Role of serum adropin measurement in the assessment of insulin resistance in obesity

Hande Erman ,[1] Ali Ozdemir,[1] Mustafa Erinc Sitar,[2] Seher Irem Cetin,[3] Banu Boyuk [4]

[1]Internal Medicine, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey
[2]Clinical Biochemistry, Maltepe Universitesi Tip Fakultesi, Istanbul, Turkey
[3]Internal Medicine, Gaziosmanpaşa Taksim Eğitim ve Araştırma Hastanesi, Istanbul, Turkey
[4]Internal Medicine, Istanbul Dr Lutfi Kirdar Kartal Egitim ve Arastirma Hastanesi, Istanbul, Turkey

Correspondence to
Dr Hande Erman, Internal Medicine, Fatih Sultan Mehmet Training and Research Hospital, Istanbul, Turkey;
handeerman@yahoo.com

Accepted 13 April 2021

ABSTRACT

Obesity has recently been mentioned as a metabolic pandemic in developed and developing countries and is an important known risk factor for type 2 diabetes and cardiovascular diseases. The main mechanism responsible for obesity is insulin resistance. Adropin is a peptide-structured regulatory hormone that is suggested to play a role in insulin resistance and metabolic regulation. We aimed to evaluate the associations of serum adropin with insulin resistance and clarify the factors affecting serum adropin concentrations. The study included 50 obese patients and 22 healthy controls. Patients with chronic disease and drug use history were excluded. Serum adropin and other metabolic parameters were obtained after overnight fasting. ELISA was used to measure serum adropin concentrations. The homeostatic model assessment-insulin resistance (HOMA-IR) index was used to calculate insulin resistance. Insulin resistance was defined as HOMA-IR >2.5. Serum adropin values were found to be low in the obese otherwise healthy patient group ($p<0.001$). Linear regression analysis revealed that age, body mass index (BMI), waist circumference (WC), high-density lipoprotein cholesterol, fasting glucose, and HOMA-IR affect serum adropin level. In multiple regression analysis, age is the most significant factor affecting serum adropin concentration. Serum adropin concentrations were negatively correlated with BMI, WC, diastolic blood pressure, fasting glucose, and insulin. Serum adropin concentrations were low in obese patients and the optimum cut-off point for adropin to indicate HOMA-IR at 2.5 is 216.7 ng/L. The findings suggest that serum adropin may contribute to the regulation of glycolipid metabolism and insulin resistance in obese patients.

Significance of this study

What is already known about this subject?

- Obesity is a growing health issue and has been known to be a risk factor for type 2 diabetes and cardiovascular disease.
- Increased visceral fat tissue and insulin resistance are the main factors responsible for poor metabolic outcomes.
- Adropin is an amino acid peptide and is thought to be important in energy homeostasis and insulin sensitivity.

What are the new findings?

- Adropin is associated with homeostatic model assessment-insulin resistance (HOMA-IR) index, which is a reliable indicator of insulin resistance.
- 216.7 ng/L is the cut-off value for serum adropin that indicates HOMA-IR at 2.5.
- Age, body mass index, waist circumference, and diastolic blood pressure affect serum adropin level; however, age is the most significant factor affecting serum adropin, suggesting an effect of aging and cumulative fat deposition.

How might these results change the focus of research or clinical practice?

- Serum adropin measurement is clinically easy and a practical way to predict insulin resistance and metabolic deterioration in obese patients.
- Current cut-off value for adropin may give an insight into adropin-based therapy for insulin resistance in obese patients.

To cite: Erman H, Ozdemir A, Sitar ME, *et al*. *J Investig Med* Epub ahead of print: [*please include* Day Month Year]. doi:10.1136/jim-2021-001796

INTRODUCTION

Obesity is a growing health issue in both developed and developing countries. It has been known to be associated with a wide range of metabolic abnormalities, including insulin resistance, pre-diabetes, atherogenic dyslipidemia, non-alcoholic fatty liver disease, and metabolic syndrome, which are risk factors for type 2 diabetes and cardiovascular disease.[1] Obesity is typically determined and classified according to body mass index (BMI); however, waist circumference (WC), waist to hip ratio (WHR), and visceral adiposity index (VAI) enhance further assessment of visceral adiposity.[2] Visceral fat tissue is thought to be the main cause of increased free fatty acid flow and metabolism and is the most important factor for the development of hyperinsulinemia, dyslipidemia, and insulin resistance.[3]

It is well known that insulin resistance is key to the development of poor metabolic outcomes in obesity. Although euglycemic hyperinsulinemic clamp is the gold standard method for assessment of insulin resistance, due to the invasiveness and complicated nature of

this technique, simple and clinically practical assessment tools such as homeostatic model assessment-insulin resistance (HOMA-IR) and HOMA-ß have been used.[4 5] The HOMA-IR index correlates with the glucose clamp technique and is the most commonly used index in population and epidemiological studies.

