THE ROLE OF LEU260PHE POLYMORPHISM OF THE RECEPTOR GENE TO GLP-1 INCRETIN IN THE PATHOGENESIS OF DIABETES TYPE 2 DIABETES WITH OBESITY

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BACKGROUND: Glucagon-like peptide-1 (GLP-1) stimulates the proliferation of β-cells, enhances their resistance to apoptosis and increases glucose-dependent insulin secretion.

AIMS: Study of the relationship of Leu260Phe polymorphism (rs1042044) of the GLP-1R gene with postprandial hormone production (C-peptide, insulin, ghrelin, GLP-1) in obese patients with type 2 diabetes.

MATERIALS AND METHODS: A total of 174 patients, 82 patients with obesity with type 2 diabetes (BMI=40.4±14.3 kg/m²) and 92 conditionally healthy donors (BMI=22.6±2.7 kg/m²) were studied. The material for the study was venous blood taken on an empty stomach and 60 minutes after the test breakfast. Genotyping was performed by PCR using the sets for determining polymorphism (rs1042044) of the GLP-1R gene (Sintol) and the amplificator (CFX96 BioRad, USA). Plasma hormone levels were evaluated by flow fluorimetry (Bio-PlexProteinAssay System, Bio-Rad, USA) using commercial test systems (Bio-PlexProHumanDiabetes 10-Plex Assay, Bio-Rad, USA). Statistical analysis and graphs were obtained at R Statistical Software.

RESULTS: A violation of postprandial production of GLP-1 and ghrelin after a test breakfast in obese patients with type 2 diabetes was found. A postprandial increase in C-peptide levels of 3.25 [1.83;4.16] ng/ml and insulin 3048 [1978;4972] ng/ml in carriers of the CC genotype compared with carriers of the CA genotype in the group of patients with obesity with type 2 diabetes. In carriers of the CA genotype, there was a decrease in the C-peptide level of 2.21 [1.8;2.49] ng/ml and insulin 1462 [1146;2304] ng/ml with a constant concentration of GLP-1. The postprandial level of ghrelin in carriers of the CA genotype of the Leu260Phe polymorphism increased to 118 [96.1;157] ng/ml compared to carriers of the AA genotype [86;109] ng/ml.

CONCLUSION: The presence of the CC genotype of the Leu260Phe polymorphism of the GLP-1 receptor gene is associated with an increase in postprandial plasma levels of C-peptide and insulin in obese patients with type 2 diabetes, and the CA genotype with a decrease in these indicators and an increase in ghrelin content.

KEYWORDS: type 2 diabetes; obesity; polymorphism; GLP-1R; insulin; ghrelin

РОЛЬ ПОЛИМОРФИЗМА LEU260PHE ГЕНА РЕЦЕПТОРА К ИНКРЕТИНУ GLP-1 В ПАТОГЕНЕЗЕ САХАРНОГО ДИАБЕТА 2 ТИПА ПРИ ОЖИРЕНИИ

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ОБОСНОВАНИЕ. Глюкагоноподобный пептид-1 (GLP-1) стимулирует пролиферацию β-клеток, усиливает их устойчивость к апоптозу и повышает глюкозозависимую секрецию инсулина.

ЦЕЛЬ. Изучение взаимосвязи полиморфизма Leu260Phe (rs1042044) гена GLP-1R с постпрандиальной продукцией гормонов (C-пептида, инсулина, грелина, GLP-1) у больных ожирением с сахарным диабетом 2 типа (СД2).

МЕТОДЫ. Обследованы 174 пациента, 82 больных ожирением с СД2 (ИМТ=40,4±14,3 кг/м²) и 92 условно здоровых доноров (ИМТ=22,6±2,7 кг/м²). Материалом для исследования служила венозная кровь, взятая натощак и через 60 минут после тестового завтрака. Генотипирование проводилось методом полимеразной цепной реакции (ПЦР) c использованием наборов для определения полиморфизма (rs1042044) гена GLP-1R (‘Синтол’) и амплификатора (CFX96 BioRad, США). Плазменный уровень гормонов оценивали методом проточной флюориметрии (Bio-Plex Protein Assay System, BioRad, США) с использованием коммерческих тест-систем (Bio-Plex Pro Human Diabetes 10-Plex Assay, Bio-Rad, США). Статистический анализ и графики были получены в R Statistical Software.

