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THE ASSOCIATION BETWEEN PRO AND ANTI-INFLAMMATORY MARKERS WITH THE COMPONENTS OF METABOLIC SYNDROME

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Abstract

Objectives. Metabolic syndrome (MetS) is a cluster of metabolic abnormalities that is linked with increased circulating markers of oxidative stress and low-grade inflammation. The link between inflammation and MetS is not yet fully understood. We aim to evaluate the relationship between the levels of pro and anti-inflammatory markers such as apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), interleukin (IL) 6, tumor necrosis factor alpha (TNF-α), fibrinogen and complement component 3 (C3) and adiponectin and MetS/MetS components.

Methods. This study was a case-control study conducted in an outpatient internal medicine clinic of the Ondokuz Mayıs University Internal Medicine Department. A total of 108 subjects (59 female, 49 male) who were not under any dietary restrictions and older than 17 years were selected and divided into two groups (54 with MetS and 54 healthy controls).

Results. Increased levels of IL-6, C3 and Apo-B/Apo-A1 ratios and decreased levels of Apo-A1 and TNF-α (except in patients with hypertriglyceridemia) were detected in the MetS group. Apo-A1 and TNF-α exhibited decreased levels, and IL-6, fibrinogen, C3 and Apo-B levels and Apo-B/Apo-A1 ratios increased as higher numbers of MetS criteria were met in the total study group.

Conclusions. We found that inflammatory marker levels were not affected by an increased number of MetS criteria met in the MetS group although these levels increased in the control group with higher numbers of MetS components. The presence of a high number of MetS components does not have an additive pro-inflammatory contribution for subjects already diagnosed with MetS.

Key words: Metabolic syndrome, inflammatory markers, abdominal obesity, hypertension, hyperglycemia, hypertriglyceridemia.

INTRODUCTION

MetS is a cluster of metabolic abnormalities characterized by the following traits: hypertension, a fasting blood glucose greater than 100 mg/dL, increased waist circumference, hypertriglyceridemia and low high-density lipoprotein (HDL) cholesterol levels (1). In most cases, MetS is accompanied by obesity. In the last decade, adipose tissue was found to have roles other than functioning as a passive storage depot, including the secretion of a variety of molecules (members of the cytokine class) and involvement in immune modulation and inflammatory responses (2). As a result, with an increase in fat tissue, obesity is also associated with low-grade inflammation and increased levels of oxidative stress markers. Additionally, MetS has been independently linked with increased oxidative stress and inflammatory burden (3). Previous studies have also shown increased secretion of apolipoprotein B (Apo-B), uric acid, fibrinogen, plasminogen activator inhibitor 1, complement component 3 (C3), and several cytokines, including interleukin (IL) 6, IL-8, resistin, tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), in addition to reduced secretion of adiponectin in MetS (2, 4-5). Inflammatory markers are not currently included in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) or World Health Organization (WHO) diagnostic criteria for MetS, but several studies claim that the pro-inflammatory state is a component of this syndrome.

The relationship between MetS and inflammation is not fully understood. One mechanism that could explain this linkage is the stimulation of hepatic CRP production from the cytokines, which originate from the adipose tissue. A second mechanism that could explain this may be related to the insulin resistance responsible for the increased production of cytokines (6).

Various inflammatory markers were evaluated in MetS patients in different studies. We aim to evaluate the relationship between MetS/MetS components and

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their associated levels of pro and anti-inflammatory markers such as apolipoprotein A (Apo-A1), Apo-B, IL-6, TNF-α, fibrinogen and C3) and adiponectin.

MATERIALS AND METHODS

Patient selection

This study was conducted in an outpatient internal medicine clinic of the Ondokuz Mayıs University Internal Medicine Department. The study protocol was approved by the Ethics Committee of Ondokuz Mayıs University and has been performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This study is a case-control study evaluating the relationship between inflammatory markers and MetS criteria. Individuals with MetS were identified by meeting at least three out of the five criteria established by the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) (1). A total of 108 subjects (59 female, 49 male) who were not under any dietary restrictions and older than 17 years were selected and divided into two groups. The first group consisted of subjects meeting compatible clinical MetS criteria (n:54) and the second group of subjects without MetS (n:54). All individuals signed informed consent forms to participate in this study and answered questions about their age and their clinical and genetic backgrounds. Subjects with known or newly diagnosed renal disease, liver disease, hyperthyroidism, hypothyroidism, malignancy, rheumatologic or connective tissue disease or with histories of smoking, trauma or infection in the last two weeks were excluded from the study. None of the subjects in the control or study group were being treated with anti-inflammatory drugs during the time of the study.

