Progress in Nutrition 2021; Vol. 23, N. 1: e2021009 DOI: 10.23751/pn.v23i1.9072

Original research

Adipokines, inflammation, oxidative stress: critical components in obese women with metabolic syndrome

Sevil Karahan Yilmaz[1], Günay Eskici[2], Cuma Mertoğlu[3], Aylin Ayaz[4]

[1]Department of Nutrition and Dietetics, Faculty of Health Sciences, Erzincan Binali Yıldırım University, Erzincan, Turkey; [2]Department of Coaching, Faculty of Sport Science, Çanakkale Onsekiz Mart University, Çanakkale, Turkey; [3]Department of Clinical Biochemistry, Faculty of Medicine, Erzincan Binali Yıldırım University, Erzincan, Turkey; [4]Department of Nutrition and Dietetics, Faculty of Health Sciences, Hacettepe University, Ankara, Turkey.

Abstract. *Objective:* Adipose tissue dysfunction, increased systemic inflammation and oxidative stress are features of metabolic syndrome. The purpose of the present study was to determine the relationship between adipokines, inflammation, oxidative stress and metabolic syndrome components in obese women. *Subjects and Methods:* A total sample of 100 obese women (BMI=32.44±1.80 kg/m^2) living in Erzincan aged 20-45 years were included in this cross-sectional survey. Serum biochemical (leptin, adiponectin, resistin, lipit profiles, fasting plasma glucose, fasting plasma insulin, high sensitivity C-reactive protein, tumor necrosis factor-alfa, interleukin-6, malondialdehyde, anthropometrical (body weight, height, waist and neck circumference) parameters and blood pressure were measured. Metabolic syndrome was defined according to National Cholesterol Education Program Adult Treatment Panel-III (NCEP-ATP III) criteria. *Results:* Results of this study indicate that waist circumference, neck circumference, systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma insulin (FPI), HOMA-IR, triglyceride (TG), high sensitivity C-reactive protein (Hs-CRP), Tumor Necrosis Factor -alfa (TNF-α), leptin, leptin: adiponectin (L:A) ratio and malondialdehyde (MAD) were significantly higher but adiponectin and HDL-Cholesterol (HDL-C) were significantly lower in obese women with metabolic syndrome than in women without the syndrome ($p < 0.05$). Waist circumference had positive correlation with Hs-CRP ($r = 0.315$, $p < 0.05$) and negative correlation with adiponectin ($r = -0.552$, $p < 0.01$). TG had highly significant positive correlation with Hs-CRP ($r = 0.305$, $p < 0.05$) but, negative correlation with IL-6 ($r = -0.347$, $p < 0.05$) and adiponectin ($r = -0.440$, $p < 0.01$). Hs-CRP was positively correlated with MDA ($r = 0.323$, $p < 0.05$) and negatively correlated with DBP ($r = -0.253$, $p < 0.05$). TNF-α was significantly and positively correlated with leptin ($r = 0.701$, $p < 0.01$), resistin ($r = 0.646$, $p < 0.01$), MDA ($r = 0.949$, $p < 0.01$) and negatively correlated with adiponectin ($r = -0.772$, $p < 0.01$). MDA had positive correlation with TNF-α ($r = 0.949$, $p < 0.01$), leptin ($r = 0.721$, $p < 0.01$), adiponectin ($r = 0.788$, $p < 0.01$) and resistin ($r = 0.694$, $p < 0.01$). Hs-CRP was significantly and positively associated with waist circumferemce ($\beta = 0.315$, $p < 0.05$), TG ($\beta = 0.307$, $p < 0.05$) and negatively associated with DBP ($\beta = -0.276$, $p < 0.05$). *Conclusion:* High leptin and low adiponectin level, L:A ratio, Hs-CRP, TNF-α and MDA may act as a diagnostic marker for metabolic syndrome in obese women.

Key words: Obesity, metabolic syndrome, adipokines, inflammation, oxidative stress

Introduction

Obesity has become, over recent decades, the most prevalent metabolic alterations such as type 2 diabetes (T2D), hypertension, dyslipidemia, and non-alcoholic fatty liver disease (NAFLD), constituting one of the main causes of death and disability (1,2). According to World Health Organization (WHO), more than 650 million people in the world were obese by 2016, and the prevalence of obesity has tribled since 1975 (3). According to Turkey Nutrition and Health Survey (TNHS) 2010 data, obesity and overweight prevalence among Turkish adults were 30.3% and 34.6%, respectively (4). Associations have been found showing that metabolic syndrome is related to being overweight or obese (5). There is a surge in the global prevalence of metabolic syndrome (MS) and its components including obesity, insulin resistance, diabetes mellitus, dyslipidemia and hypertension, as a result of reduced physical activity, excessive intake of energy-dense, high-fat foods, genetic predisposition and lifestyle factors (6,7).

Obesity and metabolic syndrome are defined medically as a condition of excessive accumulation of adipose tissue, of sufficient extent to produce adverse health consequences (8,9). Adipose tissue has been shown to be have as a highly active endocrine organ, based on its ability to secrete a wide variety of biologically active adipokines, such as leptin, adiponectin, resistin, tumor necrosis factor- alfa (TNF-α) or interleukin-6 (IL-6), which are known to be involved in different physiological processes (10). A significant role of adipokines secreted by adipose tissue and various metabolic risk markers play a important role in the development of metabolic syndrome (11). Leptin is primarily produced by adipose tissue in proportion to the amount of body fat stores being involved in the regulation of food intake, energy homeostasis and other physiological processes (12-14). Adiponectin is also secreted almost exclusively by adipocytes, and decreases in obese patients. This adipokine protects against insulin resistance and excessive hepatic lipid accumulation with anti-inflammatory effects (15). Resistin is also regarded as a potential risk factor and biomarker for MS due to its association with obesity, inflammation, insulin resistance and comorbidities of cardiovascular disease (CVD) (16). Leptin and adiponectin also have opposite's effects on inflammatory markers and thus subclinical inflammation. Leptin is considered as a proinflammatory cytokine since it up regulates pro-inflammatory cytokines such as TNF-α and IL-6. On the contrary, adiponectin displays anti-inflammatory properties by down regulation of the expression and release of proinflammatory mediators (17). Higher plasma leptin and lower adiponectin levels are well known features of the metabolic syndrome (12).

