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Original Article

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Levels of TRB3 and Sestrin 2, Paraoxonase-1 activity, and the atherogenic index of plasma in obese individuals

Abstract

Aim: Obesity is a chronic health problem characterized by excess fat accumulation. This study aimed to assess the levels of endoplasmic reticulum stress–associated Tribbles homolog 3 (TRB3), oxidative stress–associated Sestrin 2 (SESN2), paraoxonase-1 (PON1) activity, and the atherogenic index of plasma (AIP) in obese, overweight, and normal-weight individuals, and to investigate their relationship with obesity.
Materials and Methods: The study enrolled 172 individuals, who were classified into normal-weight, overweight, and obese groups based on their BMI. TRB3 and SESN2 levels were measured using ELISA, and PON1 activity was assessed using spectrophotometric methods.
Results: Obese participants exhibited reduced PON1 activity and SESN2 levels compared with normal-weight individuals ($p<0.001$ and $p=0.001$, respectively). AIP values were elevated in both obese and overweight individuals ($p=0.002$). Additionally, men had higher AIP values than women ($p<0.001$).
Conclusion: Our study shows that SESN2 and PON1 levels are decreased, whereas AIP levels are increased in obese individuals. These findings suggest that the increased cardiometabolic risk in obesity may be related to oxidative stress and lipid imbalance. Moreover, the elevated AIP levels observed in men compared to women emphasize the need to account for sex in evaluating atherosclerotic risk.

Keywords: Sestrin 2, tribbles homolog 3, paraoxonase-1, obesity, atherogenic index of plasma

INTRODUCTION

Obesity develops through the interaction of genetic, metabolic, environmental, and behavioral factors, and their occurrence is increasing worldwide (1). Oxidative stress is an important contributing factor to the onset of several metabolic disorders linked to obesity (2). In obesity, the simultaneous occurrence of metabolic disturbances, including insulin resistance, glucose intolerance, and lipid imbalances, contributes to a greater likelihood of developing type 2 diabetes and cardiovascular disease (3).

Sestrins that regulate metabolic homeostasis are upregulated under stress conditions and suppress oxidative damage (4). Sestrin 2 (SESN2) functions by inhibiting oxidative stress and proinflammatory signaling primarily through the AMP-activated protein kinase (AMPK) and mammalian target of rapamycin complex 1 (mTORC1) pathways (5). Inhibition of SESN2 has been reported to worsen atherosclerotic processes by enhancing pro-inflammatory responses and ER stress in the endothelium (6). SESN2 is considered a protective antioxidant protein induced by oxidative stress. Furthermore, SESN2 can increase lipolysis and fatty acid oxidation by regulating autophagy and mitophagy (7).

Tribbles homolog 3 (TRB3), also known as neuronal cell death–inducible protein kinase (NIPK), is the mammalian counterpart of the Drosophila Tribbles gene. It has an important function in regulating glucose balance and is present in multiple tissues, including the adipose tissue, liver, skeletal muscle, and heart. TRB3 is a pseudokinase whose expression is triggered by various cellular stress conditions, such as fasting, ER stress, oxidative imbalance, and lack nutrients (8). It has been reported that TRB3 inhibits adipocyte differentiation. In mice, TRB3 overexpression contributes to hyperglycemia by increasing hepatic glucose output (9).

Paraoxonase (PON) is an ester hydrolase enzyme of the group A aryldialkyl phosphatase class, which has three members: PON1, PON2, and PON3. Paraoxonase-1 (PON1) is an antioxidant enzyme associated with circulating HDL and inhibits lipid peroxidation (10). PON1 supports HDL's anti-atherogenic and anti-inflammatory functions by degrading lipid peroxides, thus contributing to the reduction of oxidative stress (11). In animal models of obesity and metabolic syndrome, PON1 serum activity has been shown to decrease. Expression of the PON1 gene has been associated with the restoration of enzyme activity and reductions in macrophage count, plaque volume, and lipid levels (11).

