*East African Medical Journal Vol. 88 No. 12 December 2011*
PERIPHERAL-ARTERIAL DISEASE IN RHEUMATOID ARTHRITIS PATIENTS AT THE KENYATTA NATIONAL HOSPITAL, KENYA
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# PERIPHERALARTERIAL DISEASE IN RHEUMATOID ARTHRITIS PATIENTS AT THE KENYATTA NATIONAL HOSPITAL, KENYA

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## ABSTRACT

***Objective*: To determine the magnitude of the rosclerotic arterial disease in Rheumatoid Arthritis(RA) patients at Kenyatta National Hospital.**
***Design*: Hospital based cross-sectional study.**
***Setting*: Kenyatta National Hospital Rheumatology outpatient clinic.**
***Subjects*: Rheumatoid Arthritis patients.**
***Results*: We obtained ABI measurements in 90 RA patients, among them 23(25.5% 95% CI 17.2-36.1) had obstructed lower limb arteries. Among the 23, 21(91.3%) had mild PAD, two (8.7%) had moderate PAD; none had severe PAD nor incompressible vessels. The obstruction of vessels was independent of diabetes, hypertension, dyslipidemia and cigarette smoking though these factors increased the likelihood of having PAD. Risk age( ≥45 males, ≥55 females), Established RA(> 5 year duration) and severe RA were found to be significantly associated with the likelihood of having PAD. These trends remained significant after multivariable adjustment for potential confounders. twenty five (27.7%) of the study subjects exhibited symptoms of intermittent claudication, 13(52%) of them had PAD on ABI measurements, The Edinburgh claudication questionnaire was found to have 56.5% sensitivity and 82% specificity in detection of PAD in RA patients.**
***Conclusion*: There seems to be an association between PAD in RA with chronicity and severity of the RA. This association may support the pathogenic role of accumulated systemic inflammation in atherosclerosis. Clinicians should be alert to the possibility of impared arterial function and thus subsequent cardiovascular morbidity and mortality in this group of patients.**

## INTRODUCTION

Rheumatoid Arthritis (RA) emerges as a major cause of significant morbidity and increased mortality which plagues the normal lives of millions of people all over the world. Early diagnosis of RA and prompt initiation of standard treatment has shown to improve prognosis and quality of life (1).
Patients with Rheumatoid arthritis apart from leading to irreversible joint damage and functional disability, have a two to five times increased risk of developing premature cardio-vascular disease that shortens life expectancy by five to ten years . It has been suggested that this excess mortality is mainly due to cardio-vascular disease (CVD) which accounts for nearly 50% of death causes (35-50%) (2,3).
Pooled analysis of many observational studies suggest an increase in risk of death in RA associated cardio-vascular disease (CVD) and that this has a prognosis comparable to that of triple-vessel Coronary Heart Disease (CHD) or stage 4 Hodgkin's disease (3). Intriguingly, most evidence suggests that classic cardio-vascular risk factors do not fully explain this excess vascular disease in RA (4, 5).

The risk of CVD associated with RA has been equalled to that of Type 2 Diabetes mellitus. Hence, RA itself should be regarded as a strong independent cardio-vascular risk factor for which cardi-ovascular risk management, as in DM2, should be considered (6).

Peripheral arterial disease (PAD) is a term mainly used to refer to a manifestation of systemic atherosclerosis. Data across many studies support the finding of PAD cross-sectionaly relating to cardio-vascular morbidity and mortality independent of other adjusted risk factors. Patients with PAD have a 15–30% five year mortality rate and a two to six fold increased risk of death from coronary heart disease. Mortality being highest in those with more severe PAD (7).

Recognition of PAD in clinical practice is important since it identifies patients at high risk of subsequent cardio-vascular and cerebro-vascular events and elicits symptoms of PAD which may be associated with functional disability and limb loss (9).

Detection of Ankle Brachial Index (ABI) is a standardised, non-invasive, simple reproducible and cost-effective method for detection of Peripheral Arterial disease and provides objective data both for the diagnosis and monitoring of efficacy of therapeutic interventions. American College of Cardiology 2005 guidelines state that the initial responsibility for the detection of PAD should be with primary-care providers, who are best positioned to determine an at-risk population and to initiate cardio-vascular risk reduction therapies (9).

