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The role of appetite-controlling hormones in the development of eating disorders in diabetic 2 patients

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ABSTRACT

Binge eating disorder (BED) and night eating syndrome (NES) are common eating disorders (EDs) in individuals with diabetes type 2 (DT2). They worsen metabolic control, have a negative impact on physical and mental health and reduce quality of life. The roles of appetite-controlling hormones – leptin and ghrelin – is not clear enough in EDs and need to be investigated in order to establish new approaches and markers of EDs. Aim: To assess the difference in leptin and ghrelin levels in DT2 patients with and without EDs. 57 patients with DT2 were involved in the study. After physical examination and screening for EDs, blood samples for leptin and ghrelin measuring were obtained.
Results: 19 participants (33.3%) were screened positively for ED (BE or NES). Leptin levels were higher in participants with ED ($p<0.05$). Conversely, ghrelin levels were lower in those with BE or NES ($p<0.05$).
Leptin level is increased in DT2 individuals with BED and NES, whereas ghrelin is decreased. Leptin and ghrelin alterations maintain emotional eating, increase the frequency of binge and night eating episodes. In screening for EDs, assessing leptin and ghrelin levels will facilitate obesity reduction and improve metabolic control in diabetic patients.

INTRODUCTION

Obesity is one of the largest non-infectious epidemics in the 21st century: almost a third of the world's population suffers from this medical condition. The main dangers of excessive adipose tissue are increased risks of diabetes type 2 (DT2), cardiovascular complications, paroxysmal nocturnal dyspnoea, osteoarthritis, etc. [1].

Eating disorders (EDs) can be the cause of overweight or obesity. The most common EDs in individuals with DT2 and obesity are binge eating disorder (BED) and night eating syndrome (NES). The prevalence of BED in DT2 individuals is up to 20% [2], whereas the prevalence of NES is 2.5 – 25.6% [3]. Patients with EDs can face serious obstacles in achieving the target levels of glycemia, glycated hemoglobin (HbA1c) and lipid profile [4].

The essential hormones which control food intake are leptin and ghrelin. Leptin is synthesized by adipocytes of white adipose tissue and having reached the hypothalamus, enhances pre-opiomelanocortin (POMC) neurons expression which leads to alpha-melanocyte-stimulating hormone (α-MSH) release in the satiety center (ventromedial nuclei in the hypothalamus), and hunger reduction. Ghrelin is a brain-gut hormone that is mainly produced by the stomach. It has the opposite effect on eating behavior: ghrelin increases neuropeptide Y/agouti-related peptide (NPY/AgRP) neurons expression in arcuate nuclei (ARC), and they both raise the activity of the lateral hypothalamus which is considered to be the hunger center. Furthermore, ghrelin reduces POMC expression and inhibits the feeling of satiety [5].

Our study aimed to assess the levels of leptin and ghrelin in overweight/obese patients who suffer from DT2 and hyperphagic EDs, as compared to that of overweight or obese diabetic individuals without EDs.

MATERIALS AND METHODS

The study involved 57 overweight/obese patients (37 women and 20 men) with DT2. All participants completed the Questionnaire on Eating and Weight Patterns-5 and the Night Eating Diagnostic Questionnaire. The questionnaires we used have proven effectiveness and validity [6].

The clinical trial was approved by the Commission of Danylo Halytsky Lviv National Medical University (LNMU)

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on Bioethics. Recruitment of participants was conducted on the Department of Endocrinology of LNMU. All participants signed informed consent, in accordance with the Helsinki Declaration of the World Medical Association on "Ethical principles of medical research with human participation as the object of study".

The analysis of the questionnaires showed that 19 of 57 patients (15 women and 4 men) suffered from BED (n = 11) or NES (n=8). Participants were divided into 2 groups: group 1 – patients with DT2 and without EDs (n=38 patients, 23 women and 15 men; age – 59.6±6.5 years, BMI – 31± 3 kg/m^2); group 2 – patients with DT2 and one of the EDs – BED or NES (n=19, 15 women and 4 men, mean age – 60.9±7.8 years, BMI– 26.9±1.4 kg/m^2). Exclusion criteria were: diabetes type 1, age <40 and >80 years, BMI <24.9 kg/m^2, use of antidepressants for the last 6 months. The control group consisted of 14 volunteers (10 women and 4 men, age – 48.8±8.2 years, BMI – 26.9±1.4 kg/m^2). Criteria for inclusion in the control group were: overweight or obesity; no diabetes mellitus or impaired glucose tolerance; no EDs.

All participants were examined, including height and weight measurements. Biological characteristics included fasting and postprandial glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), creatinine, glycated hemoglobin (HbA1c). The level of leptin in the serum was measured by enzyme-linked immunosorbent assay (ELISA), using a set of reagents "Sandwich ELISA Kit" (Germany). Ghrelin was measured by ELISA, using a set of reagents "Human Ghrelin Elisa Kit (Ghrelin-28)" (Germany). Before blood collection, all participants underwent fasting for 10 hours.

All calculations were performed using Statistica 6.1. Data are reported as mean ± SD. The groups were compared using an unpaired t-test. Statistical significance was set at p<0.05.

RESULTS

After processing the results, it was found that all groups of patients did not differ statistically (Table 1). Only the control group differed in the level of HbA1c. The prevalence of BED in our study was 19,3%, whereas the prevalence of NES – 14%.

Table 1. Clinical and biological characteristics of the groups included in the study

Characteristics	Group 1 M±m	Group 2 M±m	Control group M±m
Age, years	59.6±6.5; p>0.05	60.9±7.8; p_1>0.05	48.8±8.2; p_2>0.05
Height, cm	167.3±6.1; p>0.05	165.1±6.4; p_1>0.05	173±5.25; p_2>0.05
Weight, kg	87.4±7.8; p>0.05	87.7±9.1; p_1>0.05	80.5±5.25; p_2>0.05
BMI, kg/m^2	31±3; p>0.05	32.3±3.8; p_1>0.05	26.9±1.4; p_2>0.05
HbA_1c, %	10.2±1.8; p>0.05	10.3±1.3; p_1<0,01*	4.3±0.4; p_2<0.01*
ALT, U/L	29±11; p>0.05	27.3±7.1; p_1>0.05	16.7±2.5; p_2>0.05
AST, U/L	24.4±5.6; p>0.05	23.7±4.6; p_1>0.05	21.3±3.9; p_2>0.05
Creatinine, umol/L	82±12.3; p>0.05	93.1±29.5; p_1>0.05	89.4±11; p_2>0.05
Leptin, ng/ml	7.9±3.8; p<0.05	11.02±6.3; p_1<0.05	6.9±2.8; p_2>0.05
Ghrelin, ng/ml	23.3±14.4; p<0.05	14.3±11.6; p_1<0.05	21.2±10.4; p_2>0.05

Note: p – statistical significance between the 1st and 2nd group;
p_1 – statistical significance between the 2nd and control group;
p_2 – statistical significance between the 1st and control group

According to our results, leptin level in the 2nd study group was significantly higher (p<0.05) than in the 1st and control group (Figure 1). The average leptin level in group 1 was 7.9±3.8 ng/ml; in the 2nd group – 11.02±6.3 ng/ml; in the control group – 6.9±2.8 ng/ml. Ghrelin concentrations were lower in group 2 when compared with the 1st and control groups (p <0.05) (Figure 2): in the 1st group, its level was 23.3±14.4 ng/ml; in the 2nd group – 14.3±11.6 ng/ml; in the control group – 21.2±10.4 ng/ml.

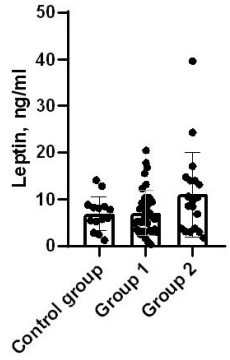

Figure 1. Dispersion of participants according to leptin levels

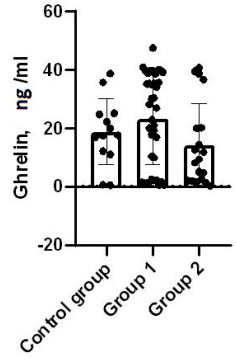

Figure 2. Dispersion of participants according to ghrelin level

DISCUSSION

EDs are very often accompanied by DT2 and obesity. BED is characterized by recurring binge eating at least once a week for over a period of 3 months while experiencing a lack of control and guilt after overeating without compensatory behaviors. The prevalence of BED in the general population is 1.5% [7], among patients with DT2 – up to 20% [2], and in our study – 19.3%.

Another type of EDs that we studied was NES – consumption of 25% or more of the total daily calorie after the evening meal [8]. This disorder includes insomnia, nocturnal hyperphagia, and morning anorexia that persist for at least 3 months [9]. The prevalence in the general population is about 1.1% [10], in DT2 individuals – 2.5 – 25.6% [3] and in our study – 14%.

Eating behavior is regulated by the complex system of arcuate (ARC), dorsomedial, paraventricular, ventromedial nuclei and lateral hypothalamus. ARC are the first-order neurons that are directly contact with appetite-related hormones, such as leptin and ghrelin [5]. Leptin is synthesized by adipocytes of white adipose tissue and it

increases POMC-neurons expression in ARC, which leads to α-MSH release in ventromedial nuclei. Moreover, leptin inhibits the orexigenic pathway by decreasing NPY/AgRP expression. This results in appetite reduction and weight loss [5]. Ghrelin is a brain-gut hormone that is mainly produced by the stomach. Ghrelin, having reached ARC, increases NPY/AgRP release in the lateral hypothalamus and decreases POMC expression. In summary, it increases hunger and provokes food consumption [5].

It would be reasonable to assume that overweight/obese individuals have low leptin and high ghrelin levels since they overeat and gain weight. However, patients with DT2 and overweight/obesity develop high levels of leptin and decreased ghrelin concentrations. High leptin levels can be explained by triggering leptin resistance due to excessive body mass and reduced sensibility of ARC to leptin. In our study, we demonstrated that individuals with BED have higher leptin levels than non-binge-eaters. In addition, leptin inhibits the dopamine system and it results in hyperactivity of dopaminergic circuits towards external reward predictive stimuli. Patients with BED often have impulsivity and reward hyposensitivity. Furthermore, leptin levels positively correlate with the frequency of binge episodes and emotional eating [11].

In our study, leptin level was high in individuals with NES. However, among the night eaters, leptin level did not reach normal values and was low during the night. This effect can explain the absence of satiety in these patients and the urge to wake up and eat in the night.

Generally, lower ghrelin levels are associated with conditions of high energy storage (hyperglycemia, insulin resistance, obesity). Binge eating behavior downregulates the ghrelin system in response to overeating or to excess body weight. This, in turn, leads to decreased ghrelin levels in BED patients. Our study reveals that overweight/obese patients with BED have lower ghrelin levels than non-binge-eaters.

Ghrelin also affects reward-related food intake: consumption of palatable food activates ventral tegmental area neurons, which are sensitive to food, alcohol and drug abuse, consequently, ghelin initiates dopamine release in the nucleus accumbens – the center of reward modulation and pleasure processing. Thus, the action of ghrelin on dopamine neuronal activity suggests its ability to influence the brain reward system and reward-related food intake [12].

There are a few studies that assessed ghrelin levels in NES individuals. In our work, ghrelin was significantly lower in the NES group, which may contribute to the tendency for frequent awakenings in persons with NES [13]. In our research, we found lower ghrelin levels in NES patients.

CONCLUSIONS

Leptin and ghrelin are the essential hormones that control food intake by affecting ARC and influencing the brain-reward system. In individuals with EDs, leptin and ghrelin alterations maintain emotional eating and increase the frequency of binge and night eating episodes. These changes have homeostatic and non-homeostatic implications in the pathogenesis of EDs. Leptin and ghrelin can be markers for BED and NES. However, further investigation of leptin and ghrelin changes during the night in individuals with NES is strongly needed to understand NES pathophysiology. Screening for EDs will facilitate obesity reduction and improve metabolic control in diabetic patients.

CONFLICT OF INTERESTS

No competing interests.

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