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Cardiovascular Risk Burden in Sub-Saharan Africans with Rheumatoid Arthritis: A Hospital-Based Study in Yaounde, Cameroon

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Abstract

Introduction: Studies on RA (rheumatoid arthritis) and cardiovascular risk in African countries are scarce. Objective: To investigate the relationship between RA and cardiovascular risk in Cameroonian patients. Methodology: In 50 Black RA patients and 51 matched healthy individuals from the general population, we studied cardiovascular risk factors validated by the WHO. Cardiovascular risks estimates were carried out using WHO risk charts for the African region. Epi-info, R and SPPS were used for the statistical analysis. Results: Overall and abdominal adiposity as expressed by increased body mass index and abdominal obesity, were all markedly increased in RA patients compared to non-RA subjects [70% vs. 47%, OR (95% CI) = 2.62 (1.16 - 5.94), p = 0.026; and 54% vs. 33%, OR (95% CI) = 2.34 (1.05 - 5.25), p = 0.045 respectively]. RA patients were more physically inactive than their non-RA counterparts (20% vs. 0, p = 0.001). Whereas RA was associated with a reduced odds of alcoholism [OR (95% CI) = 0.19 (0.06 - 0.62), p = 0.005]. Increased BMI seemed to occur independently of methotrexate (p = 0.76), hydroxychloroquine (p = 0.59), corticosteroids (p = 0.79) treatments, and independently of sex (p = 0.15), age (p = 0.67), and sedentary lifestyle (p = 0.16) in RA patients; but their BMI was weakly correlated with disease duration (r = 0.26; p = 0.074). Meanwhile, male gender was associated with a reduced odds of abdominal obesity [OR (95% CI) = 0.02 (0 - 0.4), p = 0.011]. Cardiovascular risk, comparable by proportions between RA and non-RA subjects, was low in 26 patients (78.8%) and 30 non-RA subjects (83.3%) respectively. Conclusion: Despite the high adiposity burden and a sedentary lifestyle experienced by RA patients compared to their healthy counterparts, RA was not associated with cardiovascular risk as estimated by WHO risk charts.

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Keywords

Rheumatoid Arthritis, Excess Adiposity, Physical Inactivity, Cardiovascular Risk, World Health Organization Risk Charts

1. Introduction

Rheumatoid Arthritis (RA) is a disabling systemic autoimmune disease that affects 0.24% of the world's population. The prevalence is estimated to be around 0.42% in Africa [1] [2]. The advent of effective immunomodulator treatments has reduced mortality in these patients in the past decade [3] [4]. However, mortality attributed to RA remains high compared to the general population [3]. This is closely related with the presence of comorbidities such as: infections, cancers, osteoporosis, and cardiovascular diseases (CVD) [4]. RA is increasingly being reported as an independent cardiovascular risk factor in temperate regions [5]-[11]. The reasons for implemented cardiovascular risk in RA patients are postulated to be linked with both traditional risk factors and chronic inflammation, and potentially to medications including non-steroidal anti-inflammatory drugs, corticosteroids and disease-modifying antirheumatic drugs [12]-[14]. Among traditional cardiovascular risk factors, hypertension, type 2 diabetes mellitus, dyslipidemia, smoking and obesity appear to significantly impact on the cardiovascular disease (CVD) burden in RA [12] [13]. Most importantly, chronic inflammation and immune activation (expressed by high serologic inflammatory biomarkers e.g. C-reactive protein) are crucial for the occurrence and worsening of CVD in the RA population [15]. Although ~80% of CVD now occurs in low- and middle-income countries including Sub-Saharan Africa, there are astonishingly few reports addressing the relationship between CVD and RA which remains debatable with potentially different predictors in Black Africans as compared to western population. Notably, Kirui *et al.* found hypertension as the only cardiovascular risk factor associated with RA in a Kenyan cross-sectional comparative study [16]. Similarly, a recent review summarizing evidence from South African Black RA patients reported no association between traditional risk factors and RA, despite an overall increased atherosclerotic burden [17]. Furthermore, adipokines and reduced kidney function were demonstrated to be associated with atherosclerosis in Black south African RA population, whereas, traditional risk factors were the main determinants for CVD in the White RA patients [17] [18]. Taken collectively, studies are still largely warranted to precise the putative link between CVD and RA across Sub-Saharan African countries. This work aimed to study the relationship between cardiovascular risks and RA in Cameroonian patients using the World Health Organization (WHO) and International Society for Hypertension (ISH) risk charts.

