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Cardiovascular Disease Risk Associated to Chronic Inflammatory Rheumatic Diseases in Patients Seen in Rheumatology Unit in Yaounde, Cameroon

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Abstract

Introduction: Even though there is a huge burden of both chronic inflammatory rheumatic diseases (CIRD) and cardiovascular diseases in Sub-Saharan Africa, no published study from this region has yet addressed the issue of cardiovascular diseases in a group including different CIRD to the best of our knowledge. Objective: We conducted this research with the aim to explore the association between CIRD and cardiovascular risk in a Cameroonian population based on the World Health Organization (WHO) and International Society for Hypertension (ISH) risk charts. Methods: This cross-sectional study included CIRD patients, followed at the rheumatology unit of the Yaounde Central Hospital, and, who were matched to non-CIRD subjects for sex, age and race. Cardiovascular risk factors were studied and subsequently the cardiovascular risk was estimated using the WHO/ISH risk charts. Analyses were performed in Epi-info and SPSS software and results were considered statistically significant for a p-value less than 0.05. Results: In total, 109 CIRD patients and 111 non-CIRD subjects were included. Their respective mean ages were 44.4 ± 15.2 years and 44.2 ± 15.1 years. Odds ratio 2.09, 95% confidence interval (CI) (1.07 - 4.08); high BMI OR 1.89, 95% CI (1.1 - 3.24); diabetes mellitus (p = 0.03) and physical inactivity (p < 0.001) were all markedly found in CIRD patients compared with controls. Ten (9.2%) CIRD patients had a past history of atherosclerotic cardiovascular events compared with no control (p < 0.001). The cardiovascular

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risk estimated with the WHO/ISH risk charts was low in 43 (79.6%) patients with CIRD versus 52 (88.1%) non-CIRD subjects. Conclusions: CIRD were associated with hypertension, excess overall adiposity, diabetes mellitus, and physical inactivity. A substantially increased proportion of CIRD patients with a past history of atherosclerotic cardiovascular events were noted. But the WHO/ISH risk charts broadly found a similar and globally decremented cardiovascular risk in both study groups, highlighting the need to pursue research for definite conclusions on their reliability.

Keywords

Chronic Inflammatory Rheumatic Diseases, Cardiovascular Risk, Cardiovascular Risk Factors, Cardiovascular Disease, WHO/ISH Risk Charts, Sub-Saharan Africa

1. Introduction

Chronic inflammatory rheumatic diseases (CIRD) are a heterogeneous group of disorders characterized by humoral or cell-mediated immune responses against diverse autoantigens, with prominent involvement of synovial joints [1] [2]. CIRD morbidity is increasing in developing populations, and in particular in Sub-Saharan Africa where a prevalence of 8.2% has been reported in a Cameroonian hospital setting in 2007 [3] [4]. Genetic and environmental triggers commonly interact to determine the occurrence of CIRD [1].

It is widely known that CIRD *i.e*. rheumatoid arthritis (RA), ankylosing spondylitis (AS) and other spondyloarthritides (SpA), systemic lupus erythematosus (SLE), Sjögren's syndrome, systemic sclerosis, polymyalgia rheumatica, and vasculitides are frequently associated with comorbid conditions such as cardiovascular diseases (CVD) that significantly impact on patients' life span [1] [5] [6]. CIRD may increase the cardiovascular risk through several mechanisms including nontraditional cardiovascular risk factors alongside traditional cardiovascular risk factors. Nontraditional cardiovascular risk factors are essentially genetic/epigenetic mechanisms, disease-modifying antirheumatic drugs, and more specifically immune mechanisms together with chronic inflammation [1] [6].

