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Relation between high-sensitivity C-reactive protein and cardiovascular and renal markers in a middle-income country in the African region

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Abstract

Background: High-sensitivity C-reactive protein (hs-CRP) is associated with several cardiovascular risk factors (CVRF) and with renal function markers. However, these associations have not been examined in populations in the African region. We analyzed the distribution of hs-CRP and the relationship with a broad set of CVRF, renal markers and carotid intima-media thickness (IMT), in the Seychelles (African region).
Methods: We conducted a survey in the population aged 25-64 years (n=1255, participation rate: 80.2%). Analyses were restricted to persons of predominantly African descent (n=1011).
Results: Mean and median hs-CRP serum concentration (mg/l) were 3.1 (SD 7.6) and 1.4 (IQR 0.7-2.9) in men and 4.5 (SD 6.7) and 2.2 (IQR 1.0-5.4) in women ($p < 0.001$ for difference between men and women). hs-CRP was significantly associated with several conventional CVRF, and particularly strongly with markers of adiposity. With regards to renal markers, hs-CRP was strongly associated with cystatin C and with microalbuminuria but not with creatinine. hs-CRP was not associated with IMT.
Conclusions: Serum concentration of hs-CRP was significantly associated with sex, several CVRF and selected renal function markers, which extends similar findings in Europe and in North America to a population in the African region. These findings can contribute to guide recommendations for the use of hs-CRP in clinical practice in the region.

Background

Plasma or serum concentration of high-sensitivity C-reactive protein (hs-CRP), a protein synthesized by the liver, is the most widely used biomarker of inflammation. It is well demonstrated that hs-CRP plasma concentration is associated with cardiovascular risk factors (CVRF) and with renal function (1-3). hs-CRP is also strongly associated with cardiovascular disease morbidity and mortality (4-9), but this association is generally largely attenuated upon adjustment for CVRF (1).
Carotid intima-media thickness (IMT) is a marker of atherosclerosis and a good predictor of cardiovascular events (10-12). Besides the association between hs-CRP and atherosclerosis or cardiovascular disease morbidity and mortality, the role of this marker in subclinical atherosclerosis has not been systematically demonstrated (13) and studies evaluating the association between hs-CRP and IMT have given conflicting results. In a systematic review of the literature, Baldassare et al. (13)found that a majority of studies reported an association between IMT and CRP.
However, most studies on hs-CRP have been conducted in North American and European populations. Although hs-CRP plasma concentration is higher in African than Caucasian persons residing in North America (14) and in South African black than white women (15), we are not aware of any population-based study in the African region that has focused on the distribution of hs-CRP and the association between hs-CRP and a broad set of CVRF, renal function markers and subclinical atherosclerosis. In this study, we examined the distribution of hs-CRP and whether hs-CRP is associated with CVRF, renal function markers and subclinical atherosclerosis measured by IMT in an African population of a middle-income country.

Materials and Methods

The Republic of Seychelles consists of over 100 islands located in the Indian Ocean, east to Kenya, in the African region. Around 90% of the population lives on the main island. The large majority of the population is of African descent. The GDP per capita has increased, in real values, from US$ 2927 in 1980 to US$ 5239 in 2004. A high prevalence of the main CVRF has been reported (16;17), with downward secular trends in smoking and blood pressure and upward trends in overweight and diabetes between 1989 and 2004 (18).

Sampling frame of the survey

A population-based survey of CVRF was conducted in 2004 (Seychelles Heart Study III) including 1255 participants (participation rate of 80.2%). The sampling frame, methods and main results have been described previously (17). Briefly, a sex- and age-stratified random sample of all inhabitants aged 25-64 years was used based on computerized national census data. Participants were free to participate and all gave informed consent. The survey was approved by the Ministry of Health after technical and ethical reviews. The study protocol conformed to the ethical guideline of the 1975 Declaration of Helsinki as reflected in a *a priori* institution ‘s human research committee.