2. Methodology

This was a cross sectional comparative study. RA patients aged 18 years and above, followed up in the rheumatology unit of the Yaounde Central Hospital between January 2004 and December 2014, and who gave informed consent to participate in the study were recruited from December 2013 to April 2014. The diagnosis of RA was based on ACR and/or ACR/EULAR diagnostic criteria [19] [20]. We excluded patients with mixed connective tissue disease, Human Immunodeficiency Virusinfection, hereditary dyslipidemia, chronic kidney disease, and any other active chronic inflammatory disease. Non-RA subjects were clinically healthy volunteers recruited from the community at the same time as the non-RA subjects. They were matched for sex, age, and race. Pregnant women were excluded from both groups. As it was a preliminary study, a convenient non probabilistic sampling was used. Demographic, clinical, and biological data were obtained on the same visit, during which each participant underwent a complete clinical examination (history and physical examination), and blood drawn after a fast of at least 12 hours. Blood pressure was measured with a clinically validated electronic device (Magnien B1) [21], with the cuff applied to the mid left arm, in the sitting position, after at least five minutes of rest, and no tobacco use prior to the measurements. The average of at least two blood pressure measurements was recorded. Hypertension was defined by as a systolic blood pressure $\geq$ 140 and/or a diastolic blood pressure $\geq$ 90 mmHg [22]. Body weight (kg), was measured with a mechanical scale balance (precision $\pm$ 0.5 kg) in participants barefoot, and lightly dressed. Height (m) was measured with a locally made stadiometer. Body Mass Index (BMI) was calculated using Quetelet's indices and excess adiposity was defined by BMI $\geq$ 25 kg/m^2 [23]. Waist circumference was measured with a meter tape midway between the lower border of the twelfth rib and

the antero-superior iliac spine. Abdominal obesity was defined as waist circumference ≥ 102 cm in men, and ≥ 88 cm in women [23]. Blood was drawn by venous puncture in the forearm crease after strict asepsis. Seven milliliters of this was collected in a dry tube and three milliliters in a fluorinated tube for each participant. The tubes were immediately sent to the biochemistry laboratory of the Yaounde University Teaching Hospital, and analyzed the same day for blood glucose, serum cholesterol, and uric acid.

Cardiovascular risk factors studied were those described in the literature and validated by the WHO [22]-[25]. Cardiovascular risks estimates were carried obtained from WHO/ISH charts appropriate for the Cameroonian general population [24]. These charts provide an estimate of the individual risk of cardiovascular events for the upcoming 10 years stratifying by diabetic/non Diabetic status. Further elements considered when assessing the cardiovascular risk with these charts are the sex, age (49 - 79 years) tobacco smoking status, as well as systolic blood pressure and blood cholesterol values. Accordingly, each subject fits into one of the five risk categories: low (<10%), moderate (10% to <20%), medium (20% to <30%), high (30% to 40%) and very high (≥40%) [24].

Statistical softwares used were; Epi-info version 7, SPSS version 18, and R version 3.0.1. Quantitative variables were studied using Student t test, and qualitative variables using chi square test and Fischer exact test when appropriate for the circumstances. Binary logistic regression was used to assess the main cardiovascular risk factors, with candidate predictors being: methotrexate, corticosteroids, hydroxychloroquine, male sex, advanced age (≥55 years in men, and ≥65 years in women), and sedentarity. A p-value < 0.05 was considered statistically significant.

Authorizations to recruit participants and manipulate blood samples were obtained from the hospital administrations of the Yaounde Central and University Teaching Hospitals respectively. Ethical clearance was obtained from the Institutional Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I. Signed informed consent was obtained for each participant in accordance with the Helsinki declarations.

3. Results

In all, 50 RA patients and 51 non-RA subjects were studied. The mean age was 51 ± 14.8 years for RA patients and 51.2 ± 15.3 years for non-RA subjects, p = 0.916. Their clinical characteristics are shown in **Table 1**.

