High Sensitivity C-Reactive Protein in Patients with Metabolic Syndrome and Its Relation to Metabolic Syndrome Components

Metabolik Sendromlu Hastalarda Yüksek Duyarlılıklı C-Reaktif Protein ve Bunun Metabolik Sendrom Komponentleri ile İlişkisi

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ABSTRACT Objective: High-sensitivity C-reactive protein (hs-CRP) is an important factor indicative of inflammation and predictive for atherosclerosis. In this study, we aimed to detect the association of hs-CRP with the components of metabolic syndrome and to demonstrate which components mostly contribute to the development of atherosclerosis. **Material and Methods:** A total of 527 patients (118 men and 409 women) were enrolled, and 60 of these patients were excluded due to elevated hs-CRP levels indicating an inflammatory condition. Statistically significant positive correlations were detected between hs-CRP and various clinical and laboratory markers, including systolic and diastolic blood pressure, body mass index (BMI), waist circumference (WC), fasting blood glucose (FBG), postprandial blood glucose (PBG), homeostatic model assessment of insulin resistance (HOMA-IR), low density lipoprotein (LDL)-cholesterol. **Results:** It was detected significantly positive correlation between group hs-CRP and clinical and laboratory findings such as systolic and diastolic blood pressures, BMI, WC, FBG, PBG, HOMA-IR, and LDL. There was also a statistically significant positive correlation between high risk hs-CRP levels and triglyceride (TG). A significant negative correlation between hs-CRP and high density lipoprotein (HDL) cholesterol was also noted. Subsequently, regression analysis was performed to identify the most significant parameters and the relation between hs-CRP and older age, HDL cholesterol, BMI, and PBG was seen to remain significant. When standardized regression coefficients were taken into consideration, the most significantly associated parameter with hs-CRP was found to be BMI. **Conclusion:** As a ruslt, hs-CRP can be concluded that older age, increased BMI, low HDL-cholesterol levels, and elevated PBG are important risk factors for atherosclerosis.

Key Words: Body mass index; cholesterol, HDL; C-reactive protein (164-173); insulin resistance; metabolic syndrome X

ÖZET Amaç: Yüksek duyarlılıklı CRP (hs-CRP) inflamasyonun önemli bir göstergesidir ve ateroskleroz için prediktiftir. Bu çalışmamızda hs-CRP ile ateroskleroz gelişimine katkıda bulunan metabolik sendrom komponentleri arasındaki ilişkiyi ve bu komponentler içinde ateroskleroz gelişimine en fazla katkıda bulunan değişken veya değişkenleri göstermeyi amaçladık. **Gereç ve Yöntemler:** Çalışmamızda toplam 527 hasta (118 erkek ve 409 kadın) alındı. 60 hasta inflamasyon durumunu gösteren yüksek hs-CRP düzeylerinden dolayı çalışma dışı bırakıldı. hs-CRP ile çeşitli klinik ve laboratuar bulguları arasında istatistiksel pozitif korelasyon araştırıldı; bunlar sistolik ve diyastolik kan basıncı, vücut kitle indeksi (BKİ), bel çevresi (BÇ), açlık kan şekeri (AKŞ), tokluk kan şekeri (PPG), insülin direnci (HOMA-IR), düşük densiteli lipoprotein kolesterol (LDL) idi.Bu parametreler ve hs-CRP arasında korelasyon analizleri yapıldı.Ardından değişkenlere regresyon analizi uygulandı. **Bulgular:** hs-CRP ile çeşitli klinik ve laboratuar bulguları arasında istatistiksel pozitif korelasyon saptandı; bunlar sistolik ve diyastolik kan basıncı, vücut kitle indeksi, bel çevresi, açlık kan şekeri, tokluk kan şekeri, insülin direnci, düşük densiteli lipoprotein kolesterol idi. Yüksek risk grubu hs-CRP değerleri ile trigliserid (TG) değerleri arasında da önemli pozitif korelasyon vardı. Ayrıca hs-CRP ile yüksek dansiteli lipoprotein (HDL) kolesterol arasında negatif korelasyon saptandı. Daha sonra regresyon analizi uygulandı ve hs-CRP ile en çok ilişkili parametrelerin yaş, HDL kolesterol, BKİ ve tokluk kan şekeri olduğu görüldü. Standardize regresyon katsayıları değerlendirildiğinde hs-CRP ile en sıkı ilişkinin vücut kitle indeksi arasında olduğu görüldü. **Sonuç**: Bu durumda ileri yaş, düşük HDL, artmış vücut kitle indeksi, yüksek tokluk kan şekeri değerlerinin hs-CRP ile ilişkilerine bakılarak, bu değişkenlerin yüksek ateroskleroz riski oluşturduğu sonucuna varıldı.

