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Cilazapril increases plasma ghrelin concentration in obese patients with arterial hypertension

Cilazapril zwiększa stężenie greliny w osoczu u otyłych chorych z nadciśnieniem tętniczym

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Abstract

Introduction: Ghrelin is a polypeptide hormone secreted mainly by the stomach cells, stimulating food intake and growth hormone release. Decreased plasma ghrelin concentration was found in obese subjects. Clinical and experimental data suggest that ghrelin also exerts a blood pressure lowering property. The influence of antihypertensive medication on plasma ghrelin concentration has not been studied, yet.

Material and methods: Plasma ghrelin concentration was estimated in 52 hypertensive obese (HA + O), 14 normotensive obese (O), and 15 lean healthy subjects in the fasting state, and after ingestion of a standard meal. HA + O patients were randomly allocated into 4 groups treated alternatively with: cilazapril, bisoprolol, amlodipine, or indapamide. After 6 weeks of antihypertensive monotherapy, the assessments were repeated.

Results: Similar fasting [HA + O — 780 (676–960) pg/ml; O — 751 (619–899) pg/ml] and postprandial plasma ghrelin concentrations were found in hypertensive and normotensive obese subjects. Plasma ghrelin concentrations in lean healthy subjects were significantly higher (987 (765–1366) pg/ml) in comparison to O and HA + O. Treatment with cilazapril was followed by a 28.0% increase of plasma ghrelin concentration ($p = 0.04$), while with bisoprolol, a 18.9% decrease ($p = 0.01$). No significant changes of ghrelinaemia were observed in HA + O treated with amlodipine or indapamide. No significant correlation between blood pressure and plasma ghrelin concentration before the therapy and their changes after 6 weeks of medication were found.

Conclusions:

1. Our data do not support the major role of ghrelin in blood pressure regulation in obesity.
2. An increase of plasma ghrelin concentration after treatment with cilazapril was observed.

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Key words: *ghrelin, obesity, arterial hypertension, cilazapril, antihypertensive therapy*

Streszczenie

Wstęp: Grelina jest hormonem polipeptydowym wydzielanym głównie przez komórki ściany żołądka. W warunkach fizjologicznych grelina zwiększa łaknienie i wydzielanie hormonu wzrostu. U osób otyłych stwierdzono obniżone stężenie greliny w osoczu. W badaniach doświadczalnych i klinicznych wykazano, że grelina przyczynia się do obniżenia ciśnienia tętniczego. Jak dotąd nie przeprowadzono jednak badań nad wpływem leków przeciwnadciśnieniowych na grelinemię.

Materiał i metody: U 52 otyłych chorych z nadciśnieniem tętniczym (HA + O), 14 otyłych chorych z prawidłowym ciśnieniem tętniczym (O) i 15 osób zdrowych z prawidłową masą ciała oznaczono stężenie greliny w osoczu na czczo, jak również po podaniu standardowego posiłku. Następnie chorzy HA + O zostali w sposób losowy przydzieleni do jednej z czterech grup leczonych przez 6 tygodni odpowiednio: cilazaprilem, bisoprololem, amlodipiną lub indapamidem. Po tym okresie leczenia powtórzono oznaczenia grelinemii.

Wyniki: Nie stwierdzono różnic grelinemii zarówno na czczo [HA + O — 780 (676–960) pg/ml; O — 751 (619–899) pg/ml], jak i po podaniu standardowego posiłku pomiędzy HA + O i O. Stężenie greliny w osoczu było znamiennie wyższe u osób zdrowych z prawidłową masą ciała (987 [765–1366] pg/ml) w porównaniu z O oraz HA + O. U HA + O leczenie cilazaprilem spowodowało wzrost o 28,0% ($p = 0,04$), a leczenie bisoprololem zmniejszenie grelinemii o 18,9% ($p = 0,01$). Podawanie amlodipiny lub indapamidu nie wpływało istotnie na stężenie greliny w osoczu. Nie stwierdzono występowania korelacji pomiędzy ciśnieniem tętniczym a grelinemią lub zmianami grelinemii po 6 tygodniach leczenia.

