

Original paper

Association of high sensitivity C-reactive protein and metabolic syndrome components in middle-aged subjects without overt cardiovascular disease in LitHiR primary prevention programme

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Summary

Objectives: Circulating levels of inflammatory markers such as high sensitivity C-reactive protein (hs-CRP) have been reported to be associated with increased risk of cardiovascular disease (CVD), as well as with metabolic syndrome (MetS). Therefore, our objectives were to investigate the associations between hs-CRP levels and individual MetS components as well as to analyse if hs-CRP levels are linked with the number of MetS components present in middle-aged subjects.

Design and methods: A cross-sectional study included 4628 middle-aged MetS subjects from the Lithuanian High Cardiovascular Risk primary prevention programme (LitHiR) from 2011 to 2020. MetS was diagnosed according to the National Cholesterol Education Program ATP III modified criteria. CRP was measured by a validated high-sensitivity assay. A hs-CRP cutpoint of 5 mg/l was used to differentiate high and low hs-CRP groups.

Results: The mean value of hs-CRP was 3.23 ± 4.04 mg/l, and significantly increased as the number of components of MetS increased ($p < 0.001$). The concentration of serum hs-CRP was significantly associated with waist circumference, systolic and diastolic blood pressure, and fasting blood glucose (all $p < 0.001$). However, no statistically significant associations were found between hs-CRP and serum triglycerides ($p = 0.340$) or serum high-density lipoprotein cholesterol ($p = 0.148$).

Conclusions: Serum hs-CRP increased progressively with increased waist circumference, blood pressure, fasting blood glucose in middle-aged subjects with MetS. The higher values of hs-CRP were more often present in obese subjects and women. The incremental rise in mean serum hs-CRP level was found with an increasing number of MetS components.

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Introduction

C-reactive protein (CRP) is a widely accepted biomarker of inflammation and has been trialed as a novel biomarker for cardiovascular risk prediction [1–3]. It was shown that a low but persistent level of inflammation is a significant factor for the development of atherosclerotic plaques [4–6]. Moreover, the decrease of CRP levels in the

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blood is associated with reduced cardiovascular risk [7].

The high sensitivity C-reactive protein (hs-CRP) test detects a low level of C-reactive protein in persistent low-grade inflammation. Using hs-CRP improves the sensitivity of the test and predicts the future vascular events even among the people without overt cardiovascular disease (CVD) at the time of measurement [8]. Several studies have recommended the use of hs-CRP in patients who are at high risk of CVD, particularly in those who have metabolic syndrome (MetS) [9, 10].

The increased prevalence of MetS has become a global major public health care challenge. It ranges between 20% and 45% according to the different studies [11], from 28.7% to 34.1% in our previous study [12]. The National Cholesterol Education Program ATP III (NCEP ATP-III) modified criteria guidelines suggest a definition of MetS that includes the presence of at least 3 of the following 5 components: abdominal obesity, hypertriglyceridaemia, reduced levels of high-density lipoprotein cholesterol (HDL-Ch), elevated blood pressure (BP), and elevated levels of fasting blood glucose. It was shown that these components are associated with increased levels of CRP [13–15]. Hence, it has been suggested that hs-CRP can be used as a biomarker useful to adjust therapy and modify the cardiovascular risk to prevent the development of CVD [10].

Our objectives were to investigate the associations between hs-CRP levels and individual MetS components as well as to analyse whether hs-CRP levels are linked with the number of MetS components present in middle-aged subjects.

Design and methods

Subjects and study design

A cross-sectional study analysed 4628 middle-aged MetS subjects. All enrolled subjects were participating in the Lithuanian High Cardiovascular Risk primary prevention programme (LitHiR) at Vilnius University Hospital Santaros Clinics, from 2011 to 2020. A detailed description of the LitHiR is presented elsewhere [16]. The Local Research Ethics Committee approved this study and written informed consent was obtained from all study participants. Subjects underwent a physical examination and laboratory investigations to determine the presence of MetS according to NCEP ATP-III modified criteria [17]. MetS syndrome was diagnosed when there were at least three of the five criteria: waist circumference (WC) ≥ 102 cm in men and ≥ 88 cm in women; triglyceride (TG) levels ≥ 1.7 mmol/l or special

treatment is used to treat hypertriglyceridaemia; high-density lipoprotein cholesterol (DTL-Ch) < 1.03 mmol/L in men, < 1.29 mmol/L in women; systolic blood pressure (SBP) ≥ 130 mmHg and/or diastolic blood pressure (DBP) ≥ 85 mmHg, or the diagnosis of hypertension was documented in a medical record and/or the subjects used antihypertensive drugs; fasting plasma glucose (FPG) ≥ 5.6 mmol/l. The exclusion criteria were previously diagnosed cardiovascular disease and end-stage oncological disease.

