Research article

Prevalence and associated risk factors of metabolic syndrome among rheumatoid arthritis patients attending a tertiary teaching hospital in Nairobi, Kenya

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Abstract

Background: Rheumatoid Arthritis (RA) predisposes afflicted patients to an increased risk of metabolic syndrome and cardiovascular disease. The prevalence of metabolic syndrome in RA has variably been reported in different populations.
Objective: To determine the prevalence, and associated risk factors, of Metabolic Syndrome (METS) among RA patients.
Methods: Following ethical approval, 127 patients with established RA were recruited. The following parameters were obtained/calculated for further analysis: patients' demographics, biochemical parameters, waist circumference, BMI and ten-year ASCVD risk. Presence of metabolic syndrome was ascertained as per guidelines. Appraisal of patient and disease features between patients with and those without metabolic syndrome was carried out using the Independent Student's t and Chi-square tests. Logistic regression was performed to estimate the impact of moderator variables, adjusting for age, sex and baseline characteristics. Throughout the analysis, a $p<0.05$ was considered statistically significant at a 95% CI.
Results: The mean age of the participants was 51.48±15.7 years while age at diagnosis was 43.29±13.81 years. Median duration of treatment was 6.65 years. Eighty-three patients (65.4%) had a waist circumference above the set cut off, 74 (58.26%) were overweight, 68 (53.5%) were hypertensive, 18 (14.2%) were diabetic while 38 (29.9%) patients had dyslipidaemia. Twenty-seven (21.26%) patients met the criteria for METS. A majority (55.12%) had advanced disease activity. Of the 97 patients aged above 40 years, 52.58% had advanced Cardiovascular Disease (CVD) scores. Univariate analysis, age at diagnosis (OR= 1.07, $p<0.001$), disease duration (OR= 1.08, $p=0.004$), disease activity (OR= 1.76, $p=0.004$), elevated CRP (OR= 1.01, $p=0.021$) and steroid use (OR= 2.90, $p=0.018$) were associated with METS.
Conclusion: Metabolic syndrome and its components are highly prevalent and there was sub-optimisation of many of the modifiable risk factors.

Key words: Metabolic syndrome, Rheumatoid arthritis, Cardiovascular disease

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Introduction

Rheumatoid Arthritis (RA), considered the commonest inflammatory arthritis, is an autoimmune disease of unknown cause characterised by symmetrical synovitis and joint inflammation[1]. The global prevalence of RA is approximately 1% with ranges from 0.12% to as high as 6.8% amongst native Americans[2]. Among Africans, RA's prevalence has been documented to range between 0.06% and 3.4%[1,3]. Untreated, RA is a prominent cause of chronic indisposition and is associated with major systemic complications culminating in a reduced health-associated quality of life, diminished labour capacity and increased cost of living among affected patients[1].

Patients living with RA have been reported to have a heightened risk of Cardiovascular Disease (CVD)[4]. The predisposition to CVD in these patients is precipitated by, among other factors Metabolic Syndrome (METS), a collection of interrelated disorders that include increased blood pressure, central obesity, raised blood glucose levels and dyslipidaemia[5]. The individual components of METS in RA have similarly been known to occur variably among patients with RA. Globally, the prevalence of METS in RA patients is reported to range between 14% and 64%[6]. Furthermore, the occurrence of METS in RA patients has variably been known to be determined by several factors including medication use, duration of disease and affected patient's age[7]. How these factors affect the occurrence of METS among RA patients in our local set up has similarly not been documented. Furthermore, METS has variably been shown to worsen

RA and predispose affected patients to high CVD risk. However, this association has hardly been investigated in our local population despite the different socio-economic environment. Furthermore, the strength of association of these factors with the severity of RA has been known to vary in previous studies. This study therefore aimed at determining the prevalence, and associated risk factors, of metabolic syndrome in patients living with RA.