The present study investigates the associations of SESN2 and TRB3 levels, which are linked to oxidative stress, and PON1 activity with obesity. In addition, it explores their potential as biomarkers for obesity-related cardiometabolic disorders alongside the atherogenic index of plasma (AIP).

MATERIALS AND METHODS

The study protocol received approval from the Clinical Research Ethics Committee of Ordu University Faculty of Medicine (Decision No: 2022/179). The study adhered to the ethical guidelines of the Declaration of Helsinki, and informed consent was obtained from all participants.

A total of 172 participants, aged between 25 and 59 years, attending the Internal Medicine outpatient clinic of Başakşehir Çam and Sakura City Hospital were included in the study. Based on the World Health Organization's BMI classification, participants were categorized into three groups: those with a BMI of 18.5–24.9 kg/m² were classified as normal-weight (n=58), those with a BMI of 25.0–29.9 kg/m² as overweight (n=58), and those with a BMI ≥30 kg/m² as obese (n=56). Individuals with the following conditions were excluded from the study: acute or chronic inflammatory diseases, neoplastic diseases, severe cardiovascular diseases, and other serious systemic diseases.

Data collection and analysis

Biochemical analyses were performed at the Central Laboratory of Başakşehir Çam and Sakura City Hospital, Istanbul. Routine biochemistry tests were performed using the Cobas 8000 analyzer (Roche Diagnostics, Indianapolis, USA) with original reagents. Glycated hemoglobin (HbA1c) was analyzed by multicapillary zone electrophoresis using the Sebia Capillarys 3 Tera instrument (Sebia, France). AIP=$\log_{10}$ (TG / HDL-C) (12). This index is dimensionless because it is a logarithmic ratio. Triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) concentrations were expressed in mmol/L, in accordance with the original definition of the AIP. When lipid concentrations were obtained in mg/dL, they were converted to mmol/L before calculation (TG × 0.0113; HDL-C × 0.0259).

Serum TRB3 and SESN2 concentrations were measured using commercially available ELISA kits (Bioassay Technology Laboratory, Shanghai, China). The TRB3 ELISA kit (catalog no. 201-12-8026) had an assay range of 10–2500 ng/L with a sensitivity of 9.017 ng/L. The intra- and inter-assay coefficients of variation (CVs) were 4.70% and <10%, respectively, and the TRB3 standard curve was constructed over a concentration range of 100–1600 ng/L. The SESN2 ELISA kit (catalog no. 201-12-4926) had an assay range of 0.1–30 ng/mL with a sensitivity of 0.085 ng/mL. The intra- and inter-assay coefficients of variation (CVs) were 4.53% and <10%, respectively. The SESN2 standard curve ranged from 1–16 ng/mL.

PON1 activity was measured spectrophotometrically. The assay is based on the enzymatic hydrolysis of phenylacetate, resulting in the production of phenol, which was quantified at 270 nm. The reaction mixture consisted of 50 mM Tris-HCl buffer containing 1 mM CaCl2. Following the addition of the phenylacetate substrate and an appropriate amount of enzyme, the reaction was initiated, and the increase in absorbance at 270 nm, indicating phenol formation was recorded (13). PON1 activity was calculated using the molar absorptivity of phenol, which is produced from phenylacetate in the assay.

Statistical Analysis

The Kolmogorov–Smirnov test was applied to evaluate whether the data followed a normal distribution. Levene's test was used to assess whether the variances across groups were homogeneous. Relationships between categorical variables were analyzed using the chi-square test. One-way ANOVA or Welch ANOVA was applied to compare the groups. One-way ANCOVA was conducted to assess PON1, AIP, TRB3, and SESN2, with HOMA-IR included as a covariate. Associations among continuous variables were examined using Pearson's correlation coefficient when parametric assumptions were satisfied, and Spearman's rank correlation coefficient when they were not. A type I error probability (α) of 5% was used as the threshold for statistical significance in the analysis. All statistical procedures were conducted with SPSS, version 28.0 (IBM Inc., Chicago, USA)."

