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The association of TAFI (Thrombin-activatable fibrinolysis inhibitor) with insulin resistance and components of metabolic syndrome in patients with metabolic syndrome

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Aim: To investigate the association of TAFI with components of metabolic syndrome and insulin resistance in patients with metabolic syndrome.

Materials and methods: Patients between 20 and 70 years of age, who met at least 3 of the metabolic syndrome criteria, and had no known coronary artery disease were included in the study. The control group consisted of 20 healthy subjects with demographic characteristics similar to the patients. Fasting blood glucose, HbA1c, lipid profile, insulin, microalbumin, and TAFI Ag levels were investigated in the patients and controls. Insulin resistance was calculated according to the HOMA-IR [(fasting plasma insulin (μIU/ml) × fasting plasma glucose (mmol/L))/22.5] formula.

Results: There was a significant difference ($P < 0.01$) between patients with metabolic syndrome (MS) and healthy individuals with respect to TAFI Ag levels. However, when patients with MS were divided into 2 groups according to HOMA-IR values, an indicator of insulin resistance, no association was detected between the levels of HOMA-IR and TAFI Ag. In metabolic syndrome group, there was a positive correlation only between the triglyceride and plasma TAFI Ag levels ($P < 0.05$).

Conclusion: These findings suggest that increased TAFI levels in metabolic syndrome may contribute to prothrombotic state and impaired fibrinolysis, and that hypertriglyceridemia may play part in this process.

Key words: Metabolic syndrome, TAFI, insulin resistance

Metabolik sendromlu hastalarda insulin direnci ve metabolik sendrom komponentleriyle TAFI (Thrombin activatable fibrinolysis inhibitor) arasındaki ilişki

Amaç: Metabolik sendromlu hastalarda metabolik sendrom komponentleriyle, insülin direnci ve fibrinolitik sistemin önemli bir inhibitörü olan TAFİ arasındaki ilişkiyi araştırdık.

Yöntem ve gereç: Hastalar yaşları 20-70 arasında olan, metabolik sendrom kriterlerinden en az 3'ünü taşıyan, bilinen koroner arter hastalığı olmayan kişiler arasından seçildi. Hasta grubuyla benzer demografik özellikleri taşıyan 20 sağlıklı kontrol grubu oluşturuldu. Hasta ve kontrol grubuna AKŞ, HbA1c, lipid profili (kolesterol, trigliserid, HDL kolesterol, LDL kolesterol), insülin, 24 saatlik idrarda mikroalbümin, ve TAFI Ag parametrelerine bakıldı. İnsülin ve plazma glukozu göz önüne alınarak HOMA-IR (açlık plazma insulin (μIU/mL) × açlık plazma glukozu (mmol/L)]/22.5) formülüne göre insülin direnci hesaplandı.

Bulgular: Metabolik sendromlu hastalarda, TAFI Ag düzeylerini sağlıklı grupla karşılaştırdığımızda ileri düzeyde anlamlı fark vardı ($P < 0,01$). Ama insülin rezistansının bir göstergesi olan HOMA-IR değerlerine göre metabolik sendromlu hastaları kendi içinde 2 gruba ayırdığımızda HOMA-IR düzeyi ile TAFI Ag arasında ilişki saptayamadık. Literatürden farklı olarak metabolik sendrom grubunda total kolesterol, HDL-kolesterol, LDL-kolesterol, açlık kan şekeri, BMI, bel

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çevresi, mikroalbüminüri ile plazma TAFI Ag düzeyi arasında ilişki saptayamadık. Metabolik sendromda sadece trigliserid düzeyi ile plazma TAFI Ag düzeyi arasında pozitif korelasyon saptadık (P < 0,05).

