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Original Research

Chronic subclinical inflammation in middle aged Bangladeshi population: association with low high-density lipoprotein cholesterol

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ABSTRACT

Aim: The present study was undertaken to investigate the association of chronic subclinical inflammation as assessed by high sensitivity C-reactive protein (*hs*CRP) with high-density lipoprotein (HDL) cholesterol in a middle aged Bangladeshi population. **Materials and Methods:** Total 348 adults (169 male, 179 female) were included and anthropometric data and clinical histories were recorded. Serum lipids were measured by enzymatic endpoint technique and *hs*CRP was estimated by immunoturbidimetric method. **Results:** The mean of age and body mass index (BMI) of the total subjects were 50.5 ± 11.5 years and 26.7 ± 4.5 kg/m^2 respectively. Substantial proportions (57.47%) of the subjects had low HDL cholesterol. Of the total subjects, 45.4% had *hs*CRP > 3.0 mg/l followed by 31.9% with *hs*CRP: 1.0-3.0 mg/l coupled with elevation of one or more traditional risk factors of CVDs. Lipid parameters showed no significant difference between subjects with low and moderate (*hs*CRP ≤3.0 mg/l) and high *hs*CRP (*hs*CRP > 3.0 mg/l). But BMI was significantly higher in high *hs*CRP group compared to low *hs*CRP group [25.4 (23.3-27.9) vs 27.3 (24.3-30.1) kg/m^2, $p<0.0001$)]. Compared to male, female had higher *hs*CRP [4.0 (1.9-7.6) mg/l vs 1.7 (0.84-3.9) mg/l, $p<0.0001$)]. Spearman's test and multiple regression analysis showed no significant ($p>0.05$) relationship of *hs*CRP with lipid parameters. But, when adjusted for age, sex, BMI and glycemic status, significant negative association for *hs*CRP was observed with HDL cholesterol ($\beta=-0.1654$, $p=0.0139$). **Conclusion:** This data indicated that chronic subclinical inflammation is associated with low HDL cholesterol in middle aged Bangladeshi population.

KEY WORDS: Chronic subclinical inflammation; High sensitivity C-reactive protein; Lipoprotein-lipid profile; HDL cholesterol

INTRODUCTION

Cardiovascular diseases (CVDs) are the leading causes of death in the world with rapid rise in low- and middle-income countries [1]. The occurrences of CVDs are largely influenced by variation in behavioral, traditional metabolic, sociodemographic and genetic risk factors in different regions of the globe [1,2]. Obesity due to rapid economic transitions and lifestyle changes confer a significantly elevated CVD risk in developed or developing countries [2,3] and poses greater risk in Asian [2]. Obesity induces low-grade inflammation in the body and independently advances atherosclerosis and CVDs [4]. Several studies have reported a strong association between body mass index (BMI) and C-reactive protein (CRP), the acute-phase reactant, suggesting that obesity may be a state of low-grade inflammation [5-8]. Elevated high-sensitivity C-reactive protein (*hs*CRP) is an established marker of chronic subclinical inflammation and postulated to play important role to progression of cardiovascular disease [9,10] and considered as a good predictor of future CVD events [11,12].

Among the traditional metabolic risk factors, dyslipidemia, including elevated serum total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), triglycerides (TGs), and low high-density lipoprotein cholesterol (HDL-C) levels, are modifiable major risk factors for CHD, whereas high levels of HDL-C appear to be protective [13, 14]. The nature and extent of different types of dyslipidemia and its determinants may vary substantially from population to population due to ethnic and lifestyle variations. A graded relationship between abnormal lipid levels or particular lipid abnormality and CVD has been confirmed by several studies [15-18]. It is clear that dyslipidemia is one of the leading risk factors for CVD; there is significant regional variation in the prevalence of hyperlipidemia. The link between chronic subclinical inflammation and dyslipidemia may be complex and seemed to be related to anti-inflammatory properties of HDL particles. Accumulating evidence suggests that the protective role of HDL appears to be attenuated by acute or chronic inflammation [19,20] and related to elevation of hsCRP [21]. Since, both lipid disorders and inflammation are largely influenced by eating

