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RELATIONSHIP OF ADAMTS WITH BIOCHEMICAL PARAMETERS IN METABOLIC SYNDROME

METABOLİK SENDROMDA ADAMTS'LERİN BİYOKİMYASAL PARAMETRELER İLE İLİŞKİSİ

Semiramis DOĞAN ZEYBEK[1], Adnan Adil HİŞMİOĞULLARI[2]

[1]İstanbul University, Institute of Health Sciences, Cancer Biochemistry, İstanbul, Türkiye
[2]Balıkesir University, Institute of Health Sciences, Medical Biochemistry, Balıkesir, Türkiye

ORCID ID: S.D.Z. 0000-0002-0248-2483; A.A.H. 0000-0001-9982-2714

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ABSTRACT

Objective: The aim of our study was to investigate the potential of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) proteins, which are thought to change in levels as a result of the deterioration of the extracellular matrix in the vessels due to the development of atherosclerosis, to be used as biochemical markers in individuals with metabolic syndrome and diabetes.

Material and Methods: Our study was carried out with the participation of 10 female individuals diagnosed with diabetes in the experimental group, 10 female individuals diagnosed with metabolic syndrome and 11 healthy female individuals the aged 25-65 years. Biochemical analyses and anthropometric measurements were performed and blood samples were taken. Serum was separated from the blood samples. ADAMTS-1 and ADAMTS-9 serum levels were analysed using ELISA method.

Results: When the amount of ADAMTS-1 protein was analysed, ADAMTS-1 level was found to be statistically ($p<0.01$) significantly lower when the experimental and control groups were compared. When the amount of ADAMTS-9 protein was analysed, similarly statistically significant ($p<0.01$) decreases were found between the groups.

Conclusion: This is a preliminary study showing that ADAMTS-1 and ADAMTS-9 proteins can be used in the early diagnosis and treatment of metabolic syndrome and in the pathogenesis of the disease. However, this potential needs to be investigated in detail.

Keywords: ADAMTS-1, ADAMTS-9, diabetes mellitus, metabolic syndrome, atherosclerosis

ÖZ

Amaç: Çalışmamızda ateroskleroz gelişimine bağlı olarak damarlardaki ekstraselüler matriksin bozulmasının neticesinde düzeylerinde değişiklik olabileceği düşünülen a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) proteinlerinin metabolik sendromlu ve diyabetli bireylerde biyokimyasal belirteç olarak kullanılma potansiyellerini ortaya koymaktır.

Gereç ve Yöntemler: Çalışmamız, 25-65 yaş aralığında deney grubunda diyabet tanısı konulmuş 10 kadın birey, metabolik sendrom tanısı konulmuş 10 kadın birey ve sağlıklı 11 kadın bireyin katılımıyla gerçekleştirilmiştir. Çalışmadaki bireylerin biyokimyasal analizleri ve antropometrik ölçümleri yapılıp kan örnekleri alındı. Alınan kan örneklerinden serumları ayrıldı. ADAMTS-1 ve ADAMTS-9 serum düzeyleri ELISA yöntemiyle analiz edildi.

Bulgular: ADAMTS-1 protein miktarı incelendiğinde deney ve kontrol grupları karşılaştırıldığında ADAMTS-1 düzeyi istatistiksel olarak ($p<0,01$) anlamlı derece düşük bulunmuştur. ADAMTS-9 protein miktarı incelendiğinde ise gruplar arasında yine benzer şekilde istatistiksel olarak anlamlı ($p<0,01$) azalmalar tespit edilmiştir.

Sonuç: ADAMTS-1 ve ADAMTS-9 proteinlerinin metabolik sendromda erken teşhis ve tedavi sürecinde ve hastalığın patogenezinde kullanılma potansiyellerinin mevcut olduğunu gösteren bir ön çalışma niteliğindedir. Fakat bu potansiyelin detaylı olarak araştırılması gerekmektedir.

Anahtar Kelimeler: ADAMTS-1, ADAMTS-9, diabetes mellitus, metabolik sendrom, ateroskleroz

Corresponding Author/Sorumlu Yazar: Semiramis DOĞAN ZEYBEK **E-mail:** semiramisdogan13@gmail.com

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INTRODUCTION

Metabolic syndrome (MetS) is a condition that rapidly expands its area of influence because of today's modern lifestyle and leads to significant health problems (1). Metabolic syndrome is characterised by a combination of various disorders, including abdominal obesity, insulin resistance, glucose intolerance or type 2 diabetes, hypertension, dyslipidemia, and cardiovascular diseases (2). The prevalence of this syndrome is increasing rapidly all over the world. This situation decreases the living standards of the individual and leads to an increased burden on the healthcare system (3). In this context, the early diagnosis and prevention of MetS is of great importance (4).