Wnioski:

1. Uzyskane wyniki nie potwierdzają istotnej roli greliny w regulacji ciśnienia tętniczego u osób otyłych.
2. Leczenie cilazaprilem przyczynia się do wzrostu grelinemii.

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Słowa kluczowe: *grelina, otyłość, nadciśnienie tętnicze, cilazapril, leczenie przeciwnadciśnieniowe*

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Introduction

Ghrelin is a 28-aminoacid peptide secreted mainly by the stomach cells [1]. The highest plasma ghrelin concentration is usually detected in the fasting state [2, 3]. The decrease of plasma ghrelin concentration observed after feeding is not related to gastric distension but rather to the stimulation of the cholinergic nervous system via the vagus nerve, glucose absorption, and probably insulin release [4–7]. Under physiological conditions, ghrelin stimulates growth hormone release and appetite via neuropeptide Y and agouti-related protein expressing neurons in hypothalamic nucleus arcuatus [4, 8–10]. In obese subjects, plasma ghrelin concentrations are significantly lower than in non-obese subjects [11]. Weight loss in severely obese patients after laparoscopic adjustable gastric banding (LAGB) is accompanied by an increase of plasma ghrelin concentration [12, 13]. Moreover, a negative correlation between BMI and plasma ghrelin concentration was confirmed in some clinical studies [14–16].

The results obtained in the experimental studies suggest that ghrelin also affects the function and structure of the cardiovascular system. Ghrelin decreases blood pressure. Both central and peripheral mechanisms may participate in the vascular relaxation induced by ghrelin infusion. The microinjection of ghrelin into the nucleus of the solitary tract suppresses sympathetic nerve activity and decreases blood pressure and heart rate in rats [17, 18]. Ghrelin is also a potent endothelium-dependent and endothelium-independent vasodilator [19, 20]. Ghrelin improves endothelial function by increasing endothelial nitric oxide synthesis [19]. Ghrelin is not only involved in blood pressure regulation but also prevents vascular wall injury. It was shown that ghrelin diminishes vascular oxidative stress by inhibition of NAD(P)H oxidases, and attenuates vascular calcification [21, 22].

In humans it has been reported that low plasma ghrelin concentration is associated with higher prevalence of arterial hypertension [23]. In addition, some authors have found a significant negative correlation between blood pressure and plasma ghrelin concentration [14, 24]. Nagaya et al. found that intravenous injection of ghrelin decreased mean arterial pressure by 12 mm Hg, without any significant changes in heart rate [25]. A similar haemodynamic effect was recently demonstrated with synthetic ghrelin receptor agonist [26].

The aim of this study was to assess plasma ghrelin concentrations in normotensive and hypertensive obese subjects. As the influence of antihypertensive medication on ghrelin release has not yet been studied, we aimed in this single-centre, prospective, open label study to assess the influence of 6 weeks of monotherapy with cilazapril, bisoprolol, amlodipine, or indapamide on plasma ghrelin concentrations in obese patients with arterial hypertension.

Material and methods

Patients

Fifty-two obese (BMI $\geq$ 30 kg/m^2) patients with arterial hypertension (HA + O), 14 normotensive obese (O) and 15 lean (BMI $\leq$ 25.0 kg/m^2) healthy subjects (HS) were enrolled into this study after giving informed consent. The patients' characteristics are presented in Table I. Only previously untreated patients with recently diagnosed mild to moderate arterial hypertension (blood pressure higher than or equal to 140/90 mm Hg but lower than 180/110 mm Hg) were enrolled into the HA + O group. The exclusion criteria were as follows: secondary hypertension, chronic kidney or liver disease, diabetes mellitus, gout, ischaemic heart disease, neoplasms, or infections. Secondary forms of hypertension were excluded based on careful clinical and biochemical examination.

