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Original Article

C-reactive protein, fibrinogen, prothrombin time and international normalized ratio levels as indicators of chronic inflammation in patients with metabolic syndrome

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ABSTRACT

Aims: Although it has been stated in studies conducted in patients with metabolic syndrome (MetS) that elevated serum fibrinogen and C-reactive protein (CRP) may be due to chronic inflammation, sufficient studies have not been conducted on International normalized ratio (INR) and prothrombin time (PT). The aim of this study is to examine the fibrinogen, INR and PT levels of patients with MetS and to investigate the relationship between these parameters and MetS components.

Methods: A total of 56 patients, 19 males and 37 females were included in our study who applied to the Internal Medicine outpatient clinic of Ondokuz Mayıs University Faculty of Medicine and met the MetS diagnostic criteria. The control group consists of a total of 64 people, 35 men and 29 women, who have at least one of the MetS criteria and do not have a chronic disease. Fasting blood glucose, total cholesterol (total-C), triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, thyroid stimulating hormone (TSH), PT, INR and fibrinogen levels were examined from the available samples. Data were compared between healthy and patient groups.

Results: As a result of our study, it was determined that the CRP level was significantly higher in the patient group ($p<0.01$). The average fibrinogen level was calculated as 3.56 g/L in the patient group and 2.95 g/L in the control group, and a significant difference was detected when the two groups were compared ($p<0.001$). The average PT value was 13.1 in the patient group and 12.04 in the control group and a significant difference was detected between both groups ($p<0.001$). The average INR level was 1.14 in the patient group and 1.04 in the control group and a significant difference was detected between both groups ($p<0.001$).

Conclusion: MetS is associated with high CRP. In patients with MetS, PT, INR and fibrinogen levels are also high. In the follow-up and treatment of patients with MetS, the presence of chronic inflammation and factors affecting the coagulation system should be taken into consideration.

Keywords: Prothrombin time, international normalized ratio, fibrinojen, metabolic syndrome

INTRODUCTION

Metabolic syndrome (MetS), also known as syndrome X, insulin resistance, polymetabolic syndrome, is defined by the World Health Organization (WHO) as a multisystem disease characterized by abdominal obesity, insulin resistance, hypertension and hyperlipidemia.[1] The pathophysiology of MetS involves many complex mechanisms that have not yet been fully elucidated. The pathogenesis of MetS involves multiple genetic and environmental factors, including insulin resistance and chronic low-grade inflammation.[2] IL-6 production increases with increasing body fat and insulin resistance. Increased IL-6 affects the liver, bone marrow, and endothelium, leading to increased production of acute phase reactants, including C-reactive protein (CRP). Various studies have shown a correlation between high CRP levels and the development of MetS, diabetes and cardiovascular disease.[3-5]

Endothelial dysfunction is a complex pathological condition associated with increased activity of coagulation factors, hyperactivity of platelets and decreased fibrinolysis.[6] In patients with MetS, there is increased synthesis of fibrinogen and plasminogen activator inhibitor 1 (PAI-1) in the liver as a result of hyperinsulinemia and increased IL-6 levels. Factor VII, IX and X levels also increase which occur as a result of activation of endothelial cells. These changes in hemostatic balance contribute to the susceptibility to thrombosis in MetS

and constitute the atherothrombotic process underlying acute coronary or cerebrovascular events.[2,7]

In light of all this information, while CRP and serum fibrinogen levels due to chronic inflammation are often high in individuals with MetS, very few studies have been conducted on International normalized ratio (INR) and prothrombin time (PT). The aim of this study is to evaluate fibrinogen, INR and PT levels of patients with MetS and to investigate the relationship between these parameters and MetS components. We also believe that we will contribute to future studies on prophylactic anticoagulation therapy to prevent thrombosis in patients with MetS.

METHODS

A total of 56 patients between the ages of 18 and 65, who applied to the Department of Internal Medicine at Ondokuz Mayıs University Faculty of Medicine between May 2012 and September 2013 and were diagnosed with MetS according to the National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) criteria, were included in our study. Approval for the study was received from Ondokuz Mayıs University Clinical Researches Ethics Committee (Date: 26.04.2012, Desicion no: 2012/8). Informed written consent was obtained from all participants in accordance with the principles of the Declaration of Helsinki. The control group consists of 64 healthy individuals with similar demoFigureic characteristics to the patient group in terms of age and ethnicity. Patients with a history of renal failure, liver disease, hypothyroidism, acute infection, malignancy, pregnancy, autoimmune disease and patients receiving hormone replacement therapy were excluded from the study. DemoFigureic information of the participants, such as age, gender, height, weight, body-mass index (BMI), waist circumference, education level and occupation, were recorded. Venous blood samples were collected into biochemistry tubes containing anticoagulant and without anticoagulant additives after a 12-hour fast. After the samples were centrifuged for one hour, the serum was separated and placed in the -80°C deep freezer on the same day. Data were created by looking at fasting blood glucose, total cholesterol, triglyceride (TG), high-density lipoprotein (HDL), low-density lipoprotein (LDL), creatinine, thyroid stimulating hormone (TSH), PT, INR and fibrinogen levels from the available samples. Fasting blood glucose, total cholesterol, TG, HDL and uric acid were studied in the biochemistry laboratory using Roche Diagnostics kits on a Hitachi Cobas 8000 autoanalyzer.

