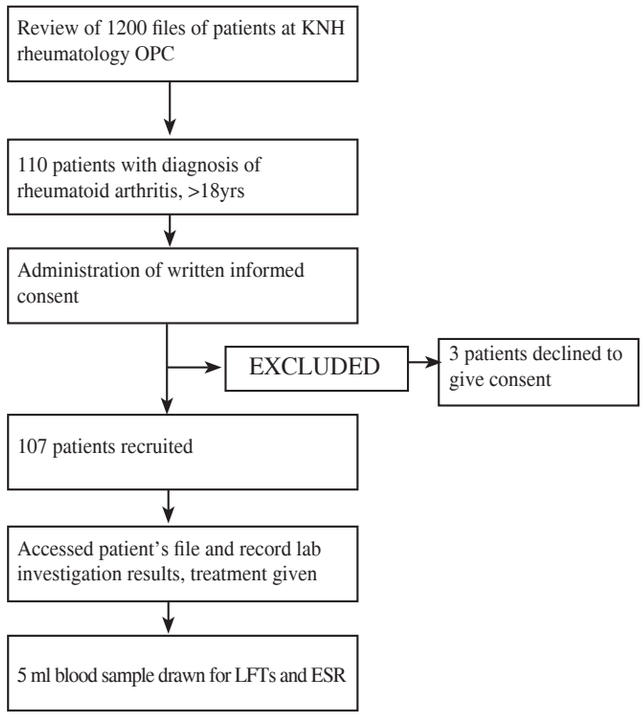
Patients were reported as having abnormal liver function tests if they had any elevations in the liver enzymes ALT, AST, ALP, GGT above the upper limit of the reference range, a rise in total or direct bilirubin above the upper limit and reduction of the albumin and protein levels below the lower limit of the reference range.

Data analysis: The prevalence of abnormal LFTs was calculated as number of abnormal LFT results as a percentage of the total number of LFT results. Association where the predictor and outcome were categorical was demonstrated using chi-square tests and odds ratios whereas Analysis of variance (ANOVA) tests were used to show relationships between categorical outcomes and continuous predictors. Where both predictor and outcome were continuous, Pearson correlation coefficients were used to characterize the association. Linear regression analysis was used to identify independent predictors of outcomes. Model building was done using a forward step-wise approach to identify the most parsimonious model. The level of significance was set at 0.05. Stata version 13 was used for data analysis.

Results

The study was done from 14th February to 21st April 2016 and enrolled 107 patients. All patients enrolled into the study gave written informed consent and had blood samples collected.

Figure 1: Shows the study flow chart



A. Demographics of the study participants

The study population was 107 patients, and 90.7% of the participants were females. The median age was 50 years, ranging from 18 to 81 years (Age of the study participants was not normally distributed and was negatively skewed; mean was therefore not described). Majority of the study participants had been diagnosed to have RA for over 5 years. Table 1 summarizes the characteristics of the study population.

Table 1: Characteristics of the study population

Variable			
Age	Median 50 (35, 62)	Min 18	Max 81
		No.	(%)
Gender	Male	10	9.3
	Female	97	90.7
Duration diagnosed with RA (years)	<1	12	11.2
	1-5	36	33.6
	>5	59	55.1

B. Medication and alcohol use

Methotrexate was the most commonly used DMARD in our population, with 60% of RA patients using it. Fourteen percent were on both methotrexate and leflunomide. Use of herbal medication was surprisingly high at 22.4%. Most study participants were non-smokers. Alcohol intake was slightly higher, with approximately 7.5% reporting current alcohol intake and 15% having stopped taking alcohol (Table 2).