Adropin is a 76-amino acid peptide which is mainly synthesized in the liver and brain. It has been hypothesized that adropin has significant roles in energy homeostasis and insulin sensitivity.[6] Furthermore, adropin is present in human circulation and participates in angiogenesis by increasing blood flow.[7] Since vascular function and insulin sensitivity are closely related to each other, it has been suggested that serum adropin can predict endothelial dysfunction.[8] Recent studies demonstrated that serum adropin concentrations are related to the presence of complications of type 2 diabetes, obesity, cardiovascular disease, and central nervous system diseases.[9–11]

Subjects without diabetes with overweight and obesity have increased cardiovascular risk. In a previous study, increased fasting blood glucose (FBG) even in the non-diabetic range is associated with septal thickening in obese subjects.[12] In addition, insulin resistance directly contributes to the development of atherosclerotic cardiovascular disease by inhibiting nitric oxide production and thus endothelial dysfunction. Asymptomatic insulin resistance causes vascular damage before the onset of diabetes and is not justified by traditional risk factors of cardiovascular disease.[13] In the present study we evaluated obese patients without a history of metabolic disease and were admitted to hospital for weight management. We aimed to assess the relationship between serum adropin concentrations and insulin resistance in obese patients and clarify the factors affecting serum adropin levels.

MATERIALS AND METHODS

Study population

In this cross-sectional study 50 (25 male, 25 female) patients with obesity and 22 (11 female, 11 male) healthy subjects were included between 2019 and 2020. Obesity was defined as BMI ≥30 kg/m^2. The obese group consists of patients with no medical disease record and no history of drug use. Patients underwent assessment for hypothyroidism, Cushing disease, type 2 diabetes, and kidney disease on admission. The exclusion criteria were presence of hypertension, hypothyroidism, Cushing disease or type 2 diabetes and regular drug use for any reason. To eliminate the effects of drugs and medication on serum adropin and insulin resistance, we designed the study with obese otherwise healthy patients. The healthy control group comprised individuals with BMI lower than 25 kg/m^2, without any illness, or not taking any drugs. Healthy subjects were randomly selected from volunteers between the ages of 18 and 35. Informed consent was taken from all subjects.

Anthropometrics

Anthropometric measurements were done according to the following standardized protocols. Subjects' systolic and diastolic blood pressure measurements were obtained with a sphygmomanometer in a seated position, twice every 5 min on the right arm, after 5 min of rest. The mean of the two readings was used in data analysis. Hypertension was defined as current use of antihypertensive drug or systolic blood pressure (SBP) ≥140 mm Hg and/or diastolic blood pressure (DBP) ≥90 mm Hg.[14] BMI was calculated using the formula weight (kg)/height (m^2). Obesity was defined as BMI >30 kg/m^2.[15] WC was measured midway between the uppermost border of the iliac crest and the lower border of the costal margin. Hip circumference (HC) was measured at the widest protrusion of the gluteal region.

Laboratory analysis

Fasting plasma samples were obtained from the patient and the control group. Serum cholesterol, triglyceride (TG), and high-density lipoprotein cholesterol (HDL-c) were measured by enzymatic colorimetric method with commercially available kit (COBAS 311, Roche Diagnostics, Mannheim, Germany), and low-density lipoprotein cholesterol was calculated according to the Friedewald formula. Serum glucose measures were determined enzymatically using the hexokinase method (Roche Diagnostics). Fasting serum concentrations of glucose and insulin were used to calculate the HOMA-IR as fasting glucose (mmol/L) × fasting insulin (mU/L)/22.5.[5] Insulin resistance was defined as HOMA-IR value greater than 2.5.[5] VAI was calculated as follows[16]: male: VAI=[waist circumference (cm)/(39.68+(1.88×BMI))]×(TG (mmol/L)/1.03)×(1.31/HDL-c (mmol/L)); female: VAI=[waist circumference/(36.58+(1.89×BMI))]×(TG/0.81)×(1.52/HDL-c). The particle-enhanced immunoturbidimetric method with Behring BN-100 Nephelometer (Behring Diagnostic, Frankfurt, Germany) was used to measure C reactive protein (CRP). In every patient, 5 mL venous blood samples were drawn in a metal-free sterile tube after 8-hour fasting condition. Blood samples were kept at room temperature for about 30 min to clot and were centrifuged at 3000 revolutions per minute for 15 min to extract the serum. The serum was placed in an Eppendorf tube and stored at −80°C until the day of study. Serum adropin was measured by human-specific ELISA kit according to manufacturer's instructions (Bioassay Technology Laboratory, Shanghai, China). The standard solutions were run for every ten-test sample to verify assay accuracy.