Despite recent interest in cardio-vascular disease in Rheumatoid arthritis, the peripheral arteries have been understudied. Central atherosclerosis has been extensively proven especially using the carotid intima media thickness studies (CIMT) (10). Few studies done have documented an increased prevalence of impaired peripheral artery function in RA patients. Peripheral arterial disease is not most common recognised clinically in Rheumatoid arthritis, perhaps because the sedentary life caused by musculoskeletal impairment may not favour exercise induced ischaemic symptoms. Pain symptoms may also be mistaken for osteoarticular pain (11,12).

## MATERIALS AND METHODS

We performed a cros-sectional analysis of data collected from Rheumatoid arthritis patients attending the rheumatology clinic at the Kenyatta National Hospital. Our institutional review board approved the study and all patients gave written, informed consent to participate in the study. From December 2010 to March 2011, we enrolled consecutive patients who met the 1987 American college of rheumatology RA classification criteria and confirmed by consultant rheumatologist at time of diagnosis. The principal investigator reviewed the medical records and administered the questionnaire. We ascertained age, sex, marital status, residence, education level and employment status all by self-report. We recorded dates of symptom onset and diagnosis of RA, history of chronic illness and confirmed these by the medical records. The principal investigator trained in examination techniques assessed for presence of pulses, abdominal and carotid bruits and performed Ankle Brachial Index(ABI) measurements.

We ascertained cardio-vascular risk factors as follows, diabetic if, self report of diabetes with supported records or use of hypoglycemic drugs with supporting file record of diabetes.

Or a fasting blood glucose of >7mmol or random blood glucose of >11.1mmol. Hypertension if known with supporting records or on treatment for hypertension with supporting records. Or a Systolic BP> 140 mmhg or Diastolic BP >90 mmhg (13). Dysplipidemia if the condition is self reported with evidence of record and or treatment for it. Or an abnormality in any of the sub-types of the measured lipid profiles and classified according to adult treatment panel III guidelines for management of serum lipids (14). Smoking status, current smokers if smoke at least 100 cigarettes in their lifetime and are still smoking or have quit within the preceding years.Formers smoker those who have smoked at least 100 cigarettes in their lifetime but quit smoking less than one year earlier and non smoker as those who have smoked less than 100 cigarettes in their lifetime or who have never smoked (15). Age as a cardio-vascular risk factor, men ≥ 45years, women ≥ 55 years. Patients duration of illness (from onset of symptoms – time of study) was classified as early Rheumatoid arthritis zero to five years, established Rheumatoid Arthritis less than five years. A measure of adult general functional status will be used to measure disease severity. The routine assessment of patient index data three (RAPID 3) subset of the health assessment questionnaire (HAQ) which comprises disability index, the visual analogue pain scale and the visual analogue scale patient global assessment of health was used (16). The total score (0-30) from the three dimensions measured in the RAPID 3 questionnaire were entered as the patients RAPID 3 cumulative score. A conversion table was used to simplify the patient's weighed RAPID three score and classify patients RA as near remission, low severity, moderate severity and high severity.

We assessed arterial function by means of the ankle–brachial index (ABI), also known as the ankle-to-arm systolic blood pressure ratio as described (17). We used a Doppler apparatus (model 841-A; Parks Medical Electronics, Aloha, OR) and a standard blood pressure cuff to detect the systolic blood pressure wave at the dorsalis pedis and posterior tibial arteries

on each lower limb. Thus, each patient could have up to four arterial measurements. We divided each lower limb artery systolic pressure by the average of the right and left brachial systolic pressures. The normal ABI lies between 0.91 and 1.30; ABI values ≤0.9 suggest the artery is obstructed, and ABI values ≥1.31 indicate incompressible vessels.

Intemittent claudication was recorded as present or absent according to patients response to the Edinburgh claudication questionnaire (18).

