Endocrine (2012) 42:132–138
DOI 10.1007/s12020-012-9599-x

ORIGINAL ARTICLE

The relationship between high-sensitivity C-reactive protein and ApoB, ApoB/ApoA1 ratio in general population of China

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Received: 13 November 2011 / Accepted: 28 December 2011 / Published online: 15 January 2012

Abstract Inflammatory biomarker high-sensitivity C-reactive protein (hsCRP) is considered as a major predictor of cardiovascular events. Apolipoprotein B (ApoB) directly reflects the number of plasma atherogenic lipoproteins, and may play a major role in vascular inflammation. We aimed to assess whether an association between ApoB and hsCRP exists and, furthermore, to examine whether ApoB is more predictive of the inflammatory status than other cardiovascular risk factors. This was a cross-sectional study, with 511 apparently healthy adult subjects enrolled. Waist circumference (WC), body mass index (BMI), and blood pressure (BP) were measured. Plasma glucose levels, hsCRP, lipid profile, and insulin were collected after 10–14 h fasting. From the lowest to the highest quartile of hsCRP, the values for BMI, WC, BP, HOMA-IR, insulin, glucose level, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), ApoB and the ApoB/apolipoprotein A1 (ApoA1) ratio were increased as the hsCRP level increased ($P < 0.01$), and high-density lipoprotein cholesterol (HDL-C) and ApoA1 levels declined as hsCRP level increased ($P < 0.0001$). Pearson's correlation analysis demonstrated that hsCRP correlated with all variables ($P < 0.01$), except for total cholesterol (TC) ($P = 0.154$) and LDL-C ($P = 0.087$). According to forward stepwise regression analysis with hsCRP as the dependent variable, WC was the only variable entered the regression model. ApoB level correlated with hsCRP level but was not the major determinant of hsCRP. WC was stronger than other cardiovascular risk factors in the associations with hsCRP. Abdominal obesity rather than atherogenic dyslipidemia was the primary cause of chronic inflammatory status.

Keywords High-sensitivity C-reactive protein · Apolipoprotein B · Inflammation · Obesity · Waist circumference

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Introduction

The view that low-level inflammatory status could promote the incidence of atherosclerotic diseases has been widely accepted. Inflammation plays an important role during all phases of atherosclerosis, from endothelial dysfunction to plaque rupture, which leads to vessel lumen occlusion and clinical events. High-sensitivity C-reactive protein (hsCRP) is an easily measured and reliable biomarker of the inflammatory status. Some clinical trials have indicated that hsCRP is an independent predictor for future cardiovascular events in apparently healthy populations [1, 2]. Similar results have also been found in patients with stable coronary artery diseases (CAD) [3]. Thus, it is important to identify the trigger of vascular inflammation to decrease the incidence of cardiovascular events.

However, previous laboratory experiments and clinical trials have not revealed the trigger of vascular inflammation. Hypertension, diabetes, and obesity participate in the process of endothelial dysfunction characterized by an impaired vasomotor response, increased vascular permeability and

platelet adhesion and aggregation, which is the first step in the development of vascular inflammation. In addition, it is also believed that elevated levels of atherogenic lipoproteins including very low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) also play an important role in inflammation [4]. Several in vitro and animal studies have shown that elevated levels of atherogenic lipoproteins result in monocytes and T lymphocytes adhering to the endothelial surface and migrating into the subendothelial spaces; moreover, these immunocytes transformed into foam cells [4, 5]. As a component of all atherogenic lipoproteins, apolipoprotein B (ApoB) directly reflects an elevated level of plasma atherogenic lipoproteins. Apolipoprotein A1 (ApoA1) is the major protein component of high-density lipoprotein cholesterol (HDL-C) and reflects the levels of plasma anti-atherogenic lipoproteins, whereas the ApoB/ApoA1 ratio reflects the cholesterol balance between potentially atherogenic and anti-atherogenic lipoprotein particles. Thus, both ApoB level and the ApoB/ApoA1 ratio are believed to be useful predictors of cardiovascular events [6]. Therefore, we hypothesized that an elevated level of plasma ApoB or the ApoB/ApoA1 ratio may be the reason for an increase in the concentration of hsCRP and the initiation of vascular inflammation in the general population. The aim of our study was to examine whether an association between the levels of ApoB and hsCRP exists in the general population of China and, furthermore, to examine whether the association between the levels of ApoB and hsCRP was stronger than other traditional risk factors of cardiovascular diseases (CVD).