Statistical analysis

Compliance with normal distribution was analyzed by Kolmogorov-Smirnov test for continuous variables. Descriptive statistics were used to describe continuous variables (mean, SD, minimum, median, maximum), and % and n were used to identify dashed variables. Associations between categorical variables were shown by χ^2 test, Fisher's exact test, and Fisher-Freeman-Halton test. Student's t-test was used to compare continuous variables showing independent and normal distribution. Mann-Whitney U test was used to compare continuous variables showing independent and abnormal distribution. Youden index was used to assess the optimal cut-off value for serum adropin to determine insulin resistance. Linear and multiple regression analyses were used to determine the effective variables on serum adropin. Receiver operating characteristics (ROC) curve analysis was performed to define the sensitivity and specificity of serum adropin in predicting insulin resistance

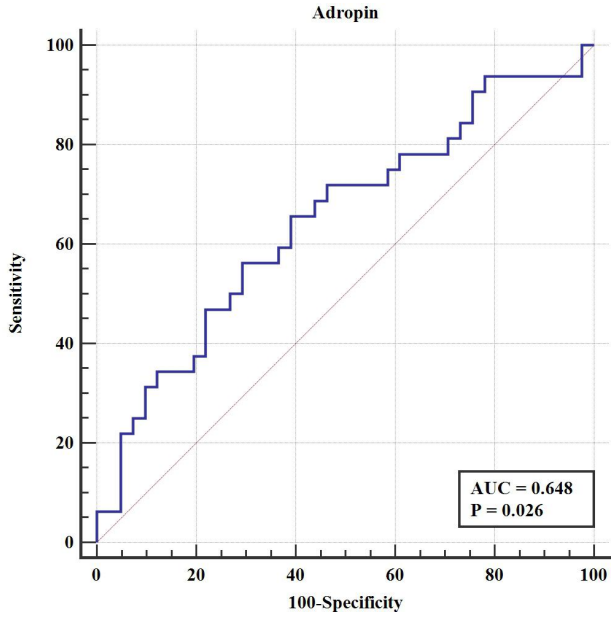

Figure 1 Sensitivity and specificity parameters for serum adropin in predicting HOMA-IR at 2.5 in obese patients. AUC, area under the curve; HOMA-IR, homeostatic model assessment-insulin resistance.

by predicting the HOMA-IR cut-off value (figure 1). Statistical significance was set at $p<0.05$. Analysis was performed using MedCalc V.19.2 statistical software (MedCalc Software, Ostend, Belgium; http://www.medcalc.org, 2020).

RESULTS

The present study included 55 obese patients with BMI >30 kg/m^2 (mean age 30±6.81 years, 50% men) and healthy subjects with BMI <25 kg/m^2 (mean age 29±5.04 years, 50% men). The baseline demographic and routine laboratory parameters of obese patients and healthy subjects are demonstrated in table 1. The age and sex distributions were similar in both groups. As expected weight, BMI, WC, HC, and WHR were significantly higher in the obese group than in the healthy with normal BMI group. In addition, SBP, DBP, alanine aminotransferase, erythrocyte sedimentation rate (ESR), CRP, glucose, uric acid, fasting insulin, HOMA-IR, HDL-c, and TG were statistically significantly different between healthy subjects and obese patients (table 1). Compared with the healthy control group, obese subjects had significantly lower serum adropin levels ($p<0.001$). The mean serum adropin concentration in obese patients was 180.63±106.89 ng/L. Obese patients had a high level of serum fasting insulin ($p<0.001$) and their mean HOMA-IR was 3.45±1.69 (table 1).

Serum adropin levels were significantly lower in the obese patient group than in healthy subjects with normal BMI ($p<0.001$). The results of the correlation analysis are summarized in table 2. In the correlation analysis serum adropin levels were significantly and negatively correlated with age ($r=-0.379$, $p=0.001$), DBP ($r=-0.294$, $p=0.011$), BMI ($r=-0.267$, $p=0.022$), WC ($r=0.274$, $p=0.019$), CRP ($r=-0.394$, $p=0001$), FBG ($r=-0.333$, $p=0.004$), fasting insulin ($r=-0.241$, $p=0.04$), HOMA-IR ($r=-0.268$, $p=0.022$), VAI ($r=-0.258$, $p=0.028$), and

Table 1 Clinical and laboratory characteristics of controls and patients with obesity