habit, lifestyle, race, physical activity, socio-economic status and heredity and study regarding interrelationship between individual lipid fractions particularly HDL-C in this population is rare, we aimed to explore the relationship between marker of subclinical inflammation and high-density lipoprotein (HDL) cholesterol with anthropometric indices and lipoprotein-lipid variables in a middle aged Bangladeshi adults.

MATERIALS AND METHODS

Study designs and population

This cross-sectional study was conducted in the department of Clinical Biochemistry, Bangladesh Institute of Health Sciences (BIHS) Hospital, Dhaka, Bangladesh during the period of January 2012 to June 2012. The target population of this study was adult subjects attending the out-patient department of BIHS general hospital during the study period. A short invitation letter was supplied to the target subjects at the out-patient department (OPD) entry point at 7:30 - 8:00 AM. Subjects willing to participate in the study were interviewed face to face by predefined questionnaire and clinical examinations were carried out by the medical officer, healthcare providers or by the researcher before data and specimen collection. Around 10 subjects were included each day and total 348 adult subjects were included purposively according to inclusion-exclusion criteria. Subjects with other comorbid diseases (infection, stroke, myocardial infarction, major surgery, severe allergy, cancer, severe illness, liver abnormalities, chronic kidney disease (CKD), pregnancy, edema, oral contraceptive or anti-inflammatory drugs users were excluded. Anthropometric data and clinical history were recorded according to standard procedure. Informed consent was taken before data collection and clinical examination. Before specimen collection clinical history (diabetes, hypertension, blood pressure), demographic variables (height and weight) and habits (smoking) or medication status of the participants were recorded.

Anthropometric measurements

Height and weight of each individual was measured to the nearest 0.1 cm and 0.1 kg using portable stadiometer and calibrated platform scales wearing light cloth without shoes and hats.

Blood pressure measurement

Mercury sphygmomanometers were used to measure blood pressure following standard procedures [22]. From two readings each of systolic and diastolic blood pressures were recorded taken at 5 minutes intervals average was taken and expressed to nearest 1 mmHg.

Glycemic measurement

Plasma glucose levels were measured by glucose oxidase method at fasting (10-12 hours) state and 2 hours after 75 g of oral glucose load. Diabetes mellitus was diagnosed by WHO diagnostic criteria for diabetes mellitus [23].

Clinical measurements

Blood samples were obtained from the antecubital vein with the subject sitting comfortably in a chair in a quiet room and transfused into vacuum tubes containing ethylenediaminetetraacetic acid (EDTA) and in tubes without anticoagulant in the morning after an overnight fasting period. After separation, blood samples were centrifuged for 10 minutes at 3000 rpm to obtain plasma/serum. Blood glucose levels were determined from plasma on the same day (CV < 2.5%) and serum was aliquoted into 2 microtubes, one preserved for lipid profile measurements and another was preserved at -20°C for *hs*CRP estimation until analysis.

Serum total cholesterol, triglyceride concentrations were measured by end point technique using Dimension® clinical chemistry system (Siemens Healthcare Diagnostics Inc. USA) using reagents (Cat. No. DF27, Siemens Healthcare Diagnostics Inc. USA). HDL cholesterol was measured by a fully automated reagent format Dimension® clinical chemistry system (Siemens Healthcare Diagnostics Inc. USA). In brief, the HDLC assay measures HDLC concentration without sample pretreatment or specialized centrifugation steps, using a two reagent format. In the first reaction, chylomicrons, very low-density lipoprotein, LDL form water soluble complexes with dextran sulfate in the presence of magnesium sulfate. Polyethylene glycol-modified cholesterol esterase and subsequently cholesterol oxidase converts HDLC to Δ4-cholestenone and hydrogen peroxide. The hydrogen peroxide thus formed reacts with 4-aminoantipyrine to form color complex that was measured by a bichromatic (600/700 nm) end-point technique. The coefficients of variation (CV) were <3% for total cholesterol, triglycerides and HDL cholesterol. LDL cholesterol concentrations in serum were calculated by Friedewald's formula [24]. *hs*CRP concentrations were determined immunoturbidimetric by using BN ProSpec® system (Siemens Healthcare Diagnostics Products GmbH, Germany) and CV was <5%. hsCRP <1.0 mg/l, 1-3.0 mg/l and >3.0 mg/l were considered as low, medium and high hsCRP [25]