RESULTS

In this study, plasma TRB3 and SESN2 levels, AIP, and PON1 enzyme activities were compared across participants

categorized as normal-weight, overweight, and obese based on BMI. When the gender distribution across the groups was examined, and no significant difference was detected (p=0.213).

Mean concentrations of biochemical parameters across the groups and the statistical significance of differences between these means were analyzed using one-way ANOVA (Table 1). Statistically significant differences were found among the groups in terms of age, BMI, insulin, ALT, triglyceride, and HOMA-IR levels (p<0.05).

In gender comparisons, males exhibited elevated BMI, glucose, insulin, urea, creatinine, ALT, AST, GGT, triglycerides, LDL, HOMA-IR, and blood pressure, whereas HDL levels were lower (p<0.05) (Table 2)."

Table 1. Comparison of study variables according to BMI.

Parameters	Normal-weight					Overweight					Obese					p
	n	Mean	SD	Min	Max.	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max	
Age, years	58	33.40	10.12	20.0	53.0	58	36.02	8.71	21.0	63.0	56	38.07	10.86	20.0	59.0	**0.062****
BMI, kg/m²	58	21.86 ^{C}	2.45	15.9	25.0	58	27.92 ^{B}	1.49	25.3	30.0	56	37.63 ^{A}	5.20	30.8	52.1	**<0.001****
Glucose, mg/dL	58	89.64	6.64	73.00	105.00	58	94.07	8.05	76.00	109.00	56	97.11	7.66	76.00	110.00	**<0.001***
Urea, mg/dL	58	24.14	5.80	13.9	39.6	57	23.32	6.75	9.9	38.0	56	23.95	7.83	10.0	44.2	0.795*
Creatinine, mg/dL	57	0.69	0.14	0.4	1.1	58	0.71	0.13	0.5	1.1	56	0.73	0.16	0.5	1.4	0.379*
ALT, U/L	58	13.59 ^{B}	6.87	2.0	35.0	58	17.24 ^{B}	8.36	7.0	39.0	56	22.98 ^{A}	9.81	5.0	43.0	**<0.001****
AST, U/L	58	15.78 ^{B}	5.91	6.0	41.0	58	16.83 ^{AB}	7.31	8.0	42.0	55	18.98 ^{A}	6.58	8.0	40.0	**0.035***
ALP, U/L	30	68.93	28.62	15.0	137.0	27	66.44	20.50	23.0	105.0	38	78.53	34.58	26.0	243.0	0.209*
GGT, U/L	33	21.12	26.71	6.0	164.0	30	31.57	36.56	6.0	161.0	37	30.54	18.63	8.0	78.0	0.246*
LDH, U/L	48	161.23 ^{B}	20.60	128.00	217.00	47	168.32 ^{AB}	29.55	13.00	213.00	42	175.60 ^{A}	25.09	118.00	226.00	**0.030***
TG, mg/dL	49	89.02 ^{B}	37.16	32.0	160.0	58	101.11 ^{B}	55.60	24.0	387.0	51	145.31 ^{A}	94.88	44.0	583.0	**0.001****
Cholesterol,mg/dL	48	174.08	24.65	109.0	200.0	58	174.90	24.94	108.0	200.0	52	181.58	21.19	117.0	200.0	0.213*
HDL, mg/dL	53	64.09 ^{A}	9.01	48.0	90.0	58	51.95 ^{B}	11.68	31.0	81.0	51	47.39 ^{B}	10.38	31.0	81.0	**<0.001***
LDL, mg/dL	48	102.52	33.87	45.0	231.0	58	110.07	32.99	40.0	198.0	50	116.92	35.44	56.0	217.0	0.116*
Insulin, uIU/mL	56	8.49 ^{A}	2.61	4.2	19.9	56	11.75 ^{B}	6.39	4.0	39.7	56	15.70 ^{C}	7.67	4.2	34.2	**<0.001****
HOMA-IR	58	1.83 ^{C}	0.60	0.0	2.5	57	2.70 ^{B}	1.56	0.0	9.3	56	3.81 ^{A}	2.00	1.0	9.0	**<0.001****
SBP (mmHg)	54	118.39	6.91	100.0	130.0	49	119.27	7.54	90.0	130.0	44	122.02	8.68	100.0	140.0	0.060*
DBP (mmHg)	54	75.98 ^{B}	6.28	60.0	85.0	49	77.08 ^{AB}	5.94	60.0	85.0	44	79.64 ^{A}	6.18	60.0	96.0	**0.014***