Clinical assessment

Physical examination and anthropometry, including height, weight, waist circumference, and body mass index (BMI) measurements were made before inclusion into the study. BMI was assessed as weight in kilograms divided by height in meters squared. Obesity was considered when BMI exceeded 30 kg/m^2 . CV risk factors (smoking, positive family history of CVD, history of primary arterial hypertension, diabetes etc.) were evaluated. Smoking was considered if the subject smoked at least one cigarette a day. Positive CVD family history was defined as having a first-degree relative (men 45 years, women 55 years old) with any CV event. Blood pressure was measured twice on the right upper arm using an automatic digital sphygmomanometer, while the patient was seated and had been resting for at least 10 minutes. The mean BP was used for analysis. After a 12-h fasting, a venous blood sample was taken for a serum lipid panel, plasma glucose, hs-CRP. CRP was measured by a validated high-sensitivity assay. A hs-CRP cutpoint of 5 mg/l was used to differentiate high and low hs-CRP groups.

Statistical analysis

Statistical analysis was performed to assess which MetS components were associated with elevated hs-CRP. All analyses were performed using STATISTICA (version 10) and R software (version 3.6.1). Descriptive statistics were computed for demographic information and characteristics of MetS. Data were expressed as mean $\pm$ standard deviation for continuous variables and as absolute and percentage values for categorical variables. Continuous variables were analyzed using Student's *t*-test, categorical variables using Pearson's chi-square test. For all tests, *p*-values less than 0.05 were considered statistically significant.

Results

Baseline characteristics

A total of 4628 middle-aged subjects participated in the study with a mean age of $53.0 \pm$

6.5 years and 2719 (58.8%) of them were female. The mean value of hs-CRP was 3.23 ± 4.04 mg/l. Table 1 presents the sociodemographic, anthropometric, clinical, and biochemical characteristics of the study cohort according to hs-CRP levels. To differentiate high and low hs-CRP groups, a hs-CRP cutpoint of 5 mg/l was used. Elevated hs-CRP was found in 805 (17.4%) subjects. Participants with hs-CRP levels above the norm were older ($p = 0.011$), and more often females ($p < 0.001$). As expected, they had a statistically significantly greater BMI and a higher prevalence of obesity, hypertension, and diabetes. A positive relationship was found between elevated hs-CRP and heart rate ($p < 0.001$). No significant association between hs-CRP and total cholesterol or LDL-Ch was found. Furthermore, we found no association with traditional CV risk factors such as smoking ($p = 0.973$), and family history of CVD ($p = 0.956$).

MetS components

As regards MetS components, we found significant associations between waist circumference, systolic and diastolic blood pressure, fasting blood glucose, and elevated hs-CRP values (all $p < 0.001$), whilst serum TG ($p = 0.340$) and serum HDL-Ch ($p = 0.148$) did not reveal significant association with hs-CRP (Table 2).

There was an incremental rise in the mean serum hs-CRP levels with an increasing number of components of the MetS. It was found that participants with four (38.9 %) components predominated in the studied population with MetS. However, in elevated hs-CRP group five MetS components statistically significantly increased compared to the low hs-CRP group (Table 3).

Discussion

Our objectives were to investigate the association between hs-CRP levels and the individual components of MetS and to explore if the higher numbers of MetS components are associated with the increased levels of hs-CRP in the middle-aged subjects without overt CVD.

In this study, we revealed statistically significant associations between the level of hs-CRP and three out of five components of MetS: central obesity, systolic and diastolic blood pressure and fasting blood glucose (all $p < 0.001$), but, unlike other studies [11,18–20], not with elevated serum TG levels ($p = 0.340$) and low HDL-Ch levels ($p = 0.148$).

One of the largest studies that examined the association between inflammation and MetS was the *National Health and Nutrition Examination*

Survey (NHANES) [20]. Its results provided evidence supporting a relationship between serum hs-CRP and the presence of MetS, hypertension, and diabetes in the general United States population. Though we investigated the subjects with diagnosed MetS, in the same way, we found an association between hs-CRP and hypertension ($p = 0.002$), and diabetes ($p < 0.001$). In the NHANES a monotonically growing trend was observed across increasing quartiles of hs-CRP level for a range of the same measures as monitored in our study, including age, gender, BMI, waist circumference, FBG, SBP, and DBP. Although authors of NHANES found increasing hs-CRP trend with total cholesterol, LDL-Ch, TG, and decreasing association with HDL-Ch, we did not.