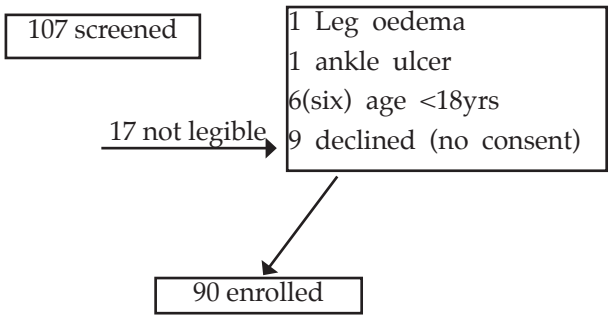
On the first contact patients five mililitres of blood was drawn from the anterior cubital fossa into a plain bottle (red cap) for lipid profiles and blood sugar measurements. The samples for the day were transported immediately to the Clinical medicine and Therapeutics laboratory. Non-haemolysed samples were centrifuged and the serum assayed with commercially available reagent kits. Erba spectrophotometer machine was used for both lipid profile and blood sugar assays. Results were printed out in strips, labelled and recorded in a book containing patient's names and study number. Results confidentiality was maintained at all times.

*Data handling and statistical analysis:* we entered all collected data and managed it in a Data pre-designed Microsoft excel database. Statistical analysis was done using statistical package for social scientists (SPSS) version 16.0. We calculated prevalence as: number of patients with PAD divided by patient total number and expressed as a percentage. Continuous data were presented as means, standard deviations, medians, proportions and frequencies. We performed univariate analysis for independent variables and presented them as proportions and frequencies. We carried out bivariate analysis using chi-square test to determine associations between PAD and each of the cardio-vascular risk factors.Multivariate analysis was used to determine independence of the significant risk factors and was carried out using binary logistic regression model. Associations were considered significant at a P-value ≤ 0.05. Odds ratios were calculated as a measure of risk magnitude. Data were presented using descriptive statistics and also using tables and bar graphs.

## RESULTS

In this four month study (December 2010 and 31st March 2011) targeting all the registered RA patients attending the KNH Rheumatology clinic, One hundred and seven patients confirmed to have rheumatoid arthritis from documentation in the file (ACR criteria and confirmed by a Rheumatologist) were consecutively screened for recruitment. Seventeen patients were not eligible for the study. Ten patients declined to be in the study, the main reason given was unwillingness to have blood drawn for laboratory tests (Figure 1).

**Figure 1**
*Enrolment flow chart*



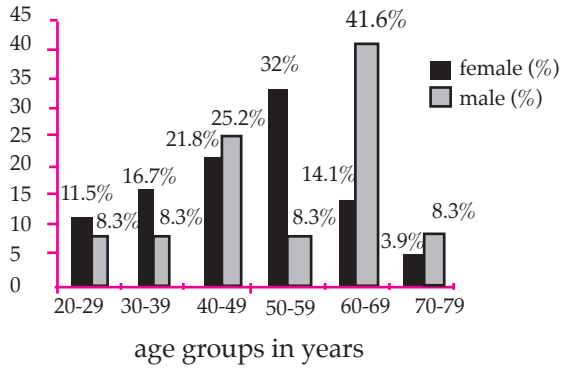

D*emographic characteristics of the study population:* The mean age of the patients was 48years median age 50 years and the age range 18 - 79 years. Most of the study participants were female 78 (86.7%) giving a female: male ratio of 6.5:1. The male patients (mean age 53 years SD 17) were on average older than their female (mean age 47 years SD14) counterparts, but this was not statistically significant (p = 0.22) (Table1).

**Table 1**
*Demographic characteristics of study participants*
*Demographic features*

| Age in years | | N(%) |
|---|---|---|
| | 18-29 years | 10 (11) |
| | >29-39 years | 14(16) |
| | >39-49 years | 20 (22) |
| | >49-59 years | 26(29) |
| | >59-69 years | 16(18) |
| | >69-79 years | 4(4) |
| Mean | 48 | SD(14 |
| Gender | Male | 12(13.3) |
| | Female | 78(86.7) |
| | Male mean age | 53 SD(17) |
| | Female mean age | 47 SD(14) |
| Residence | Nairobi | 34(38.7) |
| | Outskirts of Nairobi (central, eastern) | 33(35.2) |
| | Distant from Nairobi | 23(26.1) |
| Employment Status | Employed | 53(59) |
| | Unemployed | 37(41) |

The patients were grouped into ten year age categories. The peak age bracket for the patients was 50-59 years. The peak female age was 50-59years which was decade earlier than that for males. Females were more predominant in the younger age groups of 18-39years while males predominated in the older group between 40-69 years (Figure 2).