Study protocol

In all subjects, blood samples for the estimation of plasma ghrelin concentration were taken in the morning in the fasting state, and additionally 30, 60, and 120 minutes after the ingestion of a standard meal consisting of 250 ml of milk, 100 ml of grapefruit juice, 40 g of cornflakes, and 5 g of sugar. In addition, serum glucose, cholesterol (total and HDL fraction), triglycerides, uric acid, creatinine, and plasma insulin concentrations were estimated before ingestion of the standard meal. Blood pressure was measured with a mercury sphygmomanometer with an accuracy of 2 mm Hg. Obese patients with arterial hypertension were randomly allocated into one of four groups treated either with: angiotensin converting enzyme inhibitor — cilazapril, β-adrenergic receptor antagonist — bisoprolol, calcium channel antagonist — amlodipine, or tiazide-like diuretic — indapamide. Each group consisted of 13 patients. The initial doses of the above-mentioned antihypertensive agents were as follows: 2.5 mg of amlodipine, bisoprolol, or indapamide and 1.25 mg of cilazapril. Blood pressure and heart rate were measured in the outpatient clinic every 2 weeks. When the blood pressure was higher than 140/90 mm Hg after 4 weeks of study, the dose of each drug, except indapamide, was doubled. After 6 weeks of treatment, all the above-mentioned measurements were repeated in fasting state and after the standard meal. The study protocol was approved by the Local Ethical Committee.

Biochemical examinations

Plasma samples for estimation of ghrelin and insulin were frozen and stored at –30°C until the time of measurement. Plasma ghrelin concentration was assessed by RIA method using kits from Linco Research Inc., USA. The intra- and interassay coefficients of variations were 4.4–10.0 and 14.7–16.7%, respectively. Plasma insulin concentration was estimated by electrochemiluminescence method using Elecsys kits (Roche Diagnostics GmbH, Mannheim, Germany). Other parameters were assessed by routine laboratory methods. Homeostasis model assessment insulin resistance index (HOMA-IR) was calculated according to the formula: fasting plasma glucose concentration [mg/dl] × fasting plasma insulin concentration [μU/ml] /405. Glomerular filtration rate (eGFR) was calculated as the endogenous creatinine clearance, according to the formula by Cockcroft and Gault: eGFR = (140 — Age [years]) × body mass [kg] × 1 (for males) or 0.85 (for females)/72 × serum creatinine concentration [mg/dl] [27].

Measurement of body composition by DEXA

Body composition was measured by dual-energy X-ray absorptiometry (DEXA) using a Lunar DPX-L scanner (Lunar Radiation Corporation, Madison, WI, USA). Measurements were performed once, in a supine position, before meals. This method allowed the assessment the total fat mass (TFM) and fat mass of the trunk.

Statistical analysis

All analyses were performed using Statistica software version 7.0 (StatSoft Inc.). Non-parametrical tests were applied: the χ^2 and the Mann-Whitney U tests, to compare the analysed groups, and the Wilcoxon test for analysis of subsequent measurements. The correlation coefficient was calculated according to the Spearman correlation test. The first multiple regression analysis included all patients was performed for plasma ghrelin concentration as a dependent variable and BMI, systolic or diastolic BP, age, HOMA-IR, and eGFR as independent variables. The second multiple regression analysis focused only on patients within the HA + O group, including Δ of plasma ghrelin concentration as a dependent variable, and change of systolic or diastolic blood pressure and Δ of HOMA-R as independent variables.

Data are presented as median values and interquartile range (for comparison of analysed groups) or mean values and 95% confidence intervals (for evaluation changes in time within the same group).

