ORIGINAL ARTICLE

Effects of antihypertensive treatment on plasma apelin, resistin, and visfatin concentrations

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KEY WORDS

adipokines, antihypertensive drugs, fat tissue, hypertension, obesity

ABSTRACT

INTRODUCTION Adipose tissue has been recently recognized as an endocrine organ secreting a number of adipokines contributing to the development of atherosclerosis, hypertension, chronic kidney disease, endothelial dysfunction, insulin resistance, and vascular remodeling.

OBJECTIVES The aim of this study was to determine whether treatment with a β-blocker, calcium antagonist, thiazide-like diuretic, or angiotensin II type 1 receptor blocker influences plasma concentrations of apelin, resistin, and visfatin in obese hypertensive patients.

PATIENTS AND METHODS The study included 84 obese patients with essential hypertension. One control group included obese subjects without hypertension, and the other, lean subjects without hypertension. Patients with hypertension were randomized into 4 groups treated for 6 weeks with bisoprolol, amlodipine, indapamide, or candesartan, respectively.

RESULTS Mean daily plasma apelin concentrations in patients treated with amlodipine was significantly higher than the baseline values, whereas the difference in plasma apelin concentrations in other treatment groups was not significant. Mean daily plasma resistin concentrations were significantly lower after 6-week treatment with amlodipine, bisoprolol, or indapamide compared with the baseline values. In patients treated with candesartan, no significant differences in resistin concentrations were shown. After 6-week treatment with bisoprolol, mean daily plasma concentrations of visfatin were significantly lower compared with the baseline values. Treatment with amlodipine, candesartan, or indapamide did not significantly affect plasma visfatin levels.

CONCLUSIONS Antihypertensive treatment exerts significant and varied effects on adipokine secretion in obese hypertensive patients. Changes in apelin secretion, caused by the use of different antihypertensive drugs, may protect the cardiovascular system and kidneys. The involvement of adipokines in mechanisms of diverse protective effects of antihypertensive drugs, independently of the effect on blood pressure, requires further research.

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INTRODUCTION In recent years adipose tissue has been recognized as a dynamic endocrine organ secreting a number of hormones, cytokines, and growth factors (called adipokines) that contribute to the development of hypertension, atherosclerosis, chronic kidney disease, endothelial dysfunction, insulin resistance, and vascular remodeling. Several adipokines are preferentially expressed in visceral adipose tissue, and the secretion of proinflammatory adipokines is elevated with increasing adiposity.[1,2] In contrast, secretion of some adipokines with cardio- and nephroprotective properties is significantly reduced in patients with essential hypertension.[3]

It is suspected that a recently discovered hormone, apelin, is involved in the physiology and pathology of water balance as well as cardiovascular and metabolic disorders.[4] The cardiovascular system appears to be the primary target of apelin,[5] and changes in the expression of apelin

and the apelin receptor (APJ) have been found in patients with cardiac dysfunction.[6] Immunoactivity of apelin and its receptor have been also found in the brain, including hypothalamus.[7] This is consistent with a potential role of apelin in the control of pituitary hormone release,[8] body fluid equilibrium, and drinking behavior.[9] It has been shown that apelin expression is increased by tumor necrosis factor α (TNF-α)[10] and hypoxia-inducible factor 1-α[11] (HIF-1α) and decreased by aldosterone.[12]

A modest, although unclear, role in the control of food intake has been described for apelin, and activation of the APJ has been shown to exert a stimulatory effect on gastric and endothelial cell proliferation.[13] Further studies on the physiology of apelin are needed to provide new insights into glucose homeostasis as well as new therapies for cardiovascular complications.

Plasma levels of another adipokine, resistin, have been associated with markers of inflammation such as TNF-α or interleukin 6. Moreover, resistin has been shown in humans to be a predictive factor for coronary atherosclerosis, independent of the C-reactive protein (CRP) level.[14-16] Resistin has been shown to promote activation of endothelial cells by releasing endothelin. It induces also the expression of vascular cell adhesion molecules as well as vascular endothelial growth factor receptors.[17,18] Furthermore, it stimulates proliferation of the smooth muscle cells.[19]

In contrast to animal models, immunocompetent cells appear to be the major source of resistin in humans, rather than adipocytes,[20] and thus the presence of resistin in human adipose tissue is mostly due to its production by the nonfat stroma-vascular fraction of adipose tissue, completing a vicious circle of inflammation related to obesity.

Visfatin has the properties of a cytokine,[21] hormone,[22] and enzyme[23] with a potential influence on cellular metabolism.[24] Additionally, the influence of visfatin on the immune system has been postulated—visfatin seems to act as a growth-enhancing and colony-enhancing factor for the pre-B-cell.[25] The role of visfatin in the pathogenesis of insulin resistance is increasingly being discovered.[21]

Current guidelines equally recommend using β-blockers, calcium antagonists, thiazide-like diuretics, or renin–angiotensin–aldosterone system blockers (angiotensin II type 1 receptor) blockers [ARBs] or angiotensin-converting enzyme inhibitors [ACEIs]) as the first-line therapy in patients with hypertension.[26] Some groups of patients may benefit from selecting a specific class of medication (eg, a β-blocker in patients with ischemic heart disease or ACEI/ARB in diabetics and patients with proteinuria). It is also known that treatment with thiazide diuretics is associated with the development of diabetes, lipid disturbances, or gout. It is also well known that, at least in the first months of treatment, glucose intolerance or dyslipidemia may occur after treatment with some β-blockers. It has also been demonstrated that some ARBs may reduce serum uric acid concentrations and increase plasma adiponectin levels (the latter is also true for some ACEIs). This evidence may strongly suggest that a number of antihypertensive drugs may exert their activity also on several metabolic processes beyond their blood pressure-lowering effects. Still, more data is needed before such specific recommendations can be established.

Therefore, the aim of this study was to determine changes in plasma concentrations of selected hormones produced by adipose tissue, such as apelin, resistin, and visfatin, in obese patients with essential hypertension treated with a β-blocker, calcium antagonist, thiazide-like diuretic, or an ARB.

PATIENTS AND METHODS

The study was performed in 84 obese patients with essential hypertension (24 women, 60 men; age, 44.6 ±9.6 years; body mass index [BMI], 34.4 ±4.5 kg/m^2), in 22 obese subjects without hypertension (6 women, 16 men; age, 42.0 ±13.2 years; BMI, 33.6 ±4.0 kg/m^2), and a group of lean subjects with normal blood pressure (8 women, 13 men; age, 44.0 ±8.2 years; BMI, 22.8 ±1.5 kg/m^2). The study protocol was approved by the Ethics Committee at the Medical University of Silesia in Katowice, Poland.

Office blood pressure was measured using mercury sphygnomanometer with 2-mmHg accuracy, according to the standard conditions. The diagnosis of essential hypertension was established after excluding all secondary forms of hypertension by a clinical, biochemical, ultrasound, and radiological examination. In all patients, hypertension was diagnosed de novo, and none of the patients had a history of antihypertensive treatment. Blood pressure at baseline did not exceed 180/110 mmHg.