NCEP-ATP III components include the presence of central obesity (waist circumference >102 cm in men >88 cm in women), hypertriglyceridemia (TG ≥150 mg/dL or specific drug use), low HDL level (men<40 mg/dl, women <50 mg/dL), high fasting blood glucose (≥110 mg/dL) and high arterial blood pressure (≥130/85 mmHg). MetS is diagnosed if three or more of these components are present.

Statistical Analysis

Statistical analyzes of the data were performed using the SPSS 15 package program. Numerical data are shown as±standard deviation. Mann-Whitney U and Chi-Square tests were used to compare patient and control groups, and Spearman and Pearson correlation analyzes were used to examine the relationships between the data. Non-parametric data were interpreted with Kruskal-Wallis analysis. All analyzes were performed with a 95% confidence interval. A value of $p<0.05$ was considered as statistically significant.

RESULTS

There were 19 men and 37 women in the patient group, and 35 men and 29 women in the control group. A significant difference was detected between genders when both groups were compared. The weight, waist circumference, systolic blood pressure, diastolic blood pressure, mean blood pressure, and fasting blood glucose of the patient group were found to be statistically significantly higher than the control group (Table 1). Considering the upper limit value for CRP value as 3.3 mg/dL, it was determined that 39 people (69.6%) in the patient group were higher than the limit value and 17 people (30.4%) were lower than the limit value. In the control group, 49 people (76.4%) were found to be lower than the limit value and 15 people (23.6%) were found to be higher. The number of patients with high CRP values was found to be statistically significantly higher in the patient group ($p<0.001$) (Table 2).

Table 1. Comparison of clinical and laboratory data of the patient and control groups

	Patient group, mean±SD	Control group, mean±SD	p value
Height (cm)	160.95±10.09	167.2±9.18	<0.001
Weight (kg)	91.6±16.61	74.7±13.73	<0.001
Waist circumference (cm)	114.08±14.32	88.8±11.83	<0.001
BMI (kg/m²)	35.3±6.37	27.09±4.51	<0.001
Systolic blood pressure (mmHg)	127.14±17.5	109.69±8.91	<0.001
Diastolic blood pressure (mmHg)	76.07±9.08	70.16±7.01	<0.001
Mean blood pressure (mmHg)	93.02±10.8	83.2±6.52	<0.001
Fasting blood glucose (mg/dL)	189.34±69.64	88.6±18.95	<0.001
Triglyceride (mg/dL)	246.07±120.22	198.6±115.83	0.03
HDL (mg/dL)	31.14±11.12	47.5±14.42	<0.001
Fibrinogen	3.56±1.01	2,95 ± 0.77	<0.001
PT	13.16±2.70	12.04±1.10	<0.001
INR	1.14±0.25	1.04±0.01	<0.001

SD: Standard deviation, BMI: Body-mass index, HDL: High density lipoprotein, PT: Prothrombin time, INR: International normalized ratio

Table 2. Comparison of patient numbers in the patient and control group in terms of c-reactive protein

	Patient group n (%)	Control group n (%)	p value
CRP>3.3	39 (69.6)	15 (23.4)	<0.001
CRP<3.3	17 (30.3)	49 (76.5)	

*The CRP cut off value of our hospital is 3.3, CRP: C-reactive protein

The distribution of MetS components in the patient and control groups is shown in Figure 1.

In the patient group, the patient distribution was examined according to the number of criteria and the average fibrinogen, PT and INR levels were calculated (Figure 2).