Results

Both normotensive and hypertensive obese patients were characterised by significantly lower plasma ghrelin concentrations than lean healthy subjects (Table I, Fig. 1). Obese hypertensive and obese normotensive patients did not differ with respect to plasma ghrelin concentrations (Table I, Fig. 1). After ingestion of the standard meal, a significant decline of plasma ghrelin concentration was observed in all the examined groups. The lowest ghrelin concentrations were observed 60 minutes after ingestion of the meal (Fig. 1).

Significantly higher plasma ghrelin concentrations were observed in obese hypertensive females than in males [900 (779–1052) *v.* 743 (656–854) pg/ml, respectively; $p = 0.013$]. This difference persisted after adjustment for BMI (923 *v.* 782 pg/ml, respectively).

As expected, obese subjects were characterised by higher plasma insulin concentration and HOMA-IR values (the highest in obese hypertensive patients). Serum triglycerides and uric acid levels were also higher in obese than in lean subjects (Table I).

In all examined subjects, in univariate analysis, significant negative correlations were found between plasma ghrelin concentration and BMI ($r = –0.227$; $p = 0.04$), waist/hip ratio ($r = –0.425$; $p < 0.001$), eGFR ($r = –0.231$; $p = 0.04$), plasma concentrations of glucose ($r = –0.231$; $p = 0.04$), insulin ($r = –0.436$, $p < 0.001$), or HOMA-IR ($r = –0.454$; $p < 0.001$). Surprisingly, we did not find any significant correlation between plasma ghrelin concentration and total fat mass, trunk fat mass, and body fat content. In a similar analysis restricted only to obese hypertensive patients, similar correlations were observed between plasma ghrelin concentration and waist/hip ratio ($r = –0.314$; $p = 0.02$), and plasma insulin concentration ($r = –0.436$, $p = 0.001$) and HOMA-IR ($r = –0.444$; $p = 0.001$). Finally, no significant correlation between BMI, eGFR, and plasma glucose was found.

The univariate analysis of all examined subjects and only hypertensive obese patients separately did not reveal any significant correlation between plasma ghrelin concentration and systolic ($r = –0.122$; $p = 0.28$ and $r = –0.03$; $p = 0.98$, respectively) and diastolic ($r = –0.140$; $p = 0.21$ and $r = –0.08$; $p = 0.55$, respectively) blood pressure values.

The stepwise multiple regression analysis confirmed the lack of contribution of both systolic and diastolic blood pressure to ghrelinaemia. Only HOMA-IR ($\beta = –0.411$; $p < 0.001$) and eGFR ($\beta = –0.198$; $p = 0.05$) significantly contributed to plasma ghrelin variability ($r^2 = 0.23$).

Treatment with cilazapril, bisoprolol, amlodipine, and indapamide for 6 weeks was followed by a similar reduction of systolic and diastolic blood pressure (Table II). Treatment with cilazapril caused a significant 28.0% increase, while with bisoprolol, a 18.9% decrease of plasma ghrelin concentration was observed (Fig. 2). No significant changes of ghrelinaemia were observed

Table I. *Clinical and biochemical characteristics of the studied groups of patients (median values and interquartile range)*

Tabela I. *Kliniczna i biochemiczna charakterystyka badanych grup pacjentów (mediany i zakresy miedzykwartylowe)*