Measurement of lifestyle-related and clinical variables

Methods used to assess CVRF have been described previously (17;18). Trained survey officers administered a structured questionnaire to the participants. Current cigarette smoking was defined as smoking at least one cigarette per day. Mean daily alcohol intake was quantified in the participants reporting to drink at least once a month. Alcohol consumption was assessed by questions on drinking frequency and volume for the main available alcoholic beverages and mean daily ethanol intake was calculated. Participants were asked about their current occupation or, if not currently employed, about their occupation when they were last employed. Three categories were considered in this study: “laborer” (manual occupation with no formal training), “professional” (which included non-manual occupations with formal training such as teachers, nurses) and “intermediate” (all other categories). .

Weight and height were measured and body mass index (BMI) calculated as weight (kg) divided by height (m) squared. Waist circumference (waist) was measured at the level of the umbilicus in the standing position, with individuals in light garments. Body fat mass was measured using a noninvasive bioimpedance analyzer (Omron body fat monitor HBF-300). Blood pressure was defined as the average of the two last of three measurements, taken at intervals of at least 2 minutes, using a mercury sphygmomanometer, after participants had been seated for at least 30 minutes.

Measurement of biochemical variables

Eligible participants were requested to be fasting since midnight. A blood sample was taken in the morning, centrifuged within 2 hours and serum was immediately frozen at -20°C. Fasting plasma glucose was measured with a point-of-care analyzer (Cholestec LDX, Hayward, USA). For values ≥5.6 mmol/l in persons not known to have diabetes, an additional capillary measurement was

performed within 10 minutes with an Ascensia Elite glucometer, which adjusts values to plasma values, and the mean value of the two measures was considered, as described previously (19). Diabetes was defined as a fasting blood glucose ≥7.0 mmol/l or a personal history of current diabetes treatment (20). Except for glucose, all blood analyses were performed at the Canton Laboratory for Biochemistry and Hematology, St Gallen, Switzerland using standard techniques. LDL-cholesterol was calculated with the Friedewald formula. hs-CRP was measured by using a latex-enforced immunonephelometry using the BN II (Dade Behring) method. Of note, there is no cross-reactivity or interference known with the hs-CRP method, which we used. Microalbuminuria was assessed on the second morning urine collected at the study center using a semi-quantitative method (Clinitek Status, Bayer), as described before (21). Serum cystatin C was measured by means of a particle-enhanced immunonephelometric assay with a nephelometer (BN II, Dade Behring) (21).

Measurement of IMT

High-resolution B-mode ultrasonography was conducted in all participants ≥45 years seen during a 17-week period (n = 496) as well as in a randomly selected sample (18%, n = 57) of participants aged 35–44 years. We restricted this exam to older participants because they were more likely to have atherosclerosis and to a small randomly selected sample of younger persons (21) to limit the number of ultrasound exams in view of the availability of only one ultrasound examiner. Of these 553 participants, 497 were of African or mixed descent and 491 had hs-CRP measured and were considered in the analysis. All ultrasound exams were performed by the same investigator, blinded to the risk factor status of the participants, as described previously (19). Briefly, we used a portable ultrasound system (GE LogiqBook) connected with a 6–10 MHz linear array transducer and coupled with a software (M'ATH, ICN-metric, Paris, France) performing semi-automatic measures of IMT on frame. IMT was measured on the far wall of the right and left common carotid arteries over a length of 1 cm on a reference site located 2 cm below the bifurcation (22). The measurements on the left and right arteries were averaged to obtain a single mean value. Reproducibility of IMT measurements was assessed in 20 randomly selected participants re-examined within a few weeks interval: the coefficient of variation was 4.8%, which is consistent with other studies (23).

Statistics

Of the 1565 eligible participants aged 25-64, 1255 (80.2%) completed the clinical visit. Since hs-CRP differs between different ethnic groups (24;25) we restricted all analyses to persons categorized as being of predominantly African descent (n=1155), i.e. we excluded persons of predominantly Caucasian, Indian or Asian descent, respectively 50, 32, and 18 participants. Among these 1155 participants, 1011 had no missing data for all considered covariates and were considered in the analyses. The small number of participants of non African descent precludes inter-ethnic comparison in this study.