The pathophysiology of Metabolic Syndrome is complex and is a blend of genetic factors, environmental factors, and lifestyle. Insulin resistance (IR), which is one of its important components, leads to elevated blood glucose levels as a result of the inefficient utilisation of glucose by cells (5). Obesity, especially abdominal obesity, is one of the main components of MetS and increases IR through the unbalanced release of adipokine (2). Another important component of MetS is dyslipidemia, the deterioration of the lipid profile in the blood. This disorder includes an increase in low-density lipoprotein (LDL) cholesterol and a decrease in high-density lipoprotein (HDL) good cholesterol. In metabolic syndrome, hypertension is often seen with an increased risk of cardiovascular diseases (6, 7). Finally, coronary artery diseases may occur as an important consequence of metabolic syndrome. This is related to the progression of the atherosclerosis process (8). There are many criteria in the diagnosis of metabolic syndrome. These criteria commonly include abdominal obesity, elevated fasting blood glucose, low HDL levels, and high triglyceride levels (9).

The main aim of this study was to investigate the potential of a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) parameters as biochemical markers in metabolic syndrome. ADAMTS proteins consist of metalloproteinases that have roles in remodelling of extracellular matrix (ECM) (10). ADAMTS proteins, especially ADAMTS-1 and ADAMTS-9, are related to the disruption of the extracellular matrix of vessels and have important effects on the initiation and progression of atherosclerosis (11). In our study, we will examine the effects of these proteins in metabolic syndrome and their potential as markers by comparing ADAMTS-1 and ADAMTS-9 levels in individuals with metabolic syndrome and diabetes with those in the control groups.

MATERIAL and METHODS

Participants

The study was carried out with the participation of 10 female individuals between the ages of 25-65 who were previously diagnosed with diabetes, 10 female individuals diagnosed with MetS and 11 healthy female individuals. The experimental group was selected from female individuals diagnosed with MetS or DM because of clinical evaluations at Balıkesir University Faculty of Medicine Hospital. The control group consisted of individuals without any chronic disease and underwent regular health checks. Only female patients were included in the study because of the low number of such studies on women and in order for our study to contribute to filling this gap. In addition, it was aimed to better understand the effects of gender differences in the biochemical parameters. Patient and control group participants were informed and written consent was obtained. Approval for the research was obtained from Balıkesir University Faculty of Medicine Ethics Committee with the decision numbered 2016/111 on 16.11.2016.

Anthropometric measurements

The weight, height and waist circumference of the participants were measured and the body mass index (BMI) was calculated. These data obtained in our study were compared between the groups and the data were statistically analysed.

Anthropometric measurements of the patient and control groups were performed using standard methods. For body weight and height, a mechanical scale with a height gauge was used. The waist circumference was measured at the navel level and recorded.

Blood samples and analyses

Blood samples were taken from the participants after 8-12 hours of fasting. These samples were centrifuged at +4℃ for 10 min and the serum portion was separated. The serum portions obtained were stored at -80℃. ADAMTS-1 and ADAMTS-9 levels of the sera obtained from the blood samples were measured by ELISA test kits. In addition, the blood glucose, HbA1c, insulin, LDL, HDL, triglyceride, and total and cholesterol levels of the experimental and control groups were investigated. All biochemical analyses in the blood samples of the study group were performed using an autoanalyzer device in the Biochemistry Laboratory of Balıkesir University Health Practise and Research Hospital and the Biochemistry Laboratory of Balıkesir University Faculty of Medicine.

Statistical analysis

The analysis of the data obtained in the study was performed using the SPSS Statistical Package for Social Sciences (IBM SPSS Corp., Armonk, NY, USA) 20.0 statistical software. Numbers, mean, and percentage values were used to describe the data. The Kolmogorov-Smirnov test was employed to determine whether the variables followed a normal distribution. The non-parametric Mann-Whitney U test was used to compare the two groups. The significance of the relationship between the variables was assessed using the Spearman Correlation test. A p-value of less than 0.05 ($p<0.05$) was considered statistically significant.

