Plasma adiponectin in hypertensive patients with and without metabolic syndrome

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Abstract

Introduction. The metabolic syndrome is defined on the basis of a cluster of coexisting metabolic deteriorations, which increase the risk of cardiovascular disease. Earlier studies suggested a role of adipokines and proinflammatory cytokines in the pathogenesis of metabolic syndrome-induced complications. Some clinical studies reported the association of hypoadiponectinemia with cardiovascular diseases, diabetes mellitus, hypertension and dyslipidemia. Decreased adiponectin has been proposed as a useful biomarker of the metabolic syndrome. The aim of the study was to compare serum adiponectin levels in patients with primary hypertension with and without coexisting metabolic syndrome.

Material and methods. The study group comprised 145 patients aged 18–50 years with primary hypertension. On the basis of IDF diagnostic criteria, all patients were categorized in groups with (HTMS; n = 73) and without (HTC; n = 72) metabolic syndrome. Study protocol included anthropometric measurements including waist circumference, 24 hour blood pressure measurement, serum levels of adiponectin, uric acid, lipids, insulin and glucose, and assessment of insulin resistance using HOMA-IR index.

Results. The plasma levels of adiponectin were significantly lower in the subjects with hypertension and metabolic syndrome as compared with those without the MS (4.2 ± 3.1 μg/dL vs. 6.7 ± 6.5 μg/dL, p = 0.0026). In all patients with hypertension, adiponectin negatively correlated with insulin (r = –0.20; p = 0.014), HOMA-IR (r = –0.24; p = 0.003), triglycerides (r = –0.19; p = 0.025), uric acid (r = –0.25; p = 0.003) and positively with HDL-cholesterol (r = 0.33; p = 0.0001). In the ROC curve analysis, the cut-off value predicting metabolic syndrome in patients with hypertension was 4.1 μg/mL for adiponectin.

Conclusions. In conclusion, low adiponectin levels should be taken into account as a potential non-classical biomarker of metabolic complications in patients with primary hypertension, not only with concomitant metabolic syndrome.

Key words: adiponectin, primary hypertension, metabolic syndrome

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Introduction

The metabolic syndrome is defined on the basis of a cluster of coexisting metabolic deteriorations (visceral obesity, abnormal glucose tolerance, abnormal lipid proiles, arterial hypertension), which increase the risk of cardiovascular disease. The key role in the development of these complications play arteriosclerosis and insulin resistance. Earlier studies suggested a role of many hormonal and genetic factors as well as adipokines and proinflammatory cytokines in the pathogenesis of metabolic syndrome-induced complications. Some clinical studies reported the association of hypoadiponectinemia with cardiovascular diseases, diabetes mellitus, hypertension and