Despite the increasing burden of both CIRD and CVD in Sub-Saharan Africa collectively with extensive assessment of their relationships in temperate regions [1] [3] [5]-[7], no published study has yet addressed the issue of CVD in a group of multiple CIRD in Black African patients to the best of our knowledge. The only reports investigating the link between CIRD and CVD in Sub-Saharan Africa focused on RA [8] [9]. Moreover, their results are discrepant. In this regard and considering the need for population specific stratification [8], the potential link between various CIRD and CVD might appear theoretical in Sub-Saharan Africa and thus deserve rigorous exploration in this region. Hence, we carried out a study aiming to investigate the association between CIRD and cardiovascular risk in a Cameroonian population based on the World Health Organization (WHO) and International Society for Hypertension (ISH) risk charts.

2. Methodology

CIRD patients enrolled in this cross-sectional study are members of a large cohort designed for all aspects of research in the domain of CIRD at the Yaounde Central Hospital rheumatology unit. The cohort comprises a large array of CIRD that were all included in this research: 1) RA diagnosed according to the American College of Rheumatology (ACR)/European League against Rheumatism (EULAR) criteria [10] [11], 2) systemic lupus erythematosus (SLE) and 3) systemic sclerosis both diagnosed with respect to their respective ACR criteria [12] [13], 4) mixed connective tissue disease fulfilled the Sharp criteria [14], 5) Sjögren's syndrome (SS) diagnosed as recommended by the American-European consensus group criteria [15], 6) autoimmune polymyositis fulfilled the Hoogendjick *et al.* criteria [16], 7) spondyloarthropathies diagnosed according to the Amor *et al.* criteria [17], 8) and adult onset Still's disease diagnosed according to the Fautrel *et al.* criteria [18]. Individuals of both sexes aged $\geq$ 18 years all members of the cohort were recruited consecutively based on a non-probabilistic sampling and included in the CIRD group. Patients with human immunodeficiency virus infection, hereditary dyslipidemia, chronic kidney disease, and any other evolving chronic inflammatory disease were excluded from the study.

Clinically healthy volunteers matched to patients for sex, age (timeframe of two years) and race were recruited from the Yaounde community and included in the non-CIRD group.

Pregnant women were excluded from both groups.

Demographic, clinical and biological data were recorded during a lone visit. Blood pressure was measured with a clinically validated electronic device (Magnien B1) [19]. Hypertension was defined by a systolic (and/or a diastolic) blood pressure ≥ 140 (90) mmHg [20]. Body weight (kg) was measured with a mechanical scale balance (precision ± 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 a BMI ≥ 25 kg/m^2 [21]. Waist circumference was measured with a meter tape midway between the lower border of the twelfth rib and the antero-superior iliac spine and abdominal obesity was defined by a waist circumference ≥102 cm in men, and ≥88 cm in women [21]. Blood was drawn by venous puncture in the forearm crease after strict asepsis. 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 validated by the World Health Organization (WHO) [20]-[23] were investigated, and the cardiovascular risk was estimated from WHO/ISH risk charts appropriate for the Cameroonian general population [22]. With respect to these risk charts, 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%) risk [22].

All analyses were performed in Epi-info for windows version 7, and SPSS for windows version 18. For continuous variables, the means and standard deviations were calculated. Categorical variables were expressed as frequencies with their 95% confidence intervals (CI).

The association between CVD/risk factors and CIRD was summarized with odds ratios (OR) and their 95% CI. Multiple logistic regression (with methotrexate, corticosteroids, hydroxychloroquine, male sex, advanced age [≥55 years in men, and ≥65 years in women], and sedentarity as candidate predictors) was used to deeply question the relationship between CIRD specific factors and cardiovascular risk factors. A p-value < 0.05 was considered statistically significant.

Ethics Approval and Consent to Participate

The research protocol was in accordance with the Declarations of Helsinki. An ethical clearance was obtained from the Institutional Ethics Committee of the Faculty of Medicine and Biomedical Sciences of the University of Yaounde I. Administrative authorizations to recruit and manipulate blood samples were obtained from the Yaounde Central and University Teaching Hospitals respectively. Each participant completed a written informed consent before enrolment.

This study protocol received the approval from the institutional ethical committee of Faculty of Medicine and Biomedical Sciences of the University of Yaounde I.