We estimated the Spearman correlation coefficients between the variables of interest and hs-CRP. We further examined the association between hs-CRP and risk factors using linear regression adjusted for age and sex. Serum hs-CRP and triglycerides were log–transformed, because of positively skewed distributions. For the log transformation, undetectable hs-CRP values (n=14) were recorded as 0.05

mg/dl since the assay could detect levels as low as 0.1 mg/dl. Sensitivity analysis showed that regression estimates did not differ substantially when using models where missing hs-CRP data were coded as 0.05 or coded as missing. We used an interaction term between sex and age in multivariate analyses because hs-CRP was associated with age in men but not in women. We also used an interaction term between sex and age for their effect on IMT. There were no significant interaction between sex and microalbuminuria for their effect on log hs-CRP as well as between log hs-CRP and sex or between log hs-CRP and cystatin C for their effect on IMT. We selected a parsimonious multivariate model of "independent" variables associated with hs-CRP by using stepwise multiple regression. For each variable included in the linear regression model, we also gave the variance (i.e. the proportion of the observed variation in hs-CRP explained by the variable of interest). For the age- and sex-adjusted models, the variance was calculated as the difference between the coefficient of determination of the model adjusted for age, sex and variable of interest and the coefficient of determination of the model adjusted for age and sex only (the variance for age and sex was 7.5%). For the stepwise multiple regression models, the variance was calculated as the difference between the coefficient of determination of the model adjusted for all variables (R^2=23.1%) minus the coefficient of determination of the model adjusted for all variables except the variable of interest (the variance for age and sex was 2.4%). Similarly, we calculated the variance for the linear regression models with IMT (the variance for age and sex was 20.7% and the coefficient of determination of the model adjusted for all variables was 27.3%).
All P-values are two-sided and values less than 0.05 were considered significant. Analyses were performed using Stata 11.1 software (Stata Corp., College Station, Texas, USA).

Results

Table 1 shows the baseline characteristics of the study population and the distribution of the CVRF, renal markers and IMT stratified by sex (26).

Figure 1 shows that the distribution of hs-CRP was shifted to higher values in women than in men (our data do not include persons from Caucasian, Indian, Asian descent). Mean and median hs-CRP levels (mg/l) were 3.1 (SD 7.6) and 1.4 (IQR 0.7-2.9) in men and 4.5 (SD 6.7) and 2.2 (IQR 1.0-5.4) in women ($p < 0.001$ for tests of both the median and the mean). Mean log hs-CRP was 0.3 (SD 1.2) in men and 0.8 (SD 1.2) in women.

Association between hs-CRP and cardiovascular risk factors

Table 2 shows that most of the considered CVRF were associated with hs-CRP. The largest Spearman correlation coefficients were found for indicators of adiposity, i.e. BMI, waist, and fat mass (approximately 0.3).

Table 3 shows the associations between log hs-CRP and CVRF. We used standardized regression coefficients to enable direct comparison of the magnitude of the regression coefficients of the different markers. The standard regression coefficient indicates the change in log hs-CRP associated with one standard deviation of the explanatory variable. Consistent with findings for the Spearman correlation

coefficients (Table 2), the regression coefficients (and the proportion of variance explained by the corresponding risk factors) were largest for the adiposity markers (BMI, waist and fat mass). Alcohol intake and occupation were not associated with log hs-CRP while smoking was only marginally associated with log hs-CRP.

Association between hs-CRP and renal markers

Table 2 shows that cystatin C was strongly associated with hs-CRP but creatinine was not. These findings are confirmed by the linear regression, which shows that hs-CRP is associated with cystatin, uric acid and microalbuminuria but not with creatinine (Table 3).

