

## Association between High Sensitive-C Reactive Protein and Lipid Cardiovascular Risk Factors in Apparently Healthy Nigerian Young Adults

Research Article

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### Abstract

**Background:** CVD, in which coronary heart disease is the main manifestation, remains the major cause of morbidity and mortality worldwide. Chronic inflammatory process which starts from childhood tracking to adulthood has been reported to play a major role in the development and progression of atherogenesis leading to coronary heart disease. hs-CRP, an inflammatory marker has also been shown to best predict development of CVD even in the absence of traditional risk factors. Aim of this study is to ascertain hs-CRP as an independent risk factor as other lipid risk factors in young adults yet to develop CVD or other associated conditions.

**Methods:** 150 age-matched healthy young adults were recruited into this cross-sectional study. They were grouped into three based on the level of hs-CRP; (Group A <3.0mg/L, Group B 3.0-10.0mg/L and Group C >10.0mg/L). Anthropometric measurement, plasma Total cholesterol, Triglycerides, HDL-cholesterol, LDL-cholesterol, serum hs-CRP, Lipoprotein(a), Apolipoprotein A1, Apolipoprotein B and ApoB/A1 ratio were determined in the participants using standard methods.

**Results:** There is a significant rising trend in weight, body mass index and waist-hip ratio in proportion to the increasing level of hs-CRP ( $p=0.021$ ,  $p=0.004$  and  $p=0.029$  respectively). The HDL-cholesterol and ApoA1 levels significantly reduce in proportion to the rising levels of hs-CRP ( $p=0.000$  and  $p=0.028$  respectively). Also the total cholesterol correlates positively with hs-CRP ( $r=0.182$ ,  $p=0.026$ ), while a negative correlation exists between hs-CRP and HDL-cholesterol ( $r=-0.321$ ,  $p=0.000$ ) and ApoA1 ( $r=-0.246$ ,  $p=0.002$ ).

**Conclusions:** This study has demonstrated that increase in central or visceral adiposity, plasma total cholesterol, triglycerides, ApoB; and decreases in plasma HDL-cholesterol and ApoA1, can invoke vascular inflammation which can be detected early by rising concentration of hs-CRP even in young individuals yet to develop CVD.

**Keywords:** High-Sensitive C Reactive Protein; Lipid Cardiovascular Risk Factors; Vascular Inflammation; Healthy Young Adults.

### Introduction

Atherosclerosis remains the major cause of death in developing and developed countries, regardless of the various differences in ethnicities, habits, cultures and availability of affordable therapies [1].

It's a known fact that 50% of all myocardial infarctions occur among individuals without overt hyperlipidaemia, in spite of the strong association of lipid concentrations with coronary heart disease risk (CHD) [2]. It has been shown that about 20% of all coronary events occurred in the absence of any of the traditional risk factors, such as hypertension, diabetes mellitus,

hyperlipidaemia and smoking [3]. These findings raise the query if these conventional risk factors are sufficient to recognize individuals at increased risk of CHD. Therefore various non-lipid atherogenic markers have been suggested in an effort to better determine individuals at risk of CHD, these include markers of inflammation (high sensitivity C-reactive protein, interleukins, adhesion molecules, heat shock proteins); markers of fibrinolytic and haemostatic function (D-dimers, fibrinogen, thrombin-antithrombin III complex); homocysteine to mention but few. Of all these non-lipid risk markers available, high sensitivity C-reactive protein (hs-CRP) is considered to be the most robust tool with test uniqueness desirable and favorable for clinical use as novel marker for CHD risk [4].

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C-reactive protein (CRP) is an acute phase reactant, produced in the liver and routinely measured as an indication of acute infections, inflammatory conditions and trauma; but for the purpose of CHD, it requires the use of hs-CRP assays that have adequate sensitivity to quantify CRP throughout its normal range [5].

CHD, a manifestation of atherosclerosis and chronic inflammatory condition that most often starts at a very young age [6], plays a critical role in the development and progression of atherosclerosis at all stages [7]. Several epidemiologic studies have also shown that elevated concentrations of hs-CRP, a marker for low grade inflammation are strongly associated with risk of future coronary events [8-10]. A number of prospective studies have consistently confirmed that a single hs-CRP measurement can independently predict vascular risk both in apparently healthy men and women that are asymptomatic for traditional risk factors of cardiovascular disease (CVD) [1, 10]; and also predict risk of future coronary events in patients with acute coronary syndromes [11]. hs-CRP has been found to be the strongest predictor of coronary events compared to other novel biochemical [12] and traditional markers of CHD risks [13]. Studies have shown that there is a strong association between hs-CRP and other conditions that confers CVD risks such as metabolic syndrome, impaired glucose tolerance, type 2 diabetes mellitus and hypertension [14-17].