The leptin /adiponectin has been proposed as a marker of adipose tissue dysfunction (18). This emerging biomarker correlates with insulin resistance better than adiponectin or leptin alone being significantly reduced in patients with the metabolic syndrome (19). Moreover, the Leptin:Adiponection ratio (L:A ratio) is positively correlated with markers of low-grade chronic inflammation, such as C-reactive protein (CRP) (18). High-sensitive C-reactive protein (Hs-CRP) is a marker of a low-grade systemic inflammation (20). High-sensitive C-reactive protein levels higher than 3.0 mg/L was associated with increased risk of MS, diabetes and cardiovascular disease (21).

Oxidative stress is caused by the imbalance between free radicals (prooxidants) and antioxidant systems; it can play an important role in the pathophysiology of diabetes, cardiovascular diseases, and hypertension (22). On the other hand, some of the MS factors such as hyperglycemia and inflammation can lead to increased production of reactive oxygen species (ROS); the reactive oxygen species have toxic effects which lead to peroxidation of membrane lipids and produce malondialdehyde (MDA) (23). We aimed to investigate the relationship between indicators of adipokines, inflammation, oxidative stress and metabolic syndrome components in obese women.

Material and Methods

Participants

A cross sectional case-control study was conducted with obese women ages 20–45 years. A total of 100 obese women were enrolled in this study and

consisted of 50 women with metabolic syndrome (study group/ body mass index (BMI): 32.71±1.79 kg/m^2) and 50 women without metabolic syndrome (control group/BMI: 32.16±1.78 kg/m^2). Women who were pregnant or breastfeeding, had diabetes, a liver or kidney disease, active or past malignity, hypothyroidis or hyperthyroidis, acute or chronic inflammatory disease, severe psychiatric were excluded from this study. Participants who agreed to voluntarily contribute to this study were asked to sign a written consent form in accordance with the Helsinki Declaration. Ethical approval of the study was obtained from the Clinically Ethics Board of Erzincan University, Erzincan, Turkey (Project No:44495147-050.01.04-E.40589).

Metabolic syndrome was defined according to National Cholesterol Education Program Adult Treatment Panel-III (NCEP-ATP III) criteria (24). Three or more of the following criteria were required for categorization of subjects with MS: 1) waist circumference (WC)>88 cm; 2) triglycerides (TG)≥150 mg/dL; 3) high density lipoprotein cholesterol (HDL-C) <50 mg/dL; 4) systolic blood pressure (SBP)≥130 mmHg or diastolic blood pressure (DBP)≥85 mmHg; and 5) fasting plasma glucose (FPG)≥110 mg/dL.

Anthropometric Measurements

Body weight was measured in light clothing, with no shoes using a portable calibrated electronic scale to the nearest 0.1 kg. Height was measured with a wall-mounted stadiometer with an accuracy of 0.1 cm. Body mass index (BMI) was calculated as weight (kg) / height (m^2). The waist circumference was measured with a tape measure using the line between the lower costal border and the iliac crest as reference points (25). Neck circumference (NC) was measured with a non-elastic tape from the most protrusive point of the thyroid cartilage when the head was upright, eyes straight and shoulders held loosely (26). Using an appropriate cuff size, a physician measured blood pressure on the right arm in a sitting position after 5 min of rest.

Laboratory Measurements

Blood samples for measuring serum biochemical parameters were obtained from all women in the morning after 12 hour of fasting. Fasting plasma glucose, plasma total cholesterol, triglyceride and high-density lipoprotein-cholesterol (HDL-C) was measured by Spectrophotometer method (Beckman Coulter AU640). Low-density lipoprotein-cholesterol (LDL-C) was calculated by the Friedewald formula (27). Thyroid Stimulating Hormone (TSH) ve fasting plasma insulin (FPI) were assayed using Chemiluminescent Immunometric Assay (Siemens AdviaCentaur XP) (28). High-sensitive C-reactive protein was determined was by nephelometry (BNII N; Dade Behring, Marburg Germany (29). Tumor necrosis factor-alfa was assayed by Enzyme-Linked ImmunoSorbent Assay method using Epoch Microplate Spectrophotometer (BioTek Instruments, Inc., Winooski, VT, USA). Interleukin-6 was measured with Chemiluminescent Immunometric Assay method IMMULITE® 2000 systems (Siemens Healthcare Diagnostics Products Ltd. Glyn Rhonwy, Lianberis, Gwynedd LL55 4EL,UK). Plasma leptin, total adiponectin and resistin were measured on Epoch Microplate Spectrophotometer. Insulin resistance was evaluated using the HOMA-IR method was determined using the formula: [FPG ×FBI]/405]. HOMA-IR ≥2.5 is accepted as insulin resistance (30). We used serum MDA levels as an indicator of lipid peroxidation and oxidative stress. Malondialdehyde was measured on Epoch Microplate Spectrophotometer.

Statistical Analysis

SPSS 22 (version 22.0, SPSS Inc., Chicago, IL, USA) was used for data analysis. Data are expressed as mean ± standart deviation (SD). Differences between people with and without MS were determined by ındependent-samples T-test. Pearson correlation analysis was used to determine the relationship between the two variables. Linear regression models were performed to assess the association between components of metabolic syndrome and Hs-CRP, MDA, leptin and adiponectin. We created three different models: model 1, was adjusted for Hs-CRP; model 2 adjusted for Hs-CRP, MDA; model 3 adjusted for Hs-CRP, MDA, leptin, adiponectin. Results of regression models in the text were reported as standardized regression coefficients (β) and p value, significance level was taken as $\alpha = 0.05$ for statistical tests (31).