Anthropometric and blood pressure measurements

Subjects were wearing light clothing and no shoes while measurements were taken. Weight was determined by the nearest 0.1 kg using a standardized electronic digital scale, and height was measured to the nearest 0.1 cm using a portable stadiometer. The body mass index (BMI) was calculated by dividing the subject's weight (kg) by the square of the height (m^2). Waist circumference (WC) was measured, at the end of a gentle expiration, midway between the lowest rib margin and the iliac crest. Systolic and diastolic blood pressure was measured twice in the right arm after 15 minutes of rest in the seated position using a mercury sphygmomanometer with the cuff size adjusted to individual arm circumferences.

Metabolic evaluation

Blood samples were obtained by venipuncture into vacutainer tubes early in the morning after a 12-hour fasting period. Serum was separated by centrifugation, and total cholesterol (TC), triglycerides (TG), HDL–cholesterol (HDL-c), creatinine, alanine aminotransferase, aspartate aminotransferase and glucose were measured using the Roche Cobas Integra 800 autoanalyzer. The concentration of low-density lipoprotein cholesterol (LDL-c) was calculated using the Friedewald Equation of LDL-c = TG-(HDL-c + (TG/5)).

The serums TNF-α and IL-6 were measured using a commercially available highly sensitive enzyme-linked immunosorbent assay (ELISA) kit (DIAsource, Belgium), (Reference Range (RR): TNF-α < 0.7 pg/mL and IL-6 < 2 pg/mL). The adiponectin serum concentration was measured using the sandwich ELISA (Biovendor, The Czech Republic), (RR: < 0.47 ng/mL). The fibrinogen concentration was measured according to the modified Clauss method using a commercially available kit (Multifibren U, Siemens, Germany), (RR: 1.8-3.5 gr/dL). C3 was measured using N antisera to human complement factors (C3c, C4) (Siemens BN™ II System, Germany), (RR: 0.9-1.8 gr/L). Apo-A1 and Apo-B were measured using N antisera to human apolipoprotein A1 (RR: male: 110-205 mg/dL, female: 125-215 mg/dL) and apolipoprotein B (RR: male: 55-140 mg/dL, female: 55-125 mg/dL), (Siemens BN™ II System, Germany). All measurements were taken according to the manufacturers' recommendations.

Statistical analysis

The statistical assessment was conducted using the SPSS statistical package for Windows (version 15.0, Chicago, IL). Because of the skewed distribution of data, nonparametric methods were used. All continuous variables were shown as the mean ± standard deviation (SD) or median and interquartile range (IQR). The median values of the groups were compared using the Mann-Whitney U test to compare two groups. A p-value of < 0.05 was considered statistically significant. Correlations between variables were evaluated using Spearman's correlation coefficients.

RESULTS

In this study, 108 subjects (59 female, 49

male) were selected and divided into the following two groups: (1) the MetS group (n:54), and (2) the healthy control group (n:54). The thyroid, liver and renal function tests were within normal limits in all subjects.

Demographic characteristics of the study group (Table 1)

There were no significant differences between the groups in terms of age and sex. BMI was significantly high in the MetS group.

Comparisons between MetS and control groups (Table 2)

IL-6, fibrinogen, C3 and Apo-B/Apo-A1 were detected at significantly high levels and the TNF-α and Apo-A1 levels were detected at significantly low levels in the MetS group than in the control group ($p < 0.001$, for all markers).