Research findings have indicated that CRP enhances the expression of local endothelial cell surface adhesion molecules [18], endothelial plasminogen activator inhibitor-1 [19], endothelin-1 [20] and monocyte chemoattractant protein-1 [18]; increases the induction of monocyte tissue factors [21]; increases LDL-Cholesterol uptake by macrophages [20]; reduces endothelial nitric oxide bioactivity [22] and co-localize with the complement membrane attack complex within atherosclerotic lesion [23]. These findings suggest CRP as real contributor to atherogenesis apart from just a marker of inflammation [24].

The American Heart Association/Centre for Disease Control (AHA/CDC) Working Group on markers of inflammation in CVD has classified risk of developing CVD based on serum levels of hs-CRP, on account of data obtained from population studies. hs-CRP concentration of <1mg/L is classified as low-risk; 1-3mg/L as intermediate-risk; and levels >3mg/L as high-risk in developing CVD [25]. It is important to note that the association of hs-CRP with CVD risk may be confounded by racial/ethnic differences. Interestingly, marked racial/ethnic differences in hs-CRP levels have been reported, with individual of African origin having higher concentrations compared to Caucasians, independent of adiposity [26-28]; this might affect the interpretation of hs-CRP in risk prediction in African population. Given that chronic inflammatory process starts from childhood and tracks to adulthood; and that it plays a causative role in development and progression of atherosclerosis; and also in view of the fact that hs-CRP is both marker and aetiological factor in atherogenesis; it is important to evaluate the relationship between hs-CRP and CVD risk factors in apparently healthy young population so as to detect early the onset of atherogenesis, and to commence early intervention and preventive measures. We hypothesized that the higher the concentrations of circulating hs-CRP, the stronger its association with other markers of CVD

risks, even in apparently healthy young population who are yet to develop CVDs.

## Methods

### Study Participants

This is a cross-sectional study carried out among 150 apparently healthy young adults' aged between 18 and 25 years from South West, Nigeria over a period of 6 months. A non-random sampling technique was used to select the study participants. They were grouped into three based on the serum level of hsCRP; group A (hsCRP:  $\leq 3.0$ mg/L), group B (hsCRP: 3.0-10.0mg/L), and group C (hsCRP: >10.0mg/L) according to a study on plasma distribution of hsCRP in healthy Nigerian adults [9]. The inclusion criteria is voluntary consent to participate, while the exclusion criteria included (a) history of chronic illness or chronic use of any form of medication especially steroid/lipid lowering drugs, (b) acute illness or any treatment of inflammatory or chronic infectious disease either before or at the time of the investigation (c) social habits such as smoking, alcohol consumption. The study was approved by the University of Ibadan/University College Hospital Ibadan Health Research Ethics Committee (No. UI/EC/16/0301).

### Data Collection

A questionnaire-based interview was used to collect information on demographic characteristics, clinical measurements, personal and family medical history of diabetes mellitus, hypertension and coronary events. Informed written consent form was obtained from all participants after educating them on the benefits and relevance of the study. Clinical measurements which included weight (Kg), height (meters) were measured with participants in light clothing without shoes using a stadiometer and the stadiometer's head piece, respectively. Body Mass Index was calculated as  $\text{Weight}/\text{Height}^2$  ( $\text{kg}/\text{m}^2$ ). Waist circumference (centimeters) was measured using a non-stretch measuring tape at the midpoint between the lowest rib and the iliac crest in the horizontal plane. Hip circumference (centimeters) was measured horizontally at the level of the maximum extension of the buttocks. Waist-hip ratio (WHR) was calculated by the standard equation [ $\text{WHR} = \text{Waist circumference (cm)}/\text{Hip circumference (cm)}$ ]. Blood pressure was measured twice (10 minutes apart), on the left arm of participants in a relaxed, sitting position with the arm supported at heart level, using a standard mercury sphygmomanometer. The mean of the two readings was calculated to obtain the final blood pressure. 10mls of venous blood specimen was withdrawn from each participant in the morning between 7.00am and 9.00am, after 10-12 hours of overnight fast. 5mls was dispensed into EDTA bottle for fasting lipid profile (TC, TG, HDL-c, LDL-c) estimation and another 5mls into Gel clot activator bottle for estimation of serum hs-CRP and other lipid studies. Respective plasma and serum samples were analyzed within 3 months.

