



Ghrelin and obestatin in thyroid dysfunction

Ghrelina i obestatyna w zaburzeniach czynności tarczycy

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Abstract

Introduction: Ghrelin and obestatin derive from the same precursor. Ghrelin is an energy balance regulator and obestatin's role in metabolic processes cannot be excluded. The aim of this study was to assess plasma ghrelin and obestatin changes in thyroid disorders.

Material and methods: We evaluated plasma ghrelin and obestatin levels in severe hypothyroidism, hypothyroidism after thyroidectomy and 4-weeks L-thyroxine withdrawal, and in hyperthyroidism. We also re-evaluated plasma ghrelin and obestatin levels in patients with severe hypothyroidism and hyperthyroidism after treatment.

Results: Severe hypothyroidism was associated with a reasonably high ghrelin level ($p = 0.055$) and hyperthyroidism with a significantly lower ghrelin level ($p = 0.01$) compared to healthy subjects. Ghrelin in hypothyroid patients after L-thyroxine withdrawal did not differ from the control group ($p = 0.3$). Compared to healthy subjects, obestatin level in hyperthyroidism was decreased ($p = 0.03$) and did not differ in severe hypothyroidism due to thyroiditis ($p = 1$) or after L-thyroxine withdrawal ($p = 0.6$). Ghrelin and obestatin levels correlated positively. Both peptides levels correlated positively with TSH and negatively with free thyroid hormones. In patients with severe hypothyroidism, ghrelin level significantly decreased after treatment ($p < 0.01$) and in hyperthyroid patients significantly increased after treatment ($p = 0.04$). There were no significant changes in obestatin levels in hypo- or hyperthyroid patients after treatment.

Conclusions: Plasma ghrelin changes and its correlation with TSH and thyroid hormones may indicate a compensatory role of ghrelin in metabolic disturbances associated with thyroid dysfunction. The positive correlation between ghrelin and obestatin levels may suggest a modulatory role of obestatin in these processes. (*Endokrynol Pol* 2012; 63 (6): 456–462)

Key words: ghrelin, obestatin, thyroid, hypothyroidism, hyperthyroidism

Streszczenie

Wstęp: Ghrelina i obestatyna są peptydami pochodzącymi z tego samego prekursora. Ghrelina w istotny sposób wpływa na utrzymanie równowagi energetycznej organizmu. Rola obestatyny w tym zakresie nie jest wykluczona. Celem pracy była ocena stężeń ghreliny i obestatyny w osoczu chorych z zaburzeniami czynności tarczycy.

Materiał i metody: Badano stężenia ghreliny i obestatyny u chorych z ciężką niedoczynnością tarczycy, u chorych po strumektomii całkowitej i 4-tygodniowym odstawieniu L-tyroksyny oraz u chorych z nadczynnością tarczycy. Porównano stężenia obu peptydów u pacjentów z nadczynnością tarczycy i ciężką niedoczynnością tarczycy przed i po leczeniu.

Wyniki: W porównaniu z grupą kontrolną u chorych z ciężką niedoczynnością tarczycy wykazano wysokie stężenie ghreliny ($p = 0,055$), a u chorych z nadczynnością tarczycy — obniżone ($p = 0,01$). Stężenie ghreliny u chorych po tyreoidectomii i odstawieniu L-tyroksyny nie różniło się od wartości stwierdzanych u osób zdrowych ($p = 0,3$). Stężenie obestatyny w nadczynności tarczycy było istotnie obniżone ($p = 0,03$). W obu rodzajach niedoczynności tarczycy nie różniło się istotnie od grupy kontrolnej. Stężenia ghreliny i obestatyny korelowały dodatnio. Stężenia obu peptydów korelowały dodatnio z TSH, a ujemnie ze stężeniem wolnych hormonów tarczycy. Po leczeniu u pacjentów z ciężką niedoczynnością tarczycy stężenie ghreliny istotnie obniżało się ($p < 0,01$), a u chorych z nadczynnością tarczycy wzrastało ($p = 0,04$). Nie wykazano istotnych różnic w stężeniu obestatyny przed i po leczeniu w żadnej z tych grup.