**Figure 2**
*Age by Gender distribution of study population*




*Peripheral arterial disease:* All the 90 study patients underwent successful ABI measurement among them ,twenty three had ABI of <0.9 computing for a PAD prevalence of 25.6% (95% CI, 17.2–36.1).

The mean age of PAD patients was higher than that of their non PAD counterparts 56(±12) yrs versus 45 (±14): p = 0.001.Twelve (12) of the study participants were men and more than half of them had PAD 7(58.3%), while PAD affected only 28.2% of the females study participants, gender prevalence difference in PAD was statistically significant: p= 0.005.

All the patients were classified into categories based on PAD severity. Among the twenty three patients with PAD, majority had mild disease 21(91.3%); none of the patients had severe PAD.

**Table 2**
*PAD severity by ABI classification*

| | | Count (%) |
|---|---|---|
| ABI | <=0.4 severe PAD | 0 (0) |
| | 0.41-0.7 moderate PAD | 2 (2.2) |
| | 0.71-0.9 mild PAD | 21 (23.3) |
| | 0.91-1.3 normal | 67 (74.4) |
| | >1.3 non compressible | 0 (0) |
| | Total | 90 (100) |

*Clinical characteristics of the study population:* Half the patients had established rheumatoid arthritis, while majority (87%) of patents with obstructed vessels had established RA. More than one third (40%) of the studied patients were found to be hypertensive while two thirds (61%) of those with abnormal vessels on ABI were hypertensive. Those found to be diabetic (14%) were almost equally distributed among those with normal and abnormal vessels (1:1.1). Only seven (8%) of the patients were tobacco smokers and again they were almost equally distributed in the group with normal vessels (4) and those with obstructed vessels (3). Majority of the patients were had dyslipidemia (74%) and this large proportion was reflected both in those with normal and abnormal vessels. The most common pattern was hypercholesterolemia among those with obstructed vessels and low HDL among those with normal vessels. One third (30%) of the studied patients were at cardio-vascular risk by virtue of age, this consisted of 58% of the studied male patients and only 29% of the studied female patients. Among the male patients at risk age, only one of them was found to have normal vessels on ABI measurement. On average the studied patients had moderately severe RA. This moderate disease severity pattern was also elicited among each of the two patient groups. On an individual count basis only three (13%) of the patients with PAD had RA of low severity, while almost half (48%) of those with no PAD were found to have RA of low severity (Table 3).

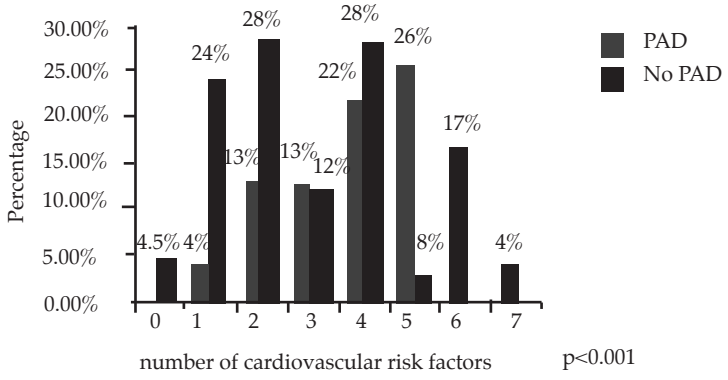
**Table 3**
*Clinical characteristics of study subjects*

| | All patients | Ankle Brachial Index <0.9(obstructed) | 0.9–1.3 (normal) |
|---|---|---|---|
| No of patients | 90 | 23 | 67 |
| Duration of rheumatoid arthritis | | | |
| Mean duration of RA | 8(±6) | 11(±4) | 5(±6) |
| > 5years -established disease | 46(51) | 20(87) | 26(39) |
| Hypertension | 36(40) | 14(61) | 22(33) |
| Diabetes | 13(14) | 6(26) | 7(10) |
| Dyslipidemia | 67(74) | 17(74) | 50(75) |
| Hypercholesterolemia | 29(43) | 10(59) | 19(38) |
| Hypertriglycerenemia | 29(43) | 7(41) | 21(42) |
| Low HDL | 28(42) | 6(35) | 22(44) |
| Smoking | 7(8) | 3(13) | 4(6) |
| Cardiovascular risk age ( > 45 years Male >55years female) | | | |
| Male | 7(8) | 6(26) | 1(2) |
| Female | 22(24) | 8(35) | 14(21) |
| Rheumatoid arthritis severity score(Rapid 3) | | | |
| Moderate- highly severe disease | 56 (62) | 20 (87) | 36 (64) |
| Mean score (interpreted score) | 9.1(moderate disease) | 12.1(moderate) | 8 (moderate) |
| ABI<0.9 | | 23(25.6%) | |
| Mean age | | 56(±12)* | 45(±14) |
| Males | | 7(30) | **5(7) |
| Intermittent claudication | | 13(52) | 12(48) |