Results

Differences between obese women with and without metabolic syndrome (Table 1), in terms of WC (104.67±9.28 cm vs. 100.09±7.56 cm), NC (39.77±3.72 cm vs. 38.03±2.20 cm), SBP (134.82±1.21 mmHg vs. 130.82±1.11 mmHg), DBP (75.21±1.11 mm Hg vs. 70.22±1.15 mmHg), FPI (17.09±10.65 μU/mL vs. 12.66±7.69 μU/mL), HOMA-IR (5.92±5.81 vs. 2.66±1.65), TG (164.50±79.01 mg/dL vs. 90.24±27.09 mg/dL), HDL-C (46.19±17.54 mg/dL vs. 52.29±12.17 mg/dL), Hs-CRP (3.92±3.65 mg/dL vs. 2.32±1.88 mg/dL), TNF-α (366.39±289.59 pg/mL vs. 265.14±242.10 pg/mL) and MDA (8.57±5.5 nmol/ml vs. 4.6±3.2 nmol/mL) were high ($p<0.05$). Further comparison of obese women with and without metabolic syndrome revealed that serum leptin levels (13.01±9.85 ng/mL vs. 8.38±4.13 ng/mL), leptin: adiponectin ratio (0.97±0.39 vs. 0.53±0.07) increased and adiponectin (16.51±14.25 ng/mL vs. 18.29±16.45 ng/mL) levels decreased with metabolic syndrome ($p<0.05$).

Correlations between anthropometric measurements of obesity, insulin resistance, blood lipids, inflammatory markers, adipokines and oxidative stress in obese women with metabolic syndrome presented

Table 1. Anthropometric measurements and biochemical parameters in obese women with and without metabolic syndrome

Parameters	MS (n = 50)	No MS (n =50)	*P*
Age (years)	32.38±7.13	33.72±7.34	0.357
BMI (kg/m^2)	32.71±1.79	32.16±1.78	0.133
WC (cm)	104.67±9.28	100.09±7.56	**0.008***
NC(cm)	39.77±3.72	32.23±1.83	**0.006***
SBP (mmHg)	134.82±1.21	130.82±1.11	**0.000***
DBP (mmHg)	75.21±1.11	70.22±1.15	**0.029***
FPG (mg/dL)	88.92±9.14	86.3±6.90	0.117
FPI (μU/mL)	17.09±10.65	12.66±7.69	**0.019***
HOMA-IR	5.92±5.81	2.66±1.65	**0.000***
Cholesterol (mg/dL)	191.41±46.16	187.81±26.95	0.245
TG (mg/dL)	164.50±79.01	90.24±27.09	**0.000***
LDL-C (mg/dL)	118.50±41.25	113.28±21.03	0.145
HDL-C (mg/dL)	46.19±17.54	52.29±12.17	**0.046***
Hs-CRP (mg/dL)	3.92±3.65	2.32±1.88	**0.003***
TNF-α (pg/mL)	366.39±289.59	265.14±242.10	**0.016***
IL-6 (pg/mL)	4.54±3.80	3.43±2.21	0.078
Leptin (ng/mL)	13.01±9.85	8.38±4.13	**0.007***
Adiponectin (ng/mL)	16.51±14.25	18.29±16.45	**0.012***
L:A ratio	0.97±0.39	0.53±0.07	**0.003***
Resistin (pg/mL)	25.47±20.36	27.98±23.89	0.572
MDA (nmol/mL)	8.57±5.5	4.6±3.2	**0.008***

*t-test for independent samples $p<0.05$, BMI: body mass index, WC: waist circumference, NC: neck circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, FPI: fasting plasma insulin, HOMA-IR: insulin resistance, TG: triglyceride, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, Hs-CRP: high sensitivity C-reactive protein, TNF-α: tumor necrosis factor -alfa, IL-6: Interleukin-6, MDA: malondialdehyde, L:A ratio: leptin: adiponectin ratio

in Table 2. Body mass index was positively correlated with WC, NC and DBP (r = 0.393, p<0.01), WC had positive correlation with NC (r = 0.577, p<0.01), Hs-CRP (r = 0.315, p<0.05) and negative correlation with adiponectin (r = -0.552, p<0.01). Neck circumference was also positively correlated with FBG (r = 0.290, p<0.05), TG (r=0.070, p<0.05), Hs-CRP (r = 0.510, p<0.01) and negatively correlated with HDL-C (r = -0.301, p<0.01). Triglyceride had highly positive correlation with Hs-CRP (r = 0.305, p<0.05) but, negative correlation with IL-6 (r = -0.347, p<0.05) and adiponectin (r = -0.440, p<0.01). High sensitivity C-reactive protein was positively correlated with MDA (r = 0.323, p< 0.05) and negatively correlated with DBP (r = -0.253, p<0.05). Tumor Necrosis Factor -alfa was positively correlated with leptin (r= 0.701, p<0.01), resistin (r = 0.646, p<0.01), MDA (r = 0.949, p<0.01) and negatively correlated with adiponectin (r = -0.772, p<0.01). Malondialdehyde had positive correlation with TNF-α (r = 0.949, p<0.01), leptin (r = 0.721, p<0.01), adiponectin (r = 0.788, p<0.01) and resistin (r = 0.694, p<0.01).

In obese women without metabolic syndrome (Table 3), BMI was positively correlated with WC and NC. Weight circumference had positive correlation with NC (r = 0.621, p <0.01).

Results of multiple linear regression models in obese women with metabolic syndrome were showed in Table 4. In model 1 Hs-CRP was positively associated with waist circumferemce (β = 0.315, p<0.05); in model 2 Hs-CRP was positively associated with TG (β = 0.307, p<0.05) and in model 3 Hs-CRP was negatively associated with DBP (β = -0.276, p<0.05).

We evaluated the means of Hs-CRP, TNF-α, IL-6, MDA, leptin, adiponectin and resistin levels based on the number of MS components. With increasing in one unit number of MetS components, threre is an increasing trend of TNF-α, MDA and resistin level and a decreasing trend of adiponectin level (Figure 1).