### Assay Methods

Plasma Total cholesterol, HDL-c and TG were determined by enzymatic methods; cholesterol-oxidase, direct HDL PEGME, and lipase/glycerol phosphate-oxidase respectively, using G Cell laboratories reagents on an automated chemistry analyzer

(LandWind C 100 plus). The Friedewald equation was used to calculate LDL-c [LDL-C (mg/dL) = Total Cholesterol- HDL-c -(TG/5)]. Serum ApoB and ApoA1 were measured using immunoturbidimetric assays (G Cell laboratories reagents) on an automated chemistry analyzer (LandWind C 100) plus). Serum hsCRP and Lp(a) levels were manually measured using enzyme linked immunosorbent assay (CALBIOTECH Diagnostics kits) on microplate reader (StatFax 4200, USA).

### Statistical Analysis

The statistical analysis was performed using Statistical Package for Social Sciences version 20.0. Data were normally distributed, after checking for normality using the Kolmogorov-Smirnov test. All results are expressed as mean (SD). One-way ANOVA was used to compare group means for anthropometric data, clinical data and lipid studies across the three groups. Pearson's correlation analysis was carried out to determine the association of hsCRP with anthropometric data and lipid cardiovascular risk factors. The level of significance was taken to be  $p < 0.05$ .

## Results

### Demographic Characteristics of the Study Population

A total of 150 apparently healthy age-matched, young adults, were recruited for this study. They were grouped into three based on their serum hsCRP level. 50 participants are in group A (hsCRP:  $\leq 3.0$ mg/L), 56 participants in group B (hsCRP: 3.0-10.0 mg/L) and 44 participants in group C (hsCRP:  $>10$ mg/L).

### Comparison of Anthropometric and Clinical Data in the three groups

The weight and BMI were significantly higher ( $p < 0.05$ ) in group C when compared to both groups A and B. Also the WHR was significantly higher ( $p < 0.05$ ) in group C when compared to group A. The height, waist circumference, hip circumference, systolic and diastolic blood pressure were not statistically different ( $p > 0.05$ ) across the three groups. Table 1.

### Comparison of lipid cardiovascular risk factors in the three groups

Total cholesterol was significantly higher in group C ( $p < 0.05$ ) when compared to group A. The HDL-C concentration was significantly lower in group C ( $p < 0.05$ ) when compared to groups A and B; while it is also significantly lower in group B ( $p < 0.05$ ) compared to that of group A. Triglycerides was significantly higher ( $p < 0.05$ ) in group C compared to group B; while ApoB and ApoB/ApoA1 ratio in group C were significantly higher ( $p < 0.05$ ) than those of group A. ApoA1 concentration was significantly higher ( $p < 0.05$ ) in group A when compared to group C. There was no significant difference ( $p > 0.05$ ) in LDL-c and Lp(a) across the groups. Table 2

### Correlation of hsCRP with anthropometric and clinical data

There was no correlation between hsCRP, measured anthropometric and clinical data in this study. Table 3

### Correlation of hsCRP with lipid cardiovascular risk factors

There was a positive correlation between hsCRP and Total cholesterol; and a negative correlation between hsCRP and HDL-c and ApoA1 in this study. Table 4

## Discussion

hs-CRP, a marker of inflammation have been shown to predict the development of cardiovascular diseases (CVD) even in the absence of traditional risk factors. It is also more robust compared to other novel markers in predicting coronary events. This study therefore looked at the relationship of hs-CRP levels and some traditional risk factors in apparently healthy young adults of African descent. The participants are yet to develop CVD, type II diabetes mellitus, metabolic syndrome or any other chronic disease condition; these could explain the relatively "normal" values obtained in this study.