Values are number(percentage) unless otherwise indicated
* P=0.001 versus normal ABI
**P=0.005 versus females with PAD

*Number of cardio-vascular risk factors per patient:* There was a step wise rise in the number of patients with PAD with the cumulative increase in number of CV risk factors. There was no PAD patient with zero CV risk factors. A large proportion (82%) of PAD patients each had ≥3 risk factors. When number of risk factors was compared between the two groups, there was statistical significance (p= <0.0001) (Figure 3).

**Figure 3**
*Number of CV risk factors in PAD and Non PAD patients*



*PAD risk association:* As a measure of association between PAD and the cardio-vascular risk factors, bivariate analysis using Chi-square test was carried out. Odds ratios were calculated as a measure of risk magnitude of getting PAD when exposed to the risk factors. The likelihood of getting PAD when exposed to the cardio-vascular risk factors of interest was more than two fold for each risk factor except for dyslipidaemia. Statistical significance was however obtained in only three of the risk factors namely mod-severe RA, established RA, and risk age (Table 4).

**Table 4**
*PAD and Cardiovascular risk factor association*

| Risk factor | Odds ratio(95% CI) | P-value |
|---|---|---|
| Risk age/not at risk age ( ≥45 male ≥55 female) | 5.4(1.9-14.9) | 0.001 |
| Established/ early rheumatoid arthritis | 10.5(2.8-38.9) | <0.0001 |
| Mod-high/ low rheumatoid arthritis severity | 5.7(1.6-21.2) | 0.005 |
| Dyslipidemia/no dyslipidemia | 0.96(0.4- 3.1) | 0.946 |
| Hypertension/no hypertension | 3.3(0.9-6.6) | 0.074 |
| Diabetes/ no diabetes | 3.0(0.9-10.2) | 0.066 |
| Cigarette smoking/no cig. Smoking | 4.9(0.8-31.3) | 0.069 |

Multivariate analysis using binary logistic regression model was carried out to determine risk factors independently associated with the presence of PAD among those that were significant at bivariate analysis (Table 4). The three factors retained statistical significance as follows age (p = 0.04), Established disease (> five years disease duration) (p = 0.001) and moderate-severe disease severity (p= 0.013) (Table 5).

**Table 5**
*Multivariate analysis for risk age, disease severity and disease duration*

| Variable | OR (95% CI) | P-value |
|---|---|---|
| Risk age | 3.3 (1.0 - 10.9) | 0.047 |
| Established RA(>5yrs) | 9.9 (2.5 – 40.1) | 0.001 |
| RA Severity (moderate–severe) | 6.2 (1.5-25.8) | 0.013 |

*Symptomatic PAD*: All 90 study participants were subjected to the Edinburgh claudication Questionnaire, 27.8% (95% CI 18.9-38.2) of them were found to have symptoms consistent with intermittent claudication. Half (52%) of those who exhibited symptoms of intermittent claudication were found to have PAD by virtue of an abnormal ABI. Presence of intermittent claudication was associated with up to a five fold risk of getting PAD using ABI measurement and this was of statistical significance (p= < 0.0001).

Intermittent claudication when measured using the Edinburgh questionnaire was found to be 56.5% sensitive and 82% specific in determining presence of ABI diagnosed PAD in RA patients (Table 6).