The content of adipose tissue was assessed by dual energy X-ray absorptiometry (Lunar Corporation, Madison, Wisconsin, United States). Anthropometric measurements were done in all participants and included weight, height, and waist and hip circumferences.

Patients with diabetes mellitus, autoimmune diseases, malignancy, renal insufficiency (estimated glomerular filtration rate <60 ml/min/1.72 m^2 according to the Modification of Diet in Renal Disease formula), liver cirrhosis, acute coronary syndromes, heart failure (New York Heart Association classes II–IV), pregnant or intending to get pregnant, or previously treated for hypertension were excluded from this study.

In all patients blood samples were obtained in a fasting state at 7 AM for the assessment of serum levels of glucose, cholesterol, triglycerides, thyroid-stimulating hormone (TSH), ferritin, CRP, insulin, and leptin, as well as plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), apelin, resistin, and visfatin concentrations, and additionally at 11 AM, 3 PM, 7 PM,

12 AM, and 4 AM for the assessment of plasma apelin, resistin, and visfatin levels.

There was no significant difference in plasma apelin, resistin, and visfatin concentrations at the specified time points, and the average of all measurements was used in further analyses as mean daily values.

Patients with hypertension were randomized into 4 groups treated with one of the following drugs as a monotherapy: 1) selective β-blocker, bisoprolol (2.5–10 mg/d [Concor, Merck]; n = 21; 7 women/14 men); or 2) long-acting calcium antagonist, amlodipine (2.5–10 mg/d [Vilpin, Pliva]; n = 21; 6 women/15 men); or thiazide-like diuretic, indapamide (1.5–3.0 mg/d [Diuresin SR, Polfarmex]; n = 21; 6 women/15 men); or 4) AT1 receptor blocker, candesartan (4–32 mg/d [Atacand, Astra-Zeneca]; n = 21; 5 women/16 men).

After 6 weeks of monotherapy, all the above biochemical and hormonal analyses were repeated. Plasma NT-proBNP and serum TSH and ferritin concentrations were assessed by a microparticle enzyme immunoassay; serum insulin concentrations, by an enzyme-linked immunosorbent assay (ELISA); and CRP concentrations, by the turbidimetric method. Plasma apelin, resistin, and visfatin concentrations were measured using commercially available ELISA kits (all Phenix Peptides, Karlsruhe, Germany). Serum leptin concentrations were measured by a radioimmunoassay (Linco Research Inc., St. Charles, Missouri, United States). Other parameters were estimated by routine laboratory methods. To inhibit the activity of proteinases, aprotinin (0.6 TIU/ml of blood) was added. Serum samples were stored at –40°C until analysis.

The homeostatic model assessment insulin resistance (HOMA-IR) index as a measure of insulin sensitivity was calculated.[27]

Statistical analysis The Shapiro–Wilk test was used for testing normality distribution of variables. For normally distributed variables, the groups were compared by the analysis of variance with a post hoc analysis (LSD test). For variables that were not normally distributed in the population, the Kruskal–Wallis analysis of ranks and then the Mann–Whitney test were used. Simple linear correlation (Pearson *r*) for seleceted variables was also performed. The results were expressed as mean ± SD as indicated. Differences were considered statistically significant at a *P* value of less than 0.05. All statistical analyses were performed using the Statistica 5.0 software (StatSoft Inc., Tulsa, Oklahoma, United States).

RESULTS There were no differences in the mean age, serum concentrations of total cholesterol, creatinine, TSH, and NT-proBNP between hypertensive patients and participants (obese and lean) with normal blood pressure.

Compared with lean subjects without hypertension, obese subjects (with or without hypertension) were characterized by significantly higher plasma concentrations of uric acid, leptin, CRP, glucose, insulin, and ferritin (TABLE 1).

After 6 weeks of antihypertensive treatment, a significantly lower blood pressure was noted in all obese hypertensive patients (TABLE 2). The BMI and serum concentration of creatinine, cholesterol, triglycerides, urea, leptin, CRP, and ferritin did not change significantly during the 6-week antihypertensive treatment. Plasma NT-proBNP levels were significantly higher after 6 weeks of treatment with bisoprolol in comparison with the baseline values (62.5 ±41.6 pg/ml vs 43.8 ±40.8 pg/ml respectively; FIGURE 1), and HOMA-IR values were significantly higher in patients treated with indapamide in comparison with the baseline values (3.93 ±2.23 vs 3.22 ±1.65, respectively; FIGURE 2).

The mean daily plasma apelin concentration did not differ significantly between the groups, although a tendency toward lower levels was observed in hypertensive patients.

No significant correlation was found between mean daily plasma apelin concentrations and plasma NT-proBNP, serum CRP, and serum insulin levels as well as the HOMA-IR index.

The mean daily plasma apelin concentration was significantly higher ($P < 0.05$) after 6 weeks of antihypertensive treatment in all obese hypertensive patients (534 ±98 pg/ml vs. 496 ±150 pg/ml at baseline). In the treatment subgroups, mean daily plasma apelin concentrations in patients treated with amlodipine was significantly higher ($P < 0.05$) than the respective baseline values (538 ±84 pg/ml vs 444 ±163 pg/ml), while the difference in other treatment groups was not significant (FIGURE 3). There was no significant correlation between the change in mean daily plasma apelin concentration and change in blood pressure after 6 weeks of antihypertensive treatment. The mean plasma resistin concentration did not differ significantly between the groups. No significant correlation was found between mean daily plasma resistin concentrations and BMI, body fat percentage, insulin concentration, and HOMA-IR.

After 6 weeks of antihypertensive treatment, mean daily plasma resistin concentrations were significantly lower than the respective pretreatment values in patients treated with amlodipine (2.01 ±0.13 ng/ml vs 2.39 ±0.45 ng/ml, $P < 0,05$), bisoprolol (1.88 ±0.48 ng/ml vs 2.36 ±0.81 ng/ml, $P < 0.001$), or indapamide (2.02 ±0.86 ng/ml vs 2.89 ±0.71 ng/ml, $P < 0.05$). The therapy with candesartan did not significantly affect plasma resistin concentrations (FIGURE 4).

The mean daily plasma visfatin concentration was higher both in obese subjects with normal blood pressure (15.3 ±4.2 ng/ml) and obese patients with hypertension (12.3 ±3.9 ng/ml), compared with lean subjects without hypertension (9.6 ±2.6 ng/ml, $P < 0.001$).