Sonuç: Bu bulgular bize metabolik sendromdaki artmış TAFI düzeylerinin protrombotik duruma ve bozulmuş fibrinolizise bir katkı sağlayabileceğini ve bu katkıda hipertrigliserideminin de rolü olabileceğini düşündürmektedir

Anahtar sözcükler: Metabolik sendrom, TAFI, insülin direnci

Introduction

Metabolic syndrome (MS), also known as insulin resistance syndrome, is defined by the clustering of several cardiovascular risk factors in an individual patient, including impaired glucose tolerance (diabetes), hypertension, dyslipidemia, and visceral obesity. Several studies have demonstrated that this syndrome strongly predicts cardiovascular disease (CVD), especially coronary heart disease, independently of LDL-cholesterol levels (1). Since the original description of metabolic syndrome in 1988, criteria diagnosis develop constantly and a complete consensus has yet to be reached on the most proper definition. Criteria suggested for MS may partly vary depending upon its pathogenesis. Insulin resistance is the main cause of metabolic syndrome. According to International Diabetes Foundation (IDF), central obesity plays a key role in the pathogenesis of MS and is the sine qua non diagnostic criterion (2). IDF stressed the presence of ethnic differences in the correlation between central obesity and other risk factors. Therefore, the criteria of central obesity were determined based on nation and ethnicity using the best available population estimates. For the people of European origin, IDF determined the threshold value for abdominal obesity ≥94 cm waist circumference in males and ≥80 cm in females. In Asian populations other than Japanese, threshold values are ≥90 cm and ≥80 cm in males and females, respectively. Probably one of the most commonly used criteria is those of National Cholesterol Education Program–Adult Treatment Panel III (NCEP ATP III). These criteria were modified in 2005 and the cut off value of fasting blood sugar was reduced from 110 mg/dL to 100 mg/dL (3). The criteria for metabolic syndrome are listed as follows:

1) Updated NCEP ATP III, 2005

Three or more of the following 5 risk abnormalities:

a) Waist circumference > 102 cm (men) or > 88 cm (women)

b) Triglycerides > 150 mg/dL

c) HDL-Cholesterol < 40 mg/dL (men) or < 50 mg/dL (women)

d) Blood pressure > 130/85 mm Hg

e) Fasting plasma glucose > 100 mg/dL

2) **IDF Criteria, 2005**

Increased waist circumference (with ethnicity-specific values for ethnic groups) plus at least 2 of the following:

a) Triglycerides >150 mg/dL or treatment for this abnormality

b) HDL-C < 40 mg/dL (men) or < 50 mg/dL (women) or specific treatment

c) Blood pressure >130/85 mm Hg or specific treatment

d) Fasting plasma glucose > 100 mg/dL or previously diagnosed type 2 diabetes

In MS, hypercoagulability is the consequence of the increase in coagulation factors, decrease in fibrinolysis, hyperactivity and thrombocytes, and endothelial dysfunction. Insulin resistance plays a central role in pathogenesis. According to the formula of homeostasis of minimal assessment of insulin resistance (HOMA-IR), a value of >2.5 is defined as insulin resistance (4). Thrombin activatable fibrinolysis inhibitor (TAFI) provides an important molecular link between the coagulation and fibrinolytic systems (5). TAFI is a 58-kD glycoprotein synthesized in the liver and can be activated by thrombin, thrombin-thrombomodulin complex, plasmin or trypsin-catalyzed proteolysis to carboxypeptidase B –like enzymes that inhibit fibrinolysis (6). It is well known that C-terminal lysines on cell-surface proteins and partially degraded fibrin enhance fibrinolysis by providing binding sites

for plasminogen. Once bound, it adopts a more activatable conformation. Activated TAFI inhibits activation of plasminogen to plasmin by removing these C-terminal lysine residues. In addition, activated TAFI might also directly inactivate plasmin, further impairing fibrinolysis (7). Since TAFI is associated with coagulation/fibrinolysis and inflammation, plasma TAFI may participate in arterial thrombosis in CVD or in venous thrombosis (8). In a previous study of patients with type 2 diabetes (9), plasma TAFI was independently correlated with components of the MS including visceral fat and the glucose infusion rate, an index of insulin resistance. However, Aubert et al. (10) suggested that plasma TAFI shows only a weak, non-independent correlation with insulin resistance. Thus, the identity of main determinants of plasma TAFI concentrations remains unclear.

Despite studies on the relationship of TAFI with thromboembolic events and coronary artery disease of various metabolic syndromes, studies on association of TAFI and neoplastic disease are limited (11-14).