	Obese hypertensive (n = 52)	Obese normotensive (n = 14)	Healthy subjects (n = 15)
Age (years)	42 (36–52)	42 (38–48)	39 (36–46)
Males/females	32/20	7/7	6/9
BMI [kg/m^2]	33.2 (31.2–36.0) ###	32.1 (30.9–32.8) ###	22.4 (21.6–24.0)
Systolic BP [mm Hg]	155 (149–160) *** ###	123 (115–130)	120 (110–120)
Diastolic BP [mm Hg]	98 (95–100) *** ##	80 (80–85) #	75 (70–80)
Total Fat Mass [kg]	35.5 (27.9–41.5) ###	34.1 (29.8–39.7) ###	17.9 (15.5–21.4)
Trunk Fat Mass [kg]	18.5 (15.3–19.9) ###	19.3 (17.0–21.0) ###	8.6 (6.7–10.0)
Body Fat Content (%)	33.4 (28.6–44.5) ##	34.8 (30.4–46.6) ##	28.7 (23.8–32.5)
WHR	0.96 (0.86–1.00) ###	0.95 (0.88–1.00) ###	0.79 (0.77–0.84)
Creatinine [mg/dl]	1.13 (0.98–1.26) *** #	0.87 (0.81–1.07)	0.92 (0.80–1.15)
eGFR [ml/min]	113 (92–129) * ##	135 (108–136) ###	95 (75–102)
Glucose [mg/dl]	104 (96–116)	91 (81–119)	86 (81–101)
Cholesterol total [mg/dl]	224 (200–258)	239 (199–276)	217 (166–246)
Cholesterol HDL [mg/dl]	43 (34–60)	45 (40–51)	54 (48–69)
Cholesterol non-HDL [mg/dl]	179 (153–214)	192 (148–220)	152 (107–198)
Triglycerides [mg/dl]	158 (118–223) ###	139 (124–206) #	88 (75–141)
Uric acid [mg/dl]	5.27 (4.30–6.24)	5.30 (4.80–5.60) ##	3.95 (3.30–5.20)
Ghrelin [pg/ml]	780 (676–960) ##	751 (619–899) #	987 (765–1366)
Insulin [μU/ml]	12.3 (8.8–16.1) * #	8.7 (6.3–12.9) ###	4.6 (3.4–5.2)
HOMA-IR	2.96 (2.17–4.46) * #	1.87 (1.38–3.05) ###	1.02 (0.72–1.23)

Statistical significance *v.* obese normotensive * $p < 0.05$; ** $p < 0.01$; ***$p < 0.001$

Statistical significance *v.* healthy subjects # $p < 0.05$; ##$p < 0.01$; ### $p < 0.001$

BMI — body mass index, WHR — waist to hip ratio, HOMA-IR — homeostasis model assessment insulin resistance index, eGFR — estimated glomerular filtration rate

Figure 1. *Baseline plasma ghrelin concentration in obese normotensive subjects (n = 14), obese patients with arterial hypertension (n = 52), and lean healthy subjects (n = 15) in fasting state before and after ingestion of the standard meal. Statistical significance* v. *healthy subjects * $p < 0.05$; ** $p < 0.01$. Statistical significance* v. *before meal # $p < 0.05$; ## $p < 0.01$; ### $p < 0.001$*

Rycina 1. *Wyjściowe stężenie greliny w osoczu u otyłych osób z prawidłowym ciśnieniem tętniczym (n = 14), u otyłych osób z nadciśnieniem tętniczym (n = 52) i u zdrowych, szczupłych osób (n = 15) oznaczone na czczo przed posiłkiem oraz po spożyciu standardowego posiłku. Istotność statystyczna* v. *osoby zdrowe *$p < 0,05$; **$p < 0,01$. Istotność statystyczna v. pomiar przed posiłkiem #$p < 0,05$; ##$p < 0,01$: ###$p < 0,001$*

Table II. *The influence of antihypertensive treatment on the systolic and diastolic blood pressure, insulin resistance (HOMA-IR), and plasma ghrelin concentration in obese hypertensive patients treated for 6 weeks with cilazapril, bisoprolol, amlodipine, or indapamide (mean values and 95% confidence intervals)*

Tabela II. *Wpływ terapii przeciwnadciśnieniowej na ciśnienie skurczowe i rozkurczowe, insulinooporność (HOMA-IR) oraz stężenie greliny w osoczu u otyłych osób z nadciśnieniem tętniczym leczonych przez 6 tygodni cilazaprilem, bisoprololem, amlodipiną lub indapamidem (średnie i 95% przedziały ufności)*