Anahtar Kelimeler: Vücut kitle indeksi; kolesterol, HDL; C-reaktif protein (164-173); insülin direnci; metabolik sendrom X

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Atherosclerosis is the most common cause of death in almost all countries. As a result, atherosclerotic risk factors are one of the major areas of interest in medicine. In this context, conventional risk factors have been defined and used for the last few decades. In recent years, new risk factors (small, dense low-density lipoprotein particles, oxidized low-density lipoprotein, and apolipoprotein B, triglycerides; triglyceride-rich lipoprotein remnants)[1,2] are being considered. Identifying atherosclerotic risk factors and having early detection of these factors are important, and directly related insulin resistance (IR) and metabolic syndrome (MS).

High-sensitivity CRP (hs-CRP) assays are needed for risk assessment of cardiovascular disease.[3] It was shown to be associated not only with conventional risk factors and MS in general, but also with several individual components of MS. It was also shown that hs-CRP might enable the prediction of atherosclerosis independently from other risk factors. Although no consensus has yet been achieved, hs-CRP most likely reflects the inflammatory process of atherosclerosis.[4,5] Despite the vast research carried out on this subject, there is still no consensus regarding the diagnostic criteria of MS.[6]

Anthropometric measures may or may not predict MS, and often differ due to ethnic variability. Cut-off values for anthropometric measures also can vary with ethnicity. Accordingly, there is still no agreement on the cut-off values or appropriate variables for both anthropometric measures and other laboratory measures with respect to MS.

This problem becomes more complicated in Turkey because there are no large-scale studies concerning anthropometric measures and no approved cut-off values. Therefore, in this study, we aimed to detect the association of hs-CRP with the components of MS and also to demonstrate which components mostly contribute to the development of atherosclerosis in a group of patients who visited our out-patient clinic.

MATERIAL AND METHODS

PATIENT POPULATION

This study enrolled 527 patients (118 men and 409 women) who visited the internal medicine out-patient clinic of Ankara Training and Research Hospital. The present study was approved by local Ethical Committee. Written informed consents were obtained from the patients for those >18 years old, or patient's parents for those <18 years old. Patients were excluded from the study if they had any acute disease or any factors that could interfere with measurements of waist circumference (such as hernia, ascites, intra-abdominal mass or pregnancy) or anthropometric measurements (such as orthopedic abnormalities). Of the 527 patients, 60 were excluded from the study since they had elevated hs-CRP levels of 10 mg/L and above, which was considered to be a secondary increase due to inflammation (such as malignancy, acute bacterial infection, collagen tissue disease).

CLINICAL AND LABORATORY MEASUREMENTS

Patients included in this study were questioned for the presence of hypertension, diabetes mellitus, dyslipidemia, coronary artery disease, family history, smoking, and drug usage. Following physical examination, their waist and hip circumferences were measured according to techniques suggested by the International Biological Program (IBP) and Anthropometric Standardization Reference Manual (ASRM).[7]

Blood pressure (BP) was measured with a mercury manometer on the right arm while patients were sitting in an upright position after at least five minutes of resting. Waist circumferences were measured in a standing position from midway between the lowest rib margin and the iliac crest at the end of a normal expiration. Hip circumferences were measured over the widest part of the hip. Height and body weight measurements were made in light clothing without shoes. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2).