Statistical Methodology

Statistical analysis was performed using MedCalc® version 11.4 for Windows, *STATISTICA* version 8.0 for windows. All data were expressed as mean±SD (standard deviation) or median with interquartile range and percentage (%) as appropriate. We used Spearman rank correlation to assess the relationship hsCRP with measured variables. To analyze the factors that affect the changes of *hs*CRP, a multivariate linear regression model was used to determine *hs*CRP as dependent variable and gender, body mass index, systolic blood pressure, diastolic blood pressure, blood lipids, serum glucose (fasting blood glucose) as independent and gender as categorical variables. The level for statistical significance was set at 0.05.

RESULTS

Clinical Characteristics

Total 348 subjects were included in this study in which 169 (48.56%) were male and 179 (51.44%) were female. The mean age of the study subjects was 50.5±11.5 years and their BMI was 26.7±4.5 kg/m^2. Of the total subjects, 289 (83.05%) were diabetic, 204 (58.62%) were hypertensive and 35 (7.87%) had a habit of smoking. Among the study subjects, 197 (56.61%) used lipid lowering drugs and 292 (83.91%) use antidiabetic agents and all hypertensive subjects use antihypertensive agents for the management of diabetes mellitus or hypertension. Characteristics of the study subjects are shown in table 1.

Table 1. Characteristics of the study subjects

Variables	n (Percentages)	Median (IQR)
Age (years)	-	50 (42-59)
Sex (Female)	179 (51.44%)	-
Body mass index (kg/m^2)	-	26.4 (23.6-28.6)
Systolic blood pressure (mmHg)	-	120 (120-130)
Diastolic blood pressure (mmHg)	-	80 (80-80)
Diabetes Mellitus (type 2)	289 (83.05%)	-
Hypertension	204 (58.62%)	-
Smoker	35 (7.87%)	-

There was no primary evidence of known allergy, edema, severe illness, cancer, infection, liver dysfunction and chronic kidney disease (CKD) according to hospital's registry or participant's information.

Lipid parameters of the study subjects

The median (interquartile range) of serum total cholesterol (TC), HDL Cholesterol, LDL cholesterol and triglycerides (TG) were 175 (IQR 148-205) mg/dl, 36 (IQR 30-40) mg/dl, 107 (IQR 82-132) mg/dl and 154 (IQR 109-210) mg/dl respectively.

Distribution of individual dyslipidemia among the study subjects

Table 2 shows the distribution of single lipid abnormality among the study subjects. Ninety nine (28.45%) subjects had elevated serum TC (>200 mg/dl), 212 (57.47%) had low HDL cholesterol (< 35 mg/dl for male and <40 mg/dl for female), 238 (68.39%) had elevated LDL cholesterol (LDL cholesterol not at goal) and 180 (51.72%) had elevated serum TG (> 150 mg/dl).

Distribution of hsCRP in the study subjects

The median (IQR) value of hsCRP was 2.4 (1.1 - 5.4) mg/l. Distribution of hsCRP according to different cut-off values is shown in table 3 of the total study subjects (n=348), 79 (22.7%) subjects had low hsCRP (hsCRP < 1.0 mg/l), 111 (31.9%) had moderate level of hsCRP (hsCRP: 1.0 – 3.0 mg/l) and 158 (45.4%) had high level of hsCRP (hsCRP > 3.0 mg/l) (Table 3).