Study design and methods

A total of 83 individuals including 63 patients from Haseki Training and Research Hospital and 20 healthy controls were included in the study. Patients with an age range of 20-70 years were selected among individuals without any known coronary artery disease, who presented to the Internal Medicine Outpatient Clinics and fulfilled at least 3 of the metabolic syndrome criteria (Updated NCEP ATP III, IDF). Presence of previous coronary cardiac disease, chronic airway disease, and impaired hepatic dysfunction, pregnancy, and presence of any acute disease were determined as exclusion criteria. Demographic characteristics of patient and control groups were similar. The study protocol was approved by the institutional ethics committee. All participants gave informed consent before recruitment. Fasting blood glucose (FBG), HbA_{1c}, lipid profile (total cholesterol, triglyceride, HDL-cholesterol, and LDL-cholesterol), insulin, 24-h urinary microalbumin, and TAFI Ag levels were investigated in the patient and control groups. Glucose, cholesterol, triglyceride, and HDL-cholesterol were measured by a spectrophotometric method with an Olympus AU 2700 device using Olympus kits, and HbA_{1c} was measured by immuno-turbidimetric inhibition method with the same device using the same kits. Insulin was measured by chemiluminescence method using an Immulite 2000 device. Insulin resistance was calculated using insulin and plasma glucose, according to homeostasis of minimal assessment of insulin resistance (HOMA-IR) [(fasting plasma insulin (μIU/mL) × fasting plasma glucose (mmol/L)) / 22.5] formula. TAFI Ag was measured by ELISA method using an Actichrome kit.

Statistical analysis

ANOVA, independent samples test, t-test, chi-square, variance analysis, and Pearson's correlation tests were used in statistical analyses using SPSS 13.0. For data evaluation, descriptive statistical methods, such as mean, standard deviation (SD), and minimum and maximum values, were used. P value of <0.05 was accepted as significant.

Results

Subjects included in the study were divided into 9 groups. The association of all groups with TAFI Ag was investigated. Results of all parameters are given for both patient and control groups in the Table.

Group 1: This group includes individuals with metabolic syndrome who do not have a known coronary artery disease and meet 3 or more of NCEP ATP III criteria (n = 63) and healthy control subjects. (n = 20). In this group, in the comparison of mean TAFI Ag levels between metabolic syndrome group and control group, they were found to be significantly higher in the MS group ($t = 3.92$, $P < 0.01$), again in this group, HOMA-IR levels were compared between the MS group and the control group and they were found significantly higher in patients with MS ($t = 5.39$, $P < 0.01$). In patients with MS, triglyceride, total cholesterol, and fasting blood glucose levels were found to be higher while HDL levels were lower than the control group ($P < 0.05$). No significant difference was found between mean LDL values. Waist circumference and BMI were found to be significantly higher in the MS group ($P < 0.01$) (Figures 1 and 2)

Group 2: Patients with MS were examined in 2 subgroups; HOMA-IR > 2.5 (n = 19) and HOMA-IR < 2.5 (n = 44) and these 2 groups were compared in

Table 1. Results of all parameters for both patients and control groups.

	MS Group n = 63	Control Group n = 20	t	P
SAP (mmHg; mean ± SD)	144 ± 24	117 ± 11	4.81	0.0005
DAP (mmHg; mean ± SD)	91 ± 15	74 ± 6	4.80	0.0005
BMI (kg/m²; mean ± SD)	33 ± 5	24 ± 3	6.26	0.0005
Waist circumference (cm; mean ± SD)	110 ± 11	83 ± 12	8.24	0.0005
FBG (mg/dL; mean ± SD)	137 ± 59	84 ± 13	6.47	0.0005
Total cholesterol (mg/dL; mean ± SD)	215 ± 42	193 ± 24	2.67	0.0010
LDL (mg/dL; mean ± SD)	129 ± 37	121 ± 18	1.32	0.192
HDL (mg/dL; mean ± SD)	44 ± 8	50 ± 13	2.42	0.018
Triglyceride (mg/dL; mean ± SD)	249 ± 208	117 ± 37	4.63	0.0005
HOMA-IR (mean ± SD)	4.3 ± 2.9	1.7 ± 1.2	5.3	0.0005
TAFI Ag (mean ± SD)	166 ± 74	114 ± 40	3.92	0.0005