Fasting plasma glucose (FPG), postprandial blood glucose (PBG), insulin, total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol, triglyceride (TG), and hs-CRP levels were evaluated in all patients. Blood samples were collected in the morning, between the hours of 090.0 and 11.00, after a fasting period of at least 12 hours. Glucose, total cholesterol, HDL-cholesterol, and TG measurements were performed on the Roche Modular DP analyzer using kits from Roche Diagnostics in the biochemistry laboratory. Low density lipoprotein cholesterol was calculated by using Friedewald formula.[8]

All patients' trigliseride levels are below 300 mg/dL. Insulin was measured by ELISA from DRG Diagnostics (DRG Instruments GmbH, Germany) and hs-CRP was measured by the Beckman Coulter Immage (Beckman Coulter Inc., USA) nephelometry kits.

Patients were separately evaluated according to the National Cholesterol Education Program (NCEP-ATP III) and International Diabetes Federation (IDF) criteria for MS.[9]

During this evaluation, detection of hypertension during examination and usage of antihypertensive drugs were both considered as fulfilling a criterion for the diagnosis of "hypertension"; detection of impaired fasting glucose or diabetes mellitus via laboratory tests and receiving antidiabetic medication were considered as fulfilling a criterion for the diagnosis of "disglycemia"; and detection of elevated cholesterol and TG levels via laboratory tests and receiving medication for dyslipidemia were considered as fulfilling diagnosis criteria for both "HDL-cholesterol" and "triglyceride". The homeostasis model assessment of insulin resistance (HOMA-IR) was applied evaluate insulin sensitivity. HOMA values of all patients were calculated by the following formula: "[Fasting blood insulin (μU/ml) x fasting blood glucose (mg/dL)]

Patients were also divided into three groups according to their hs-CRP levels, with low (<1 mg/L), moderate (1-3 mg/L), and high (3-10 mg/L) risk values. Correlations with MS and other parameters of MS were evaluated separately for these three groups.

STATISTICAL ANALYSES

Data analyses were performed with the Statistical Package for the Social Sciences (version 11.5) software. Continuous and categorical variables were expressed as mean ± standard deviation and percentages, respectively. The significance of the different hs-CRP levels between independent groups was evaluated by the Mann Whitney U test. Kruskal Wallis test was used to evaluate the differences in more than 2 groups. When the difference is statistically significant, multiple comparison test was used. The presence of a significant linear relationship between continuous variables and hs-CRP was tested with the Pearson correlation test. Whether or not the variables that significantly correlated with hs-CRP in the univariate analysis had multiple effects on hs-CRP was tested by the multiple linear regression analysis. Since the original hs-CRP variable was not normally distributed, a logarithmic hs-CRP transformation was applied. A stepwise regression method was used to obtain a model that best explains the variation in logarithmic hs-CRP. Regression coefficients and 95% confidence intervals were calculated. P values of less than 0.05 were considered as statistically significant.

RESULTS

There were 467 patients enrolled in this study. A total of 467 patients, ages 18-80 years, were evaluated. Of the 467 patients, 105 were men and 362 were women. The age and gender distribution of these patients were shown in Table 1. BMI and HDL-cholesterol levels were both significantly higher in women compared to men ($p< 0.001$ for both values). However, the hs-CRP levels were not significantly ($p= 0.357$). The BMI, WC, HDL-cholesterol, and MS frequency, which showed a statistically significant difference between genders, were separately evaluated for each gender; whereas hs-CRP, systolic BP, diastolic BP, FBG, PBG, LDL, insulin, and HOMA values were generally evaluated among all patients since they were not significantly different between genders ($p< 0.001$).

Table 2 displays the correlation values between hs-CRP and MS-related variables. Statistically significant positive correlations between hs-CRP and BMI (p< 0.001), WC (p< 0.001), systolic BP (p< 0.001), diastolic BP (p< 0.001), FBG (p< 0.001), PBG (p< 0.001), LDL (p< 0.001), insulin (p< 0.001), and HOMA (p< 0.001) were detected. Furthermore, a significant negative correlation between hs-CRP and HDL was detected (p= 0.005), while no significant linear correlation between hs-CRP and TG was detected (p= 0.067).

The presence or absence of MS was also evaluated by gender in Table 3. MS was identified in 170 (47.0%) of 362 female patients and in 34 (32.4%) of 105 male patients according to MS diagnosis criteria defined in NCEP-ATP III. Similarly, using the IDF criteria, MS was identified in 197 (54.4%) of 362 female patients and in 39 (37.1%) of 105 male patients. The difference in MS prevalence among the genders was statistically significant for both diagnosis criteria (p= 0.008 and p=0.002, respectively) (Table 3).

