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Ghrelin as a potential blood pressure reducing factor in obese women during weight loss treatment

Grelina jako potencjalny czynnik hipotensyjny u otyłych kobiet poddanych terapii odchudzającej

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Abstract

Background: In animal models ghrelin reduces cardiac afterload and increases cardiac output via receptors in the cardiovascular system. The aim of our study was to evaluate a potential relationship between weight loss treatment, blood pressure and serum ghrelin concentrations in obese women.
Material and methods: A group of 37 obese premenopausal women with no previous history of hypertension (BMI: 36.5 ± 5 kg/m^2) were involved in the study. Blood pressure and serum ghrelin levels were assessed before and after a three-month weight reduction treatment, which consisted of a diet of 1000 kcal/day and physical exercise. Body composition was determined by impedance analysis using Bodystat.
Results: Following weight loss (mean 8.9 ± 4.8 kg) SBP decreased (120 ± 13 *vs.* 115 ± 14 mm Hg, p = 0.01) and serum ghrelin levels increased significantly (66.9 ± 13.7 *vs.* 73.9 ± 15.4 pg/ml; p = 0.005). There were significant correlations between values for ghrelin levels after weight loss and SBP (r = –0.45, p = 0.02), DBP (r = –0.41, p < 0.05), and between Δghrelin levels and ΔSBP (r = 0.52, p = 0.006), ΔDBP (r = 0.53, p = 0.005). There was a positive correlation between an increase in ghrelin and a decrease in percentage body fat during weight loss (r = 0.51; p = 0.002).
Conclusion: The results seem to provide evidence that weight loss may decrease blood pressure in obese patients via a ghrelin-dependent mechanism. **(Pol J Endocrinol 2008; 59 (3): 207–211)**

Key words: *obesity, ghrelin, arterial blood pressure, weight loss*

Streszczenie

Wstęp: W modelach zwierzęcych grelina powoduje zmniejszenie obciążenia następczego serca i zwiększenie rzutu serca poprzez wpływ na receptory znajdujące się w układzie sercowo-naczyniowym. Celem badania było określenie zależności między redukcją masy ciała, ciśnieniem tętniczym a stężeniem greliny w surowicy u kobiet z otyłoscią.
Materiał i metody: Badaniem objęto 37 otyłych kobiet (wskaźnik masy ciała [BMI, *body mass index*] 36,5 ± 5 kg/m^2) bez nadciśnienia tętniczego w wywiadzie. Ciśnienie tętnicze i stężenie greliny w surowicy oznaczono przed i po 3-miesiecznej kuracji odchudzającej, która obejmowała dietę 1000 kcal/d. i ćwiczenia fizyczne. Skład ciała określono metodą analizy impedancji z użyciem aparatu Bodystat.
Wyniki: W następstwie redukcji masy ciała (średnio 8,9 ± 4,8 kg) nastąpiło istotne obniżenie SBP (120 ± 13 *vs.* 115 ± 14 mm Hg, p = 0,01) i zwiększenie stężenia greliny w surowicy (66,9 ± 13,7 *vs.* 73,9 ± 15,4 pg/ml; p = 0,005). Stwierdzono istotne korelacje między stężeniami greliny po redukcji masy ciała a SBP (r = –0,45, p = 0,02) i DBP (r = –0,41, p = 0,05) oraz między Δstężeń greliny a ΔSBP (r = 0,52, p = 0,006), ΔDBP (r = 0,53, p = 0,005). Wykazano dodatnią korelację między wzrostem stężenia greliny a zmniejszeniem procentowej zawartości tłuszczu w organizmie pod wpływem terapii odchudzającej (r = 0,51, p = 0,002).
Wnioski: Wyniki badania dowodzą, że zmniejszenie masy ciała może spowodować obniżenie ciśnienia tętniczego u osób otyłych przez mechanizm zależny od greliny. **(Endokrynol Pol 2008; 59 (3): 207–211)**

Słowa kluczowe: *otyłość, grelina, ciśnienie tętnicze, zmniejszenie masy ciała*

Introduction

Ghrelin is a growth hormone-releasing peptide isolated from the stomach and is involved in the pathogenesis of obesity. It exerts anabolic effects through growth hormone (GH) stimulation and a direct positive energy balance. Ghrelin secretion is probably up-regulated under conditions of a negative energy balance and down-regulated in the setting of a positive energy balance [1–3].

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Moreover, ghrelin is a new peptide modulating central sympathetic activity [4], a function which would seem to be of importance, because changes in the autonomic function have been implicated in the development and progress of obesity and its complications, including systemic hypertension [5].