Methods

Subjects

This was a cross-sectional study. The study was approved by the local ethical committee. All subjects were healthy volunteers recruited from the Luohuang Community in the urban area of Chongqing, which is a large city in Southwestern China, and informed consent was obtained from all subjects before participating in the study.

Only the subjects who were 20–80 years old, nonsmokers or seldom smokers and low alcohol consumers (<2 drinks per day) and who participated in structured exercise for <2 h per week were included in the study. The exclusion criteria were the following: (1) hsCRP level was >10 mg/l, (2) suffered from cancer, current renal disease, liver disease or rheumatic diseases or acute or chronic inflammatory diseases, (3) had a history of CVD or administered lipid-lowering medication, (4) use of steroid or non-steroidal anti-inflammatory drugs, (5) use of aspirin, and (6) alcohol and drug abuse. Finally, a total of 511 apparently healthy adults were enrolled.

Medical examinations and measurements

Fasting body weight was measured in kilograms with a digital scale from 0700 to 0900, and height was measured in centimeters with a metric scale. Body mass index (BMI) was calculated as the ratio of weight to the square of height. Waist circumference (WC) was measured at the midpoint between the lower edge of the costal arch and the top of the iliac crest. After a 5-min period of rest, blood pleasure (BP) was measured in the sitting position with a mercury sphygmomanometer (in mmHg); the mean of the two values was used as the measurement of BP.

A series of routine biochemical analyses were performed on all subjects participating in the study after 10–14 h fasting. A standard 75 g oral glucose tolerance test (OGTT) was completed for the subjects older than 30 years of age. Serum hsCRP was measured using high-sensitivity immunoturbidimetric assays (Orion Diagnostics, Finland). Plasma glucose was measured using hexokinase assays (Olympus Diagnostics, Japan). Insulin was measured using chemiluminescence assays (Roche Diagnostics, Germany). Total cholesterol (TC), triglyceride (TG), HDL-C, and low-density lipoprotein cholesterol (LDL-C) were measured with an enzymology assay (Wako Diagnostics, Japan); ApoB and ApoA1 were measured with nephelometry assays (Olympus Diagnostics, Japan). Insulin resistance (IR) was estimated by the homeostasis model assessment of insulin resistance (HOMA-IR), which was calculated using the following formula: Fasting insulin (Fins) (μU/ml) × Fasting plasma glucose (FPG) (mmol/l)/22.5.

Statistical analysis

Normal distribution data are expressed as the mean ± SD. Skewed distribution data are expressed as the median and interquartile ranges and were log-transformed (base 10) before statistical analysis. Mean levels of variables were compared across quartiles of hsCRP or lipids by analysis of variance (ANOVA), and the χ^2 test was used for categorical variables. Comparisons between each combination of two groups were made using the Student–Newman–Keuls test. The association between hsCRP and other variables was examined by Pearson's correlation analysis. Multivariable stepwise forward analysis was used to examine the independent correlated factor of hsCRP. A P value <0.05 using a two-sided test was considered statistically significant. All statistical analyses were conducted with the SPSS 11.0 statistical package.

Results

The baseline data are presented in Table 1. This analysis included 352 males and 159 females with an average age of 46.0 ± 11.6 years. Approximately one-fourth (25.2%) of our subjects had hypertension (i.e., hypertension history or systolic BP (SBP) ≥140 mmHg or diastolic BP (DBP) ≥90 mmHg), 9.2% had diabetes (i.e., diabetes history, FPG ≥ 7.0 mmol/l, or 2 h-OGTT plasma glucose ≥11.1 mmol/l) and 23.3% had abdominal obesity (WC ≥90 cm in males or ≥80 cm in females). According to the Chinese guidelines for the prevention and treatment of dyslipidemia in adults [7], 33.1% of the individuals had high TG (≥1.70 mmol/l), 33.1% had high TC (≥5.18 mmol/l), 18.8% had low HDL-C (<1.04 mmol/l), and 26.8% had high LDL-C (≥3.37 mmol/l).