BMI: body mass index; TG: Triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HOMA-IR: homeostasis model assessment insulin resistance; SBP: systolic blood pressure; DBP: diastolic blood pressure; *: One-way ANOVA; **: Welch ANOVA; The difference between groups with no common letter is significant (p<0.05)

Table 2. Comparison of study variables according to gender

Parameters	Female			Male			Test statistics	p
	n	Mean	SD	n	Mean	SD		
Age, years	139	35.45	10.13	33	37.27	9.72	-0.934*	**0.351**
BMI, kg/m²	139	28.41	6.98	33	31.70	8.20	-2.355*	**0.020**
Glucose, mg/dL	139	92.67	7.67	33	97.33	8.56	-3.070 *	**0.002**
Urea, mg/dL	138	22.53	6.01	33	29.12	7.42	-5.399*	**<0.001**
Creatinine, mg/dL	138	0.67	0.10	33	.88	0.17	-6.865**	**<0.001**
ALT, U/L	139	15.56	7.33	33	27.64	10.03	-6.517**	**<0.001**
AST, U/L	138	16.19	6.11	33	21.24	7.69	-4.053*	**<0.001**
ALP, U/L	72	70.67	32.17	23	76.43	18.57	-.816*	0.417
GGT, U/L	74	23.51	25.68	26	39.77	30.35	-2.646*	**0.009**
LDH, U/L	108	166.88	26.71	29	172.48	108	-1.039 *	0.301
Triglyceride, mg/dL	127	102.10	63.17	31	150.66	85.69	-2.965**	**0.005**
Cholesterol, mg/dL	126	175.67	24.77	32	181.48	18.90	-1.235*	0.219
HDL, mg/dL	129	56.63	11.81	33	46.12	11.83	4.559*	**<0.001**
LDL, mg/dL	125	106.95	32.63	31	122.00	38.72	-2.212*	**0.028**
Insulin, uIU/mL	136	11.36	6.00	32	14.60	8.41	-2.058**	**0.046**
HOMA-IR	138	2.59	1.51	33	3.49	2.24	-2.187**	**0.035**
SBP (mmHg)	117	118.99	8.07	30	122.80	5.69	-2.432*	**0.016**
DBP (mmHg)	117	76.78	6.16	30	80.03	6.18	-2.580*	**0.011**

*: t-test. **: Welch t-test

One-way ANCOVA was used to analyze differences in PON1, AIP, SESN2, and TRB3 levels among the three groups (Table 3). Superscript letters (A, B, AB) indicate the results of post hoc multiple comparison analyses. Bonferroni correction was applied to control for the probability of Type 1 error in multiple comparisons. Groups sharing the same letter are not significantly different, whereas groups with different letters differ significantly ($p<0.05$). PON1 and SESN2 levels were found to be lower in obese individuals compared to those with normal weight (PON1, $p<0.001$; SESN2, $p=0.001$). Additionally, when comparing AIP values among the groups, AIP was significantly higher in overweight and obese individuals ($p=0.002$). However, the differences in TRB3 levels between the groups based on BMI categories were not statistically significant ($p=0.117$).