	Cilazapril (n = 13)	Bisoprolol (n = 13)	Amlodipine (n = 13)	Indapamide (n = 13)
Initial systolic BP [mm Hg]	152 (147–157)	156 (152–159)	157 (152–162)	151 (148–155)
Changes of systolic BP [mm Hg]	–24 ([–29]–[–18])	–32 ([–37]–[–25])	–28 ([–35]–[–22])	–25 ([–31]–[–20])
Initial diastolic BP [mm Hg]	99 (97–101)	97 (96–100)	100 (98–103)	95 (93–96)
Changes of diastolic BP [mm Hg]	–20 ([–24]–[–16])	–20 ([–25]–[–16])	–22 ** ([–25]–[–18])	–16 ([–19]–[–14])
Initial HOMA-IR	3.99 (2.78–5.21)	3.24 (2.22–4.27)	2.97 (2.29–3.64)	2.99 (2.43–3.56)
Changes of HOMA-IR	–0.26 ([–1.92]–1.41)	–0.15 ([–0.93]–0.62)	–0.25 ([–1.00]–0.51)	0.51 ([–0.62]–1.65)
Initial ghrelin [pg/ml]	725 (657–795)	990* (767–1100)	860 (762–903)	751 (674–885)
Changes of ghrelin [pg/ml]	171 (25–318)	–204** ([–366]–[–42])	21 ([–72]–115)	51 ([–70]–173)