All subjects of this analysis were divided into four groups according to quartiles of the hsCRP level: the first group, hsCRP level <0.20 mg/l, $n = 130$; the second group, hsCRP level from 0.20 to 0.40 mg/l, $n = 126$; the third group, hsCRP level from 0.41 to 1.00 mg/l, $n = 125$; and the fourth group, hsCRP level >1.00 mg/l, $n = 130$. We compared age, WC, BMI, SBP, DBP, FPG, 2 h-OGTT-PG, Fins, HOMA-IR, ApoA1 level, ApoB level, and the ApoB/ApoA1 ratio among different groups (Table 2). With an increasing level of hsCRP, age, BMI, SBP, DBP, FPG, 2 h-OGTT-PG, fasting insulin (Fins), HOMA-IR, TG level, LDL-C level, ApoB level, and the ApoB/ApoA1 ratio increased ($P < 0.01$), whereas the levels of HDL-C and ApoA1 decreased ($P < 0.01$), and TC level neither increased nor decreased ($P = 0.062$).

The distribution of the means of hsCRP was displayed according to the quartiles of different lipid levels (Fig. 1). We found that the means of hsCRP all have significant differences among these groups ($P < 0.01$), except for TC ($P = 0.194$). The concentration of hsCRP increased with the level of TG, ApoB, and the ApoB/ApoA1 ratio and decreased with the level of HDL-C and ApoA1 ($P < 0.01$). The level of hsCRP in the highest quartile of LDL (Q4) was not greater than the lowest quartile (Q1; $P > 0.05$).

According to Pearson's correlation analysis, we found that hsCRP correlated positively with BMI, WC, BP, plasma glucose, Fins, HOMA-IR, TG level, ApoB level, and the ApoB/ApoA1 ratio ($P < 0.01$) and negatively with the levels of HDL-C and ApoA1 ($P < 0.01$). The hsCRP level was not significantly associated with TC or LDL-C (Table 3).

Finally, we used multivariate stepwise forward regression analysis to estimate the independent predictor of hsCRP. In this regression formula, BMI, WC, SBP, DBP, FPG, 2 h-OGTT-PG, Fins, HOMA-IR, TG level, HDL-C level, ApoA1 level, ApoB level, and the ApoB/ApoA1 ratio were used as independent variables, and hsCRP level was used as the dependent variable. Only WC entered the regression model when the F value was 58.432 ($P < 0.01$).

Table 1 Descriptive characteristics of subjects

Variable	Mean ± SD	Range
Age (years)	46.0 ± 11.6	22.0–76.0
BMI (kg/m^2)	23.6 ± 3.1	16.4–35.7
WC (cm)	80.8 ± 10.2	58.0–15.5
SBP (mmHg)	125 ± 17	87–186
DBP (mmHg)	78 ± 10	52–117
FPG (mmol/l)	5.12 ± 0.95	2.70–15.80
2 h-OGTT-PG (mmol/l)	6.97 ± 2.89	2.20–23.40
Fins (μU/ml)[a]	9.12 (6.00–12.99)	0.30–98.69
HOMA-IR[a]	2.01 (0.92–3.01)	0.06–21.13
TC (mmol/l)	4.86 ± 0.92	2.72–10.13
TG (mmol/l)[a]	1.21 (0.85–1.92)	0.14–21.25
HDL-C (mmol/l)	1.33 ± 0.36	0.31–2.99
LDL-C (mmol/l)	2.94 ± 0.79	0.93–8.18
ApoA1 (g/l)	1.47 ± 0.30	0.80–2.43
ApoB (g/l)	0.86 ± 0.21	0.39–1.84
the ApoB/ApoA1 ratio	0.61 ± 0.20	0.21–1.29
hsCRP (mg/l)[a]	0.39 (0.20–1.00)	0.10–8.70

[a] Data are skewed distribution and presented as median (interquartile range)

Discussion

Several studies indicated that the levels of lipoproteins and their subfractions closely correlated with atherosclerosis. Elevated concentrations of LDL-C or ApoB, an increased ApoB/ApoA1 ratio or reductions in HDL-C and ApoA1 levels would increase the risk of CVD [8, 9]. In our study, the result of the Pearson's correlation analysis demonstrated that both ApoA1 and HDL-C level were significantly and inversely related to hsCRP ($P < 0.01$). HDL could promote cholesterol efflux, which resulted in a reduction in the formation of foam cells and could inhibit cytokine-induced expression of endothelial cell adhesion molecules [10], and prevent the inflammatory response. As the major protein of HDL, ApoA1 can prevent lipopolysaccharide (LPS) from participating in inflammation after binding to a lipoprotein, downregulate neutrophil function and inhibit activated monocytes without affecting cell proliferation [11]. However, neither HDL-C nor ApoA1 was an independent predictor of hsCRP after forward stepwise analysis finally. The reason for this result may be that the anti-inflammatory effect of HDL was influenced by the hyperglycemia and obesity. HDL would lose its ability to inhibit monocyte adhesion to endothelial cells after glycation [12], the anti-inflammatory effect of HDL would be weakened in centrally obese humans [13].