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dyslipidaemia. Decreased adiponectin has been proposed as a useful biomarker of the metabolic syndrome. Adiponectin is a polypeptide hormone secreted by mature adipocytes within the adipose tissue. In plasma, adiponectin occurs in different forms, predominantly in multimeric fractions including low molecular weight (LMW) trimers, medium molecular weight (MMW) hexamers, and high molecular weight (HMW) multimers. Adiponectin exerts its activity via adiponectin-specific receptors. Literature reports two types of adiponectin receptors: AdipoR1 and AdipoR2, characterized by somewhat different location profiles. AdipoR1 is predominant in skeletal muscles while AdipoR2 is predominant in liver and skeletal muscles. In addition, some reports suggest that adiponectin is a ligand for T-cadherin. The plasma levels of adiponectin are relatively high compared to total protein levels and amount to 0.01% of total plasma proteins. Numerical values range from 1 to 30 μg/mL. Gender-related differences were reported as adiponectin levels in females are higher than those in males. Physiologically, adiponectin is involved in the metabolism of lipids and glucose. Acting via its membrane receptors, it enhances the uptake of glucose into skeletal muscles while reducing glyconeogenesis and beta-oxidation of fatty acids in liver [1–3]. These mechanisms explain the effects of increased insulin sensitivity. In addition, adiponectin is a vasoprotective agent acting via different mechanisms. It inhibits most atherosclerotic mechanisms, e.g. by suppressing TNF-α and thus reducing the adhesion of monocytes to endothelial cells, stymies proliferation of vascular smooth muscles, and reduces the formation of foam cells by means of inhibition of oxidized LDL (OxLDL) [4]. In their study conducted in a population of adult Japanese subjects, Ryo et al. demonstrated that adiponectin levels were negatively correlated with waist circumference, visceral fat, fasting glucose and insulin levels, and blood pressure measurements; on the other hand, positive correlation with HDL levels was observed. Of note was the finding that the more components of metabolic syndrome were observed in a patient, the lower were their adiponectin levels [5]. Gannage et al. demonstrated that adiponectin levels were negatively correlated with the incidence of metabolic syndrome regardless of subject's BMI [6]. Based on the currently available literature, high molecular weight (HMW) adiponectin multimers are the most active form of adiponectin. Falahi et al. suggested that HMW adiponectin may even be the most reliable biomarker in the diagnostics of metabolic syndrome [7]. Low adiponectin levels were observed in patients with arterial hypertension and left ventricular hypertrophy, ocular fundus lesions, albuminuria, and increased intima media thickness (IMT) within the common carotid artery [8–10]. Of special note is the fact that low adiponectin levels were observed with non-dipping circadian blood pressure profiles which are known to be a risk factors of organ complications [11]. Also interesting were the studies by Chow et al., who demonstrated that subjects with low baseline adiponectin levels were characterized by an increased risk of arterial hypertension within the following 5 years [12]. This may be an indirect evidence of adiponectin's role in the pathophysiology of arterial hypertension. The mechanisms of adiponectin's antihypertensive activity have not been fully elucidated. Adiponectin is postulated to have an inhibitory effect on the activity of the sympathetic nervous system [13] and a stimulatory effect on the release of vasodilator nitric oxide across vascular endotheliuum [14]. Considering the above, low adiponectin levels may be one of the risk factors of arterial hypertension. Most importantly from the clinical standpoint, this factor should be potentially modifiable. Adiponectin levels may be regulated by both pharmacological and non-pharmacological management. Hypotensive agents may exert different effects on adiponectin levels. According to numerous reports, treatment with certain angiotensin receptor blockers (ARB) such as losartan and telmisartan, or type 1 angiotensin converting enzyme inhibitors (ACEI), such as ramipril, increased the adiponectin levels [15, 16]. On the other hand, treatment with thiazide and thiazide-like diuretics (indapamide, chlorothiazide) reduced adiponectin levels [17], possibly explaining the increased risk of the development of type 2 diabetes mellitus in patients treated with these medications. Lifestyle modifications and reduction in body weight in obese patients increased their adiponectin levels [18]. In addition, lower adiponectin levels were observed in active smokers as compared to non-smokers [19]. Considering the potential for regulation of adiponectin levels by pharmacotherapeutic and non-pharmacotherapeutic methods, further studies on the role of adiponectin are warranted as they may contribute to the greater efficacy of the prevention of cardiovascular diseases in the future.

Material and methods

Study population

The study was conducted in a population of 145 residents of Zachodniopomorskie Voivodeship, aged 18–50 and diagnosed with essential arterial hyper-

tension, who were hospitalized at the Department of Hypertensiology and Internal Medicine in years 2013–2014. Secondary causes of arterial hypertension were ruled out by routine physical, biochemical, and radiological examinations. The exclusion criteria were: coronary heart disease, heart failure, kidney or liver disease, pharmacological treatment, including medication known to affect the metabolic profile. Next, the International Diabetes Federation (IDF) 2005 criteria were used to divide both study groups into subgroups of patients with (HTMS) or without metabolic syndrome (HTC).

Central obesity defined as waist circumference of ≥ 80 cm in females and ≥ 94 cm in males as well as at least two of the following additional criteria were required to qualify to the metabolic syndrome subgroups:

— increased triglyceride levels [≥ 150 mg/dL (1.7 mmol/L)],
— reduced HDL cholesterol levels [< 50 mg/dL (1.3 mmol/L) in females, < 40 mg/dL (1.0 mmol) in males],
— systolic blood pressure of ≥ 130 mmHg and/or diastolic blood pressure of ≥ 85 mmHg,
— fasting glucose level of ≥ 100 mg/dL (5.6 mmol/l).

The remaining patients who did not meet the aforementioned criteria were classified as non-metabolic syndrome patients.

The study protocol was approved by the Pomeranian Medical University Ethics Committee. All the participants gave their written consent.