**Table 6**
*Intermittent Claudication and ABI association*

| Intermittent Claudication by Edinburgh questionnaire | Abnormal ABI (PAD) n (%) | Normal ABI (No PAD) n (%) | Total | P-value | OR(95%CI) |
|---|---|---|---|---|---|
| Yes | 13(52) | 12(48) | 25 | <0.0001 | 5.9(2.1-16.8) |
| No | 10(15) | 55(85) | 65 | | |
| Total | 23 | 67 | 90 | | |

## DISCUSSION

RA is a chronic systemic inflammatory disease which has also been associated with excess cardio-vascular morbidity and mortality. Information on the prevalence of cardio-vascular disease in rheumatoid arthritis locally is unavailable.

In this study we sought evidence of peripheral atherosclerosis by ankle brachial index in RA patients. Using the technique of measuring ABI as a marker of atherosclerotic burden and a strong predictor of cardio-vascular morbidity and mortality. This is the first study of this nature done locally in this group of patients.

From our results we found a young study population of mean age 48 years of whom over two thirds were women. Our results showed a significant proportion (25% prevalence) of PAD mainly comprising of mild disease. Our PAD population was found to be significantly older, have had RA for a longer duration and to have had more severe disease as compared to their non PAD counterparts and the same three factors were found to be independently associated with PAD.

The number of patients with rheumatoid arthritis attending KNH MOPC seems to have significantly increased over the years. While in this study we were able to enrol 90 patients over a period of three months, Bagg *et al* (19) was only able to see 76 patients over 18 months in 1979. Owino *et al* was able to see 60 patients within a period of six months at KNH MOPC (20). This increase could possibly be attributed to increased awareness of the disease, improved referral systems in the country and establishment of a rheumatology clinic at Kenyatta National Hospital in 2010. The more recent worldwide trends in RA incidence are not well known, however the incidence and prevalence of RA in populations has been noted to vary substantially between geographical areas and over time (21).

In this study, females were 83.7% and the male to female ratio 1:6.5. This female gender preponderance has also been found in non local studies and confirms previous observation of the same. The mean age of male patients in our population 53(±17) years was higher than that of female patients 47 (±14) this age differences though not statistically significant coincides with what has been shown regarding the disease pattern affecting females at a younger age than males.

The mean age of our patients 48(±14) years was similar to that observed in an earlier local study by Kirui (22) (44.7 years) who in 2008-2009 identified traditional cardio-vascular risk factors in RA patients. The age characteristics found in these local studies was however younger compared to that recorded in a study of 353 RA patients in a Netherlands study comparing RA and diabetes as cardio-vascular risks (mean age of 63 years) (6). The difference could probably be explained by better health seeking behaviour of the elderly accompanied by better quality of health care systems and also a generally higher life expectancy all seen in these western countries. A racial difference could also explain this difference in age since a similar younger age group in black patients have been recorded in Nigeria by Adebajo when he compared the pattern of RA in west Africans with that of a cohort of British patients (23). This could be a pointer showing blacks get rheumatoid arthritis at an early and productive age group and thus more aggressive treatment needed.

The PAD prevalence amongst RA patients in this study was 25.5%. This finding is similar to a study in Texas by I Del Rincon *et al* who examined lower limb arteries in age and sex matched (median age 59 years) non smoking subjects with and without rheumatoid arthritis. They found 19% of the rheumatoid arthritis patients to have abnormal arteries by virtue of abnormal ABI (11). Another study with prevalence comparable to ours, was evaluating the association of bone cortical thickness to ABI involving 588 RA patients, 28% of the patients were found to have abnormal ABI (12).

Peripheral arteries in general are understudied and the same applies in rheumatoid arthritis. Our patient population has shown significant amount of peripheral arterial disease which in turn goes to show the high risk of cardio-vascular events faced by our patients which should put all clinicians on high alert for.

The comparability of our prevalence to that of the UK and USA RA populations may mean that PAD in RA may not be related to factors such as race, climate, feeding habits and poverty but to the disease related factors.

Local studies looking for PAD in other diseases found a much less PAD prevalence, Maritim *et al* in 2006 studied CKD patients, 80% of whom had advanced CKD (stage ≥3) (24). They found a PAD prevalence of 11.9%, mainly comprising of mild and moderate disease. Mugambi *et al* found a 12% prevalence of PAD when they set out to stratify patients with diabetes into risk categories for foot ulceration (25). Our study could therefore probably suggest that RA carries an almost double risk of peripheral vascular disease and thus cardio-vascular morbidity as compared to other diseases known to have high cardio-vascular risk. However ABI measurements in age- and -sex matched patients in various disease categories would be ideal to study for further comparison.

