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Relationship between plasma omentin-1 levels and newly diagnosed Stage I hypertension

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Abstract
Aim: Omentin-1 is an adipose tissue-derived cytokine with unknown biological function. The impact of omentin-1 on hypertension has been questioned due to its relation to obesity. This study is aimed to investigate omentin-1 levels in hypertensive patients.
Material and Methods: A prospective, case-control study evaluated patients admitted to outpatient cardiology clinics between January 2012 and December 2013. We designed two groups: the patient group comprised hypertensive patients with newly diagnosed stage-1 hypertension, and the control group comprised normotensive patients. The demographic and anthropometric characteristics and laboratory parameters of the patients in both groups were recorded. Plasma levels of omentin-1 were the primary outcome in this study.
Results: Patient group consisted of 52 hypertensive patients, whereas the control group consisted of 36 patients without hypertension. There was no significant difference between the groups in terms of demographic and clinical characteristics ($p>0.05$). The median omentin-1 level of the patient group was higher than that of the control group (756.2 ng/mL vs. 664.4 ng/mL); however, the difference was insignificant ($p=0.161$).
Discussion: The findings of this study did not suggest a significant relationship between the plasma omentin-1 levels and the newly diagnosed Stage I hypertension.

Keywords
Hypertension, Adipokines, Omentin

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Introduction

Omentin-1 is the major circulating isoform of an adipose tissue-derived cytokine (adipokine) expressed in the visceral adipose tissue [1]. The biological function of omentin-1 is mainly unknown; however, it has been reported to play a role in promoting insulin-mediated glucose transport in human adipocytes, and vasodilatation of blood vessels occurs [2, 3]. The fact that overweight and obese people have low levels of omentin-1 led to the hypothesis that omentin-1 may be directly related to several metabolic, endocrine, and cardiovascular diseases associated with diabetes [2].

Hypertension, smoking, diabetes, and hyperlipidemia are the risk factors for the development of coronary artery disease [4]. Given its close association with diabetes and its anti-atherogenic properties, it has been speculated that omentin-1 may function as a biomarker in the context of the development of coronary artery disease, acute myocardial infarction, atrial fibrillation, and hypertension [4-8].

The findings regarding the omentin-1 levels in atherosclerotic and hypertensive patients in the literature are contradictory. There are studies that reported low levels of omentin-1 as well as studies that reported high levels of omentin-1 [9-11]. A negative correlation of omentin-1 concentrations with waist circumference, insulin resistance, and body mass index (BMI) has been shown [6]. To date, there is no study that comprehensively investigated any possible relation between omentin-1 and hypertension. In this context, the objective of this study is to investigate and compare the plasma levels of omentin-1 in hypertensive patients and healthy normotensive subjects in view of the hypothesis that low levels of omentin-1 are associated with hypertension.

Material and Methods

Study Design

This study was designed as a prospective, case-control analysis of the plasma omentin-1 levels in hypertensive patients and control subjects. The local ethics committee approved the study (Abant Izzet Baysal University, Ethics Committee for Clinical Studies, 20.12.2012/465). Written informed consent was obtained from the patients and the control subjects. The study was carried out in accordance with the Declaration of Helsinki.

Population and Sample

The study population comprised all patients admitted to the outpatient clinics of Abant Izzet Baysal University, Faculty of Medicine, Turkey, Department of Cardiology. The patient group comprised all consecutive patients above 18 years of age with a newly diagnosed stage I hypertension. The diagnostic criteria for stage I hypertension based on the 2017 American College of Cardiology (ACC) and American Heart Association (AHA) guidelines were as follows: systolic blood pressure of 130 to 139 mmHg or diastolic blood pressure of 80 to 89 mmHg [12]. Patients with significant cardiac pathologies such as coronary artery disease, valvular heart disease, atrial fibrillation, secondary hypertension, and congestive heart failure (ejection fraction <45%), as well as patients with chronic inflammatory and rheumatoid diseases, diabetes mellitus, cerebrovascular diseases, chronic renal failure, a body mass index (BMI) ≥ 30 kg/m2, who were actively smoking, and had anti-hypertensive treatment were not included in the study. The control group consisted of normotensive individuals randomly selected from the outpatient clinic admissions without any clinical cardiological diagnosis in the same period.