Study protocol

All the participants were interviewed to obtain medical history. Physical examination were performed including measurements of height, body weight, waist circumference (WC). Fasting blood samples were obtained between 07:00 and 08:30 hours for laboratory investigations including determination of glucose, insulin, total cholesterol, low-density (LDL) cholesterol, high-density (HDL) cholesterol, triglycerides, uric acid, and adiponectin levels. All measurements were performed using commercially available assays. Adiponectin levels were measured using the sandwich enzyme-linked immunosorbent assay (ELISA). The intra-assay and inter-assay CVs for adiponectin were < 5.4% and < 5%. HOMA-IR index was calculated from fasting glucose and insulin levels. Urinary albumin-to-creatinine ratio (ACR) was measured in a spot early-morning urine sample. ACR was calculated by dividing albumin concentration in milligrams by creatinine concentration in grams. In all patients a 24-hour ambulatory blood pressure monitoring (ABPM) protocol was performed using Spacelabs Healthcare 90207 and 90217 monitors. Blood pressure was measured every 20 min during the daytime (from 06.00 to 22.00) and every 30 min at night-time (22.00–06.00). The non-dipping hypertension was diagnosed if the declines in blood pressure at night were below 10% of the daytime values.

Statistical analysis

All statistical calculations were carried out using StatSoft. Inc. (2014). STATISTICA (data analysis software system) version 12.0. The Shapiro-Wilk's test was used to check the data for normality. The quantitative variables were expressed as the arithmetic mean ± standard deviation (SD). While the qualitative variables have been shown, whereby using frequencies and percentages. The between — group differences were analyzed by the Student's T-Distribution test or the non-parametric Mann-Whitney U test. The Chi-square test for independence with Yates' correction was used for qualitative variables. The area under the receiver operating characteristic (ROC) curve (AUCs) of adiponectin levels was used to assess the diagnosis value of MS. To determine the optimal cut-off level of adiponectin for predicting metabolic syndrome, the Youden index was calculated. P-value ≤ 0.05 was considered as statistical significance.

Results

The baseline characteristics of the subjects with are shown in Table I and Table II. Based on IDF criteria, 73 subjects (50.34%) had metabolic syndrome (HTMS). Patients with MS were older (p = 0.021). In comparison to patients without metabolic syndrome, subjects with MS had significantly higher levels of fasting glucose, LDL-cholesterol, uric acid, triglycerides, nocturnal systolic blood pressure, BMI and WC, but lower HDL-cholesterol. As summarized in Table III, group HTZM had significantly higher levels of insulin (16.5 ± 14.2 µlU/mL vs. 9.7 ± 5.6 µlU/mL, p = 0.0001) and HOMA-IR (3.8 ± 3.9 vs. 2.0 ± 1.2, p = 0.0001) in comparison to HTC group. The plasma levels of adiponectin were significantly lower in the subjects with hypertension and metabolic syndrome as compared with those without the MS (4.2 ± 3.1 µg/dL vs. 6.7 ±6.5 µg/dL, p = 0.0026). The correlation between adiponectin level and metabolic parameters are shown in Table IV. In all patients with hypertension, adiponectin negatively correlated with insulin (r = –0.20; p = 0.014), HOMA-IR (r = –0.24; p = 0.003), triglycerides

Table I. Baseline characteristics of the study population

	HTMS (n = 73)	HTC (n = 72)	All (n = 145)	p-value
Women Men	24 (32.9%) 49 (67.1%)	33 (45.8%) 39 (54.2%)	57 (39.3%) 88 (60.7%)	0.1103
Age [years]	31.9 ± 6.9			**0.0210**
Body Mass Index [kg/m^2]	33.3 ± 6.8	25.3 ± 3.5	29.3 ± 6.7	**0.0001**
Waist circumference [cm]	106.5 ± 14.4	84.3 ± 8.5	95.5 ± 16.2	**0.0001**
Uric acid [mg/dL]	6.4 ± 1.4	5.1 ± 1.1	5.8 ± 1.4	**0.0001**
Glucose [mg/dL]	90.8 ± 10.1	84.6 ± 7.4	87.7 ± 9.4	**0.0004**
Total cholesterol [mg/dL]	193.7 ± 39.9	182.8 ± 37.4	188.3 ± 39.0	0.0876
LDL-cholesterol [mg/dL]	129.8 ± 37.8	114.3 ± 35.5	122.1 ± 37.4	**0.0074**
HDL-cholesterol [mg/dL]	44.3 ± 12.5	57.5 ± 12.9	50.8 ± 14.2	**0.0001**
Triglycerides [mg/dL]	167.0 ± 68.2	104.1 ± 33.7	135.8 ± 62.3	**0.0001**
Creatinine [mg/dL]	0.89 ± 0.16	0.86 ± 0.15	0.87 ± 0.15	0.3186
GFR [ml/min]	99.7 ± 15.9	100.9 ± 15.0	100.3 ± 15.4	0.6419
ACR [mg/g]	22.52 ± 76.51	6.49 ± 11.05	14.56 ± 55.24	0.5179