Wnioski: Zmiany stężenia ghreliny i korelacje z parametrami czynności tarczycy mogą wskazywać na kompensacyjną rolę ghreliny w zaburzeniach metabolicznych towarzyszących zaburzeniom czynności tarczycy. Dodatnia korelacja pomiędzy stężeniem ghreliny i obestatyny może sugerować udział obestatyny w tych procesach. (*Endokrynol Pol* 2012; 63 (6): 456–462)

Słowa kluczowe: ghrelina, obestatyna, tarczyca, niedoczynność tarczycy, nadczynność tarczycy

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Introduction

Ghrelin and obestatin are two peptides deriving from the same precursor — proghrelin [1–3]. Due to their common origin, both peptides are of particular inter-

est regarding their compatible or opposite biological functions.

Ghrelin was discovered as the first endogenous ligand for growth hormone secretagogue receptor (GHS-R) [1] and proved to be a strong, dose-dependent

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stimulator of GH release [4]. However, it also plays an important role in the regulation of metabolic processes. Ghrelin stimulates appetite by binding its receptors in the hypothalamus and increasing the release of orexigenic peptides (neuropeptide Y [NPY] and Agouti-related peptide [AgRP] [5, 6], acts as an adipogenic factor [7], accelerates gastric emptying [8, 9], and reduces energy expenditure [10].

There are two main forms of ghrelin. Acylated 28-amino acid peptide (posttranslationally *n*-octanoylated at the third residue — Ser³) is able to bind its receptor and exert biological activity [1, 11]. Unacylated ghrelin, previously considered to be inactive, has been recently shown to have some biological function [3].

Ghrelin is predominantly produced in neuroendocrine cells (X/A cells) of the gastric mucous membrane [1, 12]. However, its expression has been demonstrated also in the hypothalamus, hypophysis, small and large intestine, liver, pancreas, thyroid and many other central and peripheral organs [13–16]. Growth hormone secretagogue receptors (type GHS-R1a and GHS-R1b) are widely expressed as well [13, 16–18]. Type GHS-R1a has been described as the functional ghrelin receptor [13].

The regulation of ghrelin release is based on food intake rhythm i.e. fasting increases, and food intake reduces, ghrelin release [19]. Considering long-term metabolic disturbances, obesity is associated with low plasma ghrelin level [20]. Negative energy balance states such as cachexia, anorexia nervosa and bulimia increase ghrelin production [21–23].

Similarly to ghrelin, obestatin is predominantly produced in the stomach [24]. Its expression has been also demonstrated in the small and large intestine, pancreas, mammary ducts and in the thyroid gland [15, 25, 26]. Obestatin has been initially shown to reduce food intake and body weight gain and to suppress intestinal motility [2]. However, since its discovery, the studies describing the physiology and function of obestatin have been in constant opposition to those claiming that it does not have any biological activity and remains only a ghrelin-associated peptide [27–29]. Obestatin receptor has not been described yet [30]. Nevertheless, since obestatin level is reduced in obesity and increased in anorexia nervosa [31, 32], its direct or indirect influence on food intake and body weight cannot be excluded.

Ghrelin's involvement in energy balance regulation and the possible role of obestatin in this mechanism suggests a potential correlation between both peptides and thyroid function. It is well known that metabolic disturbances influence thyroid hormones release and, on the other hand, hyper- and hypothyroidism increases and decreases the rate of metabolism respectively. The expression of ghrelin and its receptors in the thyroid gland has been already confirmed [13–18]. Furthermore,

it has been demonstrated that exogenous ghrelin is strongly uptaken in the thyroid [33]. Obestatin also has been demonstrated in thyroid tissue [15, 26]. Therefore, a relationship between thyroid function and ghrelin and obestatin production is worth considering.

Most of the studies have revealed that hypothyroidism is associated with high ghrelin level [34–36] that decreases after treatment [35]. However, some authors did not notice any differences [37–40] or actually observed low plasma ghrelin levels [41, 42]. Hyperthyroidism, despite increased appetite and weight loss, was surprisingly associated mostly with decreased ghrelin concentration [34, 36–38, 43–47], that rose after treatment [37, 38, 43, 44, 46, 47]. Obestatin changes in thyroid dysfunction have so far been analysed only in one study. Kosowicz et al. revealed that hypothyroidism and hyperthyroidism are respectively associated with high and low obestatin levels [36].

The aim of this study was to evaluate ghrelin and obestatin plasma levels in patients with hypothyroidism and hyperthyroidism and to assess for the first time the changes of both peptides in hypothyroidism and hyperthyroidism before and after treatment.