BMI: Body Mass Index; DAP: Diastolic Arterial Pressure; FBG: Fasting Blood Glucose;
MS: Metabolic Syndrome; SAP: Systolic Arterial Pressure; SD: Standard Deviation;
TAFI: Thrombin-Activatable Fibrinolysis Inhibitor;

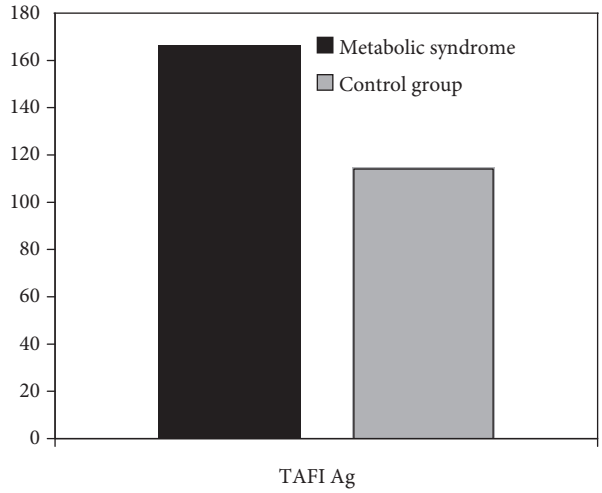

Figure 1. Mean TAFI Ag levels in both MS and control groups.

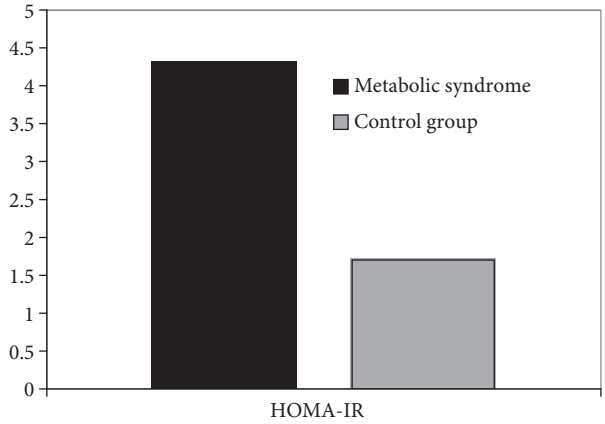

Figure 2. HOMA-IR levels in both MS and control group.

terms of mean TAFI Ag levels. Although these levels were found to be higher in the subjects with high HOMA-IR values than those with normal values, the difference was not statistically significant (Figure 3).

Group 3: MS patients were divided into 2 groups according to their total cholesterol values; subjects whose total cholesterol value < 200 mg/dL (n = 25) and those whose total cholesterol value > 200 mg/dL (n = 38). Although mean TAFI Ag values were found to be higher in the subjects with total cholesterol value of over 200 mg/dL than those with total cholesterol values below 200 mg/dL, the difference was not statistically significant. (Figure 4)

Groups 4 and 5: In group 4, although mean TAFI Ag level was higher in the subjects with a triglyceride value of over 150 mg/dL (n = 44) than those with a

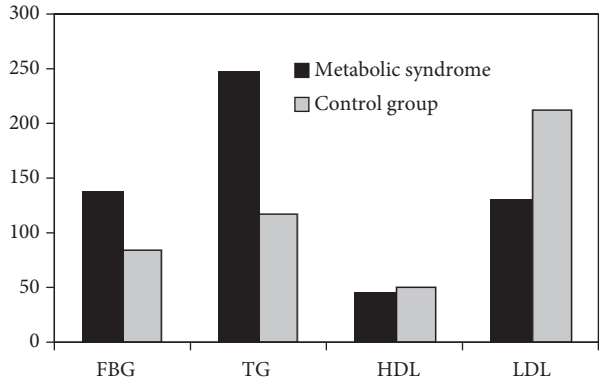

Figure 3. Fasting blood glucose (FPG), triglyceride, HDL-cholesterol and LDL-cholesterol levels compared in both MS and control groups.