Table II. 24-hour ambulatory blood pressure monitoring parameters in study population

	HTMS (n = 73)	HTC (n = 72)	All (n = 145)	p-value
SBPd [mm Hg]	135.0 ± 14.2	132.7 ± 14.2	133.9 ± 14.2	0.3487
DBPd [mm Hg]	81.3 ± 10.4	80.8 ± 9.5	81.1 ± 10.0	0.9968
MAPd[mm Hg]	97.3 ± 12.2	96.5 ± 11.7	96.9 ± 11.9	0.8930
SBPn [mm Hg]	123.4 ± 16.3	117.6 ± 13.1	120.5 ± 15.0	**0.0196**
DBPn [mm Hg]	72.2 ± 12.6	69.1 ± 8.8	70.7 ± 10.9	0.4153
MAPn[mm Hg]	88.7 ± 14.4	84.7 ± 11.1	86.7 ± 13.0	0.2442
HR [f/min]	68.8 ± 8.8	67.9 ± 8.8	68.4 ± 8.8	0.5364
Dippers	58.9% (43)	72.2% (52)	65.5% (95)	0.0916
Non-dippers	41.1% (30)	27.8% (20)	34.5% (50)	

SBPd — daytime systolic blood pressure; DBPd — daytime diastolic blood pressure, MAPd — daytime mean arterial pressure, SBPn — nocturnal systolic blood pressure; DBPn — nocturnal diastolic blood pressure; MAPn — nocturnal mean arterial pressure; HR — 24-hour mean heart rate

Table III. Adiponectin, insulin and HOMA-IR in study population

	HTMS (n = 73)	HTC (n = 72)	All (n = 145)	p-value
Insulin [μIU/mL]	16.5 ± 14.2	9.7 ± 5.6	2.9 ± 3.0	**0.0001**
HOMA-IR	3.8 ± 3.9	2.0 ± 1.2	2.9 ± 3.0	**0.0001**
Adiponectin [μg/mL]	4.2 ± 3.1	6.7 ± 6.5	5.5 ± 5.3	**0.0026**

(r = –0.19; p = 0.025), and uric acid (r = –0.25; p = 0.003) and positively with HDL-cholesterol (r = 0.33; p = 0.0001). In both studied groups, no significant correlations were found between adiponectin level and 24 hour blood pressure profile parameters (Table V). In all subjects with hypertension, adiponectin showed no significant correlation with selected markers of subclinical hypertension complications (Table VI). The area under the ROC curve (AUCs) for adiponectin levels was 0.65 [95% CI 0.56–0.74]. The cut-off value of adiponectin for predicting metabolic syndrome in patients with hypertension was 4.1 µg/ml with a sensitivity of 67.1% and specificity of 56.9% (Table VII, Fig. 1).

Discussion

Adiponectin is a protein produced by the adipose tissue. It plays a metabolic role, affects insulin resis-

Table IV. Correlation between adiponectin and 24-hour ambulatory blood pressure monitoring parameters in hypertensive patients with and without metabolic syndrome

		HTMS (n = 73)	HTC (n = 72)	All (n = 145)
Adiponectin [μg/mL]	SBPd [mm Hg]			
	r	–0.03	–0.08	–0.07
	p	0.82	0.51	0.44
	DBPd [mm Hg]			
	r	0.07	–0.13	–0.04
	p	0.53	0.28	0.65
	MAPd [mm Hg]			
	r	0.02	–0.16	–0.07
	p	0.85	0.17	0.39
	SBPn [mm Hg]			
	r	–0.06	0.02	–0.07
	p	0.59	0.86	0.39
	DBPn [mm Hg]			
	r	0.06	0.01	0.00
	p	0.64	0.93	0.98
	MAPn [mm Hg]			
	r	–0.02	0.00	–0.05
	p	0.86	0.97	0.53
	HR [f/min]			
	r	0.11	–0.09	–0.02
	p	0.35	0.43	0.80