Material and methods

The study group consisted of:

- 16 patients with severe hypothyroidism (15 women, one man) due to Hashimoto's thyroiditis or after radioiodine treatment (due to toxic goitre or Graves' disease in the past);
- 24 patients with hypothyroidism (23 women, one man), who had undergone total thyroidectomy due to differentiated thyroid cancer and were examined after 4-week L-thyroxine withdrawal — examination performed during prearranged qualification for radioiodine treatment, that required L-thyroxine withdrawal (clinical symptoms of hypothyroidism poorly manifested);
- 22 patients with hyperthyroidism (19 women, three men) due to Graves' disease or toxic goitre (typical clinical image of hyperthyroidism);
- 21 euthyroid volunteers (18 women, three men) — the control group.

Blood samples for plasma ghrelin and obestatin assessment were collected from antecubital veins after a ten-hour fast and placed into polyethylene tubes containing plasma enzymes inhibitors (aprotinin and EDTA). Total plasma ghrelin levels were measured in duplicate with a commercially available radioimmunological assay (RIA) kit (Phoenix Pharmaceuticals Inc.). Plasma obestatin levels were measured in plasma extracts as recommended by the manufacturer with a commercially available RIA kit (Phoenix Pharmaceuticals

Table I. The clinical and biochemical characteristics of the patients (1) with hyperthyroidism, (2) with hypothyroidism due to Hashimoto's thyroiditis or after radioiodine treatment, (3) with hypothyroidism after thyroidectomy and L-thyroxine withdrawal, and (4) of the control group (normal ranges: TSH 0.27–4.2 uIU/mL; fT₄ 11.5–21 pmol/L; fT₃ 3.93–7.70 pmol/L)

Tabela. I. Charakterystyka kliniczna i biochemiczna (1) pacjentów z nadczynnością tarczycy, (2) pacjentów z ciężką niedoczynnością tarczycy z powodu zapalenia tarczycy typu Hashimoto lub po leczeniu radiojodem, (3) pacjentów z niedoczynnością tarczycy po tyreoidektomii i odstawieniu L-tyroksyny i (4) grupy kontrolnej (wartości referencyjne: TSH 0.27–4.2 uIU/ml; fT₄ 11.5–21 pmol/l; fT₃ 3.93–7.70 pmol/l)

	Hyperthyroidism	Hypothyroidism (Hashimoto's thyroiditis or after radioiodine treatment)	Hypothyroidism (L-thyroxine withdrawal)	Control group
Number of patients	22	16	24	21
Sex (F/M)	19/3	15/1	23/1	18/3
Age (years)	41 ± 14	38 ± 14	41 ± 14	33 ± 7
BMI [kg/m ²]	22.3 ± 3.7	23.2 ± 3.6	23.3 ± 2.3	23 ± 2.7
TSH [uIU/mL]	0.006 ± 0.001	82.1 ± 27.1	82.7 ± 22	1.96 ± 0.85
fT ₄ [pmol/L]	38.7 ± 18.7	3.9 ± 3.4	2.1 ± 0.9	16.2 ± 1.8
fT ₃ [pmol/L]	15.8 ± 8.6	1.6 ± 1.4	0.9 ± 0.4	4.99 ± 0.6
Ghrelin [pg/mL]	205.9 ± 89.3	631.1 ± 270.6	522.5 ± 276.6	347.6 ± 121.3
obestatin [pg/mL]	21.3 ± 5.2	31.2 ± 7.9	30.4 ± 3.5	27.4 ± 3.6

Inc.). Radioactivity of the samples was measured in an automatic LKB-Wallace gamma counter. The assessment of obestatin levels in plasma extracts was technically complicated and could be completed in 71 probes. The difficulty appeared especially in the evaluation of hypothyroidism before and after treatment. The techniques of plasma ghrelin and obestatin measurement and difficulties associated with the assessment have been already described [48].

Free thyroxine (fT₄), free triiodothyronine (fT₃) and thyrotropin (TSH) levels were assessed using an electrochemiluminescence method. Serum anti-thyroglobulin (aTg), anti-thyroid peroxidase antibodies (aTPO) and anti-TSH-receptor antibodies (TRAb) were measured by radioimmunoassay (RIA).