RESULTS

Age and anthropometric measurement values of ındividuals

The mean ages of the experimental and control groups were 45.10±13.60 years, mean body weights were 87.14±22.23 kg, mean BMI (kg/m^2) was 34.60±10.21, and mean waist circumference was 101.35±23.90 cm (Table 1).

Table 1: Age and anthropometric measurements of the participants (Mean±SD)

	n	Average	±SD	Minimum	Maximum
Age (years)	31	45.10	13.60	26	71
Body weight (kg)	31	87.14	22.23	47	129
BMI (kg/m)^2	31	34.60	10.21	19.56	55.11
Waist circumference (cm)	31	101.35	23.90	63	141

BMI: Body Mass Index

Table 2: Age, height, weight and BMI values of the individuals participating in the study (Mean±SD)

	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m²)
Control (n=11)	34.5±6.2	162.3±5.1	60.2±8.4	22.9±2.3
MetS + DM (n=20)	46.7±8.9	158.7±6.0	72.4±11.3	28.7±4.6

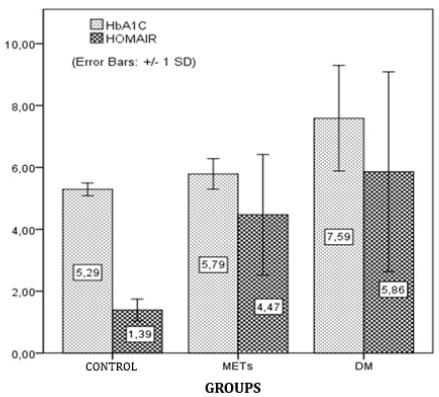

Figure 1: Mean HbA1c and HOMA-IR values of the study groups.

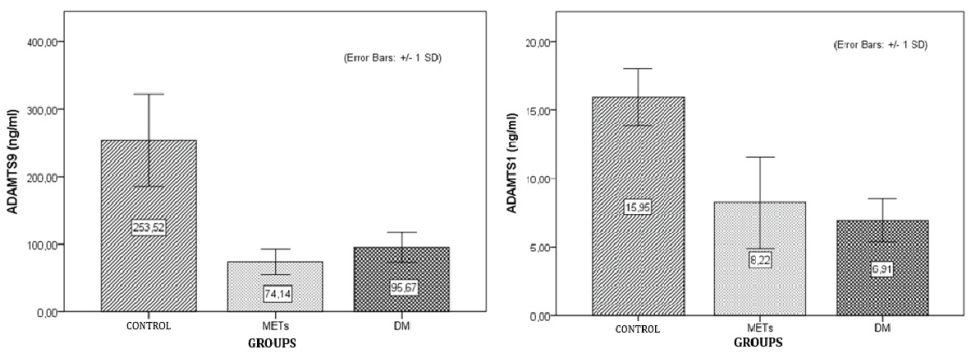

Figure 2: Mean ADAMTS-1 and ADAMTS-9 values of the study groups.

The mean age of the patient group was 45.6±10.2 years and 47.3±9.8 years, while the mean age of the control group was 42.1±8.7 years (Table 2). The waist circumference, BMI, and waist-to-hip ratio of the patient group were found to be significantly higher than those of the control group (p<0.01).

Mean HbA1c and HOMA-IR values of the study groups

The HbA1c value of the control group in the study was 5.29±0.21 ng/ml. The metabolic syndrome and diabetes groups were 5.79±0.5 ng/ml and 7.59±1.71 ng/ml, respectively (Figure 1). According to the mean HbA1c values, statistically significant differences were found between the control group and the diabetes group (p<0.01), between the control group and the metabolic syndrome group (p<0.05) and between the metabolic syndrome and diabetes groups (p<0.05).