MS variables were then analyzed for correlations when patients were separated into low, moderate, and high risk groups based on hs-CRP levels. Different risk groups of hs-CRP showed significant differences for the same parameters previously identified as correlated. In addition, although TG was found to be not significantly correlated with hs-CRP, TG levels were statistically significantly different among the low-risk group compared to the moderate and high-risk groups (p< 0.001) (Table 4).

Since positive relationships between hs-CRP and almost all metabolic variables were detected, parameters found to be correlated with hs-CRP

TABLE 1: Age and gender distribution of the patients.

Patients	n	Mean age (years)
Men	105	41.1 ± 13.2
Women	362	42.7 ± 13.5
Total	467	49.9 ± 13.6

TABLE 2: Correlation values between hs-CRP and metabolic syndrome related variables.

Variables	Mean ± SD	Correlation Coefficient	p
Age (year ± SD)	49.9 ± 13.6	0.259	<0.001
Men	41.1 ± 13.2	0.190	0.052
Women	42.7 ± 13.5	0.275	<0.001
BMI-Total (kg/m^2 ± SD)	29.1 ± 5.92	0.409	<0.001
Men	26.9 ± 4.72	0.048	0.627
Women	29.7 ± 6.09	0.486	<0.001
WC (cm ± SD)	95.6 ± 14.94	0.378	<0.001
Men	95.6 ± 12.90	0.062	0.529
Women	95.6 ± 15.49	0.451	<0.001
Systolic BP (mmHg ± SD)	136.6 ± 29.19	0.213	<0.001
Diastolic BP (mmHg ± SD)	86.7 ± 17.96	0.198	<0.001
FBG (mg/dL ± SD)	102.7 ± 42.79	0.240	<0.001
PBG (mg/dL ± SD)	130.0 ± 70.86	0.253	<0.001
LDL-cholesterol (mg/dL ± SD)	112.5 ± 40.71	0.148	<0.001
HDL-cholesterol (mg/dL ± SD)	52.3 ± 13.01	-0.128	0.005
Men	46.3 ± 11.07	-0.030	0.762
Women	54.1 ± 13.02	-0.173	<0.001
TG (mg/dL ± SD)	147.9 ± 119.72	0.085	0.067
Insulin (IU ± SD)	9.2 ± 7.87	0.166	<0.001
HOMA-IR (mean ± SD)	2.3 ± 2.07	0.234	<0.001

BMI: Body mass index, WC: Waist circumference, BP: Blood pressure, FBG: Fasting blood glucose, PBG: Postprandial blood glucose, LDL: Low density lipoprotein, HDL: High density lipoprotein, TG. Triglyceride, HOMA: Homeostatic model assessment.HOMA-IR: HOMA-insulin resistance.

were analyzed by stepwise regression analysis in order to detect the most strongly related parameters. Investigation of the multiple effects of these parameters on logarithmic hs-CRP revealed associations between hs-CRP and BMI ($p< 0.001$), age ($p< 0.001$), HDL-cholesterol ($p< 0.001$), and PBG ($p< 0.02$). Standardized regression coefficients indicated that the variation in hs-CRP was most strongly affected by BMI.

DISCUSSION

Metabolic syndrome can be defined as a cluster of problems with important complications and a physiopathology which has not yet been fully understood. Results from many studies have revealed some clues and based on these, the physiopathology of MS is beginning to be clarified. One important factor in MS is hs-CRP, which has been shown to predict the presence of atherosclerosis.[10] MS is thought to cause atherosclerosis via chronic inflammation since CRP is continuously synthesized in the liver under control of cytokines secreted from adipose tissue.[11-13]

The association between chronic inflammation and atherosclerosis has been shown in many studies.[14-17] However, an agreement has not been achieved as to which of the MS components are mostly associated with chronic inflammation. For example, in some studies, hs-CRP was shown to be

TABLE 3: Evaluations of metabolic syndrome and gender distribution.