In ten hyperthyroid patients, ghrelin and obestatin plasma levels were assessed once more, when they became clinically and biochemically euthyroid after treatment. Similarly, in nine hypothyroid patients with Hashimoto's or radioiodine-induced thyroiditis, the examination was performed again after treatment with L-thyroxine.

Hyperthyroid, hypothyroid and euthyroid groups were compared using a non-parametric Kruskal-Wallis test. The changes in ghrelin and obestatin level before and after treatment were analysed with Wilcoxon signed-ranks test. Correlations were assessed by use of Spearman's rank correlation coefficient.

The study was conducted with the permission of Poznan University of Medical Sciences' Ethical Committee. The analyses were performed in the laboratories of the

Department of Endocrinology, Metabolism and Internal Medicine of Poznan University of Medical Sciences.

Results

The clinical and biochemical characteristics of the study group are presented in Table I.

The study revealed that in severe hypothyroidism due to Hashimoto thyroiditis or after radioiodine treatment, plasma ghrelin level was high in comparison to the control group with a p-value very close to statistical significance ($p = 0.055$). Hyperthyroid patients had a significantly lower plasma ghrelin level compared to healthy subjects ($p = 0.01$), to hypothyroid patients with Hashimoto's thyroiditis or after radioiodine treatment ($p < 0.001$), and to hypothyroid patients after L-thyroxine withdrawal ($p < 0.001$). Plasma ghrelin level in hypothyroid patients after total thyroidectomy and L-thyroxine withdrawal did not differ from values observed in healthy subjects ($p = 0.3$) (Fig. 1).

Obestatin level in hyperthyroid patients was significantly decreased compared to healthy subjects ($p = 0.03$), to patients with thyroiditis ($p < 0.01$), and to patients after L-thyroxine withdrawal ($p < 0.001$) (Fig. 2). Compared to the control group, there was no difference in obestatin level in hypothyroidism due to Hashimoto's thyroiditis or after radioiodine treatment ($p = 1$), or hypothyroidism after L-thyroxine withdrawal ($p = 0.6$).

In the whole study group, including patients with thyroid disorders and the control group, ghrelin and

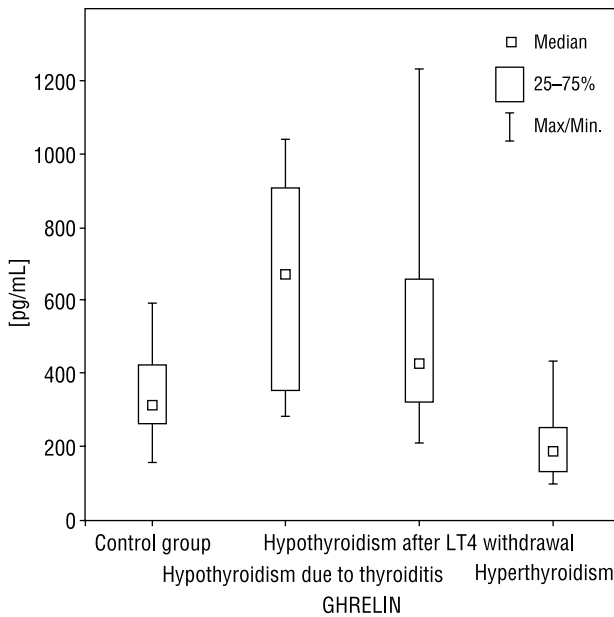


Figure 1. Plasma ghrelin levels in the control group, in patients with hypothyroidism due to Hashimoto's thyroiditis or after radioiodine treatment — 'Hypothyroidism due to thyroiditis', in patients with hypothyroidism after thyroidectomy and L-thyroxine withdrawal and in hyperthyroid patients

Rycina 1. Stężenie ghreliny w osoczu osób bez zaburzeń czynności tarczycy, w niedoczynności tarczycy z zapaleniem tarczycy typu Hashimoto lub po leczeniu radiojodem — 'Hypothyroidism due to thyroiditis', w niedoczynności tarczycy po tyreoidektomii i odstawieniu L-tyroksyny oraz w nadczynności tarczycy