Table 2. Distribution of high triacylglycerol, high total cholesterol, high LDL cholesterol and low HDL cholesterol among the study subjects

Parameters	Median (IQR)	Number (%) with
Triacylglycerol (mg/dl)	154 (109-210)	186 (51.72%)
Total cholesterol (mg/dl)	175 (148-205)	99 (28.45%)
LDL cholesterol (mg/dl)	107 (82-132)	238 (68.39%)
HDL cholesterol (mg/dl)	36 (30-40)	212 (57.47%)

High TG (TG>150 mg/dl), high total cholesterol (>200 mg/dl), high LDL cholesterol (>100 mg/dl) and low HDL cholesterol (<30 mg/dl for male, <40 mg /dl for female)

Table 3. Distribution of hsCRP in the study subjects

Concentration of hsCRP	Median (IQR)	Number of subjects (%)
Low	0.84 (0.77-0.84)	79 (22.7%)
Medium	1.9 (1.4-2.4)	111 (31.9%)
High	5.9 (4.1-8.5)	158 (45.4%)

hsCRP category: low, hsCRP<1 mg/dl; medium, hsCRP: 1 - 3 mg/dl; high, hsCRP>3 mg/dl

Comparison of lipid parameters and other variables between different hsCRP groups

Comparison of lipid parameters and other variables between hsCRP groups (*hs*CRP ≤ 3 mg/l and *hs*CRP>3.0 mg/l) is presented in table 4. Mann-Whitney tests (as appropriate) were not significant for lipid parameters and age. Only BMI differed significantly between subjects with hsCRP≤3.0 mg/l and hsCRP>3.0 mg/l.

Table 4 Comparison of lipid parameters and other variables between different hsCRP groups

Parameters	hsCRP≤3 mg/l (n=190)	hsCRP>3 mg/l (n=158)	*p value*
Age (years)	50 (42-58)	50 (42.8-60)	0.9902
BMI (kg/m^2)	25.4 (23.3-27.9)	27.3 (24.3-30.1)	<0.0001
TG (mg/dl)	152 (101-205)(	157 (117-227)	0.0993
TC (mg/dl)	174 (149-205)	177 (147-207)	0.7969
LDLC (mg/dl)	107 (84-132)	106 (79-131)	0.8418
HDLC (mg/dl)	36 (30-40)	35.5 (30-40)	0.6049

Data expressed as median with interquartile range; TC, Total cholesterol; HDLC, High-density lipoprotein cholesterol; LDLC, Low-density lipoprotein cholesterol; TG, Triglycerides; BMI, Body mass index