Measurements and Variables

Blood pressure measurements of the patient and control groups were performed twice in the outpatient room between 08.00 and 10.00 AM after they had rest for at least 10 minutes. The mean blood pressure value was regarded as the cut-off value for inclusion in the control group [6]. Peripheral blood samples to measure omentin-1 levels were taken after the patients fasted overnight. The samples were centrifuged for ten minutes at 4000 ppm and then stored in a deep freezer at – 22C˚. The plasma concentration of omentin-1 (ng/ml) was measured using a commercially available ELISA (enzyme-linked immunosorbent assay) kit (BioVendor serum/plasma omentin-1, Brno, Czech Republic).

Demographic and anthropometric characteristics of the patients (age, gender, BMI, and waist circumference) were recorded. Patients' waist circumferences were measured at the mid-level between the lower rib margin and the iliac crest [13]. The laboratory tests included the measurement of the complete blood count, biochemical analysis (fasting blood glucose, urea, creatinine, sodium, potassium, aspartate aminotransferase, alanine aminotransferase levels), lipid profile (cholesterol, high-density lipoprotein, low-density lipoprotein, triglyceride levels), and the measurement of the serum thyroid-stimulating hormone (TSH) levels. Hypertensive patients were evaluated using conventional and M-mode echocardiography (GE Healthcare, Vivid S6 Echocardiography).

Statistical Analysis

The plasma levels of omentin-1 were the primary outcome in this study. In this context, omentin-1 levels of hypertensive patients and normotensive control subjects were compared.

Descriptive statistics were expressed as mean ± standard deviation and median with minimum-maximum values in the case of continuous variables and depending on whether they conform to normal distribution. Categorical variables were expressed as numbers and percentages. Shapiro-Wilk, Kolmogorov-Smirnov, and Anderson-Darling tests were used to determine whether the numerical variables conform to normal distribution or not.

The Independent Samples t-test was used to compare two independent groups in the case of numerical variables that conform to normal distribution; otherwise, the Mann-Whitney U test was used.

Pearson's Chi-Squared test was used to compare differences between categorical variables in 2x2 tables.

For statistical analysis, "Jamovi project (2020), Jamovi (Version 2.0.0.0) [Computer Software] (Retrieved from https://www.jamovi.org) and JASP (Version 0.15) (Retrieved from https://jasp-stats.org) were used. In all statistical analyses, the significance level (p-value) was set at 0.05.

Results

The patient group consisted of 52 hypertensive patients, whereas the control group consisted of 36 patients without hypertension. The demographic and clinical characteristics of

the patients are given in Table 1. The mean age of the patient group was higher than that of the control group; however, the difference was not statistically significant (p=0.241). There was also no statistical difference between the groups in terms of gender, BMI, and waist circumference (p>0.05).

Table 1. Demographic and clinical characteristics of the healthy controls and the patients

	Healthy controls (n=36)	Hypertensive patients (n=52)	p
Age (year) †, ‡	39.8 ± 12.7	42.8 ± 14.4	0.241**
	41.5 [19.0 – 57.0]	44.5 [17.0 – 67.0]	
Sex ¶			
Female	23 (63.9)	26 (50.0)	0.284***
Male	13 (36.1)	26 (50.0)	
BMI (kg/m2) †	25.6 ± 2.4	26.0 ± 2.1	0.389*
Waist circumference (cm) †	79.2 ± 4.4	79.7 ± 5.3	0.625*

†: mean ± standard deviation, ‡: median [min-max], ¶: n (%): *. Independent Samples T-Test: **. Mann-Whitney U test: ***. Pearson Chi-Square test: BMI: body mass index