Table 2 Comparison of mean of variables in quartiles of hsCRP

Variables	Quartiles of hsCRP				*P* value
	Q1	Q2	Q3	Q4	
Age (years)	42.0 ± 10.3	46.0 ± 11.0*	47.4 ± 11.0†	48.8 ± 12.8§	<0.0001
Gender					
n male[b]	70 (53.85%)	85 (67.46%)	96 (76.80%)	101 (77.69%)	<0.0001
n female[b]	60 (46.15%)	41 (32.54%)	29 (23.20%)	29 (22.31%)	<0.0001
BMI (kg/m^2)	22.0 ± 2.6	23.4 ± 3.2*	24.7 ± 2.8†‡	24.3 ± 3.2§¶	<0.0001
WC (cm)	74.9 ± 8.6	79.5 ± 9.4*	84.8 ± 9.1†‡	84.3 ± 10.2§¶	<0.0001
SBP (mmHg)	119 ± 16	125 ± 17*	129 ± 17†	127 ± 15§	<0.0001
DBP (mmHg)	75 ± 10	77 ± 10	79 ± 11†	79 ± 9§	<0.0001
FPG (mmol/l)	4.82 ± 0.43	5.18 ± 0.95*	5.13 ± 0.85†	5.33 ± 1.29§	<0.0001
2 h-OGTT-PG (mmol/l)	5.64 ± 1.23	7.11 ± 3.02*	7.49 ± 3.19†	7.50 ± 3.17§	<0.0001
Fins (μU/ml)[a]	0.82 ± 0.33	0.95 ± 0.23*	0.94 ± 0.27†	0.99 ± 0.28§	<0.0001
HOMA-IR[a]	0.15 ± 0.34	0.31 ± 0.26*	0.29 ± 0.28†	0.36 ± 0.28§	<0.0001
TC (mmol/l)	4.68 ± 0.71	4.95 ± 1.03	4.94 ± 0.87	4.88 ± 1.00	0.062
TG (mmol/l)[a]	0.88 ± 0.25	1.31 ± 0.23*	1.46 ± 0.33†	1.47 ± 0.26§	<.0001
LDL-C (mmol/l)	2.74 ± 0.69	3.01 ± 0.95*	3.01 ± 0.74†	3.00 ± 0.73§	0.019
HDL-C (mmol/l)	1.48 ± 0.35	1.34 ± 0.39*	1.26 ± 0.35†	1.23 ± 0.28§	<0.0001
ApoA1 (g/l)	1.60 ± 0.32	1.48 ± 0.30*	1.40 ± 0.27†	1.40 ± 0.26§	<0.0001
ApoB (g/l)	0.78 ± 0.19	0.88 ± 0.22*	0.89 ± 0.22†	0.89 ± 0.20§	<0.0001
The ApoB/ApoA1 ratio	0.52 ± 0.19	0.62 ± 0.19*	0.66 ± 0.19†	0.66 ± 0.21§	<0.0001

[a] data are skewed distribution, log-transformed (base 10) before statistics

[b] count data are adopted χ^2 test

* Q2 vs. Q1, $P < 0.05$; † Q3 vs. Q1, $P < 0.05$; § Q4 vs. Q1, $P < 0.05$, ‡ Q3 vs. Q2, $P < 0.05$; ¶ Q4 vs. Q2, $P < 0.05$

In our study, hsCRP level did not correlate with LDL-C level ($P = 0.087$). The measurement of LDL-C assesses the mass of cholesterol in the LDL particle, but not the number and size of the LDL particle. LDL particle size negatively associates with its ability to cross the arterial endothelial barrier into the intimae; thus, small dense LDL (sLDL) particles are more atherogenic than large buoyant ones [4]. Therefore, the concentration of LDL-C might not reflect the severity of inflammation.

Several studies demonstrated that ApoB was better than other traditional risk factors in predicting cardiovascular events [6, 14, 15]. As the major component of atherogenic lipoproteins, the total ApoB level represents the total atherogenic particle number. However, we failed to find that ApoB was the major determinant for hsCRP. Faraj et al. [4] found that ApoB level was an independent predictor of many inflammatory biomarkers such as hsCRP, interleukin-6 (IL-6), orosomucoid, haptoglobin and α1-antitrypsin in postmenopausal, overweight and obese women, and other risk factors were less predictive. Our subjects were from the general population, and the baseline of both hsCRP and ApoB levels were lower than for an overweight or obese population; the vascular inflammation and dyslipidemia were less severe, and the risk of CVD was also lower than Faraj's study. These differences may contribute to why our results were inconsistent with those of Faraj et al.