This present study showed that the measures of adiposity (BMI, WHR) rise significantly in proportion to the increasing levels of

**Table 1. Comparison of Anthropometric and Clinical Data in the three groups.**

Parameters	Group A (n=50) (hsCRP $\leq 3.0$ mg/L) mean (SD)	Group B (n=56) (hsCRP 3.0-10mg/L) mean (SD)	Group C (n=44) (hsCRP $>10$ mg/L) mean (SD)	p value
Height (m)	1.65 (0.07)	1.64 (0.06)	1.65 (0.08)	0.915
Weight (Kg)	56.4 (10.2)	57.5 (7.87)	61.0 (8.15) <sup>a, b</sup>	0.021*
BMI (Kg/m <sup>2</sup> )	20.7 (2.77)	21.4 (2.53)	22.4 (2.56) <sup>a, b</sup>	0.004*
WC (cm)	75.1 (5.91)	75.2 (6.87)	77.9 (8.57)	0.094
HC (cm)	93.8 (5.05)	93.3 (7.86)	94.6 (7.87)	0.626
WHR	0.80 (0.06)	0.81 (0.04)	0.82 (0.04) <sup>a</sup>	0.029*
SBP (mmHg)	110 (10.65)	112 (16.42)	114 (11.75)	0.239
DBP (mmHg)	72 (10.26)	72 (10.66)	74 (8.09)	0.825

(\* $p < 0.050$ ; <sup>a</sup>significantly different from group A; <sup>b</sup>significantly different from group B; <sup>c</sup>significantly different from group C). BMI- Body Mass Index; WC- Waist Circumference; HC- Hip Circumference; WHR- Waist Hip Ratio; SBP- Systolic Blood Pressure; DBP- Diastolic Blood Pressure

Table 2. Comparison of lipid cardiovascular risk factors in the three groups.

Parameters	Group A (n=50) (hsCRP ≤ 3.0mg/L) mean (SD)	Group B (n=56) (hsCRP 3.0-10mg/L) mean (SD)	Group C (n=44) (hsCRP > 10mg/L) mean (SD)	p value
Height (m)	152 (22.13)	155 (27.50)	164 (30.98) <sup>a</sup>	0.093
Weight (Kg)	64 (11.48) <sup>b,c</sup>	60 (9.23) <sup>c</sup>	53 (10.91)	0.000*
BMI (Kg/m <sup>2</sup> )	68 (20.64)	67 (16.98)	75 (21.28) <sup>b</sup>	0.088
WC (cm)	74 (25.41)	82 (25.83)	96 (29.62)	0.635
HC (cm)	69 (22.71)	73 (18.88)	74 (18.18)	0.392
WHR	80 (22.92)	87 (19.17)	89 (23.37) <sup>a</sup>	0.08
SBP (mmHg)	173 (21.22) <sup>c</sup>	169 (12.49)	163 (17.99)	0.028
DBP (mmHg)	0.46 (0.14)	0.51 (0.19)	0.55 (0.16) <sup>a</sup>	0

(\*p < 0.050; a significantly different from group A; b significantly different from group B; c significantly different from group C). TC- Total cholesterol; HDL- High density lipoprotein cholesterol; TG- Triglycerides; LDL- Low density cholesterol; Lp(a)- Lipoprotein (a); ApoB-Apolipoprotein B; ApoA1-Apolipoprotein A1.

Table 3. Correlation of hsCRP with anthropometric and clinical data.

Anthropometric/ Clinical data	hsCRP	
	r	p
Height (m)	0.073	0.373
Weight (Kg)	0.027	0.745
BIVII (Kg/m <sup>2</sup> )	0.008	0.927
WC (cm)	0.097	0.235
HC (cm)	0.044	0.596
WHR	0.122	0.135
SBP (mmHg)	0.056	0.494
DBP (mmHg)	0.027	0.744
(*p < 0.050)		

BMI- Body Mass Index; WC- Waist Circumference; HC- Hip Circumference; WHR- Waist Hip Ratio; SBP- Systolic Blood Pressure; DBP- Diastolic Blood Pressure

Table 4. Correlation of hsCRP with lipid cardiovascular risk factors.