Table 2. Comparison of the echocardiographic measurements of the patients

Echocardiographic variables †, ‡	Hypertensive patients (n=52)	
LVDD (mm)	47.0 ± 4.1	47.0 [36.0- 60.0]
LVSD (mm)	29.0 ± 4.4	29.0 [22.0- 45.0]
IVSD (mm)	8.9 ± 2.5	9.0 [0.8- 15.0]
PWD (mm)	8.4 ± 2.2	9.0 [0.9- 13.0]
EF (%)	62.2 ± 3.5	63.0 [55.0- 69.0]
LAd (mm)	34.3 ± 2.8	35.0 [26.0- 44.0]
AO (mm)	26.8 ± 2.4	27.0 [21.0- 32.0]
Aortic velocity (m/s)	1.3 ± 0.2	1.2 [0.9- 1.8]

†: mean ± standard deviation, ‡: median [min-max]: LVDD: left ventricular end diastolic diameter, LVSD: left ventricular end systolic diameter, IVSD: Interventricular septum thickness at end-diastole, PWD: posterior wall dimension, EF: left ventricular ejection fraction, LAd: left atrium diameter, AO: aortic root.

Table 3. Comparison of the laboratory parameters between the healthy controls and the patients

	Healthy controls (n=36)	Hypertensive patients (n=52)	p
Hemoglobin (gr/dl) †	13.9 ± 1.8	14.2 ± 1.7	0.555*
White blood cell count (109/L) †	7.3 ± 1.8	7.5 ± 2.1	0.720*
Neutrophil count (109/L) ‡	4.3 [1.8 – 7.2]	4.2 [1.9 – 10.9]	0.902**
Lymphocyte count (109/L) †	2.3 ± 0.6	2.2 ± 0.7	0.401*
Platelet count (109/L) ‡	270.5 [152.0 – 423.0]	246.5 [137.0 – 535.0]	0.160**
Fasting blood glucose (mg/dl) †	92.9 ± 7.6	95.1 ± 8.3	0.206*
Urea (mg/dl) †	26.9 ± 9.1	27.2 ± 7.5	0.858*
Creatinine (mg/dl) ‡	0.7 [0.4 – 1.1]	0.7 [0.6 – 1.3]	0.070**
Sodium (mmol/L) ††	137.9 ± 1.8	137.8 ± 2.2	0.800*
Potassium (mmol/L) †	4.2 ± 0.4	4.2 ± 0.4	0.410*
AST (U/L) †	19.1 ± 5.8	19.2 ± 5.2	0.952*
ALT (U/L) ‡	20.5 [8.0 – 49.0]	19.0 [6.0 – 70.0]	0.909**
Cholesterol (mg/dl) †	185.2 ± 38.7	190.6 ± 33.3	0.498*
HDL (mg/dl) †	44.9 ± 11.2	44.4 ± 10.4	0.826*
LDL (mg/dl) †	116.1 ± 30.3	121.5 ± 30.2	0.411*
Triglyceride (mg/dl) ‡	98.0 [43.0 – 350.0]	118.0 [39.0 – 264.0]	0.344**
TSH (uIU/ml) †	1.8 ± 0.7	2.0 ± 0.8	0.283*
Omentin (ng/ml)	664.4 [331.2 – 1313.6]	756.2 [307.6 – 1928.4]	0.161**

†: mean ± standard deviation, ‡: median [min-max]: *. Independent Samples T-Test: **. Mann-Whitney U test AST: aspartate aminotransferase, ALT: alanine aminotransferase, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TSH: thyrotropin stimulating hormone.

The echocardiographic measurements of the hypertensive patients are summarized in Table 2. The mean ejection fraction was determined as 62.2 ± 3.5%.

The results of the laboratory tests are summarized in Table 3. There was no significant difference between the groups in laboratory parameters. The median omentin-1 levels were determined as 664.4 ng/mL and 756.2 ng/ml in the control and patient groups, respectively. The difference between the omentin-1 levels of the groups was insignificant (p=0.161).

Discussion

The findings of this study revealed no significant relationship between plasma omentin-1 levels and the newly diagnosed stage 1 hypertension. There was also no indication of a physiological impact of omentin-1 on the complex interactions that lead to the development of hypertension.