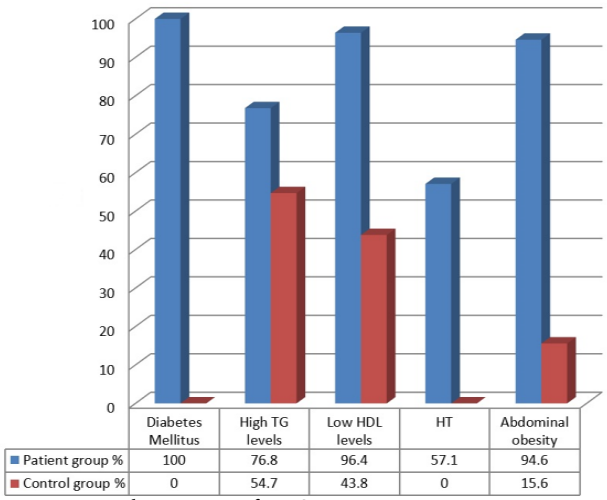

Figure 1. Distribution rates of MetS components

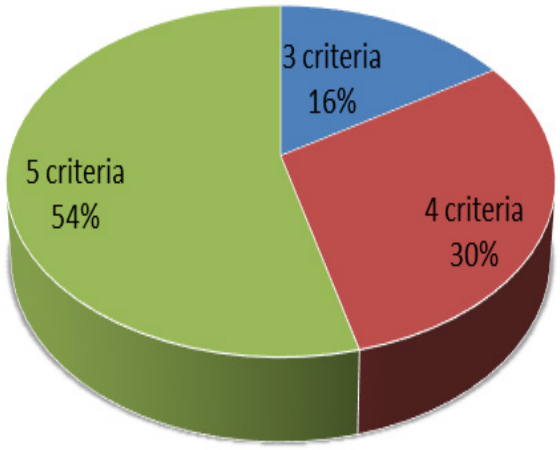

Figure 2. Distribution of patients according to metabolic syndrome criteria numbers

While fibrinogen, PT and INR levels in the female patient group were significantly higher than those in the control group, no significant difference was detected between the patient and control groups in men (Table 3).

Table 3. Comparison of PT, INR and fibrinogen levels by gender

	Female			Male		
	MetS (+)	MetS (-)	p value	MetS (+)	MetS (-)	p value
PT	13.49±2.9	11.98±0.87	p<0.01	12.49±2.16	12.10±1.28	>0.05
INR	3.57±0.82	1.03±0.01	p<0.01	3.32±0.74	2.81±0.51	>0.05
Fibrinogen	3.52±0.13	2.95±0.08	p<0.01	3.32±0.7	2.81±0.08	<0.05

PT: Prothrombin time, INR: International normalized ratio

No statistically significant difference was detected in the change in PT, INR and fibrinogen levels as the number of MetS components increased (p>0.05) (Table 4).

Table 4. Change in PT, INR and fibrinogen levels with metabolic syndrome criteria number

	3 criteria together	4 criteria together	5 criteria together	p value
PT	12.58±1.00	13.83±0.77	12.94 ±0.43	
INR	1.09±0.09	1.20±0.07	1.12±0.03	>0.05
Fibrinogen	3.51±0.29	3.73±0.21	3.33±0.12	

PT: Prothrombin time, INR: International normalized ratio

A positive correlation was found between waist circumference and PT, INR and Fibrinogen in the MetS group. Strong positive correlations were observed between fasting blood glucose and PT, INR and fibrinogen.While mean blood pressure and TG levels showed a positive correlation with PT and INR levels, these results were not statistically significant.A statistically non-significant negative correlation was observed in HDL levels with PT, INR and fibrinogen (Table 5).

DISCUSSION

MetS is a component of pathological conditions associated with metabolic, proinflammatory and prothrombotic states.[8] This syndrome involves increased levels of coagulation factors (tissue factor, factor VII and fibrinogen) as well as inhibition of the fibrinolytic pathway (increase in PAI-1 and decrease in tissue plasminogen activator activity). It also has characteristics of a hypercoagulation state. The simultaneous presence of endothelial dysfunction and dyslipidemia triggers platelet aggregation, thus further increasing the risk of thrombotic events in both the arterial and venous systems.[9]

MetS increases with age. In a meta-analysis study, the average age of MetS patients was calculated as 41 years.[10] In the study of Gündoğan et al.,[11] the average age was reported as 47 years, and the frequency of MetS increased as age increased. In our study, the average age of MetS patients was found to be 52.9±12.08 years.