Materials and methods

This study was done on adult RA patients attending the Rheumatology Clinic at the Kenyatta National Hospital (KNH). Ethical approval to conduct the study was granted by the KNH-UON Ethics and Research Committee and informed consent was obtained from all participants prior to recruitment to the study. Only patients above 18 years of age and with established RA, as defined by ACR/EULAR classification criteria for RA[8], were enrolled. Patients with the following conditions were excluded from the study: other autoimmune disorders, HIV-AIDS, chronic liver and renal disease and active malignancy. The following parameters were then extracted from the patient's medical records: prescribed medications, C-Reactive Protein (CRP), Erythrocyte Sedimentation Rate (ESR), Fasting Lipid Profile (FPL), Blood Sugar (BS) and HbA1C levels. Blood Pressure (BP) was taken twice using a digital BP machine (each reading five minutes apart) and the average taken. The weight of the patients was measured using a standard weighing scale while height was taken using a wall mounted height rod. Body Mass Index (BMI) was calculated as: mass (kg)/height^2. Waist Circumference (WC) was measured (in centimetres) at a point halfway between the inferior border of the ribcage and iliac crest[9]. Duration of disease was determined by subtracting patient's age at diagnosis from the current age of the patient. Disease activity was assessed using the DAS28 (CRP) criteria using the DAWN VISUAL DAS28 online calculator[11]. Ten-year Atherosclerotic Cardiovascular Disease (ASCVD) risk for patients above 40 years of age was be estimated as per the 2013 ACC/AHA guidelines[12] utilizing the ASCVD Risk Estimator Plus calculator developed by ACC.

Case definitions

Hypertension was defined as per the ESH/ESC hypertension (HTN) guidelines (BP consistently ≥140/90 mm/Hg or patient already taking anti-hypertensive medications)[13]. Presence of diabetes was confirmed by the presence of either of: patient taking anti-diabetic drugs, HbA1C levels above 6.5%, a Random Blood Sugar (RBS) of >11.1mmol/L or a Fasting Blood Sugar (FBS) level >7.01mmol/L[14]. BMI was categorized as underweight (<18.5), healthy (>18.5 and <25), overweight (>25 and <30) or obese (>30). Ten-year risk for ASCVD was grouped as: low-risk (<5%), borderline (5% to 7.4%), intermediate (7.5% to 19.9%) and high (≥20%). RA disease activity level was graded into four categories: remission (DAS28 ≤2.6), low/minimal (2.6 <DAS28≤ 3.2), moderate (3.2 < DAS28 ≤ 5.1) and high disease activity (5.1> DAS28) (10). Presence of METS was ascertained by the presence of any three of these five features[15]: increased waist circumference (≥ 102 cm for men and ≥ 88 cm for women); elevated BP (≥140/≥90 mmHg); high triglyceride levels (≥1.7 mmol/L) or medical therapy for elevated TG; low HDL-C (< 1.03 mmol/L for male patients and < 1.3 mmol/L for female patients); elevated Fasting Blood Sugar (FBS) (>7.01mmol/L), Random Blood Sugar (RBS) (>11.1mmol/L), HbA1C level (>6.5%), or medical therapy for raised glucose.

Data analysis

Data analysis was carried out using SPSS Version 25. Categorical data was reported as frequencies (%). Independent Student's-t test was used for comparison of quantitative patient and disease characteristics between patients with and those without METS. Comparison of categorical data was carried out using Chi-square test. Logistic regression was performed to estimate the impact of moderator variables (disease duration, disease activity, CRP levels, methotrexate use, steroid use and Nonsteroidal Anti-Inflammatory Drugs (NSAID) use), adjusting for age, sex and baseline characteristics. Further variable selection and model improvement was performed using the stepwise algorithm. Final logistic models were used to calculate adjusted Odds Ratios (ORs) with the corresponding 95% Wald Confidence Interval (CI). Throughout the analysis, a $p<0.05$ was considered statistically significant at a 95% CI.