SBPd — daytime systolic blood pressure; DBPd — daytime diastolic blood pressure, MAPd — daytime mean arterial pressure, SBPn — nocturnal systolic blood pressure; DBPn — nocturnal diastolic blood pressure; MAPn — nocturnal mean arterial pressure; HR — 24-hour mean heart rate
r — Spearman's rank correlation coefficient

tance, exerts anti-inflammatory action and prevents the formation of atherosclerotic plaque. Serum levels of adiponectin are relatively high and the molecule itself is stable and characterized by a relatively long half-life; therefore, it may act as a potential biomarker of metabolic disorders. Adiponectin levels were significantly lower in the study group of patients with arterial hypertension and concomitant metabolic syndrome. The corresponding mean values were 4.2 μg/mL in patients with metabolic syndrome and 6.7 μg/mL in patients without metabolic syndrome. The results of my study are in line with data available in the literature; of note, however, are the relatively low levels of adiponectin in both groups. Garg et al. studied adiponectin concentrations in a group of patients aged 30 to 50. Patients with metabolic syndrome were identified according to the IDF criteria. The mean adiponectin concentration in patients with MS (4.01 μg/mL) was significantly lower than that in the control group (8.7 μg/mL). Adiponectin levels dropped with the increased in the number of metabolic syndrome components. No gender-related differences were observed in the patient population. ROC curve was used in the study to determine adiponectin cut-off level in relation to metabolic syndrome. The determined value was 6.7 μg/mL and corresponded to marker sensitivity and specificity of 83% and 86%, respectively [20]. As determined in my own studies, adiponectin cut-off level as used for differentiation of AH patients in terms of the presence vs. the absence of concomitant MS (Youden's index) is 4.1 μg/mL. The area under the ROC curve was statistically significant. The sensitivity of the marker was 67.1% while its specificity was 56.9%. Hata et al. used the AFT model to determine adiponectin cut-off levels for stratification of patients into MS or non-MS groups in a population of Japanese subjects. The obtained cut-off value was 6.2 μg/mL [21]. Determination of cut-off levels for use in clinical practice requires large-population studies and consideration to ethnic differences. As known from the available literature, adiponectin levels are negatively correlated with BMI, waist circumference, insulin resistance, body

Table V. Correlations between adiponectin level and metabolic parameters in hypertensive patients with and without metabolic syndrome

		HTMS (n = 73)	HTC (n = 72)	All (n = 145)
Adiponectin [μg/mL]	Glucose [mg/dL]			
	r	0.02	–0.07	–0.09
	p	0.85	0.55	0.29
	Insulin [μIU/mL]			
	r	–0.10	–0.10	**–0.20**
	p	0.38	0.42	**0.014**
	HOMA-IR			
	r	–0.14	–0.13	**–0.24**
	p	0.23	0.27	**0.003**
	Total cholesterol [mg/dL]			
	r	0.07	0.09	0.04
	p	0.55	0.47	0.63
	LDL-cholesterol [mg/dL]			
	r	–0.06	–0.01	–0.10
	p	0.59	0.91	0.26
	HDL-cholesterol [mg/dL]			
	r	0.23	**0.25**	**0.33**
	p	0.05	**0.036**	**0.0001**
	Triglycerides [mg/dL]			
	r	–0.07	–0.09	**–0.19**
	p	0.57	0.44	**0.025**
	Uric acid [mg/dL]			
	r	**–0.34**	0.05	**–0.25**
	p	**0.0028**	0.67	**0.003**

r — Spearman's rank correlation coefficient

Table VI. Correlation between adiponectin level and renal complications in hypertensive patients with and without metabolic syndrome

	HTMS (n = 73)	HTC (n = 72)	All (n = 145)
ACR [mg/g]			
r	–0.07	–0.20	–0.13
p-value	0.5331	0.0851	0.1078
Creatinine [mg/dL]			
r	–0.13	0.07	–0.04
p-value	0.2768	0.5431	0.6217
GFR [ml/min]			
r	–0.04	–0.20	–0.10
p-value	0.7303	0.0977	0.2144

r — Spearman's rank correlation coefficient

weight, and triglyceride levels while being positively correlated with HDL cholesterol levels [20]. In my, study, adiponectin concentrations measured in all arterial hypertension patients was negatively correlated with waist circumference, BMI, fasting blood glucose levels, insulin resistance (HOMA-IR), triglycerides, and uric acid levels while being positively correlated with HDL cholesterol levels. This may prove that