Our analysis indicated that WC was the major determinant of the high CRP level in the general Chinese population, because multiple linear forward stepwise regression analysis revealed that WC was the only variable that entered into the regression formula. Earlier studies found that hsCRP level was strongly associated with parameters of visceral obesity (including WC, waist-to-hip ratio, and visceral adipose tissue accumulation measured by computed tomography), even after adjusting for age, gender, and smoking status [16, 17]. As the anthropometric index of abdominal obesity, WC reflects the storage of visceral adipose tissue, which is considered as an important endocrine organ recently. Various biologically active substances known as adipokines are produced and secreted by adipocytes. Current evidence suggests that some adipokines may trigger CRP production by endothelial cells, smooth muscle cells, and monocyte/macrophages [18]. Some adipokines have pro-inflammatory properties or anti-inflammatory properties. For example, as anti-inflammatory adipokines, adiponectin is negatively correlation with body fat mass, with visceral fat accumulation. It can reduce the ability of macrophages to develop into foam cells, limit subendothelial lipid accumulation and promote vasodilatation, these

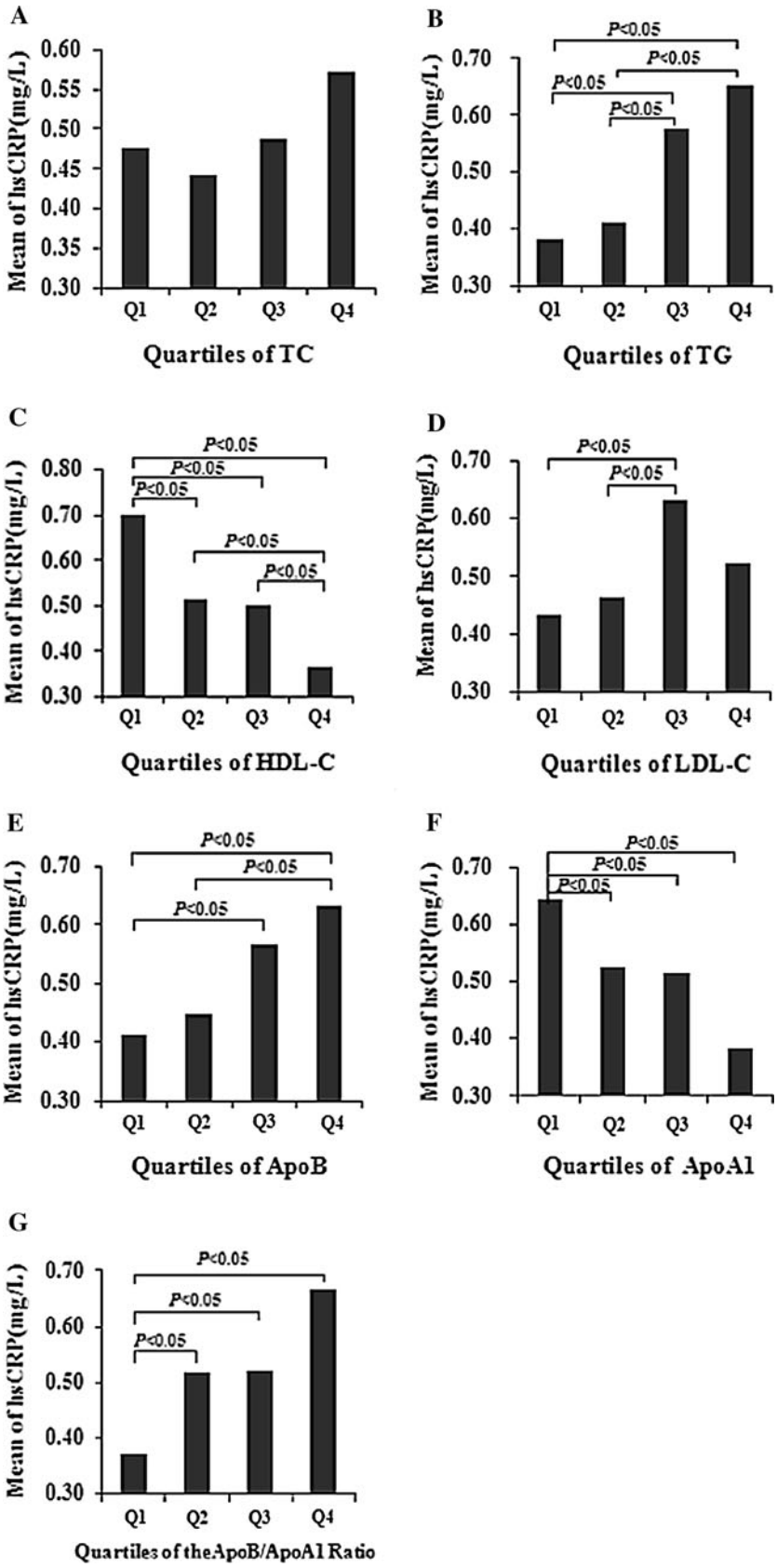

Fig. 1 Comparison of hsCRP in quartiles of different lipids. TG are skewed distribution log-transformed (base 10) before statistics. Comparison of hsCRP in quartiles of different lipid profile groups by ANOVA analysis, P values as followed, **a** $P = 0.194$, **b** $P < 0.0001$, **c** $P < 0.0001$, **d** $P = 0.015$, **e** $P = 0.002$, **f** $P = 0.001$, **g** $P < 0.0001$

Table 3 Pearson correlation between hsCRP and different variables

Variables	Correlation coefficient (r)	P value
Age	0.183	<0.0001
BMI	0.251	<0.0001
WC	0.341	<0.0001
SBP	0.147	0.001
DBP	0.137	0.002
FPG	0.174	<0.0001
2 h-OGTT-PG	0.179	<0.0001
FIns	0.151	<0.0001
HOMA-IR	0.181	<0.0001
TC	0.063	0.154
TG	0.229	<0.0001
LDL-C	0.079	0.087
HDL-C	−0.230	<0.0001
ApoA1	−0.206	<0.0001
ApoB	0.142	0.002
the ApoB/ApoA1 ratio	0.217	<0.0001

actions result in anti-atherosclerotic effect [19]. Obestatin and apelin are new adipokines. The roles of these adipokines have not yet been fully elucidated but they could have anti-inflammatory properties [20, 21]. Otherwise, several pro-inflammatory factors, including IL-1, IL-6 and tumor necrosis factor-α (TNF-α), are produced in the adipose tissue. The dysregulated synthesis and/or secretion of adipokines will lead to a state of inflammation. Thus, the individuals with abdominal adiposity may have