Discussion

This study evaluated the relationship between adipokines, inflammation, oxidative stress and metabolic syndrome components in obese women. According to the present study anthropometric measurements like WC, NC and and biochemical parameters like SBP, DBP, FPI, HOMA-IR, TG, Hs-CRP, TNF-α, leptin, L:A ratio and MDA are significantly high in obese women with MS (study group) as compared to obese women without MS (control group) where as adiponectin level and HDL-C were found to be low. In agreement with the other study which shows that in women anthropometric measurements like WC and biochemical parameters like SBP, TG, Hs-CRP, leptin, HOMA-IR, and L:A ratio were significantly lower and adiponectin level was significantly higher in subjects with regression of metabolic syndrome than in those with persistent metabolic syndrome (32). Results of another study revealed that obese MS women had significantly higher levels of biochemical parameters like SBP, DBP, HOMA-IR, TG and MDA compared to obese without MS women (33).

Waist circumference is a main feature of MS that represents visceral fat and central obesity (34). Several prior population-based studies show that neck circumference is a reliable screener and predictive tool of central obesity and, similar to WC, can anticipate metabolic abnormalities, better than other anthropometric indices (35-37). It has been shown that men with NC < 37 cm and women with NC < 34 cm probably have a less chance of developing metabolic syndrome (38). In a study; the optimal NC cut–offs for assessing MS in study population of women in different age groups (young, middle–aged, and elderly) were 34.15 cm, 33.55 cm, and 33.95 cm, respectively (39). In our study; in obese women with MS the value of NC was 39.77±3.72 cm, while in obese women without MS the value of NC was 32.23±1.83 cm (p<0.05). A positive correlation in MS women between the neck circumference and BMI (r=0.493, p<0.01), WC (r=0.577, p<0.01), FBG (r=0.294, p<0.05), TG (r=0.270, p<0.05), Hs-CRP (r=0.510, p<0.01) and negative correlation between HDL-C (r=-0.301, p<0.05) was found. This study is in agreement with the meta-analysis in which they have reported there were a positive association between neck circumference and waist circumference, triglyceride, diastolic blood pressure and FPG levels and there was a negative link between HDL-C (40). Neck circumference

Table 2. Correlations with anthropometric measurements and biochemical parameters in obese women with metabolic syndrome

Parameters	BMI	WC	NC	SBP	DBP	FBG	TG	HDL-C	Hs-CRP	TNF-α	IL-6	Leptin	Adiponectin	Resistin	MDA
BMI (kg/m²)	1														
WC (cm)	0.629**	1													
NC (cm)	0.493**	0.577**	1												
SBP (mmHg)	0.210	-0.153	-0.074	1											
DBP (mmHg)	0.393**	0.209	0.196	0.733**	1										
FBG (mg/dL)	-0.133	0.080	0.294*	0.099	0.014	1									
TG (mg/dL)	0.130	0.028	0.070*	0.024	0.121	-0.261	1								
HDL-C (mg/dL)	-0.242	-0.215	-0.301*	0.039	-0.056	-0.148	-0.080	1							
Hs-CRP (mg/dL)	-0.004	0.315*	0.510**	-0.136	-0.253*	0.090	0.305*	-0.105	1						
TNF-α (pg/mL)	-0.129	-0.132	0.128	-0.228	-0.205	-0.042	-0.136	-0.184	0.019	1					
IL-6 (pg/mL)	-0.159	-0.188	-0.035	0.042	-0.098	0.210	-0.347*	0.020	-0.088	0.072	1				
Leptin (ng/mL)	-0.135	-0.095	-0.120	-0.241	-0.286*	0.036	-0.211	-0.209	-0.085	0.701**	0.248*	1			
Adiponectin (ng/mL)	-0.304*	-0.552**	-0.037	-0.245	-0.297*	-0.035	-0.440**	-0.571**	-0.265	-0.772**	-0.337*	0.800**	1		
Resistin (pg/mL)	-0.268	-0.153	0.045	-0.320*	-0.403**	-0.026	-0.157	-0.196	-0.030	0.646**	-0.024	0.694**	0.839**	1	
MDA (nmol/mL)	-0.168	-0.165	0.120	-0.223	-0.164	0.066	-0.085	-0.187	0.323*	0.949**	0.010	0.721**	0.788**	0.694**	1

*p<0.05, **p<0.01, BMI: body mass index, WC: waist circumference, NC: neck circumference, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, Hs-CRP: high sensitivity C-reactive protein, TNF-α: tumor necrosis factor -alfa, IL-6: ınterleukin-6, MDA: malon-dialdehyde

Table 3. Correlations with anthropometric measurements and biochemical parameters in obese women without metabolic syndrome

Parameters	BMI	WC	NC	SBP	DBP	FBG	TG	HDL-C	Hs-CRP	TNF-α	IL-6	Leptin	Adiponectin	Resistin	MDA
BMI (kg/m²)	1														
WC (cm)	0.629**	1													
NC (cm)	0.617**	0.621**	1												
SBP (mmHg)	0.433**	0.268	0.053	1											
DBP (mmHg)	0.353*	0.036	0.008	0.479**	1										
FBG (mg/dL)	0.109	0.086	-0.048	-0.027	0.066	1									
TG (mg/dL)	-0.102	0.131	0.208	0.129	0.291*	0.089	1								
HDL-C (mg/dL)	0.220	0.229	0.095	0.147	0.412**	-0.254	0.012	1							
Hs-CRP (mg/dL)	0.091	0.091	0.088	-0.044	0.124	-0.037	-0.085	0.187	1						
TNF-α (pg/mL)	-0.128	-0.143	-0.186	-0.342**	-0.258	-0.046	-0.358*	-0.348*	0.076	1					
IL-6 (pg/mL)	0.228	0.099	0.092	0.134	0.080	0.102	0.409**	-0.044	0.432**	-0.024	1				
Leptin (ng/mL)	-0.232	-0.174	-0.184	-0.201	-0.239	0.078	-0.259	-0.515**	-0.029	0.083	0.122	1			
Adiponectin (ng/mL)	-0.064	-0.006	0.197	-0.302*	-0.320*	0.019	-0.008	-0.221	0.030	0.053	-0.057	0.788**	1		
Resistin (pg/mL)	-0.252	-0.239	-0.209	-0.325*	-0.370**	0.012	-0.459**	-0.558**	-0.171	0.778**	-0.287*	0.799**	0.964**	1	
MDA (nmol/mL)	-0.123	-0.081	0.198	-0.427**	-0.118	0.098	-0.340*	-0.318*	0.067	0.840**	-0.032	0.791**	0.097	0.823**	1