Caro *et al* embarked on estimating the burden of cardio-vascular risk in terms of mortality and morbidity in patients with PAD (26). They found the PAD crude five year death rate stood at 33.2 % (26.6% for index myocardial infarction; 41.8% for index stroke). This translated to our patients would mean

25.5% of our rheumatoid arthritis patients could have an estimated five year death rate of 33.2% secondary to cardiovascular events.

Our study differs from that of the USA based rheumatoid arthritis PAD studies in that our study had a sample size much smaller, period of study was much shorter and a younger patient population (11,12). However, prevalence as is known may not be affected by these factors. PAD has however been shown to be more prevalent in the black race compared to the whites (27). This racial factor could have confounded our finding of a high PAD burden. Rheumatoid arthritis still stands out as an additional and major risk factor since local PAD studies in blacks without rheumatoid arthritis patients have not recorded such high burden of disease

Correlations have been made between PAD severity and patient morbidity and mortality. Majority of our patients with PAD (91.3%) were found to have mild vascular obstruction, none of them had severe obstruction. Other studies have however recorded more severe PAD in their RA patients. Roldán JF *et al* found 10% of their study population to have severe disease (12). These patients were older and had a higher percentage of cigarette smokers which could probably explain the finding of more severe disease.

The cumulative survival after five years among our patients with mild disease is expected to be about 91%. That is 9% of these patients could have a cardio-vascular death or suffer a cardio-vascular related morbidity if deduced from the finding of Sikkink *et al* in determining the relationship between ABI and morbidity /mortality in patients with PAD (28).

In this study we set out to find if specific (those demonstrated in previous studies) cardio-vascular risk factors are associated with PAD in rheumatoid arthritis. Detailed literature search has however revealed that both traditional and novel cardio-vascular risk factors and disease-related mechanisms contribute to the RA atherosclerosis but the disease induced systemic inflammation is the major determinant of the RA vascular co-morbidity.

A local study in 2008 by Kirui demonstrated a significant burden of cardio-vascular risk factors in rheumatoid arthritis patients; he found 87% of patients had traditional cardio-vascular risk factors (22).

We analysed age, duration of disease, severity of disease, hypertension, dyslipidemia, diabetes and cigarette smoking. Each of these factors was demonstrated in our patients. Most (82%) of the PAD patients had more than three of these risk factors and there was statistical significance ($p<0.001$) in comparing PAD verses non PAD patients in terms of number of cardiovascular risk factors. This is a pointer of that these risk factors increase the chance of patients developing PAD.

On analysis of association, significant odds ratios were found in all risk factors except dyslipidaemia with the rest holding an equal or more than double risk of getting PAD. On multivariate analysis only cardio-vascular risk age ($p=0.047$), duration of RA disease ($p=0.001$) and disease severity of RA ($p=0.013$) were found to be independently associated with PAD in our study.

The independence that we found in the above three factors goes to indicate that the increased arterial obstruction in our patients reflects the cumulative inflammatory disease process that is occurring in our patients. Our findings are similar to that proven in other studies. Fietta, P., *et al* found in their detailed search of the available literature that atherosclerosis is a common finding in RA patients and positively correlates with disease duration and severity (4).

As a measure of disease severity we used the three dimensional routine assessment of patient index data three (RAPID 3) questionnaire was used. RAPID 3 is a time saving validated tool, a sub-set of the widely known five dimensional Health assessment questionnaire (HAQ) (16). This is the first time RAPID 3 has been used in a study of this kind and has shown similar results to that of JK Alkaabi *et al* who showed patients with ABI < 1.0 to have higher HAQ scores (more severe disease) compared with normal ABI (29).

Age as a cardio-vascular risk factor was independently associated with PAD in this study. Majority (67%) of our studied patients were not at cardio-vascular risk by virtue of age, however among those with PAD a significant two thirds (60.8%) were at enhanced risk by age. The prevalence of PAD increases with age: longevity also increases risk of cardio-vascular morbidity all as shown in the Framingham's heart study. Our patients are thus facing a triple edged sword (age, longevity and RA) with risks for PAD and cardio-vascular mortality. Our study results also concurred with a study conducted in Spain which showed older age and disease duration as the best predictive factors for severe morphologic expression of atherosclerotic disease in RA patients (5).