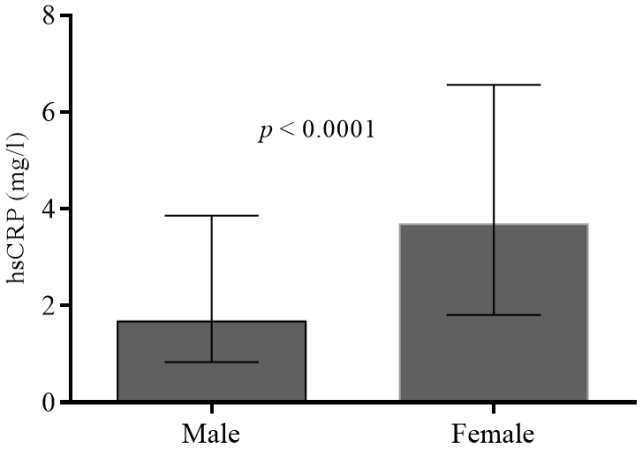

Figure 1. Comparison of hsCRP between male and female

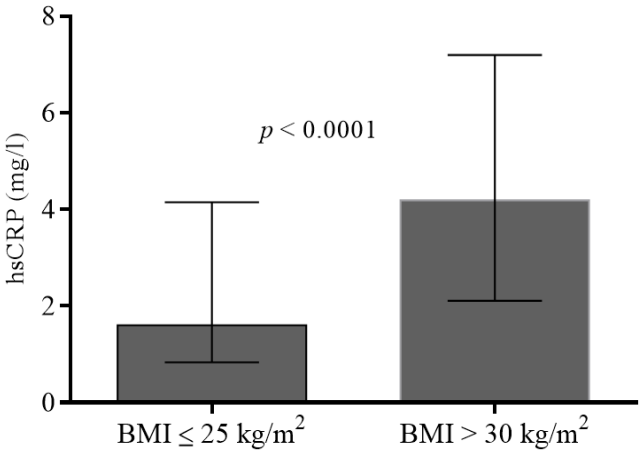

Figure 2. Comparison of hsCRP between lean and obese subjects

Comparison of hsCRP between male and female

The median (IQR) of hsCRP in male and female were 1.8 (IQR 0.84-3.8) mg/l and 3.6 (IQR 1.8-6.5) mg/l respectively. hsCRP in female was significantly higher compared to male ($p < 0.0001$, Fig 1).

Comparison of hsCRP between diabetic and nondiabetic subjects

The median (IQR) of hsCRP in subjects without type 2 diabetes mellitus was 2.6 (IQR 1.1-5.7) mg/l and in subjects with type 2 diabetes mellitus, it was 2.2 (IQR 0.99-4.2) mg/l, $p = 0.4640$.

Comparison of hsCRP between subjects with lipid lowering drugs and without lipid lowering drugs

The median and interquartile ranges of hsCRP in subjects with lipid lowering drugs and without lipid lowering drugs were 2.2 (0.94-4.8) mg/l and 2.9 (1.2-5.8) mg/l, $p = 0.0695$.

Comparison of hsCRP between lean and obese subjects

In lean (n=131, BMI≤25 kg/m^2), the median and interquartile ranges of hsCRP concentration was 1.6 (0.84-4.1) mg/l and in obese (n=61, BMI>30 Kg/m^2), hsCRP concentration was 4.3 (2.1-7.1) mg/l. hsCRP was significantly higher in lean subjects compared to obese subjects ($p < 0.0001$, Fig 2).

Correlation of hsCRP with different variables

The Spearman nonparametric correlation coefficient of hsCRP was -0.050 ($p = 0.3508$) for age, 0.291 ($p < 0.0001$) for BMI, 0.098 ($p = 0.0673$) for triacylglycerol, 0.037 ($p = 0.4917$) for total cholesterol, -0.034 ($p = 0.5267$) for HDL cholesterol and 0.008 ($p = 0.8831$) for LDL cholesterol.

Multivariate linear regression analysis

Multiple linear regression analyses considering hsCRP as dependent variable and lipid parameters as independent

Table 5. Multiple linear regression analyses of independent variables associated with hsCRP concentrations in the study subjects

Parameters	*β value*	*p value*	*β value**	*P value**	*β value***	*p value***
Age	-0.0091	0.8634	0.0015	0.9783	-0.0091	0.8718
Sex	-0.2395	<0.0001	0.0243	0.8510	0.1393	0.8279
BMI	**0.1493**	**0.0059**	**0.1471**	**0.0071**	**0.1565**	**0.0051**
Triglyceride	-0.0386	0.6669	-0.0231	0.7978	-0.0237	0.7997
Total Cholesterol	0.2045	0.3231	0.1584	0.4461	0.1757	0.8222
LDL cholesterol	-0.2114	0.2596	-0.1753	0.3515	-0.2031	0.2930
HDL cholesterol	**-0.1808**	**0.0074**	**-0.1654**	**0.0139**	**-0.1508**	**0.0296**
DM (Yes)	-	-	0.1151	0.3729	0.0164	0.9238
Sex.DM (Biased)			-0.2996	0.0188	-0.3900	0.0209
HTN (Yes)			-	-	0.1612	0.4257
LLD (No)					0.0278	0.8678