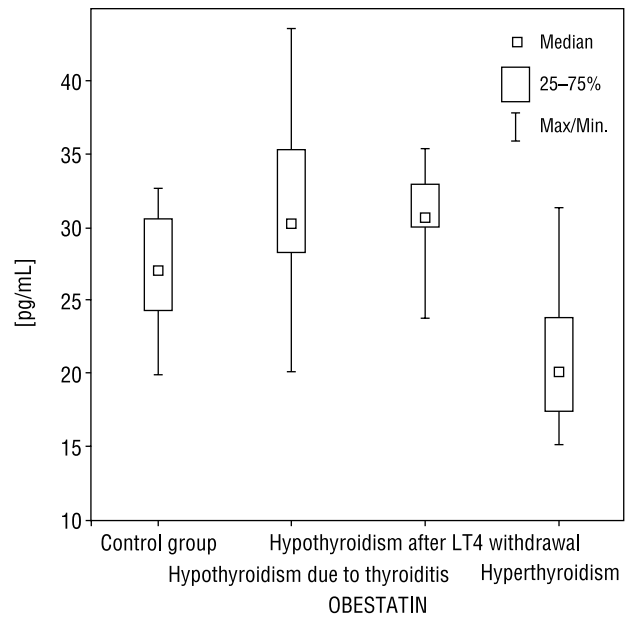


Figure 2. Plasma obestatin levels in the control group, in patients with hypothyroidism due to Hashimoto's thyroiditis or after radioiodine treatment — 'Hypothyroidism due to thyroiditis', in patients with hypothyroidism after thyroidectomy and L-thyroxine withdrawal and in hyperthyroid patients

Rycina 2. Stężenie obestatyiny w osoczu osób bez zaburzeń czynności tarczycy, w niedoczynności tarczycy z zapaleniem tarczycy typu Hashimoto lub po leczeniu radiojodem — 'Hypothyroidism due to thyroiditis', w niedoczynności tarczycy po tyreoidektomii i odstawieniu L-tyroksyny oraz w nadczynności tarczycy

Table II. The clinical and biochemical characteristics of hypothyroid patients (with Hashimoto's thyroiditis or after radioiodine treatment) and of hyperthyroid patients before and after treatment (normal ranges: TSH 0.27–4.2 uIU/mL; fT₄ 11.5–21 pmol/L; fT₃ 3.93–7.70 pmol/L)

Tabela II. Charakterystyka kliniczna i biochemiczna pacjentów z niedoczynnością tarczycy (z powodu zapalenia tarczycy typu Hashimoto lub po leczeniu radiojodem) oraz pacjentów z nadczynnością tarczycy przed i po leczeniu (wartości referencyjne: TSH 0.27–4.2 uIU/ml; fT₄ 11.5–21 pmol/l; fT₃ 3.93–7.70 pmol/l)

	Hypothyroidism (Hashimoto's thyroiditis or after radioiodine treatment)		Hyperthyroidism	
	Before treatment	After treatment	Before treatment	After treatment
TSH [uIU/mL]	83.3 ± 26.2	1.7 ± 1.7	0.005 ± 0.001	1.1 ± 0.6
fT ₄ [pmol/L]	4.5 ± 3.5	22.5 ± 3.1	44.2 ± 24.5	19.7 ± 5.2
fT ₃ [pmol/L]	1.9 ± 1.7	4.9 ± 0.9	18.4 ± 11.2	4.5 ± 0.7
BMI [kg/m ²]	24.3 ± 4	22.5 ± 3.9	20.4 ± 2.5	21.4 ± 2
Ghrelin [pg/mL]	652.9 ± 247.8	372.1 ± 124.6	206.7 ± 90.6	321.1 ± 119.9
Obestatin [pg/mL]	33.5 ± 9.5	29.4 ± 2.7	22.8 ± 6	27.6 ± 6.8

obestatin correlated positively ($r = 0.8$, $p < 0.05$). Furthermore, both peptides correlated positively with TSH (ghrelin $r = 0.6$, $p < 0.05$; obestatin $r = 0.6$, $p < 0.05$) and negatively with fT₃ (ghrelin $r = -0.7$, $p < 0.05$; obestatin $r = -0.6$, $p < 0.05$) and fT₄ levels (ghrelin $r = -0.7$, $p < 0.05$; obestatin $r = -0.6$, $p < 0.05$).

The analysis of plasma ghrelin levels in patients with severe hypothyroidism after treatment revealed

a significant decrease in peptide concentration ($p < 0.01$) (Table II, Fig. 3). In patients with hyperthyroidism who became euthyroid after treatment, we observed a significant increase in plasma ghrelin level ($p = 0.04$) (Table II, Fig. 4). There was no significant difference between plasma obestatin level in hypo- or hyperthyroid patients before and after treatment ($p = 0.7$ and $p = 0.4$, respectively).