According to HOMA-IR values, healthy individuals in the control group were 1.39±0.35 ng/ml, individuals with metabolic syndrome were 4.47±1.95 ng/ml, and individuals with diabetes were 5.86±3.23 ng/ml (Figure 1). According to this result, a sta-

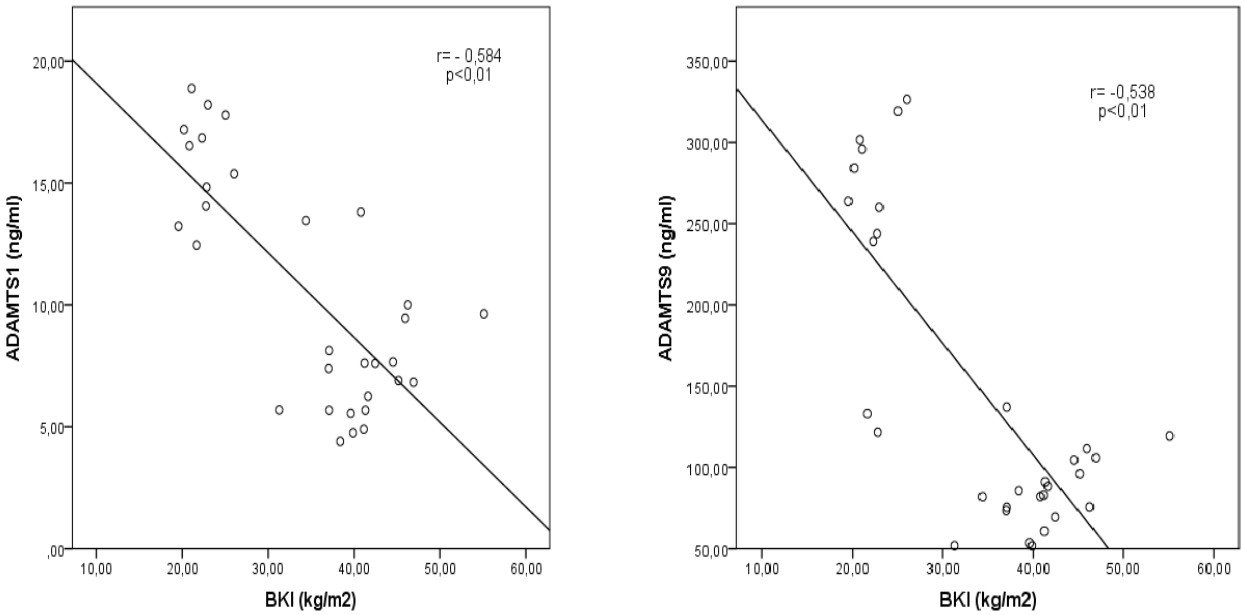

Figure 3: Relationship between BMI and ADAMTS-1 and ADAMTS-9 values

Table 3: Results of anthropometric and biochemical measurements of the study groups (Mean±SD)

	Control (n:11)		METs (n:10)		DM (n:10)	
	Average	±SD	Average	±SD	Average	±SD
Body weight (kg)	60	7.25	97.95	7.80	106.18	9.71
BMI (kg/m^2)	22.30	1.96	39.93	4.71	42.79	5.47
Waist circumference (cm)	72	6.56	114.70	8.23	120.30	11.83
Glucose (mg/dl)	89.82	6.00	104.6	15.15	153.30	48.66
Cholesterol (mg/dl)	157.64	13.58	201.20	28.28	195.10	22.73
LDL (mg/dl)	91.11	14.39	123.28	28.76	108.96	12.47
HDL (mg/dl)	52.55	9.95	50.80	11.60	56.20	17.30
TG (mg/dl)	70.27	22.07	135.60	50.76	149.70	50.50
HbA1c	5.29	0.21	5.79	0.50	7.59	1.71
HOMA-IR	1.39	0.35	4.47	1.95	5.86	3.23
ADAMTS-1 (ng/ml)	15.95	2.11	8.22	3.33	6.91	1.56
ADAMTS-9 (ng/ml)	253.52	68.59	74.14	18.79	95.67	22.25

BMI: Body Mass Index, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, TG: Triglyceride HbA1c: Haemoglobin A1c HOMA-IR: İnsülin direct test

tistically significant difference was found between the control group and the metabolic syndrome group ($p<0.05$). Again, a statistically significant difference was found between the control group and the diabetes group ($p<0.05$). However, no statistically significant difference was found between the metabolic syndrome and diabetes group ($p>0.05$).

ADAMTS levels

The mean ADAMTS-1 values of the control, metabolic syndrome and diabetes groups were 15.95±2.11 ng/ml, 8.22±3.33 ng/ml and 6.91±1.56 ng/ml, respectively (Figure 2). ADAMTS-1 levels in the patient group were significantly lower than those in the control group ($p<0.01$).