3. Results

Table 1 summarizes the demographic and clinical characteristics of participants. A total of 109 CIRD patients and 111 non-CIRD subjects were finally included. The CIRD group matched well with the non-CIRD group (mean age ± SD 44.4 ± 15.2 years vs 44.2 ± 15.5 years for CIRD patients and non-CIRD participants respectively, p = 0.82).

For cardiovascular risk factors (**Table 2**), hypertension was recorded in 27.5% of the CIRD patients and 15.3% of the non-CIRD subjects "OR 2.09, 95% CI (1.07 - 4.08), p = 0.03" excess overall adiposity reflected by high BMI was found in 63.3% of the CIRD subjects and 47.7% of the non-CIRD participants ["OR 1.89, 95% CI (1.1 - 3.24), p = 0.02" diabetes mellitus and physical inactivity were significantly noticed only in the CIRD group (7.3%, p = 0.003 and 11%, p < 0.001 for diabetes and physical inactivity respectively). The logistic regression showed that increasing age was independently associated with hypertension "adjusted OR 34.44, 95% CI (6.46 - 185.79), p < 0.001" whereas treatment with methotrexate was inversely associated with hypertension "adjusted OR 0.27, 95% CI (0.07 - 0.95), p = 0.04" (**Table 3**). Furthermore, incremented BMI was independent of age (p = 0.1), gender (p = 0.60), treatments with nonsteroidal antiinflammatory drugs (p = 0.36), corticosteroids (p = 0.16), hydroxychloroquine (p = 0.66), and methotrexate (p = 0.75) (**Table 4**).

Ten (9.2%) CIRD patients had experienced atherosclerotic cardiovascular events before the study, thus were

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

Characteristics	CIRD		p-value
	Present	Absent	
Age (mean ± SD), years	44.4 ± 15.2	44.2 ± 15.5	0.82
Sex			
-Females N (%)	39 (78)	39 (76.5)	0.88
-Males N (%)	11 (22)	12 (23.5)	
Duration* (mean ± SD), years	9 ± 7.6	N/A	
CIRD, N (%)		N/A	
-Rheumatoid arthritis	50 (45.9)		
-SLE	21 (19.3)		
-MCTD	11 (10.1)		
-Ankylosing spondylitis	11 (10.1)		
-Undifferentiated arthritis	4 (3.7)		
-Adult onset Still's disease	4 (3.7)		
-Systemic sclerosis	2 (1.8)		
-Goujerot-Sjögren's syndrome	2 (1.8)		
-Reactive arthritis	1 (0.9)		
-Polymyositis	1 (0.9)		
-Crohn's disease	1 (0.9)		
-Psoriatic arthritis	1 (0.9)		
Comorbidities, N (%)	96 (88)	N/A	
-Infections	73 (67)		
-PUD	56 (51.4)		
-Osteoarthritis	26 (23.8)		
-Cancer	3 (2.7)		
-Asthma	1 (0.9)		
-Depression	1 (0.9)		
- Parkinson's disease	1 (0.9)		
RA treatment, N (%)		NA	
-Symptomatic treatment			
Prednisone	53 (48.6)		
NSAIDS	12 (11)		
-Specific treatment			
MTX	38 (34.9)		
HCQ	31 (28.4)		
SSZ	8 (18.6)		
AZT	7 (10.1)		
LEF	1 (1.4)		
-Without treatment	28 (27.5)		

CIRD: chronic inflammatory rheumatic diseases; SD: Standard Deviation; N: number; Duration*: duration of evolution of disease; NA: not applicable; RA: rheumatoid arthritis; SLE: systemic lupus erythematosus; MCTD: mixed connective tissue diseases; PUD: peptic ulcer disease; NSAIDs: non-steroidal anti-inflammatory drugs; MTX: methotrexate; HCQ: hydroxychloroquine; AZT: azathioprine; SSZ: sulfasalazine; LEF: leflunomide.