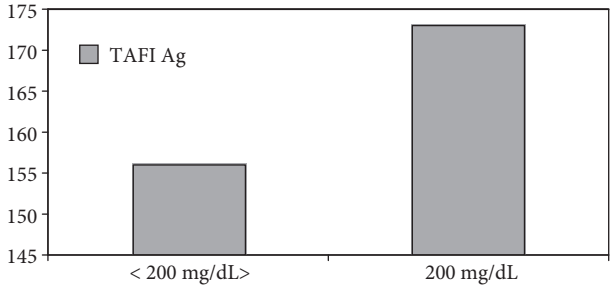

Figure 4. Mean plasma TAFI Ag levels according to total cholesterol values in MS patients.

value below 150 mg/dL (n = 19), the difference was not statistically significant. There was a positive correlation between triglyceride and TAFI Ag levels in patients with metabolic syndrome (r = 0.25, P < 0.05); i.e., TAFI Ag level increased as the triglyceride level increased. In group 4, where the patients with MS were divided into 2 subgroups according to the triglyceride levels, the lack of a significant difference in TAFI Ag levels between those with a triglyceride level below and above 150 mg/dL may be explained by the smaller number of cases with a triglyceride level < 150 mg/dL (n = 19). In group 5, although TAFI Ag level was found to be higher in the subjects with LDL level of >140 mg/dL than those under < 140 mg/dL, the relation between LDL level and ile TAFI Ag level was not significant (Figures 5 and 6).

Groups 6 and 7: In group 6, patients with MS were divided into 2 subgroups; those with microalbuminurea (n = 18) and those with normoalbuminurea (n = 45), and in group 7; those who are normotensive (n = 14) and hypertensive (n = 49). Although TAFI Ag was found to be higher in hypertensive and normoalbuminuric groups, the difference was not statistically significant.

Group 8: In group 8, patients with MS were divided into 2 subgroups by the HDL level. In subgroup 1 (n = 49), HDL level was below 40 mg/dL and 50 mg/dL in males and females, respectively. In subgroup 2 (n = 14), it was above these levels. The mean TAFI Ag level was detected to be higher in those with a low HDL level; however, the difference was not statistically significant (Figure 7).

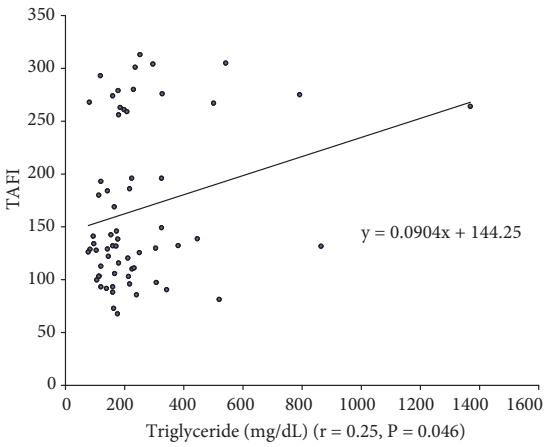

Figure 5. Relationship between triglyceride levels and plasma TAFI Ag in MS patients.

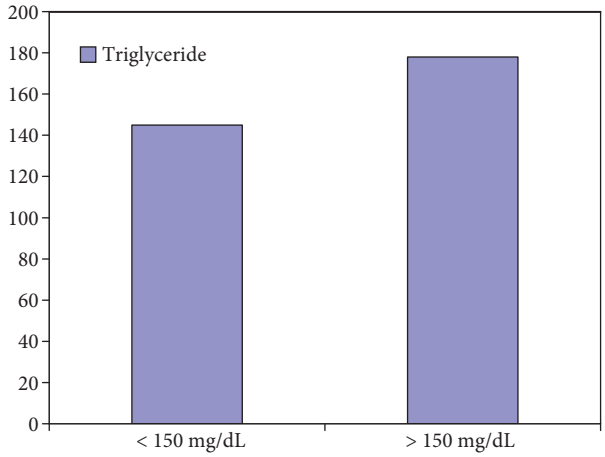

Figure 6. Mean plasma TAFI Ag levels according to triglyceride values in MS patients.