*, Multiple linear regression when adjusted for DM

**, when further adjusted for LLD and HTN

variable showed no significant association of hsCRP with these parameters. When adjusted for age, sex and BMI, β value was significant for HDLC (β= - 0.1808, p=0.0074) (Table 5) and when further adjusted for presence of diabetes mellitus, the β value was -0.1654 (p=0.0139) statistically significant.

DISCUSSION

Dyslipidemia is a prominent one among the traditional biochemical risk factor of CVDs [26-28]. The nature and extent of dyslipidemia, however, may vary depending on the ethnic, cultural and environmental background of a particular population. The present study revealed that, chronic subclinical inflammation and lipid disorders are most prevalent. While this finding is important in having an idea about the CVD risk of tertial hospital based patient, it must be cautioned that this may have considerable bias as it is not a randomized population based data. In a recent hospital based study, Thakur et al has reported similar pattern of lipid disorders in their hospital based patients [29]. Like their patients, the group of subjects in the present study may be assumed to have much higher risk of CVDs. While confirmation of this assumption needs longitudinal follow-up, it is indeed important to observe that a large proportion of subjects do have a convergence of traditional CVD risk factors like diabetes, hypertension, obesity and smoking inaddition to dyslipidemia.

The major focus of the present study was to investigate the association of chronic subclinical chronic inflammation (as evidenced by elevated serum *hs*CRP) with individual lipids. The association of hsCRP with lipid parameters, age and BMI was explored by group difference analysis and no significant difference was found for individual lipid parameters and age except BMI. In this study, hsCRP was found to be inversely related to HDL-C on adjusting confounders like diabetes mellitus [30], obesity [4-8], lipid lowering drugs [31], age, gender [32] and other clinical parameters.

Higher *hs*CRP has been found to be associated with CVDs by a number of cross-sectional studies [29] and it has been reasonably confirmed as a predictor of CVDs by substantial volume of longitudinal data. Its independent role, additional to the traditional risk factors, has also been substantiated and particularly its additive role with individual lipids, have also been published [30]. Exploration of this interrelationship is important to find out the causal connection between subclinical inflammation and lipidemic markers and, consequently to design a rational management and prevention plan.

Thus, this cross-sectional study showed that chronic subclinical inflammation is associated with HDL cholesterol. This finding is consistent with the findings of previous studies done in this population [33,34] or other population [35] and analogous to the findings of Zuliani et al [36] and Ahmad et al [37] who found inverse relationship between another inflammatory marker (IL-6) and HDL cholesterol in cross-sectional studies carried out in community-dwelling older or middle aged persons. Reduced anti-inflammatory effects due to low HDL particles may be one of the causal factors of elevated hsCRP in these subjects. Anti-inflammatory property of HDL particles is linked to its ability to limit lipid peroxidation [38] and its ability to down regulate the production of inflammatory biomarkers [38, 39]. Recent clinical trial showed that infusions of reconstituted HDL (rHDL) particles reduce the inflammatory biomarker in a dose-dependent manner [40]. The relationship between inflammation and HDL particles is likely not to be unidirectional and may be bidirectional i.e., low serum HDL or high oxLDL may be responsible for chronic subclinical inflammation, or chronic subclinical inflammation may be the cause of dyslipidemia or particularly dysfunctional HDL. From this data it may be concluded that a substantial proportion of middle aged subjects present with low HDL cholesterol which is associated with chronic subclinical inflammatory process. This may possibly posing increased risk in the development of cardiovascular diseases of these subjects.

CONFLICT OF INTEREST

The author(s) declare(s) that there is no conflict of interest regarding the publication of this paper.

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