	Obese patients (n=50) Mean±SD	Healthy controls (n=22) Mean±SD	P value
Age (years)	30±6.81	29±5.04	0.065*
Sex: male/female	25/25	11/11	
BMI (kg/m^2)	36.52±4.39	22.35±1.85	<0.001
Waist circumference (cm)	113.51±12.17	77.05±6.64	<0.001*
Hip circumference (cm)	121.06±13.27	92.77±8.95	<0.001*
WHR	0.94±0.09	0.83±0.07	<0.001*
SBP (mm Hg)	122.35±14.39	104.09±12.02	<0.001
DBP (mm Hg)	74.12±11.26	65.91±7.5	0.003
FBG (mg/dL)	99.16±8.37	88.41±5.93	<0.001*
Fasting insulin	14.43±6.73	7.65±3.4	<0.001
HOMA-IR	3.54±1.9	1.69±0.82	<0.001
AST (mg/dL)	34.1±22.21	27.18±32.65	0.029
ALT (mg/dL)	22.73±10.44	17.73±3.3	0.162
Creatinine (mg/dL)	0.77±0.12	0.76±0.12	0.548
Uric acid (mg/dL)	5.92±1.69	4.46±1.54	0.002
Total cholesterol (mg/dL)	188.56±39.73	185.09±31.08	<0.001
LDL-c (mg/dL)	112.92±44.7	112.92±44.7	0.400
Non-HDL-c (mg/dL)	145.06±40.1	126.59±36.82	<0.001*
HDL-c (mg/dL)	43.43±10.62	63.27±24.97	<0.001
Triglyceride (mg/dL)	149.1±86.15	96.34±66.34	0.001
WBC (×10^3/µL)	8.11±1.57	792±2.05	0.666*
HGB (g/dL)	14.33±1.68	14.4±1.47	0.865*
CRP (m/dL)	0.59±0.42	0.2±00.2	<0.001
ESR (mm/hour)	12.71±9.11	5.27±3.97	<0.001
VAI	2.3±1.55	0.97±0.47	<0.001
Serum adropin (ng/L)	180.63±106.89	318.75±150.26	<0.001

*Student's t-test and Mann-Whitney U test. Statistical significance at p<0.05 and p<0.001.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; FBG, fasting blood glucose; HDL-c, high-density lipoprotein cholesterol; HGB, hemoglobin; HOMA-IR, homeostatic model assessment-insulin resistance; LDL-c, low-density lipoprotein cholesterol; SBP, systolic blood pressure; VAI, visceral adiposity index; WHR, waist to hip ratio.

TG ($r=-0.238$, $p=0.042$). On the other hand no significant correlation was found between serum adropin and SBP ($r=-0.182$, $p=0.122$), ESR ($r=-0.200$, $p=0.09$), HDL-c ($r=0.155$, $p=0.192$), and uric acid level ($r=-0.066$, $p=0.963$).

To assess the discriminative value of serum adropin in detecting HOMA-IR at 2.5, an ROC curve was used for sensitivity and specificity using area under the curve (AUC) (figure 1). The ROC analysis revealed that adropin concentrations below 216.7 ng/L indicate the level of HOMA-IR index at 2.5, with a sensitivity of 70.7% and a specificity of 56% (table 3). The cut-off value for serum adropin in predicting insulin sensitivity according to the HOMA-IR index was 216.7, with a positive predictive value of 67.4% and a negative predictive value of 60% (AUC=0.649, $p=0.026$).

To determine the effect of adropin-related variables on adropin, first, simple linear regression and multiple linear regression analyses were performed with variables that were

Table 2 Correlation analysis of parameters with serum adropin in obese patients

Parameters	r	P value
Adropin–age	−0.379	0.001
Adropin–DBP	−0.294	0.011
Adropin–SBP	−0.182	0.122
Adropin–BMI	−0.267	0.022
Adropin–WC	−0.274	0.019
Adropin–CRP	−0.394	0.001
Adropin–ESR	−0.200	0.090
Adropin–glucose	−0.333	0.004
Adropin–HOMA-IR	−0.268	0.022
Adropin–VAI	−0.258	0.028
Adropin–TG	−0.238	0.042
Adropin–HDL-c	0.155	0.192
Adropin–uric acid	−0.066	0.963

Statistical significance at p<0.05 and p<0.001.
BMI, body mass index; CRP, C reactive protein; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; SBP, systolic blood pressure; TG, triglycerides; VAI, visceral adiposity index; WC, waist circumference.