CVD Parameters	hsCRP	
	r	p
TC (mg/dL)	0.182	0.026*
HDL (mg/dL)	-0.321	0.000*
TG (mg/dL)	0.138	0.092
LDL (mg/dL)	0.071	0.386
Lp (a) (mg/dL)	-0.008	0.920
Apo B (mg/dL)	0.040	0.630
Apo A1 (mg/dL)	-0.246	0.002*
ApoB/ApoA1	0.138	0.092
(*p < 0.050)		

TC-Total cholesterol; HDL- High density lipoprotein cholesterol; TG- Triglycerides; LDL- Low density cholesterol; Lp(a)- Lipoprotein (a); ApoB-Apolipoprotein B; ApoA1-Apolipoprotein A1.



hs-CRP, this is similar to the findings of [29, 30]. Finding of this study supports the body of evidence that adipose tissue is a major source of cytokines and that increased body fat is a state of low grade systemic inflammation; therefore we propose that hs-CRP production rises with increasing visceral or central adiposity which can lead to the development of CVD, even when an individual is not overweight or obese.

This study also showed a significant rising trend in total cholesterol and triglycerides with increasing tertile level of hs-CRP; this finding correlates with the reports of [31, 32]. It is known that triglyceride rich lipoproteins such as VLDL and chylomicron contain significant amount of cholesterol and infiltration of these TG rich lipoproteins in the arterial wall sub-endothelial space is a critical event that sparks an inflammatory response, promoting the development of atherosclerosis. Therefore it can be deduced from this study that even when total cholesterol and TG are within normal limits, there increasing level potentiates inflammatory response as shown by increased hs-CRP.

HDL-cholesterol is a key factor in the reverse cholesterol transport pathway and has many valuable properties, including anti-inflammatory, anti-oxidative, anti-thrombotic, anti-infectious, anti-apoptotic, intercellular communication, and pro-vasodilatory capacities. It has been clearly established in numerous epidemiological studies that an inverse relationship exists between HDL-C levels and risk of CVD. It is observed in this present study that HDL-cholesterol levels decrease as hs-CRP levels rise in agreement with the reports by [33, 34]. Rafael et al., [33] reported that “a decrease of 1 mg/dL (0.0259 mmol/L) in HDL cholesterol level increased the expected level of CRP by 14.6%”. It can be deduced therefore from this present study that the lower the HDL-cholesterol the higher the likelihood of inflammation, enhancing the development of CVD.

Studies have identified that Apo B, which represents total atherogenic particles plays a role in vascular inflammation and is a better predictor of CVD than LDL-C and non-HDL-C [35-37]. Reports have also shown that Apo A1, the major apolipoprotein in HDL-cholesterol particles has been identified as a better risk predictor than HDL cholesterol and it is considered as an anti-atherogenic marker [38, 39]. The ApoB/ApoA1 ratio reflects the balance between the opposing processes of arterial internalization of cholesterol and the reverse transport of cholesterol back to the liver [40]; such that the higher the value of the ApoB/ApoA-1 ratio, the more cholesterol is likely to be deposited in the arterial wall, thereby provoking atherogenesis and hence also increasing cardiovascular risk [41]. This study revealed that ApoB concentration and ApoB/ApoA1 ratio increase across the increasing levels of hs-CRP while ApoA1 concentration decreases; this pattern is also observed with triglycerides and HDL-cholesterol above. This discovery is similar to the findings of Wanhua et al in 2012 [42] and we can construe from this present study that elevated levels of ApoB or ApoB/ApoA1 ratio and lower concentration of ApoA1 can trigger vascular inflammation resulting in increased level of hs-CRP even when an individual is yet to develop CVD.

In this present study, hs-CRP negatively correlates with HDL-cholesterol and ApoA1; and positively correlates with total cholesterol comparable to the report by Aleksandra et al, Debdutta et al and Wanhua et al., [31, 34, 42]. This observation

supports the anti-inflammatory role of HDL-C and ApoA1; and the atherogenicity associated with increase cholesterol.

## Conclusion

The observations from this study indicate that increase in central or visceral adiposity; increase in total cholesterol, triglycerides and ApoB; and decrease in HDL-cholesterol and ApoA1, can invoke vascular inflammation which can be detected early by increasing concentration of hs-CRP even in individual without overt CVD. Therefore we propose that in the absence of other inflammatory conditions, individuals especially at risk of CVD should have routine monitoring of their hs-CRP levels. Weight reduction and ensuring optimal lipid profile can help in preventing chronic inflammation and protecting against atherogenesis.

## Study Limitations

Leukocyte count and erythrocyte sedimentation rate (ESR) were not done in this study.

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