A significant positive correlation ($P < 0.05$) was found between mean daily plasma visfatin concentrations and BMI, WHR, total fat mass, trunk fat mass, serum insulin concentration, and HOMA-IR index. A significant negative

TABLE 1 Baseline characteristics of the study groups

Parameter	Hypertensive obese (n = 84)	Normotensive obese (n = 22)	Normotensive lean (n = 21)	*P* value (ANOVA)
age, y	44.6 ±9.6	42.0 ±13.2	44.0 ±8.2	NS
male/female	60/24	16/6	13/8	–
BMI, kg/m^2	34.4 ±4.5	33.6 ±4.0	22.8 ±1.5[a,b]	<0.001
SBP, mmHg	152 ±10	122 ±7[a]	117 ±9[a]	<0.001
DBP, mmHg	94 ±5	79 ±4[a]	77 ±5[a]	<0.001
total fat mass, kg	37.2 ±10.8	37.9 ±11.1	15.8 ±4.3[a,b]	<0.001
trunk fat mass, kg	21.2 ±6.3	21.1 ±6.1	7.7 ±2.5[a,b]	<0.001
total lean mass, kg	60.9 ±11.8	63.3 ±11.6	49.2 ±12.1[a,b]	<0.001
WHR	0.92 ±0.06	0.93 ±0.04	0.84 ±0.05[a,b]	<0.001
serum creatinine, µmol/l	84.0 ±15.9	81.3 ±11.5	83.1 ±13.3	NS
eGFR (MDRD), ml/min/1.72 m^2	82 ±16	85 ±14	80 ±12	NS
serum uric acid, µmol/l	315 ±59	327 ±83	244 ±71[a,b]	0.005
total cholesterol, mmol/l	5.5 ±1.1	5.5 ±1.0	5.3 ±0.9	NS
HDL cholesterol, mmol/l	1.3 ±0.3	1.3 ±0.2	1.4 ±0.2	NS
triglycerides, mmol/l	1.8 ±1.0	1.7 ±1.0	1.4 ±0.6	NS
serum glucose, mmol/l	5.8 ±0.7	5.8 ±0.4	5.3 ±0.4[a,b]	<0.005
serum insulin, µU/ml	12.4 ±6.2	12.7 ±5.1	5.1 ±1.6[a,b]	<0.001
HOMA-IR	3.25 ±1.80	3.30 ±1.40	1.20 ±0.42[a,b]	<0.001
TSH, µIU/ml	2.35 ±1.57	2.67 ±1.23	1.82 ±0.64[b]	<0.05
CRP, mg/dl	0.36 ±0.30	0.25 ±0.23	0.05 ±0.04[a,b]	<0.001
ferritin, ng/ml	147 ±101	172 ±131	87 ±53[a,b]	<0.01
leptin, pg/ml	18.8 ±16.5	16.4 ±7.5	5.5 ±3.8[a,b]	<0.001
apelin, pg/ml	508 ±160	536 ±157	549 ±146	NS
resistin, ng/ml	2.31 ±0.88	2.37 ±0.54	2.32 ±0.66	NS
visfatin, ng/ml	12.4 ±5.1	14.9 ±6.5[a]	10.3 ±3.7[b]	<0.05
NT-proBNP, pg/ml	46.5 ±41.0	46.8 ±35.6	52.9 ±33.0	NS

Data are presented as mean ± standard deviation.

a *P* <0.05 vs obese hypertensive patients; **b** *P* <0.05 vs obese normotensive patients

Abbreviations: BMI, body mass index; CRP, C-reactive protein; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment insulin resistance; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SBP, systolic blood pressure; TSH, thyroid-stimulating hormone; WHR, waist-to-hip ratio

TABLE 2 Changes of baseline parameters in obese hypertensive patients after treatment

Parameter	Bisoprolol		Amlodipine		Indapamide		Candesartan	
	baseline	after 6-week treatment	baseline	after 6-week treatment	baseline	after 6-week treatment	baseline	after 6-week treatment
BMI, kg/m^2	33.7 ±3.4	33.6 ±3.6	33.6 ±3.2	33.1 ±4.3	35.3 ±4.6	35.2 ±4.5	35.2 ±6.2	35.0 ±6.0
SBP, mmHg	152 ±10	120 ±7[b]	156 ±10	124 ±8[b]	148 ±9	119 ±8[b]	152 ±9	122 ±15[b]
DBP, mmHg	93 ±5	75 ±5[b]	95 ±6	78 ±6[b]	92 ±3	74 ±6[b]	95 ±5	75 ±5[b]
glucose, mmol/l	5.9 ±0.5	5.5 ±0.7[a]	5.8 ±0.7	6.0 ±0.6	5.9 ±0.7	6.0 ±0.4	5.9 ±0.8	5.9 ±0.7
CRP, mg/dl	0.35 ±0.29	0.30 ±0.23	0.43 ±0.33	0.41 ±0.27	0.30 ±0.28	0.35 ±0.22	0.36 ±0.32	0.31 ±0.30

Data are presented as mean ± standard deviation.

a *P* <0.05 vs baseline, **b** *P* <0.001 vs baseline

Abbreviations: see **TABLE 1**

correlation was found between mean daily plasma visfatin concentrations and plasma NT-proBNP concentrations in all study groups (**FIGURE 5**).

The mean daily plasma concentration of visfatin in patients treated with bisoprolol was significantly lower than the respective baseline values (10.7 ±3.7 ng/ml vs 13.6 ±3.9 ng/ml, *P* <0.01).

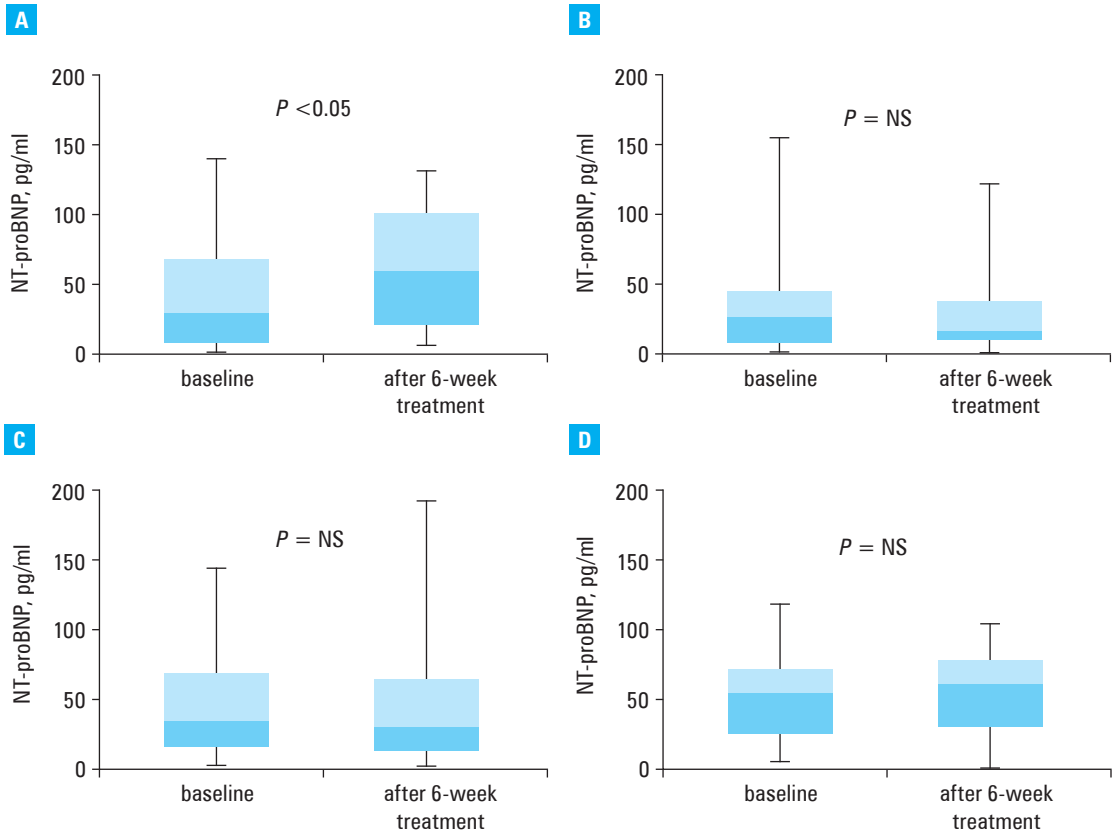

FIGURE 1 Serum N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations before and after 6 weeks of antihypertensive treatment with bisoprolol (**A**), amlodipine (**B**), indapamide (**C**), or candesartan (**D**)