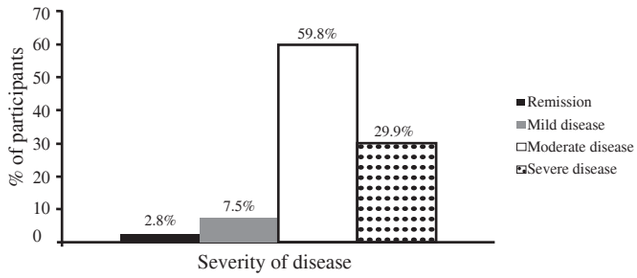
Table 2: Medication use among study participants

Drug	Use No. (%)	Duration <3 months No. (%)	3 months - 1 year No. (%)	> 1 year No. (%)
NSAID	86 (80.4)	2 (2.3)	23 (26.1)	63 (71.6)
Methotrexate	65 (60.7)	1 (1.5)	10 (15.4)	54 (83.1)
HCQS (mg/day)	44 (41.1)	1 (2.2)	6 (13.3)	38 (84.4)
Steroids - prednisone	49 (45.8)	2 (4)	7 (14)	41 (82)
Sulfasalazine (grams/day)	8 (7.5)	2 (22.2)	sz0 (0)	7 (77.8)
Leflunomide	25 (23.4)	4 (15.4)	4 (15.4)	18 (69.2)
Statin	4 (3.7)	2 (40)	0 (0)	3 (60)
Antiepileptic drugs	2 (1.9)	1 (50)	0 (0)	1 (50)
Oral contraceptive pills	8 (7.6)	1 (12.5)	2 (25)	5 (62.5)
Herbal medication	24 (22.4)	16 (15)	3 (2.8)	5 (4.7)

Disease activity among study participants

Active disease was present in 97% of the study participants and only 3% were in remission. Most of the patients, 61%, had moderate disease activity at the time of the study, despite some being on multiple DMARDs. Use of HCQS was found to be associated with a high DAS score, reflecting poor control of disease. Patients who were on HCQS were 1.7 times more likely to have poor disease control (OR=1.7, 1.14-2.55, p=0.011). A high BMI was also found to be associated with more severe disease (OR=1.06, 1.02-1.11, p=0.002). Figure 2 shows disease activity of participants.

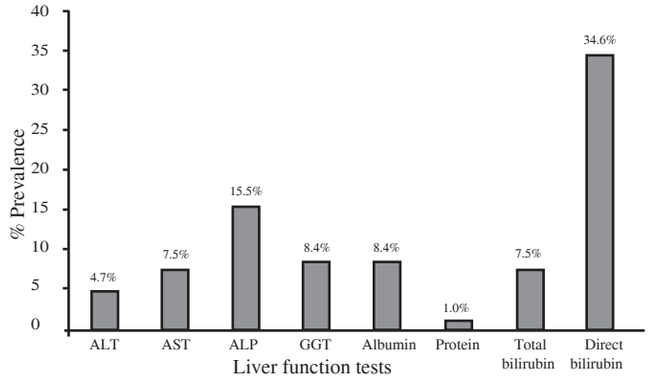
Figure 2: Disease activity of study participants



C. Prevalence of abnormal LFTs in RA

Among the RA patients, 61 (56%) had at least 1 abnormal LFT result. The most common abnormality was elevated direct bilirubin, which was found in 34.6% of RA patients. ALP was elevated in 15.5% of patients. Abnormal GGT and albumin values were found in 8.4% of patients. AST and total bilirubin were elevated in 7.5% of patients. Less than 1% of patients had low protein. Participants who had abnormality in both ALP and GGT were only 6 (5.4%). Participants who had elevations of more than twice the upper limit of normal range for the enzymes were fewer, with 5.6% having abnormal direct bilirubin, 1.9% with abnormal AST, 1.9% with abnormal GGT, 1% with abnormal ALP and total bilirubin and 0.9% with abnormal ALT. Figure 3 illustrates the prevalence of abnormal LFTs among participants.

Figure 3: Prevalence of abnormal LFTs in RA



D. Correlates of abnormal LFTs

Abnormal direct bilirubin: With longer disease duration, RA patients were almost three times more likely to have elevated direct bilirubin, OR 2.79 (1.23, 6.25), with a p value of 0.014. Though not significantly associated, being female and having a high education level seemed to be protective against development of abnormal direct bilirubin. Drugs such as HCQS, especially at high doses were also protective against abnormal direct bilirubin (Table 3).