Table 2. Prevalence of cardiovascular risk factors in CIRD patients compared to non-CIRD participants.

Variables	CIRD				OR	95% CI	p-value
	Present		Absent				
	N	%	N	%			
Hypertension	30	27.5	17	15.3	2.09	1.07 - 4.08	0. 03
BMI ≥ 25 kg/m^2	69	63.3	53	47.7	1.89	1.1 - 3.24	0.02
Abdominal obesity	48	44	35	31.5	1.71	0.98 - 2.96	0.08
Metabolic syndrome	24	22	16	14.4	1.68	0.84 - 3.37	0.16
Hyperuricemia	12	11	8	7.2	1.59	0.62 - 4.06	0.33
Dyslipidemia	59	53.1	54	48.6	1.24	0.73 - 2.11	0.42
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
Menopause	31	42.5	30	42.3	1.00	0.52 - 1.95	0.98
Alcohol misuse	9	8.3	27	24.3	0.28	0.12 - 0.63	0.001
Tobacco use	3	2.75	10	9	0.28	0.08 - 1.07	0.08
Diabetes mellitus	8	7.3	-	-	N/C	N/C	0.003
Physical in activity	12	11	-	-	N/C	N/C	<0.001
CVA/TIA*	4	3.7	-	-	N/C	N/C	0.059
Ischemic heart disease¶	7	6.4	-	-	N/C	N/C	0.007

CIRD: chronic inflammatory rheumatic diseases; OR: odds ratio; 95% CI 95%: confidence interval; N: number; BMI: body mass index; N/C: not calculable; CVA/TIA*: past history of cerebrovascular accident/transient ischemic attack; Ischemic heart disease¶: past history of ischemic heart disease.

Table 3. Predictive factors for hypertension in CIRD subjects.

	Unadjusted OR					Adjusted OR			
	OR	CI** Min	CI Max	p*		OR	CI** Min	CI Max	p*
MTX	0.59	0.23	1.50	0.27	MTX	0.27	0.07	0.95	0.04
HCQ	0.89	0.34	2.27	0.80	HCQ	0.86	0.26	2.90	0.81
Prednisone	1.89	0,80	4.43	0.15	Prednisone	1.86	0.62	5.62	0.27
NSAIDS	0.86	0.22	3.44	0.84	NSAIDS	1.95	0.33	11.63	0.46
Age	19.37	4.97	75.54	<0.001	Age	34.44	6.46	185.79	<0.001
Male gender	0.98	0.39	2.46	0.97	Male gender	0.35	0.09	1.42	0.14

OR: odds ratio; CI**: Min confidence interval minimum; CI: Max confidence interval maximum; p*: p-value; MTX: methotrexate; HCQ: hydroxychloroquine; NSAIDS: nonsteroidal antiinflammatory drugs.

Table 4. Putative predictive factors for high BMI in CIRD patients.