Group 9: In group 9, patients with MS were grouped as those with a waist circumference above and below 88 cm and 102 cm in males and females, respectively. In addition, patients with MS were also divided into 4 subgroups by their waist circumference, irrespective of gender: 80-99 cm (n = 10), 100-109 cm (n = 17), 110-119 cm (n = 24), and >120 cm (n = 12). The highest mean TAFI Ag level was detected in those with a waist circumference between 110 and 119 cm; however, no statistically significant correlation was detected between the mean TAFI Ag level and the waist circumference in any of these subgroups (Figure 8).

Discussion

In metabolic syndrome in which many disorders such as abdominal obesity, lipid metabolism disorders, hypertension, diabetes, insulin resistance with or without glucose intolerance, microalbuminurea, thrombosis or tendency to inflammation coexist, the mortality and morbidity of coronary heart disease (CHD) increase. Insulin resistance leads to susceptibility to metabolic syndrome findings, such as dyslipidemia and hypertension. In addition, it is a central metabolic disorder that leads to the development of type II diabetes. The loss of the balance between prothrombotic and fibrinolytic factors is another characteristics of metabolic syndrome. Studies investigating the nature of the interaction between hemostatic factors and the endothelial cells on the surface of blood vessels demonstrated that metabolic syndrome is a strong risk factor for arteriosclerotic cardiovascular disease. In the large scale study of Juhan V. in 2000, traditional risk factors were compared both between each other and with TAFI Ag values. In the present study, TAFI Ag values correlated positively with BMI, systolic blood pressure, diastolic blood pressure, and fibrinogen in males while they correlated with age, systolic blood pressure, total cholesterol, Apo B, fibrinogen, and IMT (intima-media thickness) in females. After correction for age, while no correlation was found in females between TAFI Ag values and other parameters, significant correlation was found between TAFI Ag values and waist-hip ratio and blood pressure (15). In the present study, TAFI Ag values were found to be significantly higher in the metabolic syndrome group than in the control group. However, no significant relation was found in the metabolic syndrome group between TAFI Ag values and BMI and hypertension. In many studies (11,14,15), significant relation has been found between TAFI and hypercholesterolemia. Yet, in the present study, although TAFI values were higher in the group with a cholesterol value of over 200 mg/dL than those with a value below 200 mg/dl, the difference was not statistically significant.

There are many studies demonstrating a positive relation between TAFI activity and TAFI Ag (16,17).

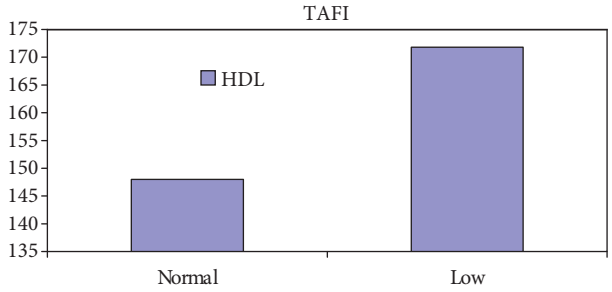

Figure 7. Mean TAFI Ag levels according to HDL-cholesterol values in MS patients.

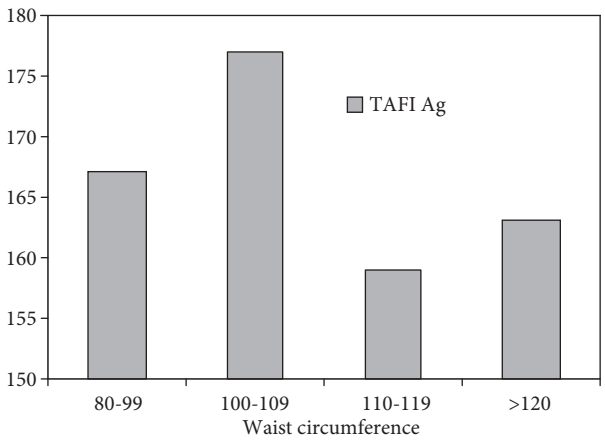

Figure 8. Mean plasma TAFI Ag levels according to waist circumference in MS patients.