been in a status of systemic inflammation, and it is necessary to measure WC in clinical practice to screen for individuals suffering from high CVD risk in the general population. Otherwise, lifestyle interventions including increased physical activity and dietary interventions should be performed for abdominally obese patients to reduce fat aggregation in the abdomen and decrease vascular inflammation, thereby preventing the incidence of CVD.

There are several limitations in the present study. First, statistics of the subjects administered antiglycemic agents and antihypertensive agents had not done in this study. Both hyperglycemia and hypertensive are important factors of inflammation, while antiglycemic agents and antihypertensive agents may affect the inflammation. The second, as is the case in any cross-sectional study, only the correlation between hsCRP and the other variables was analyzed, and thus, the causality and mechanisms could not be examined. Last but not the least, the subjects were from a random sampling from the Luohuang Power Plant Community in the Chongqing urban area; the standard of living in this area is better than the general population of Chongqing; thus, the study was not able to completely reveal information for the general population of China. Otherwise, future prospective studies should be employed to investigate the hypotheses of this study.

In summary, the ApoB level and the ApoB/ApoA1 ratio correlate with the hsCRP level, but neither were independent predictors of hsCRP level, the same as BMI, plasma glucose, BP, IR, and other traditional lipids profiles. The correlation between WC and hsCRP level was stronger than that between the other traditional risk factors and hsCRP in this general population. This study suggests that WC is an independent predictor of hsCRP level, and abdominal obesity may be the major cause of inflammation. Thus, reducing abdominal obesity may retard chronic inflammation and the development of atherosclerosis.

Acknowledgments This research was supported by grants from Chongqing Sciences and Technology Commission (grants no. 09BB5076). We thank Professor Yonghong Wang (Department of medical examination center, the First Affiliated Hospital of Chongqing Medical University) for help with collecting the specimen in her directions. We also thank Dr. Xiaojun Tang (Department of Epidemiology, Chongqing Medical University) for her advice on the statistical analysis of the data.

Institutional approval This study was approved by the Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University, Chongqing, China.

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