The mean ADAMTS-9 levels of the control, metabolic syndrome and diabetes groups were 253.52±68.59 ng/ml, 74.14±18.79 ng/ml and 95.67±22.25 ng/ml, respectively (Figure 2). ADAMTS-9 levels of the patient group were significantly lower than those of the control group ($p<0.01$). A significant decrease was found in the metabolic syndrome and diabetes groups ($p<0.05$) and no significant difference was observed between the metabolic syndrome and diabetes.

BMI and ADAMTS-1 and ADAMTS-9 values
According to Spearman's correlation analysis, a statistically significant and negative correlation was found between BMI (kg/m^2) and ADAMTS-1 (ng/ml) and ADAMTS-9 (ng/ml) measurements (r = 0.584; p<0.01) (Figure 3).

Anthropometric measurements and biochemical parameters
When the control group was compared with both the metabolic syndrome and diabetic patient group; mean HbA1c, glucose, HOMA-IR values and LDL (mg/dl), TG (mg/dl) and cholesterol (mg/dl) were found to be statistically significant (p<0.05). However, no significant difference was found in the mean HDL (mg/dl). HbA1c, ADAMTS-9 and glucose values were found to be statistically different in the metabolic syndrome and diabetic patient groups (p<0.05) (Table 3).

DISCUSSION

The results of our study indicate that ADAMTS-1 and ADAMTS-9 parameters are biochemical markers in the diagnosis of metabolic syndrome and diabetes. It is thought that the deterioration of the extracellular matrix decreases ADAMTS proteins. It is possible that this may have caused the development of atherosclerosis in the patient. This highlights that ADAMTS proteins may play a role in the formation and progression of vascular complications seen in patients with metabolic syndrome and diabetes.

These findings are consistent with other studies in the literature. For example, Santamaria et al. reported that ADAMTS-1 levels were associated with cardiovascular diseases and MetS (12). Similarly, in a study conducted by Wei et al., it was stated that ADAMTS-9 loci are associated with type 2 diabetes mellitus, insulin resistance, and coronary artery disease (CAD) risk factors. The Adamts-9 level showed a significant correlation with coronary artery disease and metabolic syndrome (13). However, as indicated in these studies, further research is required for ADAMTS proteins to be used as biochemical markers.

Low levels of ADAMTS-1 and ADAMTS-9 may be associated with increased inflammatory processes and oxidative stress. MetS and DM are known to cause increased chronic inflammation and oxidative stress. In the study of Boesgaard et al. on ADAMTS-9, the ADAMTS-9 parameter was found to be significantly lower in patients with diabetes (14). These results support the possible effect of ADAMTS-9 in diabetic complications. Wang et al. reported that ADAMTS-1 levels were low in obese individuals, and this may be associated with insulin resistance (15). This finding supports the decrease in ADAMTS-1 levels observed in our study. In a 2020 study, Li et al. examined the effect of ADAMTS-1 on cardiovascular diseases and found that low levels of ADAMTS-1 increased the cardiovascular risks of patients (16). This study shows that the ADAMTS-1' protein can be used in the early diagnosis and treatment of cardiovascular diseases.

According to the study conducted by Hoo et al., a decrease in the amount of ADAMTS-9 was observed in mice fed a high-fat diet and with increased insulin resistance. The results obtained in this study are consistent with our results (17).

However, more extensive and long-term studies are required to evaluate the potential for clinical use of ADAMTS-1 and ADAMTS-9 as biochemical markers. Future studies may show that ADAMTS proteins can be used in monitoring vascular complications and developing treatment strategies in patients with MetS and DM.

It is concluded that our preliminary study revealed that ADAMTS-1 and ADAMTS-9 proteins can be used in the early diagnosis and treatment of metabolic syndrome. However, it was concluded that this potential should be investigated in detail. Future studies need more data to better understand the clinical uses of these proteins. In addition, the potential of ADAMTS proteins to be used as therapeutic targets should also be investigated.

Ethics Committee Approval: This study was approved by Balıkesir University Faculty of Medicine Ethics Committee (Date: 16.11.2016, No: 2016/111).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

Peer Review: Externally peer-reviewed.

Author Contributions: Conception/Design of Study- A.A.H.; Data Acquisition- S.D.Z.; Data Analysis/Interpretation- S.D.Z.; Drafting Manuscript- S.D.Z.; Critical Revision of Manuscript- A.A.Ş.; Final Approval and Accountability- S.D.Z.; Supervision- A.A.Ş.

Conflict of Interest: The authors declare that there is no conflict of interest.

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