Results

Of the 127 patients recruited, 115 were female (90.6%) while 12 were male. The mean age was 51.48±15.7 years (range 18 to 83 years) while the average age at diagnosis was 43.29±13.81 years (range 15 to 74 years). Of the enrolled patients, 97 (76.38%) were above 40 years of age. The recruited patients had been on treatment for RA for a median of 6.65 years (Table 1). Fifty-five (43.3%) patients, including 53 female patients, only had primary level of education with 32 (25%) patients and 40 (31.5%) patients having attained secondary and tertiary level of education respectively. None of the patients had a previous history of smoking or cerebrovascular (CVA) accident. Forty-four (34.6%) patients were on various NSAIDS, 73 (57.5%) were on steroids while 89 (70.1%) patients were on methotrexate.

Table 1: Summaries of various study parameters

Parameter	Mean
Age (years)	51.48±15.71
Age at diagnosis (years)	43.29±13.81
Waist circumference (cm)	91.89±7.91
SBP (mmHg)	131.11±18.78
DBP (mmHg)	79.21±11.2
CRP*	7.1
ESR (mm/Hr) *	30.8
RBS (mmol/dL)	5.66±1.52
HbA1C	5.99±2.22
DAS28	3.483±1.17
BMI (Kg/M^2)	26.21±3.68
Total cholesterol (mg/dL)	166.33±34.96
HDL (mg/dL)	48.59±12.29
TG (mg/dL)	112.29±46.06

* Median

Metabolic syndrome in rheumatoid arthritis patients

A total of 27 (21.26%) patients met the criteria for METS (25 female and 2 male patients). A majority of the patients with METS only had primary level of education (77.8%) compared to the almost uniform distribution across all levels of education for RA patients without METS (Tables 2 and 3). Eighty-three (65.4%) patients had a WC above the set cut off while 58 (45.7%) and 16 (12.6%) were overweight and obese respectively. Forty-nine (59.04%) of the 83 patients on steroids had increased WC compared to 54.54% of patients not on steroids. Patients with (HTN) were much older, had a later age at diagnosis and had longer disease duration. A third of these patients with HTN were not on any anti-hypertensive medication. A majority (76.47%) had uncontrolled BP. Only one third of these patients with HTN were on NSAIDs and 25% of them had DM as a comorbidity. Moreover, more patients with primary level of education were hypertensive compared to those with secondary and tertiary level of education. All diabetic patients were on treatment, were considerably older and had a longer duration of RA treatment. Five of the diabetic patients had not achieved glycaemic control while 9 (50%) were on steroids compared to 64 (58.72%) non-diabetic patients. Of the 38 patients with dyslipidaemia, 10 were on anti-lipidemic medicines while 5 patients were on lipid-lowering drugs despite a normal lipid profile.

Table 2: Summaries of the various components of METS

Parameter	N (out of 127)	(%)
Patients with WC above cut-off	83	65.35
BMI (overweight & obese patients)	74	58.27
Patients with HTN	68	53.54
Patients with DM	18	14.17
Patients with dyslipidaemia	38	29.92
Patients with METS	27	21.26

Table 3: Differences in continuous variables between patients with METS and those without METS

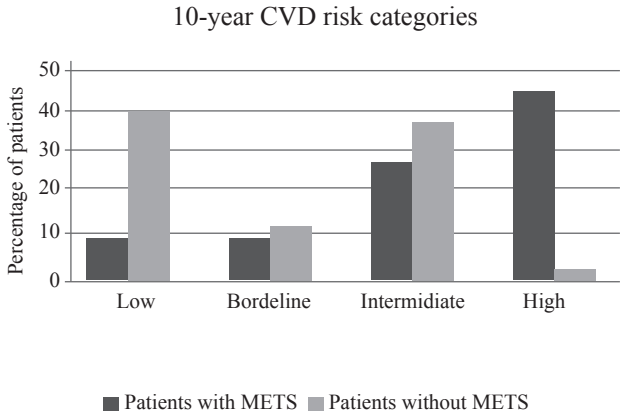
Parameter	METS (n=27)	No METS (n=100)	P-value
Age (years)	65.56±11.33	48.22±15.16	**<0.001**
Age at diagnosis (years)	51.78±9.49	41.00±13.94	**<0.001**
Duration of disease (years)	15.3	5.9	**<0.001**
Waist circumference (cm)	98.89±9.61	90±6.18	**<0.001**
CRP*	15.06	8.9	0.369
ESR*	45.3	30.8	**0.039**
SBP	146.33±17	129.55±17.67	**<0.001**
DBP	77.78±11.06	79.6±11.26	0.454
RBS	7.38±2.38	5.2±0.66	**<0.001**
BMI	28.56±4.19	25.58±3.28	**0.002**
Total cholesterol	197.17±49.64	158.01±24.07	**<0.001**
HDL	47.05±12.05	49.01±12.39	0.461
TG	141.58±57.07	104.39±39.34	**0.003**