*p<0.05, **p<0.01, BMI: body mass index, WC: waist circumference , NC: neck circumference, HOMA-IR: insulin resistance, TG: triglyceride, HDL-C: high-density lipoprotein cholesterol, Hs-CRP: high sensitivity C-reactive protein, TNF-α: tumor necrosis factor -alfa, IL-6: interleukin-6, MDA: malondialdehyde

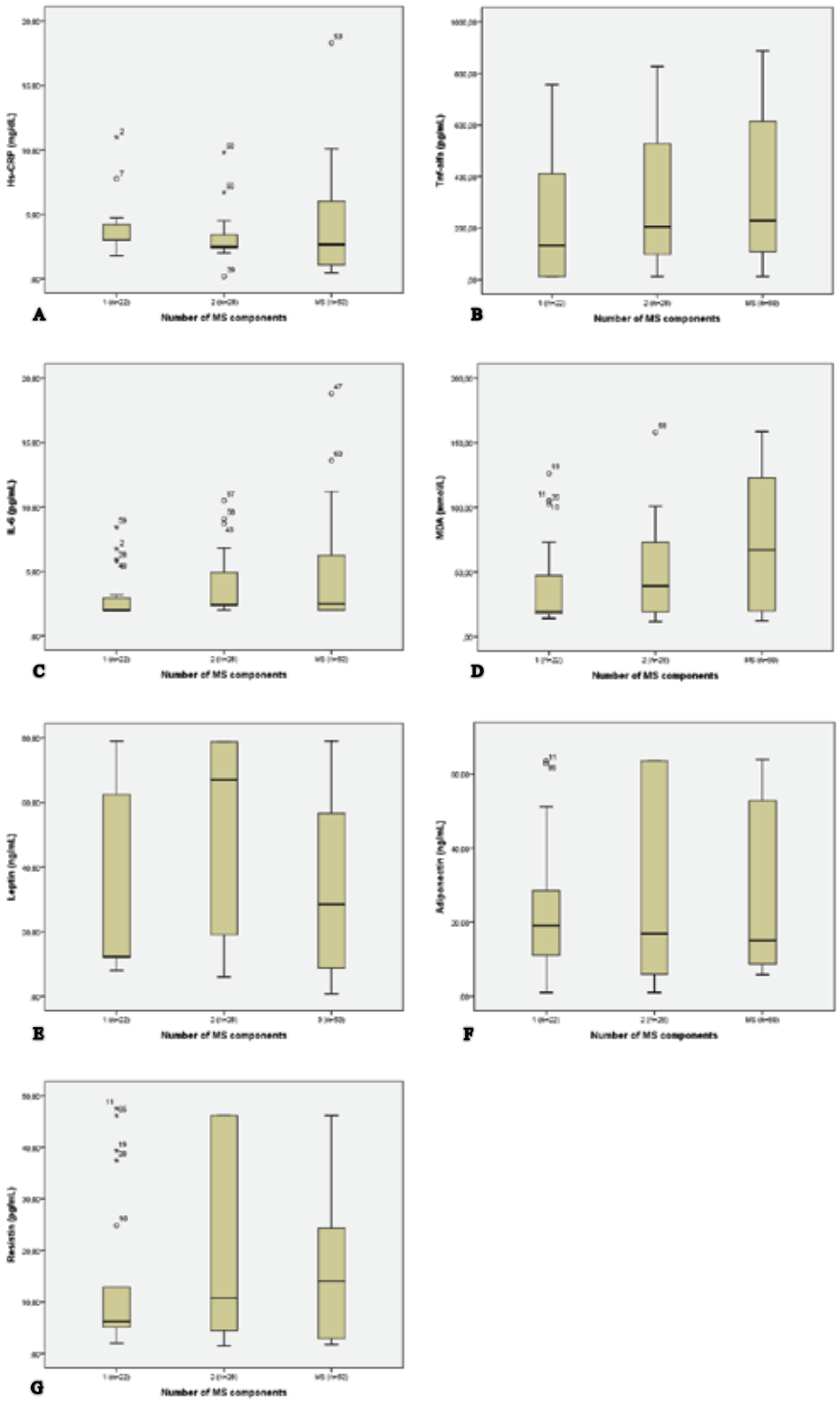

Figure 1. The comparison of mean values for A Hs-CRP, B TNF-α, C IL-6, D MDA, E Leptin, F Adiponectin and G Resistin according to the number of MS components

Table 4. Association of Hs-CRP, MDA, leptin and adiponectin with components of the metabolic syndrome in women with metabolic syndrome

Metabolic syndrome Components	Model	Hs-CRP	MDA	Leptin	Adiponectin
Waist circumference	1	**0.315***	–	–	–
	2	**0.319***	–0.172	–	–
	3	**0.312***	–0.412	–0.030	0.333
SBP	1	–0.136	–	–	–
	2	–0.131	–0.129	–	–
	3	–0.146	–0.033	–0.158	–0.092
	1	–0.253	–	–	–
DBP	2	–0.250	–0.158	–	–
	3	**–0.276***	0.267	–0.288	–0.275
	1	0.090	–	–	–
Fasting blood glucose	2	0.088	0.064	–	–
	3	0.106	0.209	0.134	–0.307
	1	0.305	–	–	–
TG	2	**0.307***	–0.092	–	–
	3	0.259	–0.088	–0.426	0.386
	1	–0.105	–	–	–
HDL-C	2	–0.101	–0.185	–	–
	3	–0.112	0.000	–0.124	–0.121

Values are presented as β, standardized regression coefficients. Model 1, adjusted for Hs-CRP. Model 2, adjusted for Hs-CRP and MDA. Model 3, adjusted for Hs-CRP, MDA, leptin and adiponectin. Hs-CRP high: sensitivity C-reactive protein, MDA: malondialdehyde, TG: triglyceride, SBP: systolic blood pressure, DBP: diastolic blood pressure, HDL-C: high density lipoprotein cholesterol, * $p < 0.05$.

can be used as a sensitive tool for metabolic syndrome and cardiovascular risk factors.