Table 3: Adjusted odds ratios for abnormal direct bilirubin

Variable	Crude OR (95% CI)	P-value	Adjusted OR	P-value
DAS28	0.593 (0.396, 0.888)	0.011	0.54 (0.34, 0.86)	0.009
RA duration	2.144 (1.099, 4.181)	0.025	2.79(1.23, 6,25)	0.014
Gender	0.313(0.082, 1.190)	0.088	0.603(0.43,1.03)	0.054
Education level	0.659(0.402, 1.081)	0.099	0.6(.33, 1.09)	0.096

Abnormal ALP: Fifteen percent of the study population had abnormal ALP. Notably, abnormal ALP was significantly associated with BMI with an adjusted OR of 0.205 (0.074, 0.57), p-value 0.002 as well as duration of disease, with an adjusted OR 1.14 (1.013, 1.29), p-value 0.031.

Other independent predictors of elevated ALP included occupation and use of oral contraceptives. Having an occupation appeared to be protective for elevated ALP, OR 0.41 (0.16, 1.01) with a p-value of 0.05. However, use of OCP was up to 22 times predictive for elevated ALP OR 22.3 (1.72, 290.12), p-value 0.018. Having been started on any DMARD and drugs such as HCQS, methotrexate and prednisone were noted to be protective against development of abnormal LFTs (Table 4).

Table 4: Adjusted ORs for abnormal ALP

Variable	OR (95% CI)	P-value	Adjusted OR	Adjusted P-value
BMI	1.168 (1.051,1.298)	0.004	0.205 (0.074, 0.57)	0.002
MTX dose	0.829 (0.683,1.008)	0.06	-	-
RA duration	0.247 (0.108, 0.564)	0.001	1.14 (1.013, 1.29)	0.031
Occupation	0.434 (0.227, 0.83)	0.012	0.405(0.16, 1.01)	0.053
Anti CCP	0.1 (0.017, 0.705)	0.02	-	-
DMARD started	0.304 (0.079, 1.166)	0.083	-	-
MTX duration	0.243 (0.061, 0.971)	0.045	-	-
Folate	0.122 (0.007, 2.19)	0.154	-	-
HCQS	0.16 (0.034, 0.748)	0.02	-	-
HCQS duration	0.105 (0.011, 1.014)	0.05	-	-
Prednisone	0.215 (0.057, 0.809)	0.023	-	-
OCP	9.577 (1.458, 62.906)	0.019	22.3 (1.72, 290.12)	0.018

Discussion

The overall prevalence of abnormal liver function tests in the study population was 57%. The most common abnormality was elevated direct bilirubin in 34.6% of participants, followed by elevated ALP in 15%. This study showed a low prevalence of ALT and AST abnormality at 4.7% and 7.5% respectively. Significant associated factors for elevated direct bilirubin included disease activity and duration of disease. Elevated direct bilirubin was more common in patients with a low disease activity and longer duration of disease. Duration of disease was a significant associated factor for both elevated ALP and direct bilirubin. Direct bilirubin and ALP may be elevated in case of liver disease and suggest intrahepatic biliary obstruction.

Previous studies have noted liver dysfunction in RA at variable levels. Lefkovitz *et al*[16] found a depressed albumin level as the most common LFT abnormality, which was in 37% of patients. Fewer patients had elevated ALP (15%) and bilirubin levels (0%). This study had a similar prevalence of ALP abnormality but higher bilirubin levels. Notably, these were patients who had not yet been started on DMARDs and the difference in this population may well be an effect of treatment. Webb *et al*[7] found that 18% of RA patients had elevated ALP, 1.9% of patients had elevated ALT and 0.5% of patients had elevated AST. In a review of RA patients on methotrexate, Amital *et al*[17] found a total of 45% of the population had at least one abnormal result, most commonly ALP and albumin. This study is similar, and shows an overall prevalence of abnormal LFTs at 57%, with the common abnormal LFTs being direct bilirubin and ALP. A study done among RA patients on a combination of methotrexate and leflunomide by Curtis *et al*[13] demonstrated LFT abnormalities in 33% of RA patients. Studies done among patients who were on DMARDs have revealed variable LFT abnormalities that have been attributed to the drug regimen, citing high dosage of drugs such as methotrexate, lack of folate supplementation and combination of drugs such as methotrexate and leflunomide. The lower prevalence of abnormal ALP in this study population of 15% in comparison to the systematic review by Salliot *et al*[19], which had a prevalence of 20%, may be explained by use of folate supplementation, which the study participants on methotrexate were on as well as the small number of patients on multiple DMARD combination. Folate supplementation is used in all our study patients on MTX

and this has been proven to reduce adverse events of MTX, including gastrointestinal effects and liver function test abnormalities [20,21].