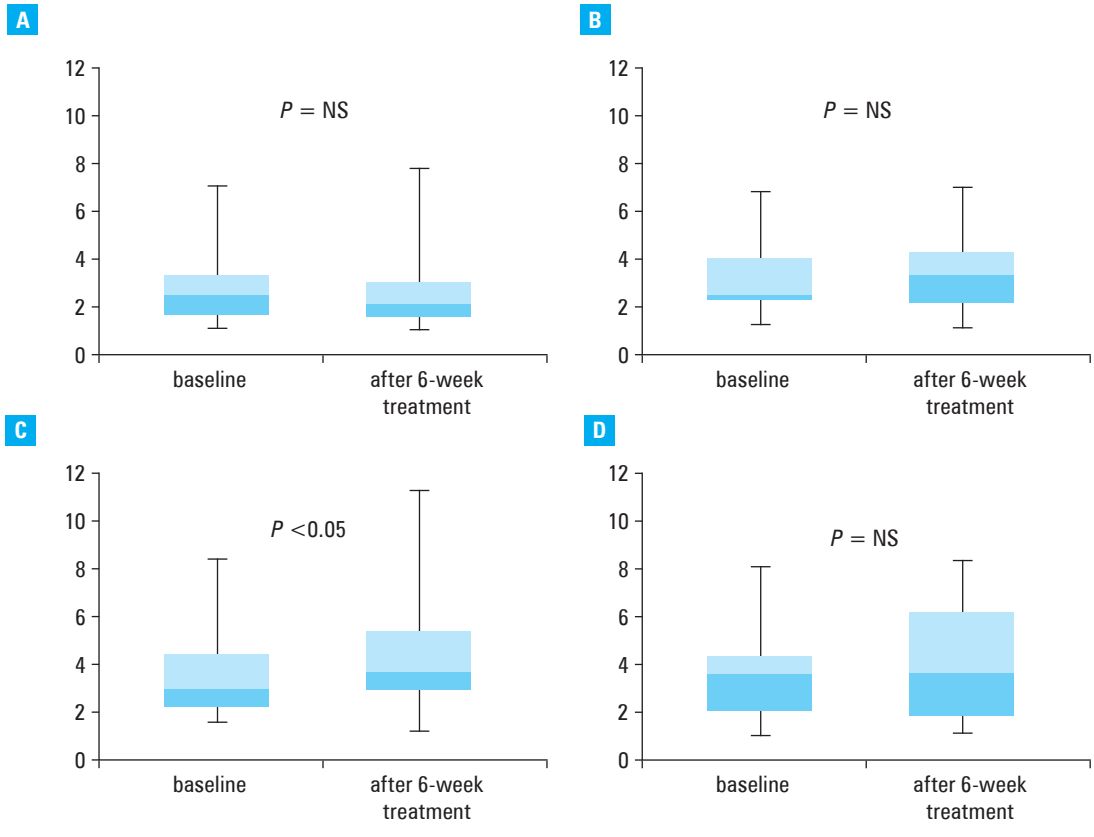

FIGURE 2 HOMA-IR index before and after 6 weeks of antihypertensive treatment with bisoprolol (**A**), amlodipine (**B**), indapamide (**C**), or candesartan (**D**)

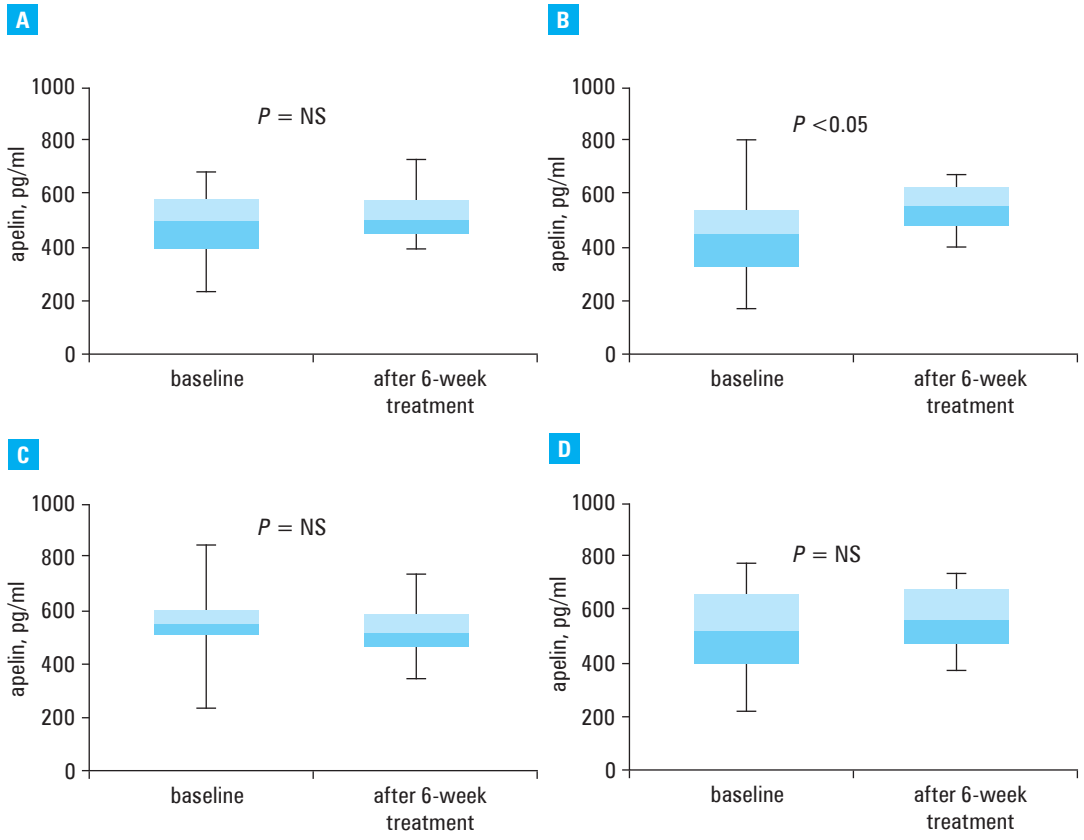

FIGURE 3 Serum apelin concentrations before and after 6 weeks of antihypertensive treatment with bisoprolol (**A**), amlodipine (**B**), indapamide (**C**), or candesartan (**D**)