Statistical significance *v.* Indapamide * $p < 0.05$; ** $p < 0.01$

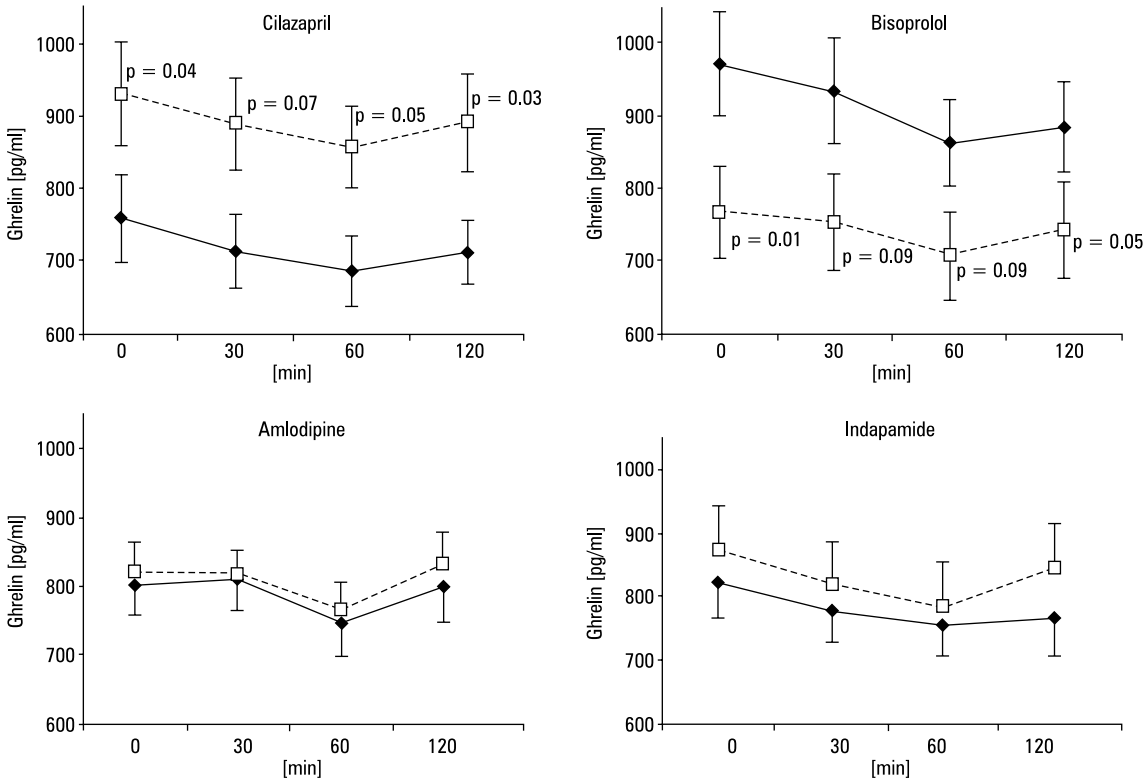

Figure 2. *Fasting (0) and 30, 60, and 120 minutes after ingestion of the standard meal plasma ghrelin concentration in obese hypertensive patients before (continuous lines and filled diamonds) and 6 weeks after (interrupted lines and empty squares) initiation of the antihypertensive medication with cilazapril, bisoprolol, amlodipine, and indapamide, respectively (means and 95% CI, statistical significance, and p value* v. *pre-treatment values)*

Rycina 2. *Stężenie greliny w osoczu na czczo (0) oraz 30, 60 i 120 minut po spożyciu standardowego posiłku u otyłych osób z nadciśnieniem tętniczym przed (linia ciagła, czarne romby) i 6 tygodni po (linia przerywana, białe kwadraty) rozpoczęciu leczenia przeciwnadciśnieniowego cilazaprilem, bisoprololem, amlodipiną lub indapamidem (średnie i 95% przedziały ufności, istotność statystyczna oraz p dla danej wartości* v. *wartość przed leczeniem)*

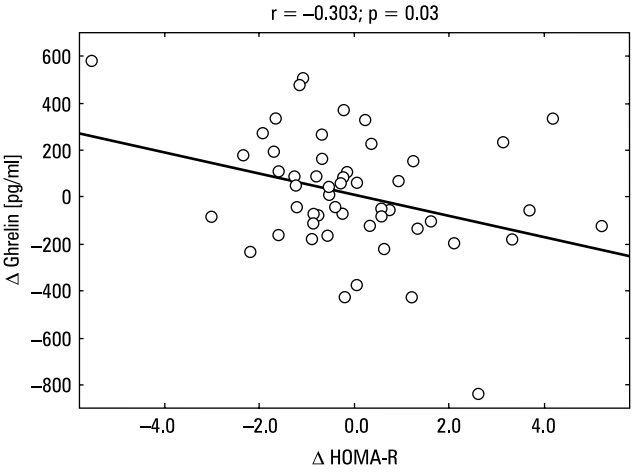

Figure 3. *Relationship between changes of homeostasis model assessment insulin resistance index (HOMA-IR) and changes of plasma ghrelin concentration after 6 weeks of antihypertensive treatment in obese humans (n = 52) (irrespective of the type of drug)*

Rycina 3. *Zależność między zmianami wartości wskaźnika insulinooporności HOMA-IR a zmianami stężenia greliny w osoczu po 6 tygodniach leczenia przeciwnadciśnieniowego u osób otyłych (n = 52) (niezależnie od rodzaju leku)*

in patients treated with amlodipine or indapamide (Fig. 2). In addition, changes in HOMA-IR were not significant (Table II). The most pronounced tendency to increase HOMA-IR was observed in patients treated with indapamide (Table II).

After 6 weeks of antihypertensive medication, no relationship was found between changes of blood pressure and changes of plasma ghrelin concentration. In contrast, a significant negative correlation was noticed between HOMA-IR changes and changes in plasma ghrelin concentration ($r = –0.303$; $p = 0.03$) (Fig. 3). Stepwise multiple regression analysis of factors potentially influencing changes of plasma ghrelin concentration ($r^2 = 0.11$) documented only the contribution of HOMA-IR changes ($\beta = –0.331$; $p = 0.017$).