Association between hs-CRP, cardiovascular risk factors and renal markers using stepwise linear regression

We used an automated variable selection method (i.e. stepwise linear regression) to define a model where all variables retained in the final model are significantly associated with the outcome (p-value <0.05). This parsimonious multivariate model included cigarette smoking, waist, fat (%), HDL cholesterol, diabetes, cystatin C, age and sex. When waist was replaced by BMI or by body fat (i.e. only one adiposity marker was considered at a time), adjusting for the same other covariates, the regression coefficient was of similar magnitude for BMI, waist and body fat. A multivariate model including only waist (or BMI or body fat), cystatin C and smoking gathered a variance (R^2= ~22.4%) almost as high as the full model.

Association between hs-CRP and IMT

In univariate and multivariate analyses (adjusted for the considered conventional CVRF) to examine the association between hs-CRP and IMT, we found that several conventional CVFR but not hs-CRP were associated with IMT (Table 4). Of note, these analyses are based on a smaller number of participants and have therefore lower statistical power to detect associations.

Discussion

In this population-based survey in the African region we found that the distribution of the serum hs-CRP concentration clearly differs according to sex, with women having higher values than men, independent of adiposity markers. We also found that hs-CRP concentration was associated with several CVRF and renal function markers, particularly cystatin C. The associations in this population in the African region are similar to those reported in America and Europe.

The gender difference in the hs-CRP distribution in the Seychelles is consistent with findings across different ethnic groups in North America and Europe (1;24;27-29). In particular, the proportion of men and women with high hs-CRP values (>10 mg/l) is similar in the Seychelles and in African Americans (27;29). Consistent with findings in other populations (27), the higher hs-CRP values in women than in men remained after adjustment for adiposity markers and other potentially confounding variables. It has been suggested that the gender difference in hs-CRP may relate to a larger impact of adiposity in

inflammation in women than in men (24;30), and a sex-specific role of leptin (an adipose derived hormone involved in energy balance) has been suggested (31).

Our study also shows strong associations between hs-CRP and several cardiovascular risk factors. Similar associations were found in Europe and North America (1;32;33). The particularly strong association between adiposity and hs-CRP in our study is consistent with findings in other populations (2;3;32-35). It has been suggested that the association between hs-CRP and adiposity reflects the production and release of pro-inflammatory cytokines, such as interleukin-6, interleukin-1 and tumor necrosis factor-α, by the adipose tissue (36) and by adipocytes themselves (37).

With regards to renal markers, we found that hs-CRP was strongly associated with cystatin C, moderately associated with microalbuminuria, but no relation was found with serum creatinine. Although not often reported in the literature, the association between hs-CRP and cystatin C has also been found in a few studies in America and Europe (38-40). Cystatin C seems to be a more sensitive marker of kidney function than creatinine (41), and its value in the prediction of acute kidney injury has been demonstrated in a recent meta-analysis (42). The stronger relation between hs-CRP and cystatin C than between hs-CRP and creatinine may suggest that hs-CRP could reflect minimal reduction in renal function, which is itself associated with a worse prognosis of kidney failure (43). In a cross-sectional community-based study in African Americans, hs-CRP was associated with chronic kidney disease (independently of other CVRF) (44), and this association has also be found in Caucasians (45).

In our study, hs-CRP was not associated with carotid IMT, which is often used as a proxy for cardiovascular outcome. A recent systematic review showed mixed results across studies. A positive univariate association between hs-CRP and carotid IMT was found in a majority of studies (13), but the association decreased or disappeared upon adjustment for CVRF. The fairly small sample size for IMT analysis in our study (n=491) underlies limited power to detect a relationship and our findings should be replicated in larger population studies in Africa.

Strengths of the study include the population-based design, the high participation rate, and the broad array of measured CVRF and renal markers. Limitations include the facts that no information was recorded on current infections and the use of anti-inflammatory drugs, hormone replacement therapy and statins, which may alter hs-CRP concentration. However, these conditions are likely uncommon in mostly healthy participants to a population survey. hs-CRP was measured once, which is typical of population-based epidemiological surveys, whereas clinical guidelines recommend measurements on two separate days (46).