Recent data indicate that ghrelin may also have beneficial haemodynamic effects. It has been demonstrated that ghrelin reduces cardiac afterload and increases cardiac output via receptors in the cardiovascular system [6]. This is not accompanied by an increase in heart rate. Experimental study has shown that ghrelin inhibits vascular superoxide production in spontaneously hypertensive rats. This effect is probably related to the inhibition of vascular NAD(P)H oxidases [7].

The results obtained by Mager et al. [8] revealed that several ghrelin gene variations were associated with blood pressure levels in subjects with impaired glucose tolerance.

On the basis of the data, we would like to put forward a novel and perhaps interesting hypothesis that weight loss may decrease blood pressure in hypertensive patients via a ghrelin-dependent mechanism.

The aim of our study was to evaluate a potential relationship between weight loss treatment, blood pressure and serum ghrelin concentrations in obese women.

Material and methods

The examinations were carried out on 37 premenopausal women with simple obesity and no previous history of hypertension (mean age 40.7 ± 11.0 years; mean body weight 96.7 ± 17.2 kg; mean body mass index (BMI) 36.5 ± 5.0 kg/m^2). Possible secondary causes for obesity were ruled out on the basis of case history, physical examination, and laboratory tests, including determination of glucose and hormone levels. Mean values of blood pressure ranged from systolic blood pressure (SBP) 119.6 ± 13.3 mm Hg, diastolic blood pressure (DBP) 80.0 ± 11.9 mm Hg. Subjective and objective (12-lead ECG and sonocardiography) examinations did not reveal any pathology within the cardiovascular systems of the obese patients.

In obese patients the examination, which included blood pressure and body composition, was carried out twice: before and after an effective three-month weight reduction treatment, which comprised a low-calorie diet (1000 kcal) with water and vitamin supplementation, constant daily sodium and potassium intake, and physical exercise. Additionally group instruction in behavioural and dietary methods of weight control was carried out every two weeks. Body composition was determined by impedance analysis (Bodystat).

The exclusion criteria included evidence of present or recent (preceding 3 months) infectious disease, fever, and drug therapy. The study was approved by the local ethical committee. All subjects gave their informed consent to their participation in the study.

The determination of ghrelin in the blood serum was carried out by enzyme-linked immunosorbent assay with Phoenix Pharmaceuticals kits. The sensitivity of ghrelin assay was less than 6.0 pg/ml. Intra- and interassay coefficients of variations (CV) were < 5.4%, and < 6.0% respectively. The measurements of insulin serum concentrations were performed by the RIA method (DPC Diagnostic Products Corporation, Los Angeles, USA).

Insulin resistance was assessed on the basis of fasting serum concentrations of glucose and insulin. The HOMA index was calculated by the formula: HOMA = = fasting serum concentration of insulin (μIU/ml) × fasting serum concentration of glucose (mmol/l)/ 22.5. The normal HOMA range is < 2.77 [9].

Samples of 6–8 ml of venous blood were collected from each subject after an overnight fast. After clot formation the samples were centrifuged (1000 g) at room temperature for 10 minutes. The serum obtained was drawn into a few plastic vials, and stored at –80°C until the time of assay.

Statistical analysis

Each variable was checked for normality of distribution by the Kolmogorov-Smirnov test. Within-group comparisons were made by a paired t test for regular data distribution, and by the Wilcoxon signed-rank test for non-normal data distribution. Values are presented as mean ± SD. Pearson's rank correlation test was applied to assess correlations between the parameters examined. Stepwise multivariate analysis was performed with serum levels of ghrelin, Δghrelin, BMI and ΔBMI, body fat and Δbody fat, free fat mass and Dfree fat mass as the independent variables and ΔSBP and ΔDBP as the dependent variables.

Differences were considered statistically significant at $p < 0.05$.

Results

A three-month weight reduction treatment, which allowed for 8.9 ± 4.8 kg weight loss, resulted in a significant decrease in BMI values (36.5 ± 5.4 kg/m^2, 33.4 ± ± 5.2 kg/m^2, respectively) and changes in body composition assessed by the impedance method (Table I).