In the present study, TAFI Ag levels were examined. It was established that, in metabolic syndrome, which is one of the most important risk factors for coronary heart disease, TAFI Ag levels were significantly higher than the control group. In the present study, unlike the study of Montserrat, higher TAFI Ag levels were found in the hypertensive group with MS than the normotensive MS group, but the difference was not statistically significant.

In the study of Yoshimasa Aso. et al. (published in the journal 'Diabetes' in 2005), it was advocated that LDL-cholesterol should be taken into account in the determination of plasma TAFI Ag in type 2 diabetes patients and that both metabolic syndrome and hypercholesterolemia accelerate inflammation in combination, thus slowing fibrinolysis. It was also established that direct inhibition of fibrinolysis was related to high levels both in TAFI and PAI-1. Unlike Yoshimasa Aso, in the present study, in patients with metabolic syndrome, higher plasma values of TAFI Ag were found in those with plasma LDL-cholesterol level over 140 mg/dL than those with a corresponding value under 140 mg/dL, but the difference was not statistically significant. Again, in patients classified as normoglicemic-impaired fasting glucose-diabetes, according to the fasting blood glucose values, no significant relation was found between fasting blood glucose and plasma TAFI Ag levels. In the present study, patients with metabolic syndrome were divided into 2 subgroups (microalbuminuric and normoalbuminuric) in that microalbuminurea has a significant relation with endothelial vessel damage and it was established that the increase in TAFI Ag levels in metabolic syndrome was independent of microalbuminurea.

When we compared triglyceride levels and TAFI Ag levels in patients with metabolic syndrome, we found a positive mild correlation between plasma triglyceride levels and TAFI ag level (i.e., triglyceride levels increased, so did TAFI Ag levels). It is not known whether increase in TAF I Ag levels in metabolic syndrome directly reflect the increase in triglyceride levels or is the result of common effect of other components of metabolic syndrome. However, in the present study, it was established that the important factor in the increase in plasma TAFI Ag levels was the increase in triglyceride levels. Y.Hori et al. investigated plasma TAFI levels and activity in order to evaluate hypofibrinolysis, which is one of the most common findings in obese type 2 DM patients. They divided DM patients into 2 groups according to their BMI (BMI > 25 obese ve BMI <25 non-obese). They found TAFI levels to be significantly higher in DM patients than in controls. In obese patients with DM, TAFI concentration and activity was found to be significantly higher than non-obese DM patients and controls. In conclusion, they found significant correlation between plasma TAFI levels and HbA1c, BMI, and insulin resistance (18). In the present study, unlike the results of Y.Hori et al., although TAFI levels were found to be significantly higher in patients with metabolic syndrome, when insulin resistance was calculated using the HOMA-IR formula. The difference in TAFI Ag levels between those with high HOMA-IR values and those with low values was not statistically significant. Juhan V. investigated cardiovasular risk factors, and found a positive correlation between TAFI ag levels and hypercholesterolemia (14). Similarly, A.Santamaria et al., in their study on patients with coronary artery disease, found a positive correlation between TAFI levels and hypercholesterolemia (19). In the present study, a positive correlation was found only between triglyceride levels, which is one of the components of metabolic syndrome, and TAFI Ag levels. No positive correlation was found between other components of metabolic syndrome and plasma TAFI Ag levels. We believe that increased TAFI Ag levels may have contributed to the prothrombotic state in metabolic syndrome and that hypertriglyceridemia may play a role in this contribution in view of the mild correlation we found between TAFI and triglycerides. In addition, other components of metabolic syndrome may contribute to the increase in TAFI levels. This contribution may be investigated with further studies including higher number of participants.

Conclusions

These findings suggest that increased TAFI levels in metabolic syndrome may contribute to prothrombotic state and hypertriglyceridemia may take part in this contribution.

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