MS Criteria		Without MS	With MS	p
NCEP- ATP III	Men (n, %)	71 (67.6)	34 (32.4)	0.008
	Women (n, %)	192 (53)	170 (47.0)	
IDF	Men (n, %)	66 (62.9)	39 (37.1)	0.002
	Women (n, %)	165 (45.6)	197 (54.4)	

MS: metabolic syndrome, NCEP: National Cholesterol Education Program, IDF: International Diabetes Federation.

TABLE 4: Metabolic syndrome related variables in low, moderate, and high-risk hs-CRP groups.

Variables	Low (n= 108)	Moderate (n= 171)	High (n= 188)	p†
Age (years ± SD)	35.8 ± 11.51	42.1 ± 13.54*	46.3 ± 12.84*,**	<0.001
BMI (kg/m2 ± SD)	25.5 ± 4.22	28.6 ± 5.22*	31.6 ± 6.21*,**	<0.001
Men	25.3 ± 5.04	27.1 ± 4.18	27.5 ± 5.12	0.165
Women	25.4 ± 4.03	29.3 ± 5.46*	32.5 ± 6.07*,**	<0.001
WC (cm ± SD)	85.9 ± 12.44	95.1 ± 13.97	101 ± 14.06	<0.001
Men	91.4 ± 14.75	96.0 ± 12.47	97.5 ± 12.14	0.169
Women	84.6 ± 11.52	94.7 ± 14.55*	102.7 ± 14.33*,**	<0.001
Systolic BP (mmHg ± SD)	126.7 ± 21.96	135.3 ± 28.77*	143.3 ± 31.47*,**	<0.001
Diastolic BP (mmHg ± SD)	81.6 ± 14.98	85.5 ± 17.81	90.7 ± 18.84*,**	<0.001
FBG (mg/dL ± SD)	94.5 ± 25.84	98.1 ± 31.77	111.5 ± 55.93*,**	<0.001
PBG (mg/dL ± SD)	108.6 ± 47.53	125.5 ± 56.96*	146.2 ± 87.88*	<0.001
Insulin (IU ± SD)	8.6 ± 6.47	8.2 ± 4.99	10.6 ± 10.22*,**	0.021
HOMA-IR(mean ± SD)	2.0 ± 1.44	2.0 ± 1.35	2.8 ± 2.73*,**	<0.001
LDL-cholesterol (mg/dL ± SD)	96.9 ± 35.73	113.3 ± 39.10*	120.8 ± 42.41*	<0.001
HDL-C (mg/dL ± SD)	57.8 ± 13.36	50.7 ± 10.98*	50.7 ± 13.70*	<0.001
Men	47.6 ± 10.54	46.3 ± 11.19	45.44 ± 11.43	0.828
Women	60.3 ± 12.79	52.3 ± 10.47*	52.0 ± 13.92*	<0.001
TG (mg/dL ± SD)	103.8 ± 58.60	164.1 ± 119.81*	158.6 ± 138.67*	<0.001
hs-CRP (mg/L ± SD)	0.47 ± 0.22	1.89 ± 0.61*	5.2 ± 1.80 *,**	<0.001

†: Kruskal Wallis test

*: Statistically significant difference between low-level hs-CRP group ($p< 0.05$).

**: Statistically significant difference between moderate level hs-CRP group ($p< 0.05$).

BMI: Body mass index, WC: Waist circumference, BP: Blood pressure, FBG:Fasting blood glucose, PBG: Postprandial blood glucose, HOMA: Homeostatic model assessment, LDL: Low density lipoprotein, HDL: High density lipoprotein, TG: Triglyceride.

associated with hypertension, WC, BMI, HOMA-IR, FBG, and lipoproteins;[11,18-22] whereas, other studies do not detect associations between hs-CRP and lipoproteins, HOMA-IR, hypertension, and WC.[17,23-25]

Results from this study revealed that there are significant positive correlations between hs-CRP and age, body weight, BMI, WC, systolic BP, diastolic BP, FBG, PBG, fasting insulin, HOMA-IR, LDL-cholesterol. In addition, there was a statistically significant positive correlation between high risk hs-CRP groups and TG. Our study also demonstrated a significant negative correlation between hs-CRP and HDL-cholesterol. hs-CRP levels were significantly higher in patients with MS compared to those without MS. However, upon stepwise regression analysis, associations between hs-CRP and age, BMI, PBG, and HDL-cholesterol remained significant; whereas, no associations were identified with other parameters.