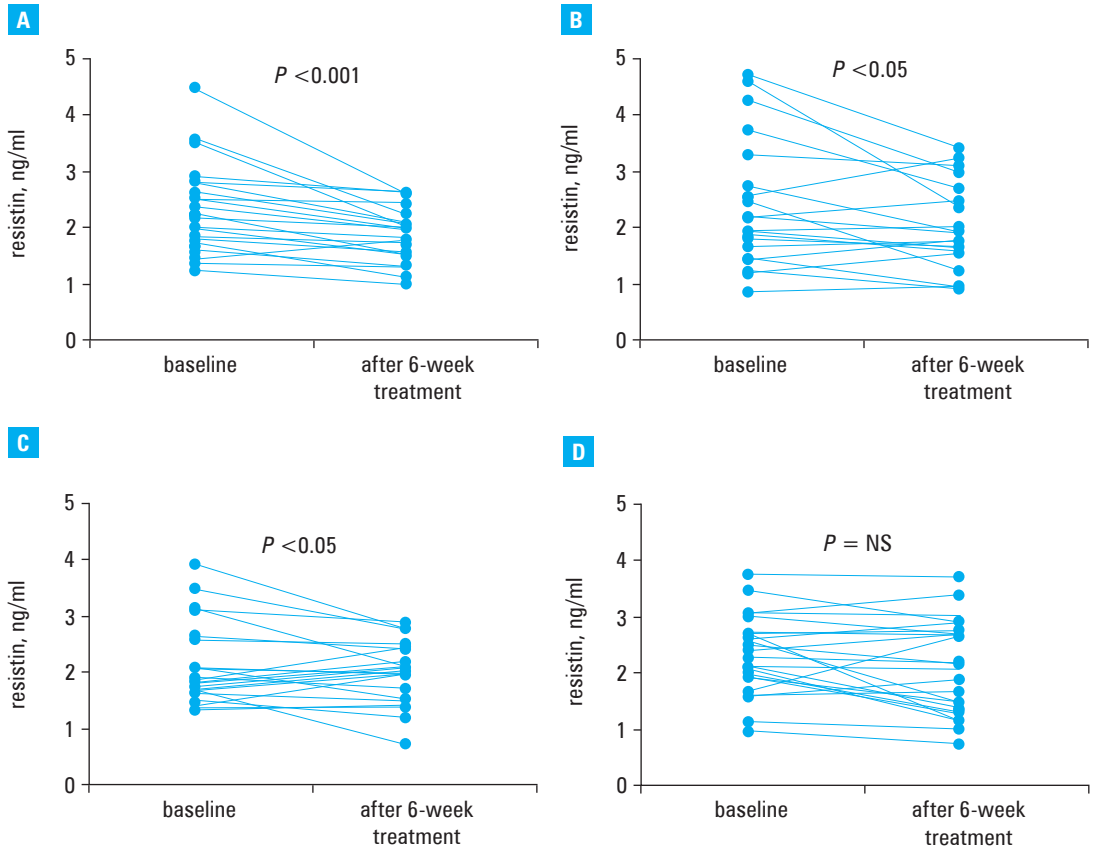

FIGURE 4 Serum resistin concentrations before and after 6 weeks of antihypertensive treatment with bisoprolol (**A**), amlodipine (**B**), indapamide (**C**), or candesartan (**D**)

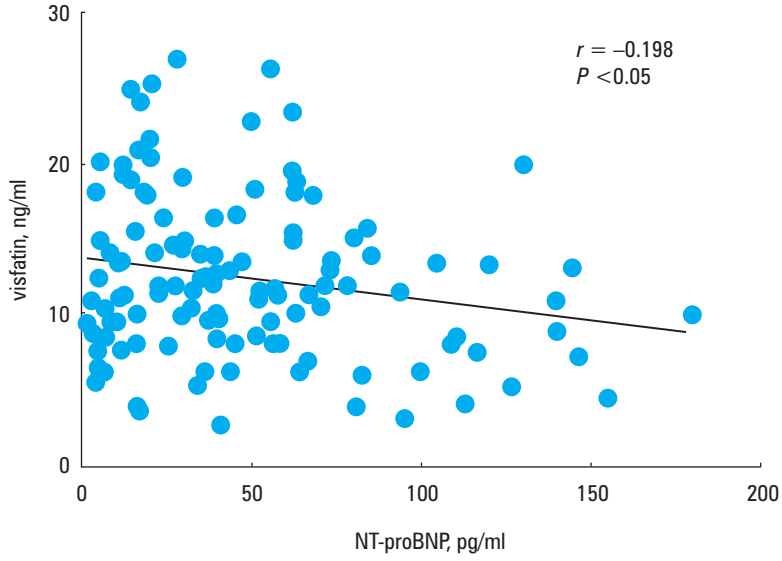

FIGURE 5 Correlation between N-terminal pro-B-type natiuretic peptide (NT-proBNP) and visfatin serum concentrations

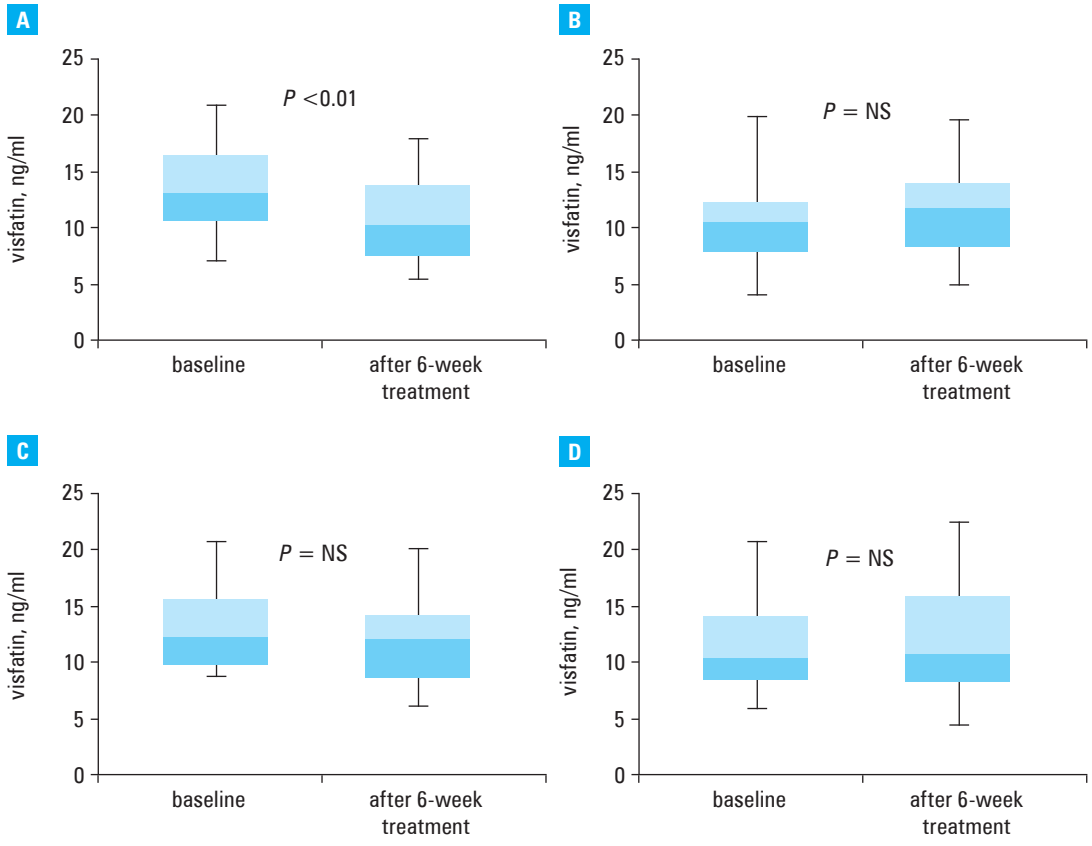

FIGURE 6 Serum visfatin concentrations before and after 6 weeks of antihypertensive treatment with bisoprolol (**A**), amlodipine (**B**), indapamide (**C**), or candesartan (**D**)

The therapy with amlodipine, candesartan, or indapamide did not significantly affect plasma visfatin concentrations (FIGURE 6).