Amongst the cardiovascular risk factors noted (**Table 2**), clinical markers of adiposity including BMI ≥ 25 kg/m^2 and abdominal obesity were respectively seen in 70% of RA patients and 47% of non-RA subjects [OR (95% CI): 2.62 (1.16 - 5.94)], and 54% of RA patients and 33% of non-RA subjects [OR (95% CI): 2.34 (1.05 - 5.25)]. Binary logistic regression analysis showed that high BMI was independent to age (p = 0.67), sex (p = 0.15), sedentarity (p = 0.16) and use of methotrexate (p = 0.76), hydroxychloroquine (p = 0.59), and corticosteroids (p = 0.79) treatments in RA patients (**Table 3**). Still, a correlation was observed between high BMI and duration of the disease in these patients (r = 0.26; p = 0.074). Furthermore, male sex was not associated with risk of abdominal obesity (p = 0.011) in RA-patients (**Table 4**).

Estimation of the cardiovascular risk using the WHO/ISH risk charts was possible in 33 RA patients and 36 non-RA subjects of both sexes aged between 40 - 79 years considering their diabetic/non diabetic status, their tobacco smoking status and their systolic blood pressure and blood cholesterol level. The 10-year risk was low in 26 RA patients (78.8%) and in 30 non-RA subjects (83.3%), moderate in three RA patients (9.1%) and three non-RA subjects (8.3%). High risk was noted in two RA patients (6.1%) and one non-RA patient (2.8%). Very high risk was seen in one RA patient (3%) and one non-RA subject (2.8%) (**Figure 1**). Rheumatoid arthritis was not associated with the cardiovascular risk.

4. Discussion

We studied the prevalence of traditional cardiovascular risk factors and assessed the cardiovascular risks in patients with RA, age and sex matched to non-RA subjects in a sub-Saharan urban central African setting. The results showed that markers of adiposity including BMI ≥ 25 kg/m^2 (p = 0.026) and abdominal obesity (p = 0.045) were more frequent in RA patients. Lombard *et al*. in a descriptive study reported the same findings involving heterogeneous population with RA [26]. This contrasted with that reported by Dessein *et al.* [27], in a black population in South Africa. This controversy could be explained by different characteristics of non-RA population. High cardiovascular risk participants were included in their non-RA group. More so, non-RA subjects had significantly higher markers of inflammation than their RA counterparts. These inflammatory markers can promote

Table 1. Demographic and clinical characteristics of the study population.

Characteristics	Rheumatoid arthritis		p-value
	Present	Absent	
Age (mean ± SD), Years	51.0 ± 14.8	51.2 ± 15.3	0.916
Sex			
-Females N (%)	39 (78)	39 (76.5)	0.855
-Males N (%)	11 (22)	12 (23.5)	
Duration* (mean ± SD), Years	9.84 ± 7.97	NA	
Comorbidity, N (%)	34 (68)	NA	
-Infections	29 (58)		
-PUD	16 (32)		
-Osteoarthris	1 (2)		
-Asthma	1 (2)		
-Cancer	1 (2)		
-Depression	1 (2)		
-Parkinson's disease	1 (2)		
Treatment of RA, N (%)		NA	
-Symptomatic treatment			
Corticosteroids	26 (52)		
NSAIDs	2 (4)		
-Specific treatment			
MTX	24 (48)		
HCQ	5 (10)		
AZT	2 (4)		
SSZ	1 (2)		
LEF	1 (2)		
-Without treatment	18 (36)		

SD: Standard Deviation; Duration*: Duration of evolution of disease; N: Number; PUD: Peptic Ulcer Disease; RA: Rheumatoid Arthritis; NSAIDs: Non-Steroidal Anti-Inflammatory Drugs; MTX: Methotrexate; HCQ: Hydroxychloroquine; AZT: Azathioprine; SSZ: Sulfasalazine; LEF: Leflunomide; NA: Not Applicable.

Table 2. Prevalence of cardiovascular risk factors in the study population.

Variables	Rheumatoid arthritis				OR	95% CI	p-value
	Present		Absent				
	N	(%)	N	(%)			
BMI ≥ 25 kg/m^2	35	70	24	47	2.62	1.16 - 5.94	0.026
Abdominal obesity	27	54	17	33	2.34	1.04 - 5.25	0.045
Hypertension	18	36	11	22	2.04	0.85 - 4.94	0.13
Hyperuricemia	8	16	5	10	1.75	0.53 - 5.78	0.39
Menopause	23	58	24	62	0.89	0.36 - 2.23	1.00
Metabolic syndrome	3	6	4	8	0.75	0.16 - 3.53	1.00
Dyslipidemia	25	50	30	59	0.7	0. 32 - 1.54	0.43
Alcohol misuse	4	8	16	31	0.19	0.06 - 0.62	0.005
Tobacco use	1	2	7	14	0.13	0.01 - 1.08	0.059
Sedentarity	10	20	-	-	NC	NC	0.001
Diabetes	5	10	-	-	NC NC	NC	0.056
CVA/TIA	3	6	-	-	NC	NC	0.12
Ischemic Heart Disease	1	2	-	-		NC	0.49