This study also reveal an elevation of direct bilirubin, which may not be explained by the effect of RA on the liver. An isolated elevation of direct bilirubin may be difficult to infer much from, though many recent studies have been evaluating elevated bilirubin as a protective factor in many inflammatory diseases such as RA, SLE, stroke, atherosclerosis and vasculitis[18]. This could explain why elevated direct bilirubin was associated with low disease activity.

This study shows no correlation of abnormal ALP with disease activity. There was however a protective effect of using DMARDs, especially prednisone and HCQS. Studies by Cockel *et al*[8] and Kendall *et al*[22] demonstrated that the abnormal LFTs, mostly ALP elevation, subsided with disease remission as well as steroid use in patients with RA. Lefkovitz *et al*[16] also demonstrated a definite relationship between abnormal albumin and high disease activity. Kendall *et al*[22] found the pathogenesis of abnormal LFT to be obscure and was unable to ascribe this to hepatotoxic drugs, alcohol or hepatitis. The high disease activity of the study population despite treatment could explain the lack of correlation. This study found that 97% of patients with rheumatoid arthritis in the rheumatology outpatient clinic have active disease. This is higher than in the study by Owino *et al* in 2007[23], who found that at least 88% of RA patients had high disease activity. High disease activity among the RA patients may not be surprising, given that patients who have been on DMARDs for a long duration will have poor response with time. The ERAN cohort in the UK similarly noted high disease activity, despite patients being on DMARDs[24].

With longer disease duration, RA patients were almost three times more likely to have elevated direct bilirubin; OR 2.79 (1.23, 6.25), with a p-value of 0.014. The effect of duration of disease could represent a cumulative effect of either the disease or the drugs on abnormal liver function. Drugs such as HCQS were protective against abnormal bilirubin results. Elevated ALP was significantly associated with BMI with an adjusted OR of 0.205 (0.074, 0.57), p-value 0.002 as well as duration of disease, with an adjusted OR 1.14 (1.013, 1.29), p-value 0.031. Kent *et al*[25] showed an effect of obesity on liver function tests in RA patients using methotrexate. Other independent predictors of elevated ALP included occupation and use of oral contraceptives. Having an occupation appeared to be protective for elevated ALP, OR 0.41 (0.16, 1.01) with a p-value of 0.05. However, use of OCP was up to 22 times predictive for elevated ALP, OR 22.3 (1.72, 290.12), p-value 0.018. Having been started on any DMARD and drugs such as HCQS, methotrexate and prednisone were noted to be protective against development of abnormal LFTs.

Study limitations: This was a cross-sectional study and we were unable to follow up patients with serial LFT measurements. We were unable to ascertain causes of liver dysfunction, especially those which may result from infection or autoimmune disease. LFTs are non-specific and were only used to detect liver dysfunction.

Conclusion

This study reveals a high prevalence of abnormal LFTS, in 57% of RA patients. Such a high burden of liver dysfunction necessitates that LFTs should be a requirement in providing quality care to any patient with rheumatoid arthritis. Abnormal direct bilirubin was associated with a low disease activity and longer duration of disease. Duration of disease was a significant associated factor for both elevated ALP and direct bilirubin. Patients with rheumatoid arthritis who have had the disease for longer should be on the health provider's watch list and LFTs should be done often. None of the patients with abnormal LFTs had clinically evident liver disease, which therefore illustrates the importance of frequently monitoring LFTs among these patients. Moreover, most of the study population did not have previous liver function test results. This study therefore recommends regular monitoring of liver function tests in patients with rheumatoid arthritis, especially in those who have long-standing disease. Establishment of a prospective cohort would also be useful as well to determine the intervals at which monitoring liver function should be done.

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