DISCUSSION Boucher et al[28] were the first to report that the plasma apelin concentration positively correlates with the visceral fat area in humans and suggested apelin as a potential link between obesity and variations in insulin sensitivity. This observation was confirmed by a study by Castan-Laurell et al,[29] who observed elevated plasma apelin concentrations in obese women compared with lean controls. Moreover, a significant reduction of plasma apelin concentration was observed after calorie restriction and weight loss.[29] Furthermore, insulin affected apelin mRNA and peptide secretion in cultured adipocytes in vitro, suggesting an essential role of insulin in the regulation of apelin expression.[28] Daviaud et al[10] found that TNF-α may act as a direct regulator of apelin expression in human adipocytes, and Wei et al[30] demonstrated that

a glucocorticosteroid (dexamethasone) decreases apelin mRNA synthesis in 3T3-L1 adipocytes.

Although plasma apelin concentrations only tended to be lower in hypertensive patients in this study, they were shown to be lower in patients with essential hypertension.[31]

We found a positive correlation between plasma apelin concentration and insulin resistance measured by the HOMA-IR model. Moreover, changes in insulin resistance in patients treated with indapamide were accompanied by similar changes in plasma apelin concentrations. This confirms a functional link between apelin and insulin, which has been demonstrated in experimental animals.[32,33]

In obesity, an abnormal and chronic increase in proinflammatory cytokine production in adipose tissue can have a profound impact on whole-body energy balance.[34,35] The negative influence of TNF-α on insulin sensitivity[36] and a positive influence on apelin secretion[10] have been well documented.

In vitro studies in cultured adipocytes showed that dexamethasone significantly increases visfatin mRNA[37] and decreases apelin mRNA[30] in 3T3-L1 adipocytes. Furthermore, glucocorticoids play an important role in determining adipose tissue distribution and function and are overexpressed in central obesity,[38] owing to the increased activity of 11β-hydroxysteroid dehydrogenase type 1 caused by overproduction of TNF-α, interleukin 6, and leptin[39] in obese subjects.

Treatment with a thiazide-like diuretic, indapamide, was shown to reduce plasma apelin concentrations along with increasing insulin resistance, similarly as it was reported for adiponectin.[40]

Apelin causes endothelium-dependant vasodilatation by triggering the release of vasodilators, such as nitric oxide, from endothelial cells[41] and counterregulates the renin–angiotensin–aldosterone system activity by interaction between its receptor (APJ) and AT1R as well as by stimulating ACE2.[42] Reduced plasma apelin concentrations after indapamide treatment may therefore result in less effective blood pressure-lowering after prolonged therapy ("escape" phenomenon).

In rodents, resistin is derived largely from adipose tissue. In contrast to animal model, immunocompetent cells rather than adipocytes appear to be the major source of resistin in humans.[20] Heilbronn et al[43] have shown that neither fat cell size nor percent body fat is related to serum resistin concentrations, which is consistent with the results of our study. Salvage et al[44] reported no difference in serum resistin levels among lean, obese, and obese hypertensive patients, despite wide variations in insulin sensitivity. Resistin expression in adipose tissue from morbidly obese patients is significantly higher compared with that from lean subjects but does not correlate with BMI. A possible explanation for this could be a higher proportion of mononuclear cells expressing resistin mRNA in the adipose tissue of obese individuals.

For the first time, we described the influence of different antihypertensive drugs on plasma resistin concentrations in obese patients with arterial hypertension. As shown in this study, the mean daily plasma resistin concentration did not change after 6 weeks of antihypertensive treatment with candesartan. However, the mean daily plasma resistin concentration in patients treated with amlodipine, bisoprolol, and indapamide was significantly lower than the respective baseline values. As high resistin levels have been correlated with increased incidence of cardiovascular disease,[45] this would be an additional pathway by which some antihypertensive drugs may reduce the cardiovascular risk independently of their blood pressure-lowering effects.

Some evidence suggests that catecholamines impair insulin sensitivity and that increased activity of the sympathetic nervous system contributes to insulin resistance and diabetes mellitus.[46] Several mechanisms by which catecholamines induce insulin resistance have been suggested, including molecular interactions on different levels between adrenergic and insulin signaling cascades,[47] or upregulation of interleukin 6.[48] Therefore, the effect of bisoprolol, as a β1 receptor antagonist, may facilitate the effects of endogenous catecholamines on β2, β3, or/and α receptors, thus exerting their suppressive effect on resistin secretion.

Fukuhara et al[22] for the first time reported that serum levels of visfatin correlate positively with the visceral fat area in humans. This observation has been in agreement with the study by Haider et al,[49] who found elevated serum visfatin levels in morbidly obese patients compared with lean controls. Finally, a significant reduction of serum visfatin concentrations was observed 6 months after gastric banding and significant weight loss.

Berndt et al[50] demonstrated that although serum visfatin concentrations in humans correlated positively with visceral adipose tissue, visfatin mRNA expression, BMI, and percent of body fat, there was no significant correlation between circulating visfatin levels and waist-to-hip ratio or the amount of visceral fat. Furthermore, other recent reports have suggested that although visceral adipose tissue and visfatin mRNA may correlate with BMI, circulating levels of visfatin do not show the same association with BMI. Instead, serum visfatin levels negatively correlated with BMI.[51]

In agreement with the observation in elderly patients,[52] plasma visfatin concentrations did not correlate with blood pressure but correlated with the degree of insulin resistance. Contrary to the observation by Lan et al,[53] we observed no significant changes in plasma visfatin concentrations after treatment with ARB and amlodipine. However, Lan et al[53] described that in leaner patients (a BMI of approximately 25 kg/m^2 versus approximately 35 kg/m^2 in this study) insulin sensitivity during the treatment period was also improved. We also demonstrated in our study that treatment with

bisoprolol resulted in lower plasma visfatin concentrations. Considering the fact that high plasma visfatin concentrations have been correlated with cerebrovascular disease,[54] this could translate into an additional benefit for patients with high risk of stroke.