Table 4 Regression analysis of factors affecting serum adropin concentration

	Linear regression		Multiple regression	
	ß	P value	ß	P value
Age (years)	−0.352	0.002	−0.326	0.009
Sex	−0.118	0.320		
Weight	−0.256	0.029	0.102	0.740
BMI (kg/m^2)	−0.364	0.002	−0.384	0.194
WC (cm)	−0.328	0.005	0.113	0.714
WHR	−0.193	0.101		
SBP (mm Hg)	−0.223	0.058		
FBG (mg/dL)	−0.385	0.001	−0.105	0.488
TG (mg/dL)	−0.223	0.058		
Fasting insulin	−0.091	0.446		
HOMA-IR	0.269	0.021	0.088	0.479
HDL-c (mg/dL)	0.314	0.007	0.200	0.149

Statistical significance at p<0.05 and p<0.001.
BMI, body mass index; FBG, fasting blood glucose; HDL-c, high-density lipoprotein cholesterol; HOMA-IR, homeostatic model assessment-insulin resistance; SBP, systolic blood pressure; TG, triglycerides; WC, waist circumference; WHR, waist to hip ratio.

significant (table 4). Linear regression analysis showed that the following factors interfered with serum concentrations of adropin: age (ß=−0.352, p=0.009), weight (ß=−0.256, p=0.029), BMI (ß=−0.364, p=0.002), WC (ß=−0.328, p=0.005), FBG (ß=−0.385, p=0.001), HOMA-IR index (ß=0.269, p=0.021), and HDL-c (ß=0.314, p=0.007). Only age (ß=−0.326, p=0.009) was independently associated with serum adropin concentrations in obese patients.

DISCUSSION

We aimed to evaluate the potential clinical importance of circulating adropin as a biomarker of insulin resistance in obese patients. We investigated serum adropin level and its correlations with clinical and biochemical determinants of obesity. Our results demonstrate that serum adropin concentrations in obese patients were lower than non-obese healthy individuals. Serum adropin negatively correlates with fasting glucose, fasting insulin, and HOMA-IR. We suggest that serum adropin has an ability to identify insulin resistance in obesity.

The definition of obesity is currently based on BMI measurement which considers different clinical and biochemical subtypes in the same category.[17] However visceral adipose tissue is thought to be responsible for the development of poor cardiovascular outcomes due to its proinflammatory properties.[18] Many studies suggest using other anthropometric measurements such as WC and WHR and biochemical indexes such as VAI for better assessment of the amount of visceral adipose tissue.[19] WC, WHR, and VAI are useful parameters in the assessment of visceral adipose tissue accumulation and are associated with insulin resistance and cardiometabolic risk.[20] Furthermore VAI is suggested to predict the conversion of metabolically healthy obesity to an unhealthy phenotype.[21] Choi and Yim[22] demonstrated that serum adropin has a negative correlation with BMI and WC. Similarly we found serum adropin is negatively correlated with WC and BMI, but not WHR. There are limited data on the association of serum adropin with VAI. In the current study VAI is negatively correlated with adropin, which suggests that visceral adipose tissue accumulation may downregulate serum adropin concentrations. On the other hand elevated uric acid levels are closely related to both visceral fat accumulation and insulin resistance.[23] In our study patients with obesity have significantly higher serum uric acid levels in comparison with the healthy group with normal BMI (table 1). However serum adropin has no correlation with serum uric acid (table 2). As far as we know, obese patients with insulin resistance, hypertension, and hyperlipidemia are prone to cardiovascular complications more frequently than metabolically healthy obese subjects. Multiple factors contribute to metabolic health; however, increased insulin resistance and visceral adiposity are the key factors most responsible.[21] Therefore, it is important to recognize metabolic risks and future deterioration of obese patients in order to provide appropriate clinical management. It has been known that the gold standard method to measure insulin resistance is the euglycemic

Table 3 ROC analysis and diagnostic screening tests were used to determine the cut-off point for serum adropin to predict HOMA-IR at 2.5

HOMA-IR at 2.5	AUC	P value	Cut-off	Sensitivity	Specificity	PPV	NPV
Adropin	0.648	0.026	≤216.7	70.7	56.2	67.4	60

Statistical significance at p<0.05 and p<0.001.
AUC, area under the curve; HOMA-IR, homeostatic model assessment-insulin resistance; PPV, positive predictive value; ROC, receiver operating characteristics curve.

clamp technique.[5] Since HOMA-IR was first introduced and evaluated in comparison with euglycemic hyperinsulinemic clamp method in 1985 by Matthews *et al*,[5] it has been used in most epidemiological studies. Although the cut-off values for HOMA-IR vary from 1.7 to 3.8 due to ethnic diversity, 2.5 is the commonly accepted value.[24]