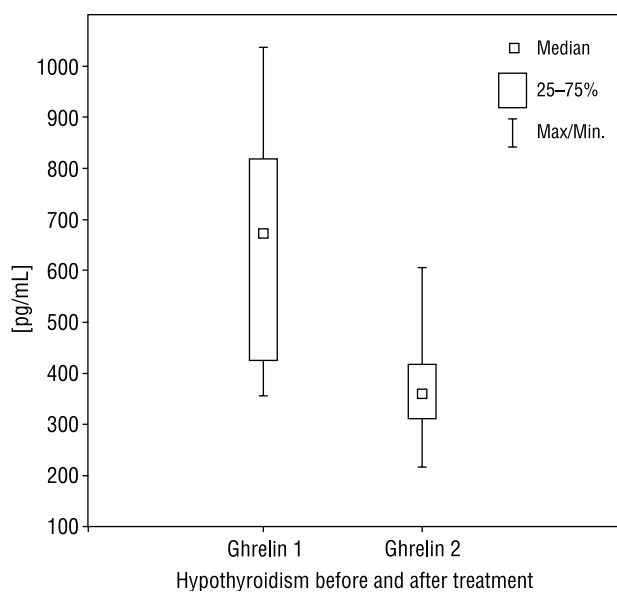


Figure 3. Plasma ghrelin levels in hypothyroid patients (with Hashimoto's thyroiditis or after radioiodine treatment) before (ghrelin 1) and after treatment (ghrelin 2)

Rycina 3. Stężenie ghreliny w osoczu chorych z niedoczynnością tarczycy (z zapaleniem tarczycy typu Hashimoto lub po leczeniu radiojodem) przed (ghrelin 1) i po leczeniu (ghrelin 2)

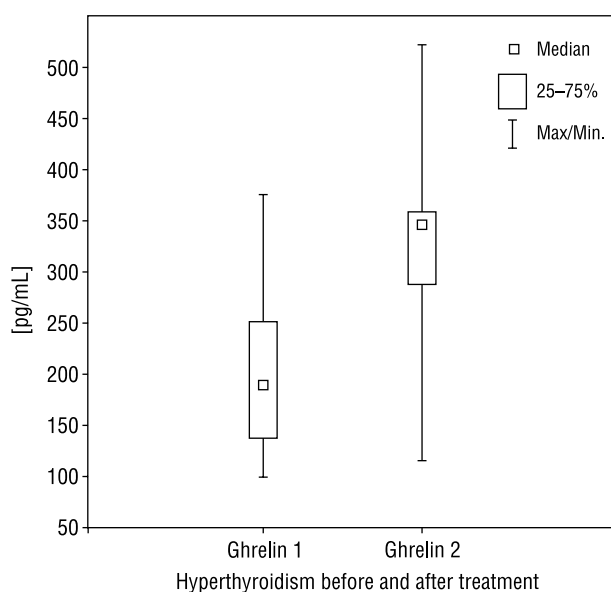


Figure 4. Plasma ghrelin levels in hyperthyroid patients before (ghrelin 1) and after treatment (ghrelin 2)

Rycina 4. Stężenie ghreliny w osoczu chorych z nadczynnością tarczycy przed (ghrelin 1) i po leczeniu (ghrelin 2)

Discussion

Since food intake and body weight are the main factors regulating ghrelin secretion, we might have expected low ghrelin concentrations in hypothyroid patients, who usually gain weight, and high ghrelin level in hyperthyroid patients, who complain of increased appetite and weight loss. However, our results are compatible with most previous studies, that also revealed a high plasma ghrelin concentration in hypothyroid patients [34–36] and low ghrelin level in hyperthyroid patients [34, 36–38, 43–47].

The possible explanation for such results requires a thorough analysis of metabolic disturbances in patients with thyroid dysfunction. It is worth noting that, despite increased body weight, hypothyroidism is not a state of positive energy balance. Thyroid hormones insufficiency does not permit for appropriate use of energy resources. This situation can be compared to starvation, when authentic energy substrates deficiency is observed. Thus, hypothyroidism may be considered as a condition of negative energy balance, such as anorexia nervosa, bulimia and cachexia.