Conclusions Our study showed that antihypertensive therapy seems to exert a profound effect on secretion of some adipokines in obese patients with essential hypertension. These effects of antihypertensive drugs may potentially protect against cardiovascular and kidney diseases. However, such additional beneficial effects of some antihypertensive drugs, beyond blood pressure reduction, should be assessed in future studies.

Contribution statement AS designed the study and collected the data. AS and GP were responsible for statistical analysis, data interpretation, and final revision of the manuscript. AW conceived the idea for the study and contributed to data interpretation and final revision of the manuscript.

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REFERENCES

1 Larsson B. Obesity, fat distribution and cardiovascular disease. Int J Obes. 1991; 15 Suppl 2: 53-57.

2 Lau DC, Dhillon B, Yan H, et al. Adipokines: molecular links between obesity and atheroslcerosis. Am J Physiol Heart Circ Physiol. 2005; 288: H2031-H2041.

3 Adamczak M, Wiecek A, Funahashi T, et al. Decreased plasma adiponectin concentration in patients with essential hypertension. Am J Hypertens. 2003; 16: 72-75.

4 O'Carroll AM, Lolait SJ, Harris LE, et al. The apelin receptor APJ: journey from an orphan to a multifaceted regulator of homeostasis. J Endocrinol. 2013; 219: R13-R35.

5 Medhurst AD, Jennings CA, Robbins MJ, et al. Pharmacological and immunohistochemical characterization of the APJ receptor and its endogenous ligand apelin. J Neurochem. 2003; 84: 1162-1172.

6 Chen MM, Ashley EA, Deng DX, et al. Novel role for the potent endogenous inotrope apelin in human cardiac dysfunction. Circulation. 2003; 108: 1432-1439.

7 Hosoya M, Kawamata Y, Fukusumi S, et al. Molecular and functional characteristics of APJ. Tissue distribution of mRNA and interaction with the endogenous ligand apelin. J Biol Chem. 2000; 275: 21061-21067.

8 Reaux-Le Goazigo A, Alvear-Perez R, Zizzari P, et al. Cellular localization of apelin and its receptor in the anterior pituitary: evidence for a direct stimulatory action of apelin on ACTH release. Am J Physiol Endocrinol Metab. 2007; 292: E7-E15.

9 De Mota N, Reaux-Le Goazigo A, El Messari S, et al. Apelin, a potent diuretic neuropeptide counteracting vasopressin actions through inhibition of vasopressin neuron activity and vasopressin release. Proc Natl Acad Sci U S A. 2004; 101: 10464-10469.

10 Daviaud D, Boucher J, Gesta S, et al. TNFalpha up-regulates apelin expression in human and mouse adipose tissue. FASEB J. 2006; 20: 1528-1530.

11 Glassford AJ, Yue P, Sheikh AY, et al. HIF-1 regulates hypoxia- and insulin-induced expression of apelin in adipocytes. Am J Physiol Endocrinol Metab. 2007; 293: E1590-1596.

12 Jiang H, Ye XP, Yang ZY, et al. Aldosterone directly affects apelin expression and secretion in adipocytes. J Mol Endocrinol. 2013; 51: 37-48.

13 Wang G, Anini Y, Wei W, et al. Apelin, a new enteric peptide: localization in the gastrointestinal tract, ontogeny, and stimulation of gastric cell proliferation and of cholecystokinin secretion. Endocrinology. 2004; 145: 1342-1348.

14 Yaturu S, Daberry RP, Rains J, et al. Resistin and adiponectin levels in subjects with coronary artery disease and type 2 diabetes. Cytokine. 2006; 34: 219-223.

15 Burnett MS, Lee CW, Kinnaird TD, et al. The potential role of resistin in atherogenesis. Atherosclerosis. 2005; 182: 241-248.

16 Reilly MP, Lehrke M, Wolfe ML, et al. Resistin is an inflammatory marker of atherosclerosis in humans. Circulation. 2005; 111: 932-939.

17 Mu H, Ohashi R, Yan S, et al. Adipokine resistin promotes in vitro angiogenesis of human endothelial cells. Cardiovasc Res. 2006; 70: 146-157.

18 Verma S, Li SH, Wang CH, et al. Resistin promotes endothelial cell activation: further evidence of adipokine-endothelial interaction. Circulation. 2003; 108: 736-740.

19 Calabro P, Samudio I, Willerson, JT, et al. Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. Circulation. 2004; 110: 3335-3340.

20 Patel L, Buckels AC, Kinghorn, IJ, et al. Resistin is expressed in human macrophages and directly regulated by PPAR gamma activators. Biochem Biophys Res Commun. 2003; 300: 472-476.

21 Hug C, Lodish HF. Medicine. Visfatin: a new adipokine. Science. 2005; 307: 366-367.

22 Fukuhara A, Matsuda M, Nishizawa M, et al. Visfatin: a protein secreted by visceral fat that mimics the effects of insulin. Science. 2005; 307: 426-430.

23 Revollo JR, Grimm AA, Imai S. The regulation of nicotinamide adenine dinucleotide biosynthesis by Nampt/PBEF/visfatin in mammals. Curr Opin Gastroenterol. 2007; 23: 164-170.

24 Sethi JK. Is PBEF/visfatin/Nampt an authentic adipokine relevant to the metabolic syndrome? Curr Hypertens Rep. 2007; 9: 33-38.

25 Jia SH, Li Y, Parodo J, et al. Pre-B cell colony-enhancing factor inhibits neutrophil apoptosis in experimental inflammation and clinical sepsis. J Clin Invest. 2004; 113: 1318-1327.

26 Mancia G, Fagard R, Narkiewicz K, et al. 2013 ESH/ESC guidelines for the management of arterial hypertension: the Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). Eur Heart J. 2013; 34: 2159-2219.

27 Belfiore F, Iannello S, Volpicelli G. Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. Mol Genet Metab. 1998; 63: 134-141.

28 Boucher J, Masri B, Daviaud D, et al. Apelin, a newly identified adipokine up-regulated by insulin and obesity. Endocrinology. 2005; 146: 1764-1771.

29 Castan-Laurell I, Vitkova M, Daviaud D, et al. Effect of hypocaloric diet-induced weight loss in obese women on plasma apelin and adipose tissue expression of apelin and APJ. Eur J Endocrinol. 2008; 158: 905-910.

30 Wei L, Hou X, Tatemoto K. Regulation of apelin mRNA expression by insulin and glucocorticoids in mouse 3T3-L1 adipocytes. Regul Pept. 2005; 132: 27-32.

31 Sonmez A, Celebi G, Erdem G, et al. Plasma apelin and ADMA Levels in patients with essential hypertension. Clin Exp Hypertens. 2010; 32: 179-183.

32 Yue P, Jin H, Aillaud M, et al. Apelin is necessary for the maintenance of insulin sensitivity. Am J Physiol Endocrinol Metab. 2010; 298: E59-67.

33 Attane C, Foussal C, Le Gonidec S, et al. Apelin treatment increases complete Fatty Acid oxidation, mitochondrial oxidative capacity, and biogenesis in muscle of insulin-resistant mice. Diabetes. 2012; 61: 310-320.

34 Hotamisligil GS. Inflammation and metabolic disorders. Nature. 2006; 444: 860-867.

35 Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest. 2006; 116: 1793-1801.