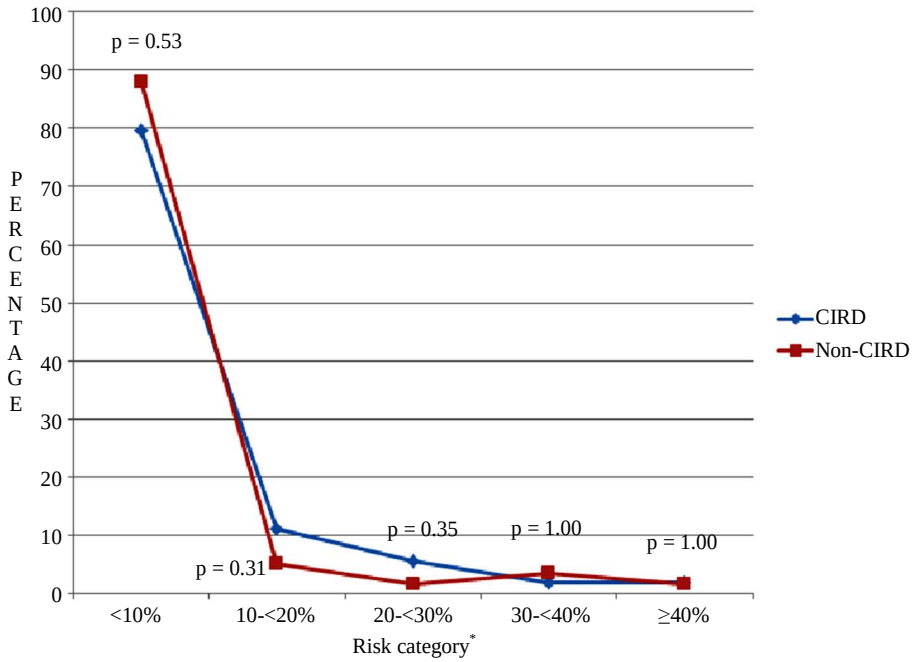
	Unadjusted OR					Adjusted OR			
	OR	CI** Min	CI Max	p*		OR	CI Min	CI Max	p*
MTX	1.18	0.52	2.69	0.69	MTX	1.16	0.47	2.82	0.75
HCQ	0.73	0.31	1.72	0.47	HCQ	0.81	0.31	2.12	0.66
Prednisone	0.67	0.31	1.46	0.31	Prednisone	0.54	0.23	1.28	0.16
NSAIDs	0.54	0.16	1.80	0.32	NSAIDs	0.54	0.14	2.05	0.36
Age	2.86	0.76	10.74	0.12	Age	3.26	0.81	13.05	0.1
Male gender	0.85	0.37	1.97	0.7	Male gender	0.76	0.28	2.10	0.60

OR: odds ratio; CI**: Min confidence interval minimum; CI: Max confidence interval maximum; p*: p-value; MTX: methotrexate; HCQ: hydroxychloroquine; NSAIDS: nonsteroidal antiinflammatory drugs.

considered "at very high risk individuals", and no participant from the non-CIRD group had ever experienced such events ($p < 0.001$ for this comparison). Based on gender, age, diabetic/non diabetic status, tobacco smoking status, systolic blood pressure and blood cholesterol values in absence of previous atherosclerotic cardiovascular events [22], the cardiovascular risk could be estimated with WHO/ISH risk charts only in 54 CIRD patients versus 59 non-CIRD subjects (**Figure 1**). According to this estimation, the cardiovascular risk was low in 43 (79.6%) CIRD patients vs 52 (88.1%) non-CIRD participants ($p = 0.53$), moderate in six (11.1%) CIRD patients vs three (5.1%) non-CIRD participants ($p = 0.31$), medium in three (5.6%) CIRD patients vs one (1.7%) non-CIRD subject (0.35), high in one (1.8%) CIRD patient vs two (3.4%) non-CIRD subjects ($p = 1.00$), and very high in one (1.8%) CIRD patient and one (1.7%) non-CIRD participant ($p = 1.00$). In summary, the number of CIRD people with previous cardiovascular events was significantly incremented in comparison with the non-CIRD group. But when the cardiovascular risk was estimated with the WHO/ISH risk charts, there was no association between the cardiovascular risk and CIRD.

4. Discussion

We studied both the cardiovascular risk factors and the CVD risk in a Black African cohort of patients with CIRD from an urban Cameroonian setting, with aim to explore the relationship between multiple CIRD and CVD risk. Resultantly, CIRD were associated with hypertension, excess overall adiposity, diabetes mellitus and physical inactivity. A Dutch study including 3356 CIRD patients and 6708 matched controls similarly reported a significantly higher prevalence of hypertension in the group of CIRD patients compared with controls (12% vs 9%, "Hazard ratio 1.3, 95% CI (1.1 - 1.5), $p = 0.001$" [24]. Furthermore, excess adiposity has also been previously reported in Black African RA patients and could be a risk factor for arthritis development and progression [8] [25]. Like in the general population [26], excess adiposity and most importantly increased age might substantially favor the development of hypertension in the context of CIRD. Notably, increased age was over 34 times independently associated with hypertension in CIRD patients. But astonishingly, treatment with methotrexate reduced by 73% the risk of developing hypertension in CIRD patients. This sheds light on a potential new role of methotrexate as an effective antihypertensive drug in the CIRD population alongside angiotensin receptor blockers. Along this line, it is possible that methotrexate—an anti-inflammatory drug-decrement blood pressure level in CIRD patients by inhibiting the renin-angiotensin system which is suggested to play an important