*median. Bold is statistically significant

Cardiovascular disease risk in rheumatoid arthritis

Of the 97 patients aged above 40 years, only 33 (34.02%) had a low 10-year CVD risk score (Figure 1).

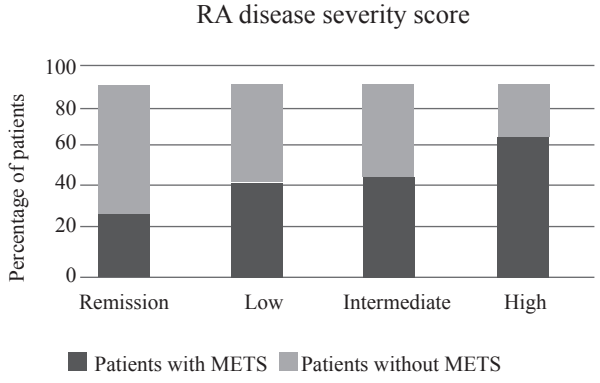
Figure 1: Differences in 10-year CVD risk between patients with METS and those without METS



Rheumatoid arthritis disease severity

A majority (55.12%) of the patients had either moderate or high disease activity compared to the 44.88% of the participants who had either a low or remission category of disease severity (Figure 2). Patients under study were either on 1 or 2 disease modifying antirheumatic drugs (DMARDS) (39.4% and 51.2% respectively) while two patients were not any DMARDS. The most commonly prescribed DMARDS were methotrexate (prescribed in 89 patients) and various steroid formulations (used by 73 patients). NSAID prescriptions were encountered in only 44 patients.

Figure 2: Differences in RA disease severity between patients with METS and those without METS



Results for logistic regression analysis

Univariate (unadjusted analysis), age at diagnosis (OR= 1.07, p<0.001), disease duration (OR= 1.08, p=0.004), disease activity (OR= 1.76, p=0.004), elevated CRP (OR= 1.01, p=0.021) and steroid use (OR= 2.90, p=0.018) were associated with metabolic syndrome (METS). After adjusting for potential confounders, age at diagnosis (OR= 1.08, p= 0.007), disease duration (OR= 1.08, p=0.030), elevated CRP (OR= 1.02, p=0.040) and steroid use (OR= 3.75, p=0.035) remained as significant predictors of development of METS.

Discussion

The prevalence of RA in Africa and particularly in Kenya has been on an upward trend in the recent past[3]. Affected patients have a lower quality of life and are at an increased risk of CVD and mortality, of which RA patients have a two-fold greater risk relative to the general population[1]. Among the established causes of CVD in RA patients is METS[5].

The current study reported a disproportionately higher number of female patients (F:M=9:1) compared to the 6:1 ratio reported in an earlier meta-analysis of studies done from Africa[16]. Nonetheless, our findings are similar to results from Asian studies[17] and would be attributed to a poorer health-seeking behaviour among male patients and misdiagnosis of RA as other arthropathies[5]. Furthermore, RA is an autoimmune inflammatory disease that mainly affects women with variably reported prevalence rates. Majority of the participants in the current study had an advanced age at diagnosis, a longer duration of treatment and primary level of education. A dearth of awareness of connective tissue diseases coupled with a lower number of trained rheumatologists in Africa has in the past been attributed not only with the low prevalence of rheumatic diseases in the continent but also a later age of diagnosis[16]. Similarly, delays in specialist referrals for RA patients of up to 12.9 years have been reported in African studies contrasting starkly with delays of between 1 and 3 months reported in studies from western Europe[16]. This might further explain the higher average age at diagnosis seen in our patients. This late diagnosis of RA has been associated with greater disease activity and delayed initiation of DMARDS, and as seen in our analysis, the predisposition to the various components of METS[18]. However, recent improvement in patient care has resulted, as reflected in our findings, in patients living with RA for long.