Adropin is coded by the Enho (energy homeostasis-associated) gene and was first isolated in the liver and brain tissue. Its synthesis is thought to be regulated by dietary macronutrient intake and associated with insulin resistance, energy homeostasis, and lipid metabolism.[25] The pathophysiological mechanisms underlying the association between serum adropin and insulin resistance are unclear yet. Studies on animals suggest that adropin regulates the effects of hepatic lipogenic genes and adipose tissue peroxisome proliferator-activated receptor gamma, and therefore interferes with the metabolic adaptation to fasting and dietary fat intake. In mice with diet-induced obesity, systemic adropin treatment attenuates hepatosteatosis and insulin resistance independently from adiposity and food intake.[25] In accordance with the literature, we found low serum adropin concentrations in obese patients, with a mean value of 180.63±106.89 ng/L. Correlation analysis revealed that serum adropin was associated with the HOMA-IR index. Serum adropin levels lower than 216.7 ng/L in obese patients predict insulin resistance with a sensitivity of 70.7% and a specificity of 56.2%. We suggest that serum adropin concentrations may be used to predict insulin resistance. More importantly, the cut-off values of serum adropin for insulin resistance had been conflicting in previous studies. The current study suggests a cut-off point of serum adropin concentration which indicates a HOMA-IR level of 2.5 in obese patients. Kumar *et al*[25] suggested that serum adropin has a role in adapting substrate metabolism and fat intake. Therefore, when the adropin levels decline in obesity, the balance between lipid metabolism and dietary fat intake may be impaired. Therefore low adropin promotes steatosis, dyslipidemia, and insulin resistance. Our results suggest a cut-off value of adropin which indicates deterioration of metabolic balance and further onset of insulin resistance.

Serum adropin has been shown to be associated with lipid metabolism in both animal and human studies.[26 27] In our study serum TG concentrations were negatively correlated with serum adropin. Our results obtained from the obese patient group are consistent with the results obtained by Butler *et al*,[28] where adropin levels were found to be negatively correlated with TG concentrations. Butler *et al*[28] observed subjects after Roux-en-Y gastric bypass surgery and found that those with lower plasma adropin exhibited the largest reductions in plasma TG; therefore, they hypothesized that adropin may have interfered with the synthesis or clearance of TG both in mice and humans. However, in a study on children, lipid profiles were similar in both groups with low and high adropin. They hypothesized that since dietary fructose intake is thought to be inversely associated with serum adropin level, high dietary fructose intake might interfere with the results.[29 30] Our study revealed that aging is an important factor for low adropin concentrations. According to these data, besides dietary fructose intake, fat exposure time and age of obesity important in atherogenic lipid profile.

Atherosclerosis is regarded as a result of chronic inflammatory disease state and endothelial dysfunction.[31] Adropin has been shown to suppress atherosclerosis by a non-lipid-driven mechanism. In animal studies, it has been demonstrated that chronic administration of adropin to Apoe$^{-/-}$ mice attenuates the development of atherosclerotic lesions of the aorta and reduces both the intraplaque monocyte/macrophage infiltration and smooth muscle cell content.[32] The messenger RNA expression of proinflammatory cytokines such as tumor necrosis factor-α (TNF-α) and interleukin 6 (IL-6) in pancreas tissue was diminished by adropin via inducible nitric oxide synthase expression.[33] Adropin is found to be associated with CRP levels in our patient group. TNF-α, IL-6, and CRP are inflammatory biomarkers that have already been associated with obesity-related inflammation.[34 35] Therefore, increased CRP and ESR levels in our obese patients might be associated with lipoinflammation.

In previous studies, low adropin levels were found to be negatively correlated with blood pressure due to endothelial dysfunction, which is thought to be the possible mechanism.[36] We found that adropin is inversely related to DBP but not to SBP. Together with knowledge on the effect of adropin on vascular endothelium, blood pressure and atherogenic dyslipidemia are associated with high-risk atherosclerotic vascular disease in the obese patient group of the current study. A recently published study pointed out a correlation between low adropin concentrations and endothelial dysfunction based on flow-mediated dilatation in patients with type 2 diabetes.[37] According to another study, it seems that decrease in serum adropin indicates endothelial dysfunction and may be a potential predictor of coronary artery disease both in patients with and without diabetes.[38] The low concentration of adropin in the obese patient group may be an indicator of endothelial dysfunction and suggests urgent lifestyle improvement and weight control even in class 1 obesity.

Some limitations should be acknowledged in this study. First, due to the cross-sectional design of the study, causal relationship cannot be established. Second, the correlation of HOMA-IR index and the results of glucose clamp technique has been shown before; however, the HOMA-IR index does not show whether the insulin resistance is peripheral or central. Third, this study is on the associations between serum adropin and insulin resistance in obesity by means of the HOMA-IR index. Although patients with overt type 2 diabetes were excluded from the study, oral glucose tolerance test was not performed. On the other hand, the effect of eating habits on adropin concentrations in obesity and the changes in adropin levels after weight intervention in obese subjects are important issues that should be clarified in further studies. Finally, since the study group represents obese patients with BMI between 30 and 40 kg/m^2, our results may not be generalized to morbidly obese patients.