The Quest RA study multivariate models found hypertension, dyslipidaemia, diabetes and smoking as independent factors associated with cardio-vascular morbidity and mortality (30). As much as these factors have also been found to be strong risk factors of PAD, our study found no independent association between these three risk factors and PAD in rheumatoid arthritis patients. This apparent lack of association could be due to the fact that we had a small sample size and the number of patients with each of these risk factors was almost equally distributed among the PAD and the non PAD group, of note is that we did not calculate LDL levels since the lipid profiles obtained were spot and not fasting

and this is known to affect triglyceride levels. The studied population was also relatively young and also this being a descriptive study was possibly not sufficiently powered to assess traditional risk factors and associations. Our findings are also not surprising since a literature search reveals association but no any strong independence between these three risk factors and PAD in rheumatoid arthritis patients (11,31).

Accumulating clinical and epidemiological evidence suggests that the atherogenetic cardio-vascular mortality and morbidity associated with RA is due to disease specific factors, rather than to ascertainment bias or to con-founders such as traditional cardio-vascular risk factors (4).

Both asymptomatic and symptomatic peripheral arterial disease have been found to be consistent and powerful independent predictors of coronary and cerebrovascular events and mortality. Using the Edinburgh Claudication questionnaire (18) we found 56% of our PAD patients exhibited a clinical picture compatible with intermittent claudication. On further analysis , intermittent claudication was found to be a predictor of abnormal ABI ($p \leq 0.001$).

If symptoms alone were to be used, a diagnosis of PAD could have been missed in 44% of the PAD patients diagnosed by ABI, this finding goes further to prove what has been documented before that in general, less than 20% of PAD patients are symptomatic; this makes symptoms not a useful tool in excluding PAD and also that the available intermittent claudication questionnaires have a low degree of sensitivity and therefore might tend to underestimate the true prevalence of intermittent claudication (18).

Our patients however recorded a relatively high prevalence of intermittent claudication and this might have been confouded by the osteoarticular pain symptoms and painful neuropathy of multiple causes among rheumatoid arthritis patients being mistaken for intermittent claudication, hence the symptom of calf pain might not be a useful aspect to rely on in this patient population.

We have documented a significant prevalence of impaired peripheral artery function in this sample of patients with rheumatoid arthritis. These findings are in line with existing evidence that patients with RA are prone to central and peripheral atherosclerosis.

We used the ABI, a simple, reliable and validated non-invasive technique, to assess the function of the lower limb arteries.

The increased frequency of arterial impairment that we have encountered in this rheumatoid arthritis group is apparently not explained for by most traditional cardiovascular risk factors. The associated factors that we have found could means that the patient with most severe rheumatoid arthritis and longer disease duration is more prone to occlusive atherosclerotic process. Thus our findings suggest that arterial impairments occur in patients with the greatest level of accumulated systemic inflammation. This supports a pathogenic role of systemic inflammation in atherosclerosis.

One strength of the study is that we studied all the RA patients registered in the clinic at this point in time and that this RA cohort was a good representation of the RA population in the country, since patients Nairobi and outside Nairobi were well represented. The results of this study are thus unlikely to be explained by selection bias.

Our data has extended earlier work in different fronts. This PAD finding is novel in that unlike in the western countries it has not been described before in RA patients locally and in Africa as a whole. In 2009 cardio-vascular risk factors were described in RA patients; we have now gone ahead and shown presence of PAD (a cardio-vascular disease).

In conclusion, we set out to find the prevalence of PAD among our RA patients; we found a high prevalence (25%) which consisted mainly of mild PAD. PAD in this population was associated with age, duration of RA and severity of RA. Intermittent claudication as a symptom of PAD was only elicited among half (50%) of those RA patients who PAD. All clinicians should be alerted to look at rheumatoid arthritis patients as having a high cardio-vascular risk illness. Rheumatoid arthritis patients require early and aggressive management to reduce the risk of development of cardio-vascular disease. Those with chronic disease and severe disease are the most deserving of attention for symptoms and signs of atherosclerotic cardio-vascular disease.

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