Adiponectin and leptin as indicator of MS and obesity respectively (41). Leptin and adiponectin are important pathophysiological factors for the obesity and metabolic syndrome (42). These findings have been explained by the pro-inflammatory effects of leptin and anti-inflammatory effects of adiponectin (43). Low leptin and high adiponectin levels could provide protection against the development of metabolic disorders (44).

Indeed lower adiponectin levels have been found to be significantly associated with metabolic syndrome. In the other hand, metabolic syndrome is found to be associated with higher levels of leptin (45-47). High leptin level in people with obesity correlates with body fat mass and is a good predictor of MS. This study showed that serum leptin concentration predicts the development of MS.

Findings of the present study are total adiponectin were decreased in obese women with the MS. This was in agreement with the previous study conducted among S~ao Paulo and Porto Alegre cohort where serum adiponectin was significantly lower in subjects diagnosed with MS compared to non-MS subjects (48). A prospective cohort study of the rural area in Korea also found that baseline serum adiponectin concentration was significantly lower in subjects who developed MS, compared to those subjects without MS progression (44).

Leptin: Adiponectin ratio (L:A ratio) has been shown to be associated with insulin resistance,

metabolic syndrome (18,49). In the current study, high L: A ratio was associated with metabolic syndrome. Result of this study L:A ratio might be a powerful diagnostic marker of obese women with metabolic syndrome and L:A ratio has better capacity in the classification of subjects with and without metabolic syndrome than adiponectin or leptin alone.

Leptin and adiponectin also have different effects on inflammatory markers (17). In the present study a significant positive correlation in MS women between the leptin and TNF-α and IL-6, in the contrary a negative correlation in MS women between the adiponectin and TNF-α and IL-6 was found. Decreased adiponectin levels or adiponectin signaling may serve as an upstream pathway of increased inflammation in the development of the MS. A negative correlation of adiponectin levels with oxidative stress was found.

Our study showed that the high levels of adiponectin are associated with a considerable decrease in anthropometrics measurements like BMI, WC, FPG, TG, DBP with MS and declined in HDL-C. In a study, a significant inverse correlation was observed between serum adiponectin and other MS components such as WC, systolic and diastolic BP, FPG, TG and HDL-C (50). The present study was in agreement with the other study which reported a negative correlation between serum adiponectin and BMI, WC, FPG and TG (48).

Inflammation is proved to be one of the underlying mechanisms of MS. Abdominal obesity also independently leads to the development of MS. Hs-CRP levels higher than 3.0 mg/L was associated with increased risk of MS, diabetes, and cardiovascular disease (51,52). This study found that the association between CRP and MS is stronger in women. Which is new in this study, and in contrast to the common concepts, as we have demonstrated here already a relatively low level of Hs-CRP around 2.0 mg/dL is found in the MS, in which chronic inflammation leads to well-known health complications. At the same time, however, it is lower than this level in simple obesity, where the clinical outcome, prognosis, and possible complications are much more favourable, and where the chronic inflammatory process is absent, or almost absent. Interestingly, this level is lower than 3.0 mg/dL, which is considered the cutoff value for low-grade inflammation (53). It has been reported that the MS is associated with increased levels of CRP, and the association and influence of this marker appeared to be cumulative; i.e. the higher the number of MS components, the higher levels of

CRP (54).

We have found that MS is associated with an alteration in serum Hs-CRP, a biomarker of inflammation, and MDA, a measure of prooxidantantioxidant status and like insulin resistance. In this study; MDA was found to be strongly associated with Hs-CRP and TNF-α. Furthermore, serum MDA and Hs-CRP were independently associated with the presence of MS. Metabolic syndrome is accompanied by a chronic pro-inflammatory state and increased oxidative stress. Tumor Necrosis Factor -alfa, IL-1, IL-6, IL-8 and MDA have been proposed as mediators of the expanded adipose tissue-mediated increase in systemic inflammation and oxidative stress (55,56).

Conclusion

The present study found an association between adipokines, inflammation, oxidative stress and MS. Authors suggest that neck circumference, high leptin and low adiponectin level, L:A ratio, Hs-CRP, TNF-α and MDA may act as a diagnostic marker for metabolic syndrome in obese women.

Limitation

This was a single-centred cross-sectional study. This study include the small sample size, a larger multicentric study with both women and men should be done in future.

Conflicts of interest: There are no conflicts of interest.

Funding: This research supported by Erzincan University.B.A.B. (TSA-2016-354).