CONCLUSION

In summary we found that serum adropin was low in obese patients and is negatively correlated with age, WC, BMI, FBG, and HOMA-IR. Serum adropin concentrations at 216.7 ng/L predict insulin resistance as it indicates HOMA-IR index at 2.5. Fasting adropin concentrations

were significantly affected by age in obese patients, drawing attention to the cumulative effect of fat accumulation and aging of endothelium. Nevertheless, novel studies on adropin and other myokines will further clarify the prediction of insulin resistance in obesity and the role of endothelium-mediated metabolic and cardiovascular complications of obesity.

Contributors Study concept and design: HE, AO. Analysis and interpretation of data: MES, BB. Drafting of the manuscript: HE, SIC.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Ethics approval The study has been approved by the University of Health Sciences, Istanbul Fatih Sultan Mehmet Education and Research Hospital (approval number of ethics committee 2018-73) and was conducted with the Declaration of Helsinki.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement All data relevant to the study are included in the article or uploaded as supplementary information. Data are available upon request to handeerman@yahoo.com.

ORCID iDs
Hande Erman http://orcid.org/0000-0001-7213-9624
Banu Boyuk http://orcid.org/0000-0001-7794-4411

REFERENCES

1 Li Q, Blume SW, Huang JC, *et al*. Prevalence and healthcare costs of obesity-related comorbidities: evidence from an electronic medical records system in the *United States*. *J Med Econ* 2015;18:1020–8.
2 Dong H, Xu Y, Zhang X, *et al*. Visceral adiposity index is strongly associated with hyperuricemia independently of metabolic health and obesity phenotypes. *Sci Rep* 2017;7:8822.
3 Kamada Y, Nakamura T, Funahashi T, *et al*. Visceral obesity and hypoadiponectinemia are significant determinants of hepatic dysfunction: an epidemiologic study of 3827 Japanese subjects. *J Clin Gastroenterol* 2009;43:995–1000.
4 DeFronzo RA, Tobin JD, Andres R. Glucose clamp technique: a method for quantifying insulin secretion and resistance. *Am J Physiol* 1979;237:E214–23.
5 Matthews DR, Hosker JP, Rudenski AS, *et al*. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985;28:412–9.
6 Chen M, Ouyang F, Zhou S. Adropin as a novel energy factor likely has the ability to regulate blood pressure. *Med Hypotheses* 2015;85:234.
7 Oruc CU, Akpinar YE, Dervisoglu E, *et al*. Low concentrations of adropin are associated with endothelial dysfunction as assessed by flow-mediated dilatation in patients with metabolic syndrome. *Clin Chem Lab Med* 2017;55:139–44.
8 Lovren F, Pan Y, Quan A, *et al*. Adropin is a novel regulator of endothelial function. *Circulation* 2010;122:S185–92.
9 Li L, Xie W, Zheng X-L, *et al*. A novel peptide adropin in cardiovascular diseases. *Clin Chim Acta* 2016;453:107–13.
10 Ganesh Kumar K, Zhang J, Gao S, *et al*. Adropin deficiency is associated with increased adiposity and insulin resistance. *Obesity* 2012;20:1394–402.
11 Shahjouei S, Ansari S, Pourmotabbed T, *et al*. Potential roles of Adropin in central nervous system: review of current literature. *Front Mol Biosci* 2016;3:25.
12 Zupo R, Castellana F, Sardone R, *et al*. Impaired fasting plasma glucose is a risk indicator of interventricular septum thickening among non-diabetic subjects with obesity. *Diabetes Res Clin Pract* 2020;169:108436.
13 Adeva-Andany MM, Ameneiros-Rodríguez E, Fernández-Fernández C, *et al*. Insulin resistance is associated with subclinical vascular disease in humans. *World J Diabetes* 2019;10:63–77.
14 2018 ESC/ESH guidelines for the management of arterial hypertension. *Rev Esp Cardiol* 2019;72:160.
15 Physical status: the use and interpretation of anthropometry. Report of a WHO expert Committee. *World Health Organ Tech Rep Ser* 1995;854:1–452.
16 Amato MC, Giordano C, Galia M, *et al*. Visceral adiposity index: a reliable indicator of visceral fat function associated with cardiometabolic risk. *Diabetes Care* 2010;33:920–2.