Similar results to the NHANES were reported in a large Iranian study. The Mashhad stroke and heart atherosclerotic disorder study (MASHHAD) found that hs-CRP values of ≥ 3 mg/l were associated with older age and were more common in women [19]. An increase in serum hs-CRP was also associated with obesity, waist circumference, high fasting blood glucose, high systolic, and diastolic blood pressure (all $p < 0.001$). The strongest association was observed with blood glucose concentration. Though in the MASHHAD study the researchers found a hs-CRP association with total cholesterol, TG, and LDL-Ch (all $p < 0.001$), but not with HDL-Ch. This is in line with our results concerning HDL-Ch.

On the contrary, a cross-sectional analysis of 1165 healthy subjects with central obesity done by den Engelsen *et al.* showed hs-CRP association with WC, BMI, TG, and HDL-Ch, but not with LDL-Ch, BP, and FBG [21].

In smaller sample studies from different countries, results are more variable. Belfki *et al.* from Tunisia reported statistically significant positive correlations between CRP and WC and TG in both sexes, and significant contribution of HDL-Ch only in women [22]. Hoeksta *et al.* in a general population of 605 Dutch elderly individuals aged 65–84 years, found that hs-CRP in normal-weight women was significantly associated with BMI and HDL-Ch [23]. However, in overweight women, these relationships were weak and not statistically significant. Findings were similar in men, although less pronounced than in women. In a study by Garcia *et al.* WC and HDL-Ch were identified as independent predictors of increased serum hs-CRP levels in Brazilian subjects with MetS risk factors [24]. Moreover, women with MetS risk factors presented higher hs-CRP levels than men with the same risk factors.

Gender and age seem to be some of the factors, which might explain the differences in results among various studies. Most of them [11,18–24],

Table 1.

Baseline characteristics of the subjects stratified by high sensitivity C-reactive protein levels.

Characteristic	Total population (N = 4628)	hs-CRP ≤ 5 mg/l (N = 3823)	hs-CRP > 5 mg/l (N = 805)	p-value*
Sex (female), N (%)	2719 (58.8)	2196 (57.4)	523 (65.0)	<0.001
Age, years	53.0 ± 6.5	52.9 ± 6.2	53.6 ± 6.2	0.011
Height, m	1.70 ± 0.10	1.70 ± 0.10	1.69 ± 0.09	<0.001
Weight, kg	92.6 ± 15.7	91.6 ± 15.3	97.2 ± 16.4	<0.001
BMI, kg/m ²	32.02 ± 4.40	31.58 ± 4.14	34.13 ± 4.93	<0.001
HR, beats/min	67.5 ± 10.7	66.8 ± 10.4	70.9 ± 11.7	<0.001
TC, mmol/l	6.44 ± 1.38	6.44 ± 1.36	6.42 ± 1.45	0.776
LDL-Ch, mmol/l	4.16 ± 1.18	4.16 ± 1.18	4.16 ± 1.15	0.885
Hs-CRP, mg/l	3.23 ± 4.04	1.91 ± 1.20	9.49 ± 6.28	<0.001
Smoker, N (%)	1122 (24.2)	925 (24.2)	197 (24.5)	0.973
Obesity (BMI >30 kg/ m ²), N (%)	3065 (66.2)	2412 (63.1)	653 (81.1)	<0.001
PAH, N (%)	4339 (93.8)	3565 (93.3)	774 (96.2)	0.002
Diabetes, N (%)	854 (18.5)	647 (16.9)	207 (25.7)	<0.001
Family history of CVD, N (%)	1501 (32.4)	1237 (32.4)	264 (32.8)	0.956

*Student's *t*-test or Pearson's chi-square test as appropriate.

Hs-CRP – high sensitivity C-reactive protein; BMI – body mass index; HR – heart rate; TC – total cholesterol; LDL-Ch – low-density lipoprotein cholesterol; PAH – primary arterial hypertension; CVD – cardiovascular disease.

Table 2.

Relationship between high sensitivity C-reactive protein and components of metabolic syndrome.

MetS components	Total population (N = 4628)	hs-CRP ≤ 5 mg/l (N = 3823)	hs-CRP > 5 mg/l (N = 805)	p-value*
WC, cm	105.8 ± 10.2	104.9 ± 9.7	110.2 ± 11.6	<0.001
HDL-Ch, mmol/l	1.19 ± 0.29	1.19 ± 0.29	1.18 ± 0.30	0.148
TG, mmol/l	2.41 ± 2.23	2.39 ± 1.95	2.48 ± 3.26	0.434
FBG, mmol/l	6.39 ± 1.54	6.31 ± 1.42	6.76 ± 1.98	<0.001
SBP, mmHg	140.6 ± 16.0	139.90 ± 15.7	143.7 ± 17.0	<0.001
DBP, mmHg	85.2 ± 10.8	85.00 ± 10.6	86.4 ± 11.4	<0.001

*Student's *t*-test.