In conclusion, the results of the distribution of hs-CRP and the association with a broad panel of CVRF and renal markers in a population-based study in the African region extend previous knowledge gained in Europe and in North America. The strong association between hs-CRP and cystatin C, a finding not often reported so far, is consistent with the association between hs-CRP and impaired renal function, although the underlying mechanisms and implications are not yet fully understood. There is much debate on the usefulness of hs-CRP in clinical practice (46-49). Our study suggests that clinical significance of hs-CRP does not differ in sub Saharan Africa as compared to other populations.

Further evaluation and guidelines will be needed to guide the use of hs-CRP in clinical practice in the African region.

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The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology (45).

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Table 1. Baseline characteristics of the study population according to sex

		Men	Women	Total
N		465	546	1011
Age	mean (SD)	45.1 (10.8)	44.9 (11.1)	45.0 (11.0)
Occupation				
Intermediate/professional	%	71.0	50.2	59.7
Labourer	%	29.0	49.8	40.3
Daily cigarette smoker	%	31.4	3.1	14.1
Alcohol intake (g/day)				
0	%	37.9	82.1	61.7
1-29.9	%	22.2	14.0	17.7
30-59.9	%	20.2	2.8	10.8
≥60	%	19.8	1.3	9.8
hs-CRP (mg/l)	mean (SD)	3.1 (7.6)	4.5 (6.7)	3.9 (7.4)
	median	1.4	2.2	1.8
Anthropometric measures				
Body mass index (kg/m2)	mean (SD)	25.9 (4.8)	28.7 (6.1)	27.4 (5.7)
Waist circumference (cm)	mean (SD)	90.3 (12.2)	91.5 (14.0)	91.0 (13.2)
Fat (%)	mean (SD)	19.6 (6.7)	33.8 (7.2)	27.3 (9.9)
Cardiovascular risk factors				
Systolic BP (mmHg)	mean (SD)	134.1 (19.0)	127.7 (20.2)	130.6 (19.8)
Diastolic BP (mmHg)	mean (SD)	87.4 (12.1)	82.6 (12.0)	84.8 (12.3)
LDL cholesterol (mmol/l)	mean (SD)	3.5 (1.2)	3.7 (1.2)	3.6 (1.2)
Apoprotein B (g/l)	mean (SD)	1.1 (0.4)	1.1 (0.3)	1.1 (0.3)
HDL cholesterol (mmol/l)	mean (SD)	1.4 (0.5)	1.4 (0.4)	1.4 (0.5)
Apoprotein A1 (g/l)	mean (SD)	1.6 (0.4)	1.5 (0.3)	1.5 (0.4)
Triglycerides (mmol/l)	median	0.9	0.8	0.9
Insulin (µmol/l)	median	10.7	12.3	11.6
Diabetes (yes)	%	14.4	15.0	14.7

Renal markers				
Creatinin (µmol/l)	mean (SD)	92.6 (20.1)	73.4 (12.6)	82.2 (19.0)
Cystatin C (mg/l)	mean (SD)	0.9 (0.2)	0.8 (0.2)	0.8 (0.2)
Uric acid (µmol/l)	mean (SD)	407.3 (92.5)	298.2 (81.6)	348.4 (102.4)
Microalbuminuria (yes)	%	14.0	14.7	14.3
IMT				
N		220	271	491
IMT (mm)	mean (SD)	0.7 (0.1)	0.7 (0.1)	0.7 (0.1)

Results are presented as percentage (prevalence), mean or median.