36 Sethi, JK, Hotamisligil, GS. The role of TNF alpha in adipocyte metabolism. Semin Cell Dev Biol. 1999; 10: 19-29.

37 Kralisch S, Klein J, Lossner U, et al. Hormonal regulation of the novel adipocytokine visfatin in 3T3-L1 adipocytes. J Endocrinol. 2005; 185: R1-8.

38 Bujalska IJ, Kumar S, Hewison M, et al. Differentiation of adipose stromal cells: the roles of glucocorticoids and 11beta-hydroxysteroid dehydrogenase. Endocrinology. 1999; 140: 3188-3196.

39 Tomlinson JW, Moore J, Cooper MS, et al. Regulation of expression of 11beta-hydroxysteroid dehydrogenase type 1 in adipose tissue: tissue-specific induction by cytokines. Endocrinology. 2001; 142: 1982-1989.

40 Piecha G, Adamcz M, Chudek J, et al. Indapamide decreases plasma adiponectin concentration in patients with essential hypertension. Kidney Blood Press Res. 2007; 30: 187-194.

41 Tatemoto K, Takayama K, Zou MX, et al. The novel peptide apelin lowers blood pressure via a nitric oxide-dependent mechanism. Regul Pept. 2001; 99: 87-92.

42 Folino A, Montarolo, PG, Samaja, M, et al. Effects of apelin on the cardiovascular system. Heart Fail Rev. 2015.

43 Heilbronn LK, Rood J, Janderova L, et al. Relationship between serum resistin concentrations and insulin resistance in nonobese, obese, and obese diabetic subjects. J Clin Endocrinol Metab. 2004; 89: 1844-1848.

44 Savage DB, Sewter CP, Klenk ES, et al. Resistin / Fizz3 expression in relation to obesity and peroxisome proliferator-activated receptor-gamma action in humans. Diabetes. 2001; 50: 2199-2202.

45 Muse ED, Feldman DI, Blaha MJ, et al. The association of resistin with cardiovascular disease in the Multi-Ethnic Study of Atherosclerosis. Atherosclerosis. 2015; 239: 101-108.

46 Facchini FS, Stoohs RA, Reaven GM. Enhanced sympathetic nervous system activity. The linchpin between insulin resistance, hyperinsulinemia, and heart rate. Am J Hypertens. 1996; 9: 1013-1017.

47 Klein J, Fasshauer M, Ito M, et al. beta(3)-adrenergic stimulation differentially inhibits insulin signaling and decreases insulin-induced glucose uptake in brown adipocytes. J Biol Chem. 1999; 274: 34795-34802.

48 Fasshauer M, Paschke R. Regulation of adipocytokines and insulin resistance. Diabetologia. 2003; 46: 1594-1603.

49 Haider DG, Schindler K, Schaller G, et al. Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. J Clin Endocrinol Metab. 2006; 91: 1578-1581.

50 Berndt J, Kloting N, Kralisch S, et al. Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. Diabetes. 2005; 54: 2911-2916.

51 Pagano C, Pilon C, Olivieri M, et al. Reduced plasma visfatin/pre-B cell colony-enhancing factor in obesity is not related to insulin resistance in humans. J Clin Endocrinol Metab. 2006; 91: 3165-3170.

52 Kocelak P, Olszanecka-Glinianowicz M, Owczarek A, et al. Plasma visfatin/nicotinamide phosphoribosyltransferase levels in hypertensive elderly - results from the PolSenior substudy. J Am Soc Hypertens. 2015; 9: 1-8.

53 Lan J, Chen X, Chen X, et al. The relationship between visfatin and HOMA-IR in hypertensive patients, and the effect of antihypertensive drugs on visfatin and HOMA-IR in hypertensive patients with insulin resistance. Diabetes Res Clin Pract. 2011; 94: 71-76.

54 Kong Q, Xia M, Liang R, et al. Increased serum visfatin as a risk factor for atherosclerosis in patients with ischaemic cerebrovascular disease. Singapore Med J. 2014; 55: 383-387.

ARTYKUŁ ORYGINALNY

Wpływ leczenia przeciwnadciśnieniowego na stężenie apeliny, rezystyny i wisfatyny w osoczu

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SŁOWA KLUCZOWE

adipokiny, nadciśnienie tętnicze, otyłość, tkanka tłuszczowa

STRESZCZENIE

WPROWADZENIE W ostatnich latach wykazano, że tkanka tłuszczowa pełni funkcje wewnątrzwydzielnicze i wytwarza wiele adipokin, które przyczyniają się do rozwoju miażdżycy, nadciśnienia tętniczego, przewlekłej choroby nerek, dysfunkcji śródbłonka, insulinooporności i przebudowy naczyń.

CELE Celem tego badania była ocena, czy leczenie β-blokerem, blokerem kanału wapniowego, diuretykiem tiazydopodobnym lub blokerem receptora AT1 wpływa na stężenie w osoczu apeliny, rezystyny i wisfatyny u otyłych chorych na nadciśnienie tętnicze.

PACJENCI I METODY Do badania włączono 84 otyłych chorych na samoistne nadciśnienie tętnicze. Do jednej z grup kontrolnych włączono osoby otyłe bez nadciśnienia tętniczego, a do drugiej grupy kontrolnej włączono osoby bez otyłości i bez nadciśnienia tętniczego. Chorzy na nadciśnienie tętnicze zostali losowo przydzieleni do jednej z 4 grup leczonych przez 6 tygodni odpowiednio: bisoprololem, amlodypiną, indapamidem lub kandesartanem.

WYNIKI Średnie w ciągu dnia stężenie apeliny w osoczu chorych leczonych amlodypiną było znamiennie wyższe w porównaniu z wartościami sprzed rozpoczęcia leczenia, podczas gdy w pozostałych leczonych grupach stężenie apeliny w osoczu nie uległo istotnej zmianie. Średnie w ciągu dnia stężenie rezystyny w osoczu było znamiennie niższe po 6-tygodniowym leczeniu amlodypiną, bisoprololem lub indapamidem w porównaniu do wartości wyjściowych. U chorych leczonych kandesartanem nie obserwowano istotnych różnic stężenia rezystyny w osoczu przed i po leczeniu. U chorych leczonych bisoprololem obserwowano znamiennie niższe stężenie wisfatyny w osoczu po 6-tygodniowym leczeniu w porównaniu do wartości wyjściowych. Leczenie amlodypiną, kandesartanem lub indapamidem nie wpłynęło istotnie na stężenie wisfatyny w osoczu.

WNIOSKI Leczenie przeciwnadciśnieniowe powoduje istotne i zróżnicowane zmiany wydzielania adipokin u otyłych chorych na nadciśnienie tętnicze. Zmiana wydzielania adipokin w następstwie stosowania różnych leków przeciwnadciśnieniowych może wpływać ochronnie na układ sercowo-naczyniowy i nerki. Udział adipokin w mechanizmie zróżnicowanego działania ochronnego leków przeciwnadciśnieniowych, niezależnie od wpływu na ciśnienie tętnicze, wymaga jednak dalszych badań.

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