References

1. Bray GA, Frühbeck G, Ryan DH, Wilding JP. Management of obesity. Lancet 2016; 387: 1947–56.

2. Frühbeck G, Toplak H, Woodward E, Yumuk V, Maislos M, Oppert JM. Obesity The gateway to ill health—An easo position statement on a rising public health, clinical and scientific challenge in Europe. Obes Facts 2013; 6: 117–120.
3. World Health Organization (WHO). WHO global ınfobase online [Internet]. 2018 [accessed 02.09.2010]. Access address: https://www.who.int/en/news-room/fact-sheets/detail/obesity-and-overweight.
4. Sağlık Bakanlığı Sağlık Araştırmaları Genel Müdürlüğü, Hacettepe Üniversitesi Sağlık Bilimleri Fakültesi Beslenme ve Diyetetik Bölümü, Ankara Numune Eğitim ve Araştırma Hastanesi. Türkiye Beslenme ve Sağlık Araştırması 2010: Beslenme Durumu ve Alışkanlıklarının Değerlendirilmesi Sonuç Raporu. Ankara (Turkey): Sağlık Bakanlığı; 2014. Report no 931.
5. Ansar H, Mirzaei K, Malek A, Najmafshar A, Hosseinnezhad A. Possible resting metabolic rate modification by the circulating RBP4 in obese subjects. Diabetes Metab Syndrome 2015;9(1):19-23.
6. Han TS, Lean ME. A clinical perspective of obesity, metabolic syndrome and cardiovascular disease. JRSM Cardiovasc Dis 2016; 5. http://www. ncbi.nlm.nih.gov/pmc/articles/PMC4780070/ [accessed 27 Nov 2016].
7. Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population. Int J Med Sci 2016;13(1): 25–38.
8. Hebebrand J, Holm JC, Woodward E, et al. A proposal of the European association for the study of obesity to improve the ICD-11 diagnostic criteria for obesity based on the three dimensions etiology, degree of adiposity and health risk. Obes Facts 2017; 10: 284–307.
9. Al-Hamodi Z, AL-Habori M, Al-Meeri A, Saif-Ali R. Association of adipokines, leptin/adiponectin ratio and C-reactive protein with obesity and type 2 diabetes mellitus. Diabetol Metab Syndr 2014; 16;6(1):99.
10. Lancha A, Frühbeck G, Gómez-Ambrosi J. Peripheral signalling involved in energy homeostasis control. Nutr Res Rev 2012; 25: 223–48.
11. Kumari R, Kumar S, Kant R. An update on metabolic syndrome: Metabolic risk markers and adipokines in the development of metabolic syndrome. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2019; 13(4): 2409-17.
12. Blüher M, Mantzoros CS. From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. Metabolism 2015; 64:131–145.
13. Rodríguez A, Ezquerro S, Méndez-Giménez L, Becerril S, Frühbeck G. Revisiting the adipocyte: A model for integration of cytokine signaling in the regulation of energy metabolism. Am J Physiol Endocrinol Metab 2015; 309:691–714.
14. Ghadge AA, Khaire AA. Leptin as a predictive marker for metabolic syndrome. Cytokine 2019; 121:154735.
15. Stern JH, Rutkowski JM, Scherer PE. Adiponectin, leptin and fatty acids in the maintenance of metabolic homeostasis through adipose tissue crosstalk. Cell Metab 2016; 23: 770–84.
16. Asgary S, Ziaedin S, Ghorbani A, Keshvari M, Sahebkar A, Sarrafzadegan N. Relationship between serum resistin with metabolic syndrome and its components in an Iranian population. Diabetes, Metab Syndrome 2015; 9: 266-70.
17. López-Jaramillo P, Gómez-Arbeláez D, López-López J, et al. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Horm Mol Biol Clin Investig 2014;18(1):37–45.
18. Frühbeck G, Catalán V, Rodríguez A, Gómez-Ambrosi J. Adiponectin-leptin ratio: A promising index to estimate adipose tissue dysfunction. Relation with obesity-associated cardiometabolic risk. Adipocyte 2018; 7: 57–62.
19. Frühbeck G, Catalán V, Rodríguez A, et al. Involvement of the leptin-adiponectin axis in inflammation and oxidative stress in the metabolic syndrome. Sci. Rep 2017;7: 6619.
20. Czarnywojtek A, Owecki M, Zgorzalewicz-Stachowiak M, et al. The role of serum C-reactive protein measured by high-sensitive method in thyroid disease. Arch Immunol Ther Exp 2014; 62 (6): 501–9.
21. Kovaroma M, Koller T, Štvrtinová V, Payer J. Thyroid-stimulating hormone concentration as an independent risk factor of venous thromboembolism regardless of thyroid function. Endokrynol Pol 2015;66(6):474-9.
22. Birben E, Sahiner UM, Sackesen C, Erzurum S, Kalayci O. Oxidative stress and antioxidant defense. World Allergy Organ J 2012;5(1):9–19.
23. Demircan N, Gurel A, Armutcu F, Unalacak M, Aktunc E, Atmaca H. The evaluation of serum cystatin C, malondialdehyde, and total antioxidant status in patients with metabolic syndrome. Med Sci Monit 2008;14(2):97–101.
24. Grundy SM, Cleeman JI, Daniels SR, et al. Diagnosis and management of the metabolic syndrome: an American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Circulation 2005;112(17):2735–52.
25. Pekcan G. Beslenme durumunun saptanması. Baysal A, Aksoy M, editörler. Diyet el kitabı. 7.baskı. Ankara: Hatiboğlu Basım ve Yayım San. Tic. Ltd. Şti.; 2013.
26. Stabe C, Vasques AC, Lima MM, et al. Neck circumference as a simple tool for identifying the metabolic syndrome and in-sulin resistance: results from the Brazilian Metabolic Syndrome Study. Clin Endocrinol 2013; 78: 874-81.
27. Nauck M, Warnick GR, Rifai N. Methods for measurement of LDL-cholesterol: a critical assessment of direct measurement by homogeneous assays versus calculation. Clin Chem 2002;48(2):236-54.
28. Starr J, Mako M, Juhn D, Rubenstein A. Measurement of serum proinsulin-like material: cross-reactivity of porcine and human proinsulin in the insulin radioimmunoassay. J Lab Clin Med 1978;91(4):683-92.
29. Roberts WL, Sedrick R, Moulton L, Spencer A, Rifai N. Evaluation of four automated high-sensitivity C-reactive protein methods: implications for clinical and epidemiological applications. Clin Chem 2000;46(4):461-8.