Heart rate slowed down as compared to baseline values (76.6 ± 3.0 *vs.* 71.2 ± 2.4 bpm, $p = 0.05$). Post-treatment SBP was significantly lower than pre-treatment

Table I. *Patient characteristics*
Tabela I. *Charakterystyka chorych*

	Pre-treatment	Post-treatment	p
Body mass [kg]	96.7 ± 17.2	87.9 ± 15.7	0.001
BMI [kg/m²]	36.5 ± 5.4	33.4 ± 5.2	0.001
FFM [kg]	53.8 ± 6.9	51.5 ± 6.8	0.05
FFM (%)	56.4 ± 7.9	59.3 ± 5.9	0.01
Fat tissue [kg]	42.2 ± 13.6	35.6 ± 10.6	0.001
Fat tissue (%)	43.2 ± 7.9	40.3 ± 6.0	0.01

BMI — body mass index; FFM — fat-free mass

Table II. *Mean heart rate and blood pressure*
Tabela II. *Średnie wartości częstości rytmu serca i ciśnienia tętniczego*

	Pre-treatment	Post-treatment	p
HR [bpm]	76.6 ± 3.0	71.2 ± 2.4	0.05
SBP [mm Hg]	119.6 ± 13.3	114.8 ± 13.8	0.01
DBP [mm Hg]	80.0 ± 11.9	77.4 ± 9.7	NS

HR — heart rate; SBP — systolic blood pressure; DBP — diastolic blood pressure

values (p = 0.01). There were no differences between baseline and post-treatment DBP values (Table II).

Mean serum ghrelin concentrations significantly increased after the three-month weight reduction treatment (66.9 ± 13.7 *vs.* 73.9 ± 15.4 pg/ml; p = 0.005). The serum insulin concentration and HOMA index value were comparable before and after follow-up (Table III).

Pre-treatment correlations

Statistical analysis of the baseline parameters revealed no correlation between ghrelin levels and the clinical data assessed.

Insulin levels and HOMA index values correlated positively with weight (r = 0.43, p = 0.02 and r = 0.45, p = 0.01 respectively), and BMI (r = 0.42, p = 0.03; r = 0.45, p = 0.02).

The baseline SBP correlated with age (r = 0.47, p < 0.01), BMI (r = 0.55, p < 0.005), and body composition indices. The baseline DBP correlated with BMI (r = 0.45, p < 0.05) and body composition indices (Table IV).

Post-treatment correlations

The analysis of post-treatment data revealed that SBP correlated negatively with ghrelin levels (r = –0.45; p < 0.05) and positively with insulin levels and HOMA index value (r = 0.44, p = 0.02; r = 0.47; p = 0.03 respectively). Similar to the baseline findings, the post-treatment SBP also correlated with age (r = 0.48, p < 0.01), BMI (r = 0.52; p < 0.005) and indices of body composition (Table V).

Table III. *Mean ghrelin and insulin serum concentrations*
Tabela III. *Średnie stężenia greliny i insuliny w surowicy*

	Pre-treatment	Post-treatment	p
Ghrelin [pg/ml]	66.9 ± 13.7	73.9 ± 15.4	0.005
Insulin [uUl/ml]	15.7 ± 7.2	14.4 ± 10.5	NS
Glucose [mmol/l]	4.8 ± 0.4	5.1 ± 0.5	NS
HOMA	3.8 ± 0.2	3.4 ± 0.2	NS

Table IV. *Pre-treatment correlations of SBP and DBP*
Tabela IV. *Korelacje miedzy SBP i DBP przed terapią*

	Age	BMI	Fat tissue	FFM
SBP	r = 0.47**	r = 0.55***	r = 0.59****	r = –0.57***
DBP		r = 0.45*	r = 0.47*	r = –0.58***

SBP — systolic blood pressure; DBP — diastolic blood pressure, * p < 0.05; ** p < 0.01; *** p < 0.005; **** p < 0.001

There were also significant correlations between DBP and ghrelin (r = –0.41, p < 0.05) and insulin levels and HOMA index value (r = 0.45, p < 0.05; r = 0.51, p < 0.01 respectively). Additionally, DBP correlated with BMI (r = 0.49, p < 0.01) and FFM (r = –0.46, p < 0.05).

There were significant correlations between post-weight loss values of ghrelin levels and SBP (r = –0.45, p < 0.05), DBP (r = –0.41, p < 0.05), and between Δghrelin levels and ΔSBP (r = 0.52, p = 0.006), ΔDBP (r = 0.53, p = 0.005). There was a positive correlation between an increase in ghrelin and a decrease in body fat percentage during weight loss (r = 0.51; p = 0.002).

A stepwise multivariate regression analysis using ΔSBP and ΔDBP as dependent variables was also performed. The ΔSBP was related positively to Δghrelin (r = 0.26; F = 11.55; p = 0.001) and Δbody fat (kg) (r = 0.23; F = 14.57; p = 0.002). The ΔDBP was related positively to Δghrelin (r = 0.28; F = 10.56; p = 0.002) and Δbody fat (kg) (r = 0.28; F = 16.67; p = 0.003).