N: Number; OR: Odds Ratio; 95% CI: 95% Confidence Interval; BMI: Body Mass Index; WC: Waist Circumference; HC: Hip Circumference; HTN: Arterial Hypertension; NC: Not Calculable; CVA/TIA: Cerebro Vascular Accident/Transient Ischemic Attack.

Table 3. Eventual predictive factors of high BMI in RA patients.

	OR	95% CI	p*
MTX	1.24	0.31 - 4.96	0.76
HCQ	0.56	0.07 - 4.74	0.59
Corticosteroids	1.22	0.28 - 5.21	0.79
Age	1.52	0.23 - 10.2	0.67
Male sex	5.13	0.54 - 0,52	0.15
Sedentarity	4.9	48.33 - 45.98	0.16

OR: Odds Ratio; 95% CI: 95% Confidence Interval; p*: p-value; MTX: Methotrexate; HCQ: Hydroxychloroquine.

Table 4. Predictive factors of abdominal obesity in RA patients.

	OR	95% CI	p*
MTX	1.31	0.31 - 1.69	0.71
HCQ	1.47	0.12 - 2.92	0.76
Corticosteroids	1.27	0.28 - 1.75	0.76
Age	3.56	0.33 - 38.34	0.29
Male Sex	0.02	0 - 0.73	0.011
Sedentarity	7.14	0.4 - 69.39	0.09

OR: Odds Ratio; 95% CI: 95% Confidence Interval; p*: p-value; MTX: Methotrexate; HCQ: Hydroxychloroquine.

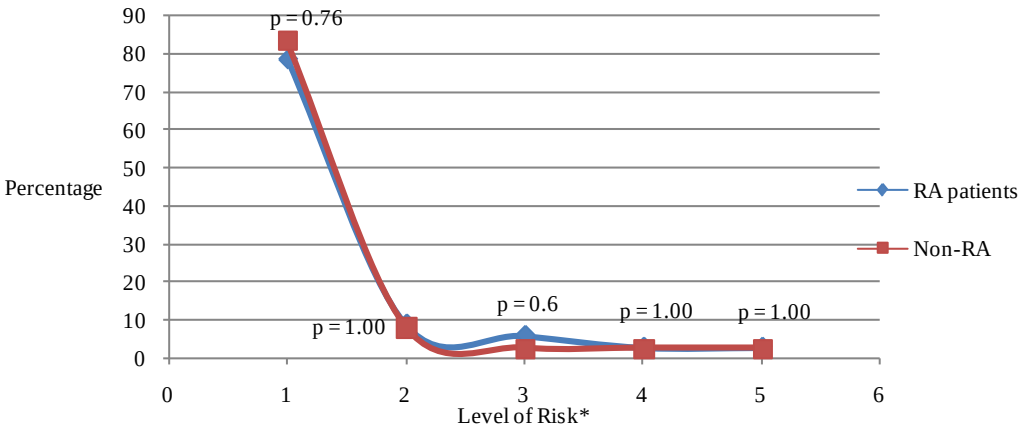

Figure 1. Cardiovascular risks of the study population; 1: <10%; 2: 10% to <20%; 3: 20% to <30%; 4: 30% to <40%; 5: ≥40%; *Risk estimated for 33 RA patients and 36 non-RA subjects.

the development of cardiovascular risk factors such as overweight and obesity [28]. We noted that increasing BMI weakly correlated with the duration of RA, independently of treatments of RA, age, sex, sedentarity and disease-specific treatments. Similar findings have been reported in a Moroccan study [29], and contrasts with that of the general population [30] [31]. However, it is possible that structural damages due to X-rays, rheumatoid factor, anti-CCP anti-bodies, and DAS 28 could also correlate with BMI values along with disease duration in these patients [29]. Furthermore, more than half of the RA patients had abdominal obesity. Female sex seemed to be a risk factor. Surprisingly [29], abdominal obesity occurred independently to treatments of RA, age, and physical inactivity. This suggests the possible interaction of both factors inherent to RA patients and RA-specific factors.