30. Wallace TM, Levy JC, Matthews DR. Use and abuse of HOMA modeling. Diab Care 2004; 27: 1487-95.
31. Kılıç İ, Ural A. Bilimsel araştırma süreci ve SPSS ile veri analizi. Ankara: Detay Yayıncılık; 2013.
32. Kang DR, Yadav D, Koh SB, Kim JY, Ahn SV. Impact of serum leptin to adiponectin ratio on regression of metabolic syndrome in high-risk individuals: the ARIRANG study. Yonsei Med J 2017; 58(2), 339-46.
33. Zakı ME, Kamal S, Youness E, et al. Association between serum visfatin, oxidative stress, ınflammation and metabolic syndrome in obese premenopausal women. J Clin Diagn Res 2019;13(2): 10-14.
34. Bener A, Yousafzai MT, Darwish S, Al-Hamaq AO, Nasralla EA, Abdul-Ghani M. Obesity index that better predict metabolic syndrome: body mass index, waist circumference, waist hip ratio, or waist height ratio. J Obes 2013;2013:269038. doi: 10.1155/2013/269038.
35. Hingorjo MR, Zehra S, Imran E, Qureshi MA. Neck circumference: a supplemental tool for the diagnosis of metabolic syndrome J Pak Med Assoc 2016; 66 (10): 1221-26.
36. Assyov Y, Gateva A, Tsakova A, Kamenov Z. A comparison of the clinical usefulness of neck circumference and waist circumference in individuals with severe obesity. Endocr Res 2017;42 (1):6-14.
37. Abdolahi H, Iraj B, Mirpourian M, Shariatifar B. Association of neck circumference as an indicator of upper body obesity with cardio-metabolic risk factors among first degree relatives of diabetes patients. Adv Biomed Res 2014; 3: 237.
38. Jensen MD. Lipolysis: contribution from regional fat. Annu Rev Nutr. 1997; 14: 127–39.
39. Cui T, Yan BH, Liu Z, Yang H, Gyan M, Ma YX. Neck circumference: A valuable anthropometric measurement to detect metabolic syndrome among different age groups in China. Diabetes Metab Res Rev 2018;34(3).
40. Namazi N, Larijani B, Surkan PJ, Azadbakht L. The association of neck circumference with risk of metabolic syndrome and its components in adults: a systematic review and meta-analysis. Nutr Metab Cardiovasc Dis 2018; 28(7), 657-74.
41. Yosaee S, Khodadost M, Esteghamatı A, et al. Adiponectin: an indicator for metabolic syndrome. Iran J Public Health 2019;48(6):1106-1115.
42. Lopez-Jaramillo P, Gomez-Arbelaez J, Lopez C, et al. The role of leptin/adiponectin ratio in metabolic syndrome and diabetes. Horm Mol Biol Clin Investig 2014;18(1):37-45.
43. Fantuzzi G. Adipose tissue, adipokines, and inflammation. J Allergy Clin Immunol 2005;115:911-9.
44. Kim JY, Ahn SV, Yoon JH, et al. Prospective study of serum adiponectin and incident metabolic syndrome: the ARIRANG study. Diabetes Care 2013; 36:1547-53.
45. Srikanthan K, Feyh A, Visweshwar H, Shapiro JI, Sodhi K. Systematic review of metabolic syndrome biomarkers: a panel for early detection, management, and risk stratification in the West Virginian population. Int J Med Sci 2016;13(1):25–38.
46. Zhang J, Kho P, Ov K, Chenghe S. Adiponectin, resistin and leptin: possible markers of metabolic syndrome. Endocrinol Metab Syndr 2015; 4:4.
47. Lopez-Jaramillo P. SSA 04-3 leptin/adiponectin in cardiometabolic disease. J Hypertens 2016;34(Suppl 1-ISH 2016 Abstract Book : e7)
48. von Frankenberg AD, do Nascimento FV, Gatelli LE, et al. Major components of metabolic syndrome and adiponectin levels: a cross-sectional study. Diabetol Metab Syndr 2014;6: 26.
49. Gauthier A, Dubois S, Bertrais S, et al. The leptin to adiponectin ratio is a marker of the number of metabolic syndrome criteria in French adults. J Metab Syndr 2011; 31: 1–6.
50. Shafiee G, Ahadi Z, Qorbani M, Kelishadi R, Ziauddin H, Larijani B. Association of adiponectin and metabolic syndrome in adolescents: the caspian- III study. J Diabetes Metab Disord 2015;14: 89.
51. Emerging Risk Factors Collaboration. C-reactive protein, fibrinogen, and cardiovascular disease prediction. N Engl J Med 2012; 367: 1310–20.
52. Kovářová M, Koller T, Štvrtinová V, Payer J. Thyroid-stimulating hormone concentration as an independent risk factor of venous thromboembolism regardless of thyroid function. Endokrynol Pol 2015;66(6):474-79.
53. Kucharska A, Sawicka-Gutaj N, Owecki M. New lower cutoff for serum high sensitive C-reactive protein in obese women indicates the risk of metabolic syndrome. Arch Physiol Biochem 2019; 125(1): 30-34.
54. Mirhafez SR, Ebrahimi M, Saberi Karimian M, et al. Serum high-sensitivity C-reactive protein as a biomarker in patients with metabolic syndrome: evidence-based study with 7284 subjects. Eur J Clin Nutr 2016;70: 1298–1304.
55. Crewe C, An YA, Scherer PE. The ominous triad of adipose tissue dysfunction: inflammation, fibrosis, and impaired angiogenesis. J Clin Invest 2017;127:74–82.
56. Frühbeck G, Catalán V, Rodríguez A, et al. Normalization of adiponectin concentrations by leptin replacement in ob/ob mice is accompanied by reductions in systemic oxidative stress and inflammation. Sci Rep 2017; 7(1): 2752.

Correspondence
Sevil KARAHAN YILMAZ
Department of Nutrition and Dietetics,
Faculty of Health Sciences,
Erzincan Binali Yıldırım University, Erzincan, Turkey.
Phone: +90 446 2265861/15006; Fax: +90 446 2265862
Mobile Phone: +90 530 3634182
Email: karahany.sevil12@gmail.com