Discussion

The results of the present study do not support the hypothesis regarding the importance of the role of low plasma ghrelin concentration in the pathogenesis of elevated blood pressure in obese humans. We found similar plasma ghrelin concentrations in obese subjects suffering or not suffering from arterial hypertension. There was also no significant relationship between blood pressure and plasma ghrelin concentration and changes of blood pressure during the treatment and ghrelinaemia, respectively. A strong methodological point of our study is that our hypertensive patients did not previously receive any antihypertensive drugs.

One clinical study which clearly demonstrated an association between blood pressure and plasma ghrelin concentration was the substudy of OPERA (Oulu Project Elucidating Risk of Atherosclerosis) [23]. However, in this study there was only a 5 mm Hg difference of systolic and 2 mm Hg of diastolic blood pressure between extreme ghrelin quartiles [23]. In addition, a significant negative correlation between blood pressure and plasma ghrelin concentration was reported [14, 24]. In contrast to the above-mentioned studies, we did not find such a correlation. The cause of these discrepancies is unclear. Of note, we found similar concentrations of plasma ghrelin in hypertensive and normotensive obese humans. Therefore, the importance of ghrelin in obesity-related hypertension is not crucial.

In the interventional part of this study, a significant increase of plasma ghrelin concentration after treatment with cilazapril was noticed. However, monotherapy with indapamide or amlodipine did not influence plasma ghrelin concentration. Therefore, changes of plasma ghrelin concentration were not directly related to the blood pressure lowering effect.

There are several experimental and clinical observations suggesting that plasma ghrelin concentration is related to the degree of insulin resistance [5, 24, 28]. In the present study, in the entire group, a significant negative correlation was noticed between HOMA-IR changes and changes in plasma ghrelin concentration (Fig. 3). The significant increase of plasma ghrelin concentration after treatment with cilazapril, and the decrease after bisoprolol therapy, may be explained, however, only partially, by changes in insulin sensitivity as no significant changes in mean HOMA-IR in any of the groups were noticed.

What is the possible clinical implication of the increase of plasma ghrelin concentration after treatment with cilazapril? The beneficial cardiovascular effect of angiotensin-converting enzyme inhibitors is claimed to exceed the blood pressure lowering mechanism [29]. In experimental models it has been shown that ghrelin diminishes vascular oxidative stress, reduces inflammatory endothelial response, attenuates vascular calcification, and prevents left ventricular hypertrophy [21, 22, 30, 31]. We can only speculate that the increase in plasma ghrelin concentration after cilazapril treatment leads to cardio- and vasculo-protection. Such an attractive hypothesis concerning the novel mechanisms of angiotensin-converting enzyme inhibitor action needs further studies.

Contrary to cilazapril, bisoprolol therapy reduces plasma ghrelin concentrations. This decrease could potentially have orexogenic effect. However, the meta-analysis by Sharma et al. showed that treatment with β-adrenergic antagonists led to weight gain [32]. The

relationship between β-adrenergic antagonists and regulation of appetite is much more complex. Beta-adrenergic antagonists also decrease plasma leptin concentrations, and through this mechanism may stimulate appetite [33]. Both ghrelin and leptin regulate satiety by modulation of neuropeptide Y release from the neurons located in the arcuate nucleus [9, 34]. As these peptides have the opposite influence, the improvement of appetite by β-adrenergic antagonists may be only very mild.

There are several limitations of our study. We did not measure plasma catecholamines and angiotensin II concentrations. Thus, we could not prove or deny the concept concerning the interrelation between these two strong vasoconstrictive agents and plasma ghrelin concentrations. Moreover, we only estimated insulin sensitivity by calculation of HOMA-IR indexes, instead of the more accurate euglycaemic-hyperinsulinemic glucose clamp technique. Therefore, we are not able to exclude minor changes in insulin sensitivity after antihypertensive treatment.

Conclusions

The results of our study do not confirm the major role of ghrelin in blood pressure regulation in obesity. The increase of plasma ghrelin concentration after treatment with cilazapril may be a novel, potentially cardioprotective mechanism of angiotensin-converting enzyme inhibitor action.

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