Sedentarity was significantly noted in 20% of RA patients (p = 0.001). Desse in *et al.* have also reported substantial reduction in weekly physical activities in South African Black RA patients [27]. Remarkably, patients present late with invalidating polyarthralgia in our settings [32] [33].

RA patients had a low cardiovascular risk, similarly to their non-RA counterparts. This low cardiovascular risk in RA patients based on general population calculators has already been reported by Crows on *et al.* [34]. Indeed, RA patients from their cohort had a low cardiovascular risk as calculated by the Framingham equation at baseline, contrasting with an increased cardiovascular risk eight years later at the end of the study. Similarly, Gomez-Vaquero *et al.* have reported a low cardiovascular risk in Spanish RA patients when using the SCORE (Systematic Coronary Risk Evaluation) and REGICOR (Framingham-Register GIRONI del COR) estimation methods [35].

Only markers of adiposity and prevalence of physical inactivity differed between RA patients and non-RA subjects. In the general population, excess adiposity reflected by high BMI and abdominal obesity were shown to be predictors of high cardiovascular mortality [30]. This linear relationship has not been fully elucidated in black Africans with RA [17]. Our findings, comparable with previous studies [17], present the later as obese RA subjects without necessarily having high cardiovascular risk. With respect to the literature, there is a link between overproduction of adipokines and alteration of cardiovascular risk in obese subjects. In black RA patients, Salmon *et al.* have reported some adipokines to be correlated with markers of atherosclerosis [17].

It is thus possible that cardiovascular risk in obese Black RA subjects is rather linked to adipokines but not to BMI, corollary to abdominal obesity that seems to be linked to endothelial activation, the initial step of atherosclerosis [17]. In this light, we can speculate that the WHO risk charts underestimated the cardiovascular risk in this population of patients with RA population, as was previously described with other evaluation tools of cardiovascular risk in the general population [18] [34]-[40]. This hypothesis could be verified in future studies where the cardiovascular risks will be estimated using the WHO risk charts and simultaneously compared to measured clinical markers of atherosclerosis (Carotid plaques, intima-media thickness of the carotid arteries). Meanwhile, methods for evaluation of the cardiovascular risks specific to Black Africans recently proposed by Solomon *et al.* [17] [18] could be more useful. They include the systematic Doppler ultrasound of the carotid arteries, use of biomarkers such as adipokines, intereukin-6 and kidney disease markers. These biomarkers could therefore be evaluated in subsequent prospective studies including Black RA patients, in view of incorporating these in specific risk equations, before making strong recommendations for their systematic use in Africans or Afro-Americans with RA populations. As an alternative, more accessible and validated biomarkers in Caucasian cohorts with RA like apolipoprotein-A1 could be measured [40]. However, risk equations specific to RA under development such as ATACC-RA, will permit in better classifying patients following an adapted stratum during follow up visits of RA in the near future [36].

This research has many drawbacks that could jeopardize definite conclusions. The small sample size and the cross-sectional nature do not allow us to make inferences of causality, nor to generalize the results. Lack of auto antibody study in the non-RA group could be a source of selection bias. The prevalence of past history of cardiovascular events could be wrongly estimated due to recall bias, despite the use of consecrated questionnaire for public use by WHO [23]. Still, we did not study the correlation between BMI and activity indices, Sharp score, and inflammatory markers, to completely elucidate the association between RA and high BMI. Beyond all those limits, findinds of this study are strengthened by the fact that most patients with established RA in Yaounde and its environs have likely been included in the study considering the rheumatology unit of the Yaounde Central Hospital as the lone rheumatology unit which centralizes the majority of RA patients from Yaounde. Besides, the non-RA subjects issued from the community were rigorously selected excluding all possible potential confounders. These contributed to data reliability.

5. Conclusion

Despite the excess adiposity burden and the high prevalence of sedentarity in RA patients, RA was not associated with cardiovascular risk as estimated by WHO risk charts. Prospective studies should be carried out on larger samples, so as to attain two main objectives: first of all, to evaluate the reliability of WHO cardiovascular risk predicting charts as against measured markers of atherosclerosis; then, to evaluate the relationship between specific markers and atherosclerosis, abdominal obesity and the different stages of atherosclerosis in RA patients. Along with this, we would better predict cardiovascular risk in Black African RA patients in the future.

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