Table VII. AUC value and cut-off value for adiponectin

	Study Group
Adiponectin	
AUC	0.65
95% CI	[0.56; 0.74]
P-value	0.0015
Youden Index	4.1
Sensitivity	67.1%
Specifity	56.9%

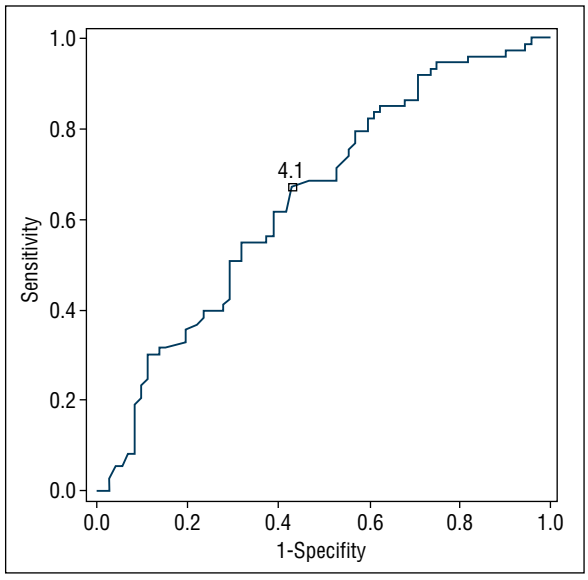

Figure 1. ROC curve of adiponectin levels for prediction of metabolic syndrome in patients with hypertension

reduced adiponectin levels may negatively impact the metabolic profiles in both groups regardless of metabolic syndrome status. Adiponectin has proven antidiabetic and antiatherosclerotic activity. Also postulated in the available literature reports is the impact of hypoadiponectinemia on blood pressure values and profiles as well as on the pathogenesis of essential arterial hypertension [22, 23]. The mechanisms of hypotensive activity of adiponectin are conformed in experimental studies. Evidence is available for adiponectin's impact on the activity of the sympathetic nervous system [13] and on the release of NO from vascular endothelial cells [14, 24]. Some clinical studies demonstrated correlation between low adiponectin levels and complications of arterial hypertension such as myocardial hypertrophy [8], ocular fundus lesions [9], and albuminuria [10]. Particularly interesting were studies confirming lower adiponectin levels in the group of patients with higher risk of essential arterial hypertension, which suggests that adiponectin is involved in the pathogenesis of arterial hypertension [12]. In the study, any significant correlations between adiponectin concentrations, non-dipping circadian blood pressure profiles, and renal complications such as microalbuminuria, creatinine levels, or GFR values were observed. Of note is the fact that all patients in my study had been diagnosed with arterial hypertension and the study groups were well-selected in terms of concomitant metabolic syndrome status. The absence of any correlation may be due to the fact that the determinations pertained to total concentration of adiponectin rather than to the concentration of individual adiponectin fractions. On the basis of some studies, it was postulated that high molecular weight (HMW) adiponectin multimers are characterized by particularly strong antiatherosclerotic properties as compared to total adiponectin [25]. Baumann et al. demonstrated lower HMW adiponectin levels in patients with arterial hypertension compared to healthy controls [26]. Changes in adiponectin levels may be due to the use of hypotensive or hypolipidemic drugs as well as to non-pharmacological management. Of note are the inhibitory effects of the sympathetic nervous system on adiponectin secretion [27–29], the increase in adiponectin levels as the result of moderate physical effort [30], and low adiponectin levels in active smokers [19]. These non-pharmacological factors were not taken into account in this study. On the other hand, reports consistent with the results of my study, i.e. showing no difference between adiponectin levels in patients with arterial hypertension and normotensive control subjects [31]. Different results being obtained in the studies of adiponectin's impact on blood pressure values may indirectly point to the complexity of the mechanisms behind the pathophysiology of essential arterial hypertension.

Despite the limitations of this study, it appears that low adiponectin levels should be taken into account as a potential non-classical biomarker of metabolic complications in patients with arterial hypertension, not only with concomitant metabolic syndrome. Determination of specific cut-off values requires further prospective clinical trials being carried out in a large population of patients.

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