Even though the prevalence of METS in RA occurred in about 21% of the participants, some of the individual components were more prevalent. The global prevalence of METS in RA has been estimated at 32% (range 8.2% to 44%) but shows significant regional differences with the highest rates reported in Asia and Europe while studies from Africa report lower rates with an average prevalence of 28% (range 14% to 33.2%)[7]. The reported prevalence in the current study (21.26%), though lower than the African average, is higher than the 18% reported in a Moroccan study[19]. Past research on METS in RA has attributed this discrepancy in the prevalence rates to the selection of cut-offs for the various components of METS, the exact definition of METS used and age heterogeneity of study participants in the various published works[20]. The burden of METS in RA can, however, not be ignored since it increases adverse cardiovascular outcomes by 2 times and enhances mortality risk by 1.5 times.

The observation in the current study that patients with METS were likely to have greater disease activity, an advanced age at diagnosis, and have had a longer duration of RA treatment has been variably reproduced in the past[7]. Similarly, and as previously reported, male sex and the use of methotrexate and NSAID did not seem to predispose patients to METS[21]. Nonetheless, a high inflammatory habitus as reflected by high DAS-28 scores and raised CRP values, was strongly correlated with predisposition to METS. This observation has been seen with other joint diseases including osteoarthritis and has been shown to precipitate insulin resistance and reduced vascular compliance exposing RA patients to components of METS[22]. Furthermore, affected patients tend to have a high disease activity resulting in chronic pain and a sedentary lifestyle[23]. We further showed, and as reported in past publications, that various components of METS occur at varied frequencies independent of each other whether or not the patient has METS[7]. This observation is further compounded by the realization that a majority of METS components in the current study, including HTN and markers of visceral adiposity, were poorly controlled. The need to modify for the risk factors for METS in RA can therefore not be overemphasized.

Rheumatoid arthritis disease activity has traditionally been reported to be worse among female patients[24]. On the contrary, male patients in the current study had greater DAS28 scores and were characterised with more joint deformities and tenderness besides having higher CRP and ESR readings. Consequently, male patients had higher CVD risk scores. This was in spite of the fact that none of the male patients in the current study had a positive history of smoking, a known determinant of adverse disease activity and CVD among RA patients[25]. The current study was nevertheless done in an apex referral hospital that treats patients with likely advanced disease which would explain this deviation. Nonetheless, our study findings are concordant with findings of a larger, more recent Chinese study that found that male patients had a more active disease with higher DAS28 scores, inflammatory markers and a propensity to adverse outcomes including strokes[26].

Patients with RA have been known to have an enhanced risk of CVD relative to the general population. The up to 2-fold risk emanates from the additive effects of the chronic inflammation and the numerous CVD risk factors that are preferentially found in these patients[27]. The overall ASCVD score for the current study was slightly lower than a scores reported in other studies done mainly among Caucasian populations[28]. The higher scores in previous studies might be explained by the inclusion of participants who were active smokers unlike the present study where none of the patients had a positive history of smoking. High CVD risk scores in RA patients reflect subclinical atherosclerosis and have been correlated with carotid intima-medial thickening[29] putting affected patients at the risk of CVA and myocardial infarctions. The risk of CVD is higher among male patients and those with a severer inflammatory status as reflected by high DAS-28 scores and greater CRP and ESR readings[30]. This observation is reflected in the current study where men had higher DAS-28 scores and CRP levels.

Conclusion

METS and its components are highly prevalent among RA patients in our locale. There is however sub-optimisation of many of the easily modifiable risk factors placing affected patients at higher CVD risk. Greater emphasis during follow up should therefore be accorded to RA patients in order to identify and manage modifiable risk factors.

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