Заключение. Наличие генотипа СС полиморфизма Leu260Phe гена GLP-1R ассоциировалось с повышением постпрандийных плазменных уровней C-пептида и инсулина у больных ожирением с СД2, а генотипа АА – со снижением этих показателей и ростом содержания грелина.

Ключевые слова: сахарный диабет 2 типа; ожирение; полиморфизм; GLP-1R; инсулин; грелин.

Abdominal obesity is the primary risk factor for the development of type 2 diabetes mellitus (DM2) [1]. In insulin resistance, the ability of insulin to have an effect on target tissues decreases, which impairs metabolic processes [2]. Many biologically active substances with systemic and local actions, such as leptin, glucagon, ghrelin and incretins, are involved in the development of insulin resistance.

Secretion of orexigenic hormone, known as the 'hunger hormone,' decreases postprandially. This hormone participates in the regulation of energy balance, including glucose metabolism [3]. In contrast, incretins are secreted postprandially by cells of the small intestine and stimulate glucose-dependent insulin secretion [4]. Incretin-stimulated postprandial production of insulin (the 'incretin effect') accounts for 20% to 50% of insulin secretion [5]. In addition, incretins contribute to the proliferation of pancreatic β-cells and inhibit their apoptosis [5]. In particular, the anti-diabetic effects of glucagon-like peptide 1 (GLP-1) incretin consist of glucose-dependent stimulation of insulin by enhancement of transcription of its gene [6].

GLP-1 exerts physiological effects by activating the GLP-1R receptor, which belongs to subclass B of the GPCR family [8]. GLP-1R is predominantly expressed in Langerhans islet cells and is also expressed in other tissues, including the fat depot [9]. GLP-1R contributes to depolarisation of the β-cell membrane by inhibiting K+ channels, which increases the influx of Ca2+ into the cells, resulting in exocytosis of insulin from β-cells [8]. Thus, GLP-1R activation is associated with important components of insulin biosynthesis and secretion [8].

The objectives of this study were to search for associations between the Leu260Phe polymorphism of the GLP-1R gene and an increased risk of developing obesity in patients with DM2, and to evaluate the relationship of genotype variants of the polymorphisms under study with serum levels of insulin, C-peptide, GLP-1 and ghrelin in patients of the Slavic population.

AIM

This study aimed to assess the relationship between Leu260Phe polymorphic variants (rs1042044) of the GLP-1R gene and postprandial production of hormones of the gastroduodenal zone (insulin, C-peptide, ghrelin and GLP-1) in obese patients with DM2.
without sugar (150 g), containing 9.1 g protein, 88.1 g carbohydrate and 10.6 g fat. The total caloric content of the breakfast was 466 kcal.

Recording of outcomes
A diagnosis of DM2 was established based on examination in a specialised hospital, guided by the criteria for diagnosis of diabetes mellitus and other types of hyperglycaemia of the World Health Organization (WHO) (1999–2013). According to the criteria recommended by the WHO (1999, 2000), the diagnosis of obesity was established.

Genomic DNA was isolated from blood cells using the QIAampDNA Minikit (QIAGEN, Germany). Genotyping was performed by real-time polymerase chain reaction (PCR) using the sets for determining the Leu260Phe polymorphism (rs1042044) of the GLP-1R gene (Syntol) and the amplificator CFX96 (BioRad, USA). The single nucleotide polymorphism Leu260Phe is localised in the seventh exon of the GLP-1R gene; in the wild type, the CC genotype encodes the amino acid phenylalanine, and in the mutant (minor) variant of the AA genotype, it encodes leucine [10].

The glucose level was studied using an automatic biochemical analyser Furuno CA-180 (Furuno Electric Company, Japan) and DiaSys test systems (DiaSys Diagnostic Systems, Germany). To assess insulin sensitivity, the HOMA-IR (homeostasis model assessment–insulin resistance) index was calculated by the formula HOMA-IR = (Ins x GI) / 22.5, where Ins is fasting plasma insulin (μU/ml) and GI is fasting plasma glucose (mmol/l). The plasma levels of insulin, C-peptide, ghrelin and GLP-1 in the fasted state and after a test breakfast were studied by flow fluorimetry (Bio-PlexProHumanDiabetes 10-Plex Assay, Bio-Rad).