Table 3. Descriptive statistical values and comparison results for PON1, AIP, TRB3, and SESN2

Parameters	Normal-weight					Overweight					Obese					F	p
	n	Mean	SD	Min	Max.	n	Mean	SD	Min	Max	n	Mean	SD	Min	Max.		
PON1, U/L	58	66.32A	1.78	63.1	73.3	58	64.07B	1.66	60.3	67.2	56	63.55B	2.27	59.2	68.3	31.434	**<0.001**
AIP	49	0.16B	0.15	0.0	0.5	58	0.27AB	0.23	0.0	1.1	50	0.44A	0.28	0.0	1.2	6.371	**0.002**
SESN2, ng/mL	58	3.01A	2.96 A	0.6	7.9	58	1.72B	1.66	0.6	7.9	56	1.54B	1.62	0.6	7.9	7.152	**0.001**
TRB3, pg/mL	58	229.79	184.94	97.4	705.0	57	292.01	289.04	50.3	900.0	53	296.17	293.72	58.9	900.0	2.178	**0.117**

F: One-way ANCOVA, The difference between groups with no common letter is significant ($p<0.05$)

In our study, according to the results of one-way ANCOVA with HOMA-IR considered as a covariate, the parameters PON1, SESN2, and TRB3 were not affected by gender (Table 4). There were no statistically significant differences between male and female patients in terms of PON1, TRB3, and SESN2 levels (p=0.352, p=0.478, and p=0.079, respectively). However, AIP values were significantly higher in males than in females within the same BMI category (p<0.001). AIP levels were classified into low-, medium-, and high-risk categories across normal-weight, overweight, and obese individuals (Table 5).

Table 4. Comparison results of PON1, AIP, TRB3, and SESN2 variables according to gender

Parameters	Female			Male			Test statistics	p
	n	Mean	SD	n	Mean	SD		
PON1	139	64.77	2.22	33	64.20	2.38	0.871	0.352
AIP	126	0.24	0.22	31	0.48	0.29	13.691	<0.001
TRB3	135	266.91	257.70	33	292.00	271.34	0.505	0.478
SESN2	139	2.26	2.40	33	1.41	1.40	3.129	0.079

F: One-way ANCOVA

Table 5. AIP distribution by group

BMI category	Low risk (AIP < 0.11)		Medium risk (0.11 ≤ AIP ≤ 0.21)		High risk (AIP > 0.21)	
	n	%	n	%	n	%
Normal-weight	24	51.1	2	4.3	21	44.7
Overweight	13	23.6	11	20.0	31	56.4
Obese	5	10.2	6	12.2	38	77.6

Correlation analysis revealed a significant negative correlation between SESN2 and age (r=- 0.378, p=0.003). PON1 exhibited a positive correlation with HDL (r=0.652, p<0.001), while TRB3 was negatively correlated with ALP (r=-0.379, p=0.027). AIP showed positive correlations with age (r=0.425, p=0.002), glucose (r=0.508, p<0.001), insulin (r=0.509, p<0.001), HOMA-IR (r=0.532, p<0.001), GGT (r=0.601, p<0.001), and triglycerides (r=0.916, p<0.001), and a negative correlation with HDL (r=-0.724, p=0.009).

DISCUSSION

Obesity, whose prevalence is steadily increasing worldwide, has been closely linked to elevated oxidative stress (1). This study analyzed plasma levels of SESN2, TRB3, and PON1 to explore their potential relevance to obesity, given their roles in regulating metabolic balance. Our results showed that, compared to individuals with normal weight, obese individuals had lower levels of PON1 and SESN2, and higher levels of AIP.

In obesity, the increased adipose tissue contributes to impaired insulin sensitivity by secreting proinflammatory cytokines and free fatty acids (FFA) (14). Studies have demonstrated that as BMI increases, HOMA-IR levels also rise significantly (15). Our study similarly revealed that insulin resistance increases with obesity. Insulin resistance promotes hepatic triglyceride synthesis by enhancing the delivery of circulating free fatty acids (FFA) to the liver. Furthermore, the diminished regulatory effect of insulin on lipoprotein lipase impairs triglyceride breakdown, contributing to dyslipidemia (16). The increase in triglyceride levels, along with a decrease in HDL cholesterol, leads to a rise in the AIP. AIP has recently gained importance as an indicator of cardiovascular risk and is elevated in obese individuals in numerous studies (17). Several investigations have demonstrated a significant link between AIP and BMI, as well as a strong relationship with metabolic syndrome (18). Huang et al. reported that men had significantly higher AIP levels than women, which was associated with an increased risk of cardiovascular disease (19). In our study, triglyceride and AIP levels showed a marked elevation in participants with obesity, with a more pronounced increase in AIP observed among males compared to females.