*The risk category has been estimated for 54 CIRD and 59 non-CIRD subjects

Figure 1. Cardiovascular risk of CIRD patients compared to non-CIRD subjects.

role in the development of endothelial dysfunction and hypertension in CIRD through induction and worsening of vascular oxidative stress and inflammation [27] [28]. On the other hand, the association between CIRD and diabetes found here is supported by a meta-analysis of Wang *et al.*, who found inflammatory markers including interleukin 6 (IL-6) and C-reactive protein (CRP) as risk factors for type 2 diabetes mellitus [29]. Indeed, CRP synthesis is driven by IL-6 and IL-6 may contribute to the pathophysiology of type 2 diabetes mellitus through its interaction with insulin-signaling pathways and β-cell function [29] [30]. Physical inactivity significantly prevalent in these CIRD patients has been described elsewhere in RA patients. The long diagnosis delay when patients already experience invalidating joint pain might be an explanation to this finding.

Recent insights have clearly demonstrated that CIRD patients have an incremented CVD risk [5] [6] [31]. The results of our study further support this knowledge. In fact, a significant proportion of CIRD patients had already experienced atherosclerotic cardiovascular diseases *i.e.* cerebrovascular accidents/transient ischemic attacks and/or ischemic heart disease, thus had a very high CVD risk. However, when estimating the cardiovascular risk with the WHO/ISH risk charts, CIRD patients did not significantly differ from their non-CIRD counterparts, and similarly had a broadly reduced cardiovascular risk. Remarkably, many cardiovascular risk calculators appropriate for the general population have been tested in RA patients [8] [27] [32] [33], but not in the other CIRD populations. Almost all of those studies have reported a low CVD risk and substantial underestimation of the CVD risk when using those calculators. Our results seem consistent with those reports in a CIRD population at large. However, we found CIRD associated with traditional CVD risk factors, contrasting with the estimated global low cardiovascular risk. Furthermore, CIRD patients frequently have an increased carotid intima-media thickness and high carotid plaque prevalences correctly suggestive of increased atherosclerosis burden [31]. Taken together, the WHO/ISH risk charts could have underestimated the CVD risk in our CIRD population. Hence, measurements of the aforementioned surrogate markers of atherosclerosis (carotid-intima media thickness and carotid plaque) as well as longitudinal studies are largely warranted for definite conclusions. In particular, cross-sectional studies confronting the WHO/ISH risk charts estimations with concomitant measures of surrogate markers of atherosclerosis and longitudinal studies verifying if CVD outcomes/status predicted by the WHO/ISH risk charts occur in the future would be helpful.

Our study had limitations:

- Caution must be exercised when interpreting results of this study. Indeed, causality of the observed associations cannot be guaranteed.
- Additionally, we cannot rule out the recall bias concerning the report of individual's previous cardiovascular events in spite of the use of adapted questionnaires developed by the WHO [21].
- Nevertheless, we studied the cardiovascular risk in an extensive CIRD population.

5. Conclusion

We found CIRD associated with hypertension, excess overall adiposity, diabetes mellitus and physical inactivity. In addition, a considerable proportion of CIRD patients reported previous atherosclerotic cardiovascular events. However, CIRD may not be associated with an increased CVD risk according to the WHO/ISH risk charts. Thus, definite conclusions require further rigorous research to precise if we can or not rely on the WHO/ISH risk charts to predict the CVD outcome in Black African patients with CIRD.

Competing Interests

The authors declare that they have no competing interests.

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