Comparisons concerning the number of MetS criteria met (Table 3)

We evaluated the correlations between the inflammatory marker levels and the number of MetS criteria met in each group (MetS, control and total study groups). We found that the inflammatory marker levels were not affected by increases in the number of MetS criteria met in the MetS group. In the control group, Apo-A1 was lower while Apo-B and Apo-B/Apo-A1 yielded higher levels with an increased number of MetS criteria met. In the total study group, we found that Apo-A1 and TNF-α were in low levels, but IL-6, fibrinogen, C3, Apo-B and Apo-B/Apo-A1 exhibited

Table 1. Demographic characteristics of the study group

	Control Group (n: 54)	MetS Group (n: 54)	P value
Age (Years) (Mean ± SD, Median, IQR)	52.9 ± 13.3, 55.0, 13.3	51.8 ± 5.7, 51.0, 6.0	0.132*
Female (n)	26 (48.1 %)	33 (61.1 %)	0.246**
Male (n)	28 (51.9 %)	21 (38.9 %)	
Body Mass Index (kg/m²) (Mean ± SD)	35.0 ± 6.6	26.4 ± 3.9	**< 0.001***

Abbreviations: n, number; SD, standard deviation; IQR, interquartile range. In non-normally distributed data Mann-Whitney-U test* and for frequency comparisons Chi-square test** were used.

Table 2. Levels of pro and anti-inflammatory markers in control and MetS Groups

Parameters	Control Group (n: 54) Median (IQR)	MetS Group (n: 54) Median (IQR)	P value*
TNF-α (pg/mL)	8.7 (4.6)	1.6 (12.3)	**< 0.001**
IL-6 (pg/mL)	0.00 (59.7)	74.7 (81.4)	**< 0.001**
Adiponectin (ng/mL)	8.3 (5.7)	7.0 (6.0)	0.191
Apo-A1 (mg/dL)	147.5 (34.3)	117.0 (22.0)	**< 0.001**
Apo-B (mg/dL)	89.9 (34.1)	102.0 (27.0)	0.154
Apo-B/Apo-A1 ratio	0.60 (0.33)	0.85 (0.27)	**< 0.001**
Fibrinogen (gr/dL)	3.0 (0.56)	3.36 (1.0)	**< 0.001**
C3 (gr/L)	1.67 (0.6)	2.32 (0.8)	**< 0.001**

Abbreviations: See Table1. *Mann-Whitney U test to compare two groups was used.

Table 3. Relationship between the levels of pro and anti-inflammatory markers and the increased number of MetS criteria

		Total Study Group (n:108) P value*	Control Group (n: 54) P value*	MetS Group (n: 54) P value*
Number of MetS Criteria	**TNF-α (pg/mL)**	**< 0.001**	0.654	0.645
	IL-6 (pg/mL)	**< 0.001**	0.199	0.149
	Adiponectin (ng/mL)	0.168	0.959	0.541
	Apo-A1 (mg/dL)	**< 0.001**	**0.002**	0.748
	Apo-B (mg/dL)	**0.014**	**< 0.001**	0.461
	Apo-B /Apo-A1 ratio	**< 0.001**	**< 0.001**	0.727
	Fibrinogen (gr/dL)	**0.001**	0.632	0.828
	C 3 (gr/L)	**< 0.001**	0.227	0.066

Abbreviations. See Table1. *Correlations between variables were evaluated using Spearman's correlation coefficients.

high levels with higher numbers of MetS criteria met. Evaluation of the inflammatory marker levels in the presence of each of the MetS criteria (Table 4).

IL-6, Apo-B/Apo-A1 and C3 levels were found to be significantly high and Apo-A1 levels were low in subjects with any of the MetS criteria. Fibrinogen levels were significantly high in subjects with hypertriglyceridemia, hyperglycemia and increased abdominal obesity. TNF-α levels were low in subjects with any of the MetS criteria except for hypertriglyceridemia. Apo-B levels were significantly high in subjects with hypertriglyceridemia and low HDL-C states. Adiponectin levels were in low level only in subjects with hypertriglyceridemia.

DISCUSSION

One of the roles of adipose tissue is secreting a wide range of protein factors and signals, referred to as adipokines, such as adiponectin, IL-1 beta, IL-6 and IL-8 (2, 7). Pro-inflammatory cytokines, including IL-1 beta, IL-6 and TNF-α, are released during an inflammatory response, activating the hepatic genes that encode acute phase reactants, such as fibrinogen, CRP and serum amyloid A (8). CRP is a nonspecific but sensitive marker of infection and tissue inflammation. It activates the complement system, mediates phagocytosis and regulates inflammation. CRP, serum amyloid A and fibrinogen all increase in subjects with obesity (9-11). In our study, we found increased levels of fibrinogen in the MetS group and in subjects with any of the following three MetS criteria: hypertriglyceridemia, hyperglycemia and abdominal obesity.