Previous studies have focused on the relationship of omentin-1 levels with several endocrine diseases, including diabetes, metabolic syndrome, obesity [4, 9, 14]. Lower omentin-1 levels were associated with diabetes and its complications. The impact of omentin-1 on the development and progression of cardiac diseases such as myocardial infarction, coronary artery disease, carotid atherosclerosis has also been studied [1, 7, 15, 16]. The omentin-1 levels were found to be significantly lower in patients with the said diseases [1, 4, 7, 9, 15]. Baig et al. [7] demonstrated that omentin-1 is an independent risk factor for the development of myocardial infarction. A negative correlation has been reported between the omentin-1 levels and the severity of coronary artery disease [17]. It is the belief of the authors of this study that clinically significant endocrine and coronary diseases, i.e., diabetes with diabetic complications, metabolic syndrome with atherosclerosis, and angiographically diagnosed coronary artery disease, are significantly associated with lower levels of omentin-1. Nevertheless, the nature and extent of this association are not clear. Thus, prospective studies are needed to clarify whether omentin-1 is involved in the pathogeneses of these studies or whether it is an end-product generated secondary to such diseases.

The results of the relevant animal studies revealed that omentin-1 has a vasodilating effect on the isolated blood vessels mediated via the endothelium-derived nitric oxide [2]. Lower levels of omentin-1 would be expected in hypertensive patients considering the action mechanism of omentin-1. Celik et al. [6] reported decreased omentin-1 levels in hypertensive patients. Nevertheless, contrary to this study, they included both the patients with stage 1 and stage II hypertension in their study and found the lowest levels of omentin-1 in Stage II patients. They attributed this finding to the endothelial dysfunction, which was determined to be positively correlated with the hypertension stage [18]. Sanlialp et al. [14] speculated that omentin-1 level might be a reliable predictive factor for the development of metabolic syndrome in hypertensive patients. They evaluated all hypertensive patients in respect of the coexistence of metabolic syndrome.

Contrary to the results of the above-mentioned studies, [6,

14] Cinemre et al. [11] found higher omentin-1levels in the patients with stage I to stage 3 hypertension than in the healthy control subjects. In comparison, there was no difference between the omentin-1 levels of hypertensive patients and the control subjects in this study. It is possible that the severity and duration of hypertension in patients included in this study were insufficient to obtain the desired outcomes. Thus, large-scale prospective studies are needed to clarify the impact of omentin-1 on the development of hypertension.

Several authors have suggested that gender is effective on omentin-1 levels. In parallel, Liu et al. [1] demonstrated higher omentin-1 levels in women with metabolic syndrome. The differences between the serum levels of patients of different genders reported in the literature are contradictory [19]. In one of these studies, a population-based study conducted with 864 unselected middle-aged, elderly adults, Onat et al. [13] found that the lower omentin-1 levels were associated with lower systolic blood pressure, HbA1c, and glucose levels. Additionally, they found that omentin-1 was an independent predictive factor for hypertension and diabetes, yet only in male patients. Systolic blood pressure values were 128.6 ± 17, 134±21, and 134±21 mmHg in adults with tertiles of omentin-1 from 1 to 3. There was no significant difference in diastolic blood pressure measurements. Therefore, these findings should be considered as a piece of pathophysiological evidence without hypertension's clinical significance. Contrary to the findings reported in other studies, no correlation was found between gender and omentin-1 levels in the patient and control groups in this study [14]. It is possible that the differences between the characteristics of the study samples have led to such conflicting outcomes.

Study Limitation

The study's small sample size and single-center study design were its primary limitations. Secondly, only the repeated office blood pressure measurements were used to diagnose hypertension. The 24-h ambulatory blood pressure monitoring could be of more help in terms of getting better results.

Conclusion

In conclusion, the findings of this study did not suggest a significant relationship between the plasma omentin-1 levels and the newly diagnosed Stage I hypertension. Further studies with extensive and diverse samples are needed to verify the findings of this study.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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