The frequency of MetS is increasing all over the world. According to the National Health and Nutrition Research Survey (NHANES) in the USA, it is known that 35% of adults and 50% of the population over the age of 60 are diagnosed with MetS (30.3% in men and 35.6% in women). While the European Met prevalence is 41% in men and 38% in women, in the Middle East it has been reported as 20.7-37.2% in men

Table 5. Relationship of metabolic syndrome components with PT, INR and fibrinogen

	PT		INR		Fibrinogen	
	Sperman correlation coefficient	p	Sperman correlation coefficient	p	Sperman correlation coefficient	p
Waist circumference (cm)	0.251**	0.007	0.250**	0.007	0.195*	0.036*
Blood pressure (mm/Hg)	0.070	0.456	0.062	0.510	0.220	0.018
FBG (mg/dL)	0.279**	0.002	0.283**	0.002	0.239**	0.010
HDL (mg/dL)	-0.049	0.603	-0.048	0.609	-0.113	0.229
TG (mg/dL)	0.059	0.530	0.077	0.413	0.045	0.633

**Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed), FBG: Fasting blood sugar, HDL: High density lipoprotein, TG: Triglyceride

and 32.1-42.7% in women.[12] According to the TEKHARF 2000 follow-up database in Turkey, it was reported as 27% in men and 38.6% in women, while according to the METSAR research conducted in 2004, it was found to be 28% in men, 39.6% in women and 33.9% in total. The prevalence of MetS increased with age in men, and while it was found to be 10.7% in those aged 20-29, it increased to 49% in people over 70 years of age. The prevalence in women also increased with age, from 9.6% in those aged 20-29 to 74.6% in those aged 60-69. When we evaluated the PURE data in 2009, it was observed that the prevalence of MetS was between 36.7% and 43.6%.[13-15] In our study, 33.9% of 56 patients were male and 66.1% were female.

When the components of MetS were evaluated, it was reported that abdominal obesity and high blood pressure were the most common metabolic findings in the METSAR study, abdominal obesity and low HDL in Tabatabaie et al.'s[16] study, and low HDL in Sharifi's study.[17] In the study of Gündoğan et al,[11] the most common component of MetS in our country was found to be hypertension. In our study, the distribution rates of MetS components were found to be high fasting blood sugar 100%, hypertension 57.1%, hypertriglyceridemia 76.8%, low HDL 96.4%, and abdominal obesity 94.6%.

Various pathogenic pathways that contribute to the development of MetS lead to the increase in various inflammatory markers such as IL-6, CRP and TNF-α seen in patients with MetS.[3] In the study of Weisberg et al,[18] it was shown that the increase in IL-6 level increased with insulin resistance and obesity.[19] In the study of Malik et al,[20] they found that the CRP level increased in patients with MetS and diabetes, and that this increase was more pronounced in people with cardiovascular disease. In our study, CRP elevation was found to be statistically significantly higher in the patient group.

MetS has a complex pathophysiology associated with an increased risk of both atherothrombotic cardiovascular events and venous thromboembolism. In addition to affecting the thrombogenicity of circulating blood as a result of the inflammatory state accompanying MetS, dyslipidemia and fat accumulation in the liver, a procoagulant and hypofibrinolytic state has been described.[21] In MetS, high IL-6 levels also increase fibrinogen levels and causes a prothrombotic state.[2] High fibrinogen levels have been reported in many MetS studies. In the TEKHARF study, which started in 1998 and included 2516 participants, the mean plasma fibrinogen level was found to be 3.12±1.11 g/L. It was also reported in the study that fibrinogen levels significantly increase with age in both genders.[13] In the study of Imperatore et al.,[22] fibrinogen values were associated with BMI, waist-hip ratio, systolic and diastolic blood pressure, plasma total cholesterol, LDL cholesterol, triglycerides, insulin and HDL. Khunger et al.[23] reported fibrinogen as the most sensitive coagulation parameter in MetS. In our study, fibrinogen levels increased significantly in the MetS group compared to the healthy group. Additionally, a significant positive correlation was found between fasting blood sugar and waist circumference.

PT, one of the indicators of the extrinsic coagulation system in MetS, and activated partial thromboplastin time (APTT), which is the intrinsic coagulation system, have been reported to be significantly low in many studies.[23] Injury to endothelial cells has been held responsible for this prothrombotic state by causing an increase in the levels of factors VII, IX and X, prothrombin and PAI-1.[19] The fact that PT and INR are significantly higher in MetS suggests that it may be in a hypocoagulant state rather than a procoagulant state. In a study conducted by Habib et al.[24] in patients with alcoholic hepatitis, INR and PT levels were found to be higher in the patient group with MetS than in the patient group without MetS. Similar to this study, PT and INR values were found to be significantly higher in the patient group in our study.

Limitations

Our study has some limitations. These limitations are the small number of patients and the lack of more parameters indicating clotting factors. Although our study has a low sample size, it has several important implications.

CONCLUSION

In our study, high fibrinogen values indicate the presence of hypercoagulopathy in patients with MetS, while high PT and INR values seem to indicate hypocoagulopathy. There are no current guidelines regarding the administration of prophylactic anticoagulation in MetS.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was approved by the Ondokus Mayıs University Clinical Researches Ethics Committee (Date: 26.04.2012, Desicion no: 2012/8).

Informed Consent

The patient signed and free and informed consent form.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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