Discussion

Literature data and our previous observations suggest that ghrelin may be regarded as a new challenge in clinical research on metabolic syndrome [1–3, 10]. Moreover, there are some data that indicate that ghrelin may exert positive haemodynamic effects, both central and peripheral [6].

The present study evaluates potential relationships between the concentrations of ghrelin and the blood

Table V. *Post-treatment correlations of SBP and DBP*
Tabela V. *Korelacje między SBP i DBP po terapii*

	Age	BMI	Fat tissue	FFM	Insulin	Ghrelin
SBP	r = 0.48**	r = 0.52***	r = 0.39*	r = –0.64****	r = 0.44*	r = –0.45*
DBP		r = 0.49**		r = –0.46*	r = 0.45*	r = –0.41*

SBP — systolic blood pressure; DBP — diastolic blood pressure, * $p < 0.05$; ** $p < 0.01$; *** $p < 0.005$; **** $p < 0.001$

pressure values in obese women undergoing complex obesity treatment. At the enrolment we observed no correlation between the above-discussed parameters. However, following weight loss treatment significant negative correlations were noted between ghrelin serum levels and SBP, DBP values. We did not find any similar reports in the literature.

A variety of evidence seems to suggest that ghrelin participates not only in feeding behaviour but also in cardiovascular and sympathetic regulation. By central nervous system mechanisms ghrelin suppresses sympathetic activity and decreases blood pressure. Furthermore, it modulates heart rate and baroreflex control of renal sympathetic nerve activity [11].

In animal models a decrease in arterial pressure without a change in heart rate has been observed following intravenous ghrelin administration [12]. Similar to our findings, a negative correlation was revealed by Makino et al. [13] between plasma ghrelin concentration and SBP in normal pregnant women. However, they observed that higher levels of ghrelin in pregnant women induced hypertension in comparison with those of normal pregnant women. Recently Poykko et al. [14] revealed that ghrelin was independently associated with type 2 diabetes, insulin concentration and elevated blood pressure. They measured fasting plasma ghrelin levels in a large sample of the middle-aged population and concluded that low ghrelin levels constituted a risk factor for diabetes and hypertension.

Finally, it is unclear what mechanism, whether vascular, myocardial or both, may be responsible for the ghrelin haemodynamic effects observed in our study. Taking into account the literature data [6], we may speculate that if ghrelin is acting to decrease afterload it could decrease blood pressure. Secondly, if ghrelin suppresses sympathetic activity and decreases heart rate it could decrease blood pressure. However, from the cardiac output increase it could exert the opposite results too.

The results of other studies further clarify the role of ghrelin in obesity development. Ghrelin is inversely related to fasting insulin levels as well as waist-hip-ratio, a useful index of central obesity [14, 15]. Furthermore, there are studies supporting the concept that basal ghrelin levels are directly related to insulin sensitivity; these are suppressed in obesity, which is generally associated with increased insulin resistance [15]. The results of our study seem to be in accordance with the above-mentioned data. The observed decrease of blood pressure after weight loss may also be a result of the increase in ghrelin levels.

Parallel to studies on obesity, those on anorexia nervosa confirm the hypothesis that ghrelin secretion is regulated by energy balance. Shiiya et al. [2] found elevated ghrelin levels in patients with anorexia nervosa (*i.e.* with a negative energy balance) when compared to those of healthy subjects.

Interesting findings were also reported in patients with cardiac cachexia. Nagaya et al. [16, 17] found significant correlations between ghrelin, GH, and tumour necrosis factor α (a positive correlation), and BMI (a negative correlation). Changes in ghrelin concentrations were related to body mass in cachectic patients, and an increase in ghrelin levels was observed following cachexia development. The results suggest that not only absolute value of fat mass but also progressive weight loss may influence plasma ghrelin levels.

The above reports are in accordance with our observations that weight loss in obese subjects results in an increase in ghrelin levels. Considering the fact that activation of the ghrelin-GH axis exerts anabolic effects, we suggest that the elevation of ghrelin levels after weight loss may constitute a secondary, counter-regulatory mechanism preventing further weight loss.

In summary, an increase in ghrelin levels after weight loss might be responsible for the haemodynamic effects of weight reduction treatment. The results of our study suggest that weight loss may also decrease blood pressure in obese patients by a ghrelin-dependent mechanism. This constitutes a novel aspect of the study.

Conclusion

The results seem to form evidence that weight loss may decrease blood pressure in obese patients via a ghrelin-dependent mechanism.

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