Table 2. Spearman's correlations coefficients between hs-CRP and conventional cardiovascular risk factors and other characteristics (n=1011)

	Men		Women	
	Coefficient	P	Coefficient	P
Anthropometric measures				
Body mass index (kg/m2)	0.25	<0.001	0.38	<0.001
Waist circumference (cm)	0.34	<0.001	0.38	<0.001
Fat (%)	0.34	<0.001	0.37	<0.001
Cardiovascular risk factors				
Systolic BP (mmHg)	0.20	<0.001	0.09	0.02
Diastolic BP (mmHg)	0.20	<0.001	0.08	0.05
LDL cholesterol (mmol/l)	0.15	<0.001	0.09	0.02
Apoprotein B (g/l)	0.21	<0.001	0.15	<0.001
HDL cholesterol (mmol/l)	0.19	<0.001	0.18	<0.001
Apoprotein A1 (g/l)	-0.15	<0.001	-0.10	<0.001
Triglycerides (mmol/l)	0.27	<0.001	0.26	<0.001
Insulin (µmol/l)	0.22	<0.001	0.30	<0.001
Glucose (mmol/l)	0.22	<0.001	0.18	<0.001
Renal markers				
Creatinin (µmol/l)	0.04	0.30	0.05	0.17
Cystatin C (mg/l)	0.19	<0.001	0.24	<0.001

Table 3. Association between log hs-CRP and conventional cardiovascular risk factors and other characteristics (n=1011)

	Age- and sex-adjusted			Stepwise multivariate		
			Variance			Variance
	β[1]	P	(%)	β[1]	P	(%)
Sex				0.70	<0.001	
Age (year)				-0.16	<0.001	
Sex*age				0.62	<0.001	
Occupation[2]	0.01	NS	0.0			
Smoking	0.07	0.045	0.4	0.10	0.001	0.8
Alcohol intake (g/day)			0.4			
129.9	-0.03	NS				
30-59.9	0.004	NS				
≥60	0.03	NS				
Anthropometric measures						
Body mass index (kg/m^2)	0.35	<0.001	10.8			
Waist (cm)	0.38	<0.001	12.5	0.24	<0.001	2.1
Fat (%)	0.47	<0.001	9.5	0.18	0.003	0.7
Cardiovascular risk factors						
Systolic BP (mmHg)	0.12	<0.001	1.2			
Diastolic BP (mmHg)	0.12	<0.001	1.1			
LDL cholesterol (mmol/l)	0.11	<0.001	1.3			
Apoprotein B (g/l)	0.16	<0.001	2.4			
HDL cholesterol (mmol/l)	-0.18	<0.001	3.3	-0.07	0.02	1.0
Apoprotein A1 (g/l)	-0.10	0.001	1.0			
Triglycerides (mmol/l)	0.24	<0.001	5.3			
Insulin (µmol/l)	0.21	<0.001	4.5			
Diabetes (yes/no)	0.15	<0.001	2.1	0.09	0.002	0.7
Renal markers						
Creatinin (µmol/l)	0.04	NS	0.1			
Cystatin C (mg/l)	0.19	<0.001	3.3	0.15	<0.001	2.2
Uric acid (µmol/l)	0.21	<0.001	3.0			
Microalbuminuria (yes/no)	0.14	<0.001	1.8			

[1]β = standardized linear regression coefficient

[2]Occupation is "laborer" category compared to "intermediate/professionals" categories.

Table 4. Association between hs-CRP and carotid intima-media thickness (IMT)

	Age- and sex-adjusted			Multiple linear regression[1]		
	B[2]	P	Variance	B[2]	P	Variance
Log hs-CRP (mg/l)	0.03	ns	0.10	-0.04	ns	0.10
Smoking	-0.05	ns	-0.47	-0.01	ns	0.01
BMI (kg/m^2)	0.12	0.005	1.26	0.06	ns	0.23
Systolic BP (mmHg)	0.14	0.002	1.60	0.1	0.02	0.81
LDL cholesterol (mmol/l)	0.15	<0.001	1.55	0.12	0.005	1.19
HDL cholesterol (mmol/l)	-0.16	<0.001	2.51	-0.1	0.02	0.89
Diabetes	0.14	0.001	1.72	0.09	0.03	0.73

[1]Adjusted for smoking, BMI, systolic BP, LDL and HDL cholesterol and diabetes

[2]β = standardized regression coefficient

Figure 1. Cumulative distribution of serum hs-CRP in men and women (range 0-10 mg/l)