MetS – metabolic syndrome; hs-CRP – high sensitivity C-reactive protein; WC – waist circumference; HDL-Ch – high-density lipoprotein cholesterol; TG – triglycerides; FBG – fasting blood glucose; SBP – systolic blood pressure; DBP – diastolic blood pressure.

Table 3.

Relationship between high-sensitivity C-reactive protein and the number of metabolic syndrome components.

Number of MetS components	Total population (N = 4628)	hs-CRP ≤ 5 mg/l (N = 3823)	hs-CRP > 5 mg/l (N = 805)	p-value*
3	1657 (35.8%)	1410 (36.9%)	247 (30.7%)	<0.001
4	1800 (38.9%)	1509 (39.5%)	291 (36.2%)	
5	1171 (25.3%)	904 (23.7%)	267 (33.2%)	

*Pearson's chi-square test.

MetS – metabolic syndrome; hs-CRP – high sensitivity C-reactive protein.

including our study, reported a high prevalence of elevated hs-CRP in women and association with older age (all $p < 0.001$).

In a large-scale study, the Women's Health Study (WHS) during 8-year prospective follow-up of 14,719 initially healthy women, a strong association was found between an increase of hs-CRP and all MetS components: obesity, hypertriglyceridemia, low HDL-Ch, high blood pressure, and hyperglycemia (all $p < 0.0001$) [13]. Moreover, this study demonstrated that at all levels of severity of the MetS, hs-CRP added important and independent prognostic information in terms of future cardiovascular risk.

Some research results suggest that all inflammatory processes start with adiposity. Obesity and waist circumference may be major determinants of elevated serum hs-CRP concentration. Most of the studies investigating hs-CRP and MetS components reported hs-CRP association with BMI, WC, and obesity [11,18–24]. According to our data, hs-CRP was significantly higher in obese (BMI > 30 kg/m²) subjects ($p < 0.001$). However, the *Korea National Health and Nutrition Examination Survey* (KNHANES), aimed to identify the associations between hs-CRP and MetS and its components in obese and non-obese men and women, concluded that the hs-CRP level plays a major role in the development of MetS independent of adiposity in women [25].

According to the literature, patients who are smoking have an elevated concentration of hs-CRP [26], especially those with MetS [27]. Jamal et al. found that smokers compared to non-smokers had a 55 % increase in hs-CRP compared to the general population and a 2-fold increase in the presence of MetS [27]. Other studies also showed a significant increase in hs-CRP levels for smokers [21,28]. Yet this question is not clear, as such studies with a large sample as the NHANES and the MASHHAD reported contrary results – smoking was not found to be associated with an increase in hs-CRP [18,19]. In line with them, we did not observe a significant relationship between serum hs-CRP and the current smoking habit ($p = 0.973$).

Although there are some discrepancies concerning separate MetS components and their correlation with hs-CRP, numerous studies found an incremental increase in mean serum hs-CRP levels with a higher number of MetS components [13–15,18–21]. Our findings are in line with them: we revealed a statistically significant association between the level of hs-CRP and the increasing number of MetS components.

In the NHANES in subjects with MetS three components were more prevalent than four and five, accordingly 58.7%, 32.0%, and 9.3%. A very similar distribution was in the WHS. However,

our cohort of MetS distributed more evenly – three components – 35.8%, four – 38.9%, and five – 25.3%. This might be one of the reasons, why we did not find the hs-CRP association with a lipid panel. A detailed analysis is needed concerning the combinations of MetS components and hs-CRP associations.

Conclusions

Our data demonstrate that serum hs-CRP levels increased with increased waist circumference, blood pressure, fasting blood glucose but not triglycerides levels, and lower HDL-cholesterol levels. The higher values of hs-CRP are more present in obese subjects and women. The incremental rise in mean serum hs-CRP levels was associated with an increasing number of MetS components.

Limitations

This study examined samples from different age groups: men aged 40–55 years and women aged 50–65 years. The data analysis was done without regard to gender. The limitations of this study also include the fact that the data were obtained only from the cross-sectional study and not the long-term follow-up, which could reveal the influence of long-term inflammatory conditions on the progression of MetS components and development of CVD. A prospective study should be performed in the future to answer this question.

Conflict of interest

The authors have no conflicts of interest to declare.

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