Moreover, previous studies revealed that chronic starvation is accompanied by high ghrelin level and low triiodothyronine concentration [21–23, 49]. Analysing metabolic disturbances not resulting from thyroid dysfunction, such hormonal changes can be explained as two ways of energy saving. Starving increases ghre-

lin secretion to stimulate prometabolic action, and low thyroid hormones level reduces energy expenditure.

In hypothyroidism, thyroid gland is not able to respond to metabolic changes in an appropriate way and ghrelin may act as one of the factors compensating energy balance disturbances.

In our study, the ghrelin level was noticeably high in patients with severe hypothyroidism due to Hashimoto's thyroiditis or after radioiodine treatment. In patients after total thyroidectomy with hypothyroidism induced by 4-week L-thyroxine withdrawal, plasma ghrelin level did not differ from values observed in the control group. The difference between these groups could be explained by the severity of energy balance disorders. The patients with hypothyroidism due to Hashimoto's thyroiditis or after radioiodine treatment had been developing the clinical symptoms over a long period of time. Advanced metabolic changes in this group resulted in considerably increased ghrelin production, and appropriate treatment with L-thyroxine normalised metabolic rate and decreased plasma ghrelin level. The patients after total thyroidectomy were examined after 4-week L-thyroxine withdrawal. Such short discontinuation of hormonal therapy was not able to induce serious metabolic abnormalities. Thus, the clinical image of this group was definitely better and their plasma ghrelin level, although slightly tending to increase, was not significantly higher than in the control group.

Metabolic disturbances could also be responsible for plasma ghrelin changes in hyperthyroid patients, whose metabolism rate, energy expenditure and thermogenesis are considerably increased. In this situation plasma ghrelin reduction may be associated with a transition to a more energy-efficient state, as previously suggested by Riis et al. [43].

Our study revealed that ghrelin correlated positively with TSH and negatively with fT_3 and fT_4 levels. Previously, Kluge et al. demonstrated that exogenous ghrelin increases fT_4 and decreases TSH level in humans [50]. These observations additionally support the hypothesis of possible compensatory role of ghrelin in thyroid dysfunction.

Nevertheless, plasma ghrelin changes may also result from other factors. It is important to underline kidney dysfunction associated with thyroid disorders [51], what may obviously influence ghrelin elimination.

It is worth noting that acylated ghrelin circulates in plasma bounded by lipoproteins [52]. Thyroid dysfunction may alter cholesterol fractions, and this could be another possible explanation for plasma ghrelin changes in hyper- and hypothyroidism.

Previous studies have suggested the influence of insulin level on ghrelin concentration in thyroid disorders [37, 43, 46]. High insulin level observed in hyperthyroid patients due to insulin resistance was suspected to decrease ghrelin release.

The analysis of obestatin changes in thyroid dysfunction revealed significantly lower peptide concentration in hyperthyroid patients. We did not observe any differences between hypothyroid groups and healthy subjects. Furthermore, obestatin correlated positively with TSH and negatively with free thyroid hormones. It is still unclear whether obestatin is a biologically active peptide. However, we cannot exclude that obestatin released together with ghrelin modulates its activity, what has been suggested by Zizzari et al. [53].

Since ghrelin and obestatin have been shown to derive from the same precursor, the studies usually revealed parallel changes of both peptides concentrations [32, 36]. However, recent studies have shown that ghrelin and obestatin may be produced independently and alternative transcription of the preproghrelin gene could lead to an excess of one of the sibling peptides [54].

In our study, ghrelin and obestatin levels correlated positively in the whole study group, which rather confirms the common origin of both peptides. Moreover, such an observation probably disproves the primary hypothesis of opposite biological effects of ghrelin and obestatin, because in this case the rise of one peptide should rather cause the decrease of the other.

Ghrelin and obestatin plasma levels are technically difficult to assess [48]. However, it is worth the effort to conduct further studies considering their biological function in humans.

Conclusions

Plasma ghrelin changes in thyroid dysfunction may indicate a compensatory role of this peptide in metabolic disturbances. In a state of severe hypothyroidism, high ghrelin concentration may lead to appropriate use of energy resources. In hyperthyroidism, which is accompanied by increased metabolic rate and energy expenditure, low ghrelin level may be associated with the transition to a more energy-efficient state, as previously suggested by Riis et al. [43]. The positive correlation between ghrelin and obestatin concentrations may suggest a modulatory role of obestatin in these processes.

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