17 Flegal KM. Body-Mass index and all-cause mortality. *Lancet* 2017;389:2284–5.
18 Liberale L, Bonaventura A, Vecchiè A, *et al*. The role of adipocytokines in coronary atherosclerosis. *Curr Atheroscler Rep* 2017;19:10.
19 Vecchié A, Dallegri F, Carbone F, *et al*. Obesity phenotypes and their paradoxical association with cardiovascular diseases. *Eur J Intern Med* 2018;48:6–17.
20 Jabłonowska-Lietz B, Wrzosek M, Włodarczyk M, *et al*. New indexes of body fat distribution, visceral adiposity index, body adiposity index, waist-to-height ratio, and metabolic disturbances in the obese. *Kardiol Pol* 2017;75:1185–91.
21 Kang YM, Jung CH, Cho YK, *et al*. Visceral adiposity index predicts the conversion of metabolically healthy obesity to an unhealthy phenotype. *PLoS One* 2017;12:e0179635.
22 Choi H-N, Yim J-E. Plasma Adropin as a potential marker predicting obesity and obesity-associated cancer in Korean patients with type 2 diabetes mellitus. *J Cancer Prev* 2018;23:191–6.
23 Tsushima Y, Nishizawa H, Tochino Y, *et al*. Uric acid secretion from adipose tissue and its increase in obesity. *J Biol Chem* 2013;288:27138–49.
24 Ziaee A, Esmailzadehha N, Oveisi S, *et al*. The threshold value of homeostasis model assessment for insulin resistance in Qazvin metabolic diseases study (QMDS): assessment of metabolic syndrome. *J Res Health Sci* 2015;15:94–100.
25 Kumar KG, Trevaskis JL, Lam DD, *et al*. Identification of adropin as a secreted factor linking dietary macronutrient intake with energy homeostasis and lipid metabolism. *Cell Metab* 2008;8:468–81.
26 Butler AA, Zhang J, Price CA, *et al*. Low plasma adropin concentrations increase risks of weight gain and metabolic dysregulation in response to a high-sugar diet in male nonhuman primates. *J Biol Chem* 2019;294:9706–19.
27 Niepolski L, Grzegorzewska AE. Salusins and adropin: new peptides potentially involved in lipid metabolism and atherosclerosis. *Adv Med Sci* 2016;61:282–7.
28 Butler AA, Tam CS, Stanhope KL, *et al*. Low circulating adropin concentrations with obesity and aging correlate with risk factors for metabolic disease and increase after gastric bypass surgery in humans. *J Clin Endocrinol Metab* 2012;97:3783–91.
29 Chang J-B, Chu N-F, Lin F-H, *et al*. Relationship between plasma adropin levels and body composition and lipid characteristics amongst young adolescents in Taiwan. *Obes Res Clin Pract* 2018;12:101–7.
30 Stevens JR, Kearney ML, St-Onge M-P, *et al*. Inverse association between carbohydrate consumption and plasma adropin concentrations in humans. *Obesity* 2016;24:1731–40.
31 Hansson GK, Libby P. The immune response in atherosclerosis: a double-edged sword. *Nat Rev Immunol* 2006;6:508–19.
32 Sato K, Yamashita T, Shirai R, *et al*. Adropin contributes to Anti-Atherosclerosis by suppressing monocyte-endothelial cell adhesion and smooth muscle cell proliferation. *Int J Mol Sci* 2018;19:1293.
33 Akcilar R, Kocak FE, Simsek H, *et al*. Antidiabetic and hypolipidemic effects of adropinin streoptozotocin-induced type 2 diabetic rats. *Bratisl Lek Listy* 2016;117:100–5.
34 Gholami M, Sharifi F, Shahriari S, *et al*. Association of interleukin-6 polymorphisms with obesity: a systematic review and meta-analysis. *Cytokine* 2019;123:154769.
35 Chen F, Chen D, Zhao X, *et al*. Interleukin-6 deficiency facilitates myocardial dysfunction during high fat diet-induced obesity by promoting lipotoxicity and inflammation. *Biochim Biophys Acta Mol Basis Dis* 2017;1863:3128–41.
36 Gu X, Li H, Zhu X, *et al*. Inverse correlation between plasma Adropin and ET-1 levels in essential hypertension: a cross-sectional study. *Medicine* 2015;94:e1712.
37 Topuz M, Celik A, Aslantas T, *et al*. Plasma adropin levels predict endothelial dysfunction like flow-mediated dilatation in patients with type 2 diabetes mellitus. *J Investig Med* 2013;61:1161–4.
38 Wu L, Fang J, Chen L, *et al*. Low serum adropin is associated with coronary atherosclerosis in type 2 diabetic and non-diabetic patients. *Clin Chem Lab Med* 2014;52:751–8.