IL-6 is produced by many cell types and is the principal procoagulant cytokine. It affects hematopoiesis, regulation of B and T cell function, secretion of immunoglobulins and acute phase inflammatory reactions (12, 13). Adipose tissue is one of the major sources of plasma IL-6 (14). Some studies have also shown a direct correlation between IL-6 and obesity (15-17). Several studies have noted elevated levels of IL-6 in individuals with insulin resistance syndrome and type 2 diabetes mellitus. Acute hyperglycemia has also been shown to affect the concentration of plasma cytokines IL-6 and TNF-α in humans (18). In our study, high levels of IL-6 were found in the MetS group, as well as in subjects exhibiting any criteria of MetS or increased numbers of MetS criteria.

TNF-α is a well-known pro-inflammatory cytokine that can be released in response to a variety of stimuli, including other cytokines (19). Increased levels of TNF-α have been reported in MetS, healthy hyperlipidemic individuals, insulin resistance and diabetes mellitus (2, 20-21). Conversely, some previous reports have found that serum TNF-α and IL-6 were not significantly associated with MetS (22-23). Our study found that low levels of TNF-α in the MetS group and in subjects with three of the MetS criteria, excluding hypertriglyceridemia and low HDL states.

Table 4. Comparison of pro and anti-inflammatory marker levels in each of the MetS criteria

Parameters	Hypertriglyceridemia			Hypertension			Hyperglycemia			Low HDL-C			Abdominal obesity		
	Positive (n: 72) Median (IQR)	Negative (n: 36) Median (IQR)	P Value	Positive (n: 27) Median (IQR)	Negative (n: 81) Median (IQR)	P Value	Positive (n: 54) Median (IQR)	Negative (n: 54) Median (IQR)	P Value	Positive (n: 75) Median (IQR)	Negative (n: 33) Median (IQR)	P Value	Positive (n: 54) Median (IQR)	Negative (n: 54) Median (IQR)	P Value
TNF-α (pg/mL)	6.84 (11.5)	8.27 (5.2)	0.263	0.37 (13.0)	8.36 (6.33)	**0.006**	1.6 (12.3)	8.7 (4.6)	**< 0.001**	5.8 (11.9)	9.1 (5.0)	**0.029**	1.78 (10.1)	8.7 (5.0)	**< 0.001**
IL-6 (pg/mL)	59.65 (99.9)	0.0 (57.4)	**0.001**	77.9 (81.4)	16.1 (64.1)	**< 0.001**	74.7 (81.4)	0.00 (59.7)	**< 0.001**	57.4 (84.6)	0.0 (55.8)	**< 0.001**	69.5 (85.5)	0.0 (59.7)	**< 0.001**
Adiponectin (ng/mL)	7.1 (5.0)	9.77 (8.5)	**0.029**	8.65 (8.62)	7.6 (5.9)	0.458	7.0 (6.0)	8.3 (5.7)	0.191	7.3 (6.0)	8.4 (4.7)	0.162	7.7 (6.0)	8.3 (5.6)	0.253
Apo-A1 (mg/dL)	121.0 (28.0)	147.5 (42.0)	**< 0.001**	117.0 (23.0)	133.0 (37.3)	**< 0.001**	117.0 (22.0)	147.5 (34.3)	**< 0.001**	120.0 (26.0)	161.0 (29.8)	**< 0.001**	117.0 (22.5)	146.5 (32.3)	**< 0.001**
Apo-B (mg/dL)	104.0 (30.4)	80.8 (28.2)	**< 0.001**	98.2 (26.1)	94.0 (34.5)	0.800	102.0 (27.0)	89.9 (34.1)	0.154	101.0 (29.4)	82.3 (35.6)	**0.016**	98.6 (28.6)	92.5 (34.8)	0.311
Apo-B/Apo-A1 ratio	0.85 (0.29)	0.57 (0.24)	**< 0.001**	0.84 (0.29)	0.71 (0.34)	**0.031**	0.85 (0.27)	0.60 (0.33)	**< 0.001**	0.84 (0.28)	0.52 (0.19)	**< 0.001**	0.84 (0.24)	0.61 (0.36)	**< 0.001**
Fibrinogen (gr/dL)	3.24 (0.75)	3.0 (0.6)	**0.037**	3.34 (1.11)	3.1 (0.68)	0.059	3.36 (1.0)	3.0 (0.56)	**< 0.001**	3.22 (0.84)	3.1 (0.55)	0.104	3.35 (1.15)	3.0 (0.57)	**< 0.001**
C3 (gr/L)	2.15 (0.97)	1.7 (0.63)	**0.001**	2.3 (0.91)	1.81 (0.75)	**0.002**	2.32 (0.8)	1.67 (0.6)	**< 0.001**	2.16 (0.93)	1.71 (0.6)	**0.004**	2.28 (0.88)	1.68 (0.59)	**< 0.001**