While many studies have detected an association between hs-CRP and IR, which is a central component of MS,[18,19,26] this relation was not identified in other studies.[22,23] In the present study, we found that hs-CRP was not significantly related to insulin or HOMA. Nevertheless, we found that a high level of PBG, which is an indicator of IR, was one of the most related parameters to hs-CRP levels. These contradictory results raise the question of how efficiently the HOMA method reflects IR.

A strong association between high levels of PBG and hs-CRP was expected. Non-enzymatic glycosylation leads to atherosclerosis by causing endothelial dysfunction. Advanced glycation end products are correlated with HbA1c levels.[27] It has also been shown that HbA1c production is mostly influenced by PBG. In fact, a strong correlation between HbA1c and hs-CRP was found in a study with diabetic patients.[24] These results indirectly suggest that high PBG levels give rise to a chronic inflammation secondary to non-enzymatic glycosylation. Based on these results, we suggest that PBG is a more important indicator of MS risk than FBG, and thus, it should be included in the list of MS components.

In our study, age was one of the most strongly associated parameters with hs-CRP. It is well known that the frequency of atherosclerosis is increased in older patients,[28] which support the relation between long term inflammation and atherosclerosis.

Consistent with previous studies, we also detected a negative correlation between hs-CRP and HDL-cholesterol. Increased adipose tissue and possibly decreased physical activity in patients with MS may explain the increased hs-CRP accompanied by decreased HDL-cholesterol.[29,30]

According to our results, BMI was the most strongly associated MS component with hs-CRP. Visceral adipose accumulation is one of the central components of MS since it causes IR. There is also much evidence that suggests visceral adipose can increase CRP secretion by synthesizing interleukin 6 (IL-6) and thus, it is an important risk factor for atherosclerosis.[31] However, our results revealed that BMI was more associated with hs-CRP than WC. Pradhan et al. also reported this observation.[22] However, these findings did not demonstrate that WC is less important in MS and atherosclerosis. Adipose tissue outside of the visceral region is hormone-active and, due to cytokine synthesis, it might produce additional effects on chronic inflammation that result from visceral adipose accumulation.[25]

It has not yet been clarified whether CRP is the cause of or the result of atherosclerosis development. If CRP is the cause of atherosclerosis development, then adipose accumulation in peripheral tissues is also a risk factor for atherosclerosis and visceral adipose accumulation.[24,25] On the other hand, if CRP increases as a result of atherosclerosis, then peripheral adipose accumulation would not be important for the development of atherosclerosis and visceral adipose accumulation would lead to atherosclerosis through other mechanisms. In fact, the importance of WC in the development of atherosclerosis has been demonstrated.[21-23] Therefore, although it is known that BMI increases hs-CRP levels and contributes to WC, its role in atherosclerosis still needs further investigation.

In conclusion, in this study we detected a significant positive correlation between hs-CRP and

age, body weight, BMI, WC, systolic BP, diastolic BP, FBG, PBG, fasting insulin, HOMA-IR, LDL cholesterol, and between high risk hs-CRP groups and TG; and a significant negative correlation between hs-CRP and HDL-cholesterol. In addition, hs-CRP levels were significantly different between patients with MS and those without. Regression analysis was also performed in order to investigate parameters that are most strongly associated with hs-CRP. Investigation of the multiple effects of these variables on logarithmic hs-CRP levels revealed that the relation of hs-CRP with BMI, age, HDL-cholesterol, and PBG remained significant. Variation in hs-CRP was mostly affected by BMI in respect of standardized regression coefficients.

Results of this study support the opinion that IR, which is a component of MS, is associated with a systemic inflammatory response and that chronic systemic inflammation has an important role in the pathogenesis of atherosclerosis. However, among the many parameters leading to MS, which parameter is mostly associated with chronic inflammation is still unclear. We aimed to clarify this issue in our study and we found that parameters associated with hs-CRP are increased BMI (which was the strongest association), older age, low HDL-cholesterol levels, and high PBG levels. According to these findings, we can conclude that age, BMI, HDL-cholesterol, and PBG are the most important risk factors for atherosclerosis.

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