The loss of endogenous sestrins has been linked to several metabolic disorders, such as impaired insulin signaling, excessive fat deposition, and increased oxidative stress (20). A study revealed that SESN2 deficiency negatively impacts metabolic sensitivity, disrupts glucose regulation, promotes oxidative damage, and accelerates the onset of type 2 diabetes in obese mice fed a lipid-rich diet (20). In a study conducted by Nourbakhsh et al. involving 70 children and adolescents, SESN2 levels were found to be reduced in obese participants

relative to their normal-weight peers (21). SESN2 is suggested to exert a protective effect against obesity by activating AMPK. Decreased SESN2 expression could facilitate obesity progression by downregulating AMPK activity (21). SESN2 deficiency has been shown to aggravate the progression of atherosclerosis by enhancing inflammatory signaling and inducing endoplasmic reticulum stress within endothelial cells (6). In our study, lower plasma SESN2 levels in obese individuals may be interpreted as an indicator of the oxidative stress burden accompanying obesity.

PON1 is an important antioxidant enzyme that degrades lipid peroxidation products and thus slows down the atherosclerotic process by inhibiting LDL oxidation (22). In their study, Ferretti and colleagues observed a marked reduction in PON1 function linked to obesity in adults, noting that this decline was associated with elevated lipid peroxides in LDL and HDL (23). Considering PON1's antioxidant and anti-inflammatory characteristics, reduced enzyme activity may exacerbate oxidative stress and inflammatory responses associated with obesity. It has been suggested that increased reactive oxygen species due to visceral fat accumulation may impair the structural integrity of PON1, thereby reducing its activity (24). Evidence from multiple studies points to the potential role of PON1 activity in identifying obesity-induced conditions, including type 2 diabetes and metabolic syndrome (24). In our study, the lower PON1 activity observed in obese individuals is consistent with previous findings in the literature.

TRB3 expression is induced by ER stress, hypoxia, insulin resistance, and elevated glucose levels, and advanced glycation end products (25). One study observed higher TRB3 concentrations in obese children (21). Although TRB3 levels were elevated in association with obesity in this study, the increase was not statistically significant. It has been suggested that the effect of TRB3 may be tissue- and stress-specific, and that interindividual genetic variations, the duration of obesity, and environmental factors may influence TRB3 levels (26). TRB3 is an intracellular pseudokinase that primarily functions at the cytoplasmic or nuclear level; its release into the plasma is limited, and its measurability at the systemic level has been reported to be low (9).

Since the research was conducted at a single center and lifestyle factors such as nutrition, exercise, smoking, alcohol use, and medication use were not examined, this represents a limitation of the study. Therefore, we believe that multicenter studies that include lifestyle variables will provide a clearer understanding of their role in obesity.

CONCLUSION

In conclusion, this study revealed that SESN2 and PON1 levels were significantly decreased, whereas AIP was increased in obese individuals. These findings suggest that the elevated cardiometabolic risk observed in obesity may be closely associated with a reduced antioxidant defense capacity and increased AIP. These parameters may be valuable for improving the understanding of obesity-related metabolic disorders and for stratifying individuals by cardiometabolic risk.

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Conflict of Interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that there is no financial support.

Ethical Approval
The study protocol received approval from the Clinical Research Ethics Committee of Ordu University on 22 July 2022 (Decision No: 2022/179).

Patient Consent
Informed consent was obtained from all participants.

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