Abbreviations. See Table1. *Mann-Whitney U test to compare two groups was used in this table.

Adiponectin is secreted by adipose cells and is an anti-inflammatory cytokine that plays a role in regulating insulin sensitivity and lipid metabolism and inhibiting many steps in the inflammatory process (24-25); therefore adiponectin is considered a key molecule in the pathogenesis of MetS (26-27). Decreased levels of adiponectin have been found in subjects with obesity and diabetes (28), and these decreased levels could be a culprit in the development of both atherosclerosis and insulin resistance (29). Decreased levels of adiponectin were only found in hypertriglyceridemic individuals in our study.

We found that TNF-α levels were lower than expected in the MetS group, and no significant difference in adiponectin levels was found between groups, despite our expectation of discovering decreased levels in MetS subjects. Circulating TNF-α has been reported as not representing its biological function accurately because it may instead function as a paracrine (30). Additional reports claim that circulating TNF-α might not be an appropriate marker of MetS (31). In our study, decreased levels of TNF-α may have caused increased levels of adiponectin in the MetS group because adiponectin and TNF-α are known to reciprocally inhibit their productions in adipose tissue (32). Adiponectin exhibited decreased levels only in hypertriglyceridemic individuals in our study.

C3 is also an important inflammatory marker related to coronary artery disease. It has been associated with dyslipidemia, obesity, type 2 diabetes mellitus and hypertension (33). In our study, increased C3 levels were found in the MetS group and in subjects with each of the MetS criteria, which was consistent with the findings of previous studies.

Studies have suggested that the Apo-B/Apo-A1 ratio predicts cardiovascular risk more accurately than any of the cholesterol indices. High Apo-B/Apo-A1 ratios were detected in individuals with greater waist circumferences, hypertension, obesity, hyperlipidemia and hyperglycemia. The Apo-B/Apo-A1 ratio also increased significantly with increased numbers of MetS components (34). In our study, we also found increased Apo-B/Apo-A1 ratios and decreased Apo-A1 in the presence of MetS and in the presence of each of the MetS components.

Our findings also suggest that IL-6, C3 and MetS are all closely related. The increased Apo-B/Apo-A1 ratios and decreased Apo-A1 levels in our study also support an increased cardiovascular risk in the MetS group and in the presence of each MetS component.

We found that inflammatory marker levels were not affected by an increase in the number of MetS criteria in the MetS group, but their levels increased in the control group with higher numbers of MetS components.

Our study has several limitations. We did not evaluate physical activity or possible drug usages of the patients. The populations of the study and control group are relatively small. Although our findings are consistent with previous studies to a considerable extent, further examination of the association between the number of MetS syndrome criteria and pro and anti-inflammatory markers, in a larger cohort may provide a better assessment. To our knowledge, no other study exists evaluating the pro and anti-inflammatory markers levels of each MetS component and the relationship of those pro and anti-inflammatory markers with the number of MetS criteria.

In conclusion, we suggest that the presence of a high number of MetS components does not have a higher pro-inflammatory contribution for subjects already diagnosed with MetS.

Conflict of interest

The authors declare that they have no conflict of interest.

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