Ethical considerations
All participants in the study signed informed voluntary consent forms. Permission to conduct the study was obtained from the local ethical committee (protocol No. 2 of the Immanuel Kant Baltic Federal University, March 6, 2017).

Statistical analysis
Sample size calculation
Sample size was not preliminary calculated.

Data analysis
Statistical analysis was performed using the R Statistical Software (version 3.3.1) programme. Normal distribution of data was evaluated by the Kolmogorov–Smirnov test. For normally distributed values, hypotheses on the equality of the average sample values were tested using Student’s t-test. For non-normally distributed values, the significance of differences between the samples was calculated using the nonparametric Mann–Whitney test. Relationships between the studied parameters were examined using correlation analysis by Spearman’s method. Differences were considered significant if \( p < 0.05 \).

RESULTS

Participants
The study included 174 participants; 82 had alimentary-constitutional obesity with abdominal localisation and DM2 (body mass index [BMI] 40.4 ± 14.3 kg/m², age 46.5 ± 10.1 years, 27 men and 55 women), and 92 were conditionally healthy donors with normal anthropometric and biochemical parameters (BMI 22.6 ± 2.7 kg/m², age 37.5 ± 5.1 years, 57 men and 35 women).

Primary study outcomes
We found no significant differences between obese patients with DM2 and age- and gender-matched control participants in biochemical parameters, content of hormones in the blood plasma and the results of genotyping. In DM2 patients, the serum glucose level was 7.80 [6.64; 10.39] mmol/l, significantly greater than the control group value of 5.23 [4.90; 5.45] mmol/l (\( p < 0.05 \)) (Table 1). In DM2 patients, the HOMA-IR index value was 12.4 [9.7; 23.5] relative units, significantly greater than the control group value of 1.17 [0.79; 1.65] relative units (\( p < 0.05 \)). As expected, the contents of C-peptide, insulin and glucose in plasma or serum in DM2 patients were significantly greater than the control group values (\( p < 0.05 \)). Postprandial changes in C-peptide and insulin (2.35 [1.83; 3.7] and 2017 [1356; 3900] ng/ml, respectively) were significantly greater in DM2 patients than in the control group (\( p < 0.05 \)) (Fig. 1).

In the control group, after the test breakfast, the plasma level of GLP-1 increased 1.5 times to 264 [248; 302] ng/ml compared with the fasting level of 200 [190; 221] ng/ml (\( p < 0.05 \)), and the plasma level of ghrelin decreased compared with its fasting level (\( p < 0.05 \)) (Fig. 1). In obese patients with DM2, the plasma level of ghrelin in the fasted state did not significantly change after the test breakfast. The postprandial ghrelin level in obese patients with DM2 significantly exceeded that in the control group (\( p < 0.05 \)). The presence of correlations between the levels of ghrelin and GLP-1 in the fasted state and after the test breakfast was noted (\( r = 0.83 \) and \( r = 0.83 \), respectively; \( p < 0.01 \)) (Fig. 2).

Next, the levels of the metabolites under study in relation to the genotype of the rs1042044 polymorphism of the GLP-1R gene were investigated. The frequency distribution of alleles and genotypes of the rs1042044 polymorphism of the GLP-1R gene is presented in Table 2.

Among obese patients with DM2 who were carriers of the CC and CA genotypes, increases in postprandial insulin levels to 3048 [1978; 4972] and 1462 [1146; 2304] ng/ml, respectively, compared with the fasting levels were noted (\( p < 0.05 \)). At the same time, postprandial increases in C-peptide levels to 3.25 [1.83; 4.16] ng/ml and in insulin levels to 3048 [1978; 4972] ng/ml were noted; the increases were almost twofold greater in the CC genotype carriers (Leu/Leu) than in the CA genotype carriers (Leu/Phe) (\( p < 0.05 \)) (Table 3).

The postprandial level of ghrelin in DM2 patients increased in carriers of the CA genotype of the Leu260Phe polymorphism of the GLP-1R gene to 118 [96.1; 157] ng/ml, compared with 98 [86; 109] ng/ml in carriers of the AA genotype (\( p < 0.05 \)).

DISCUSSION

Summary of the primary result of the study
A disruption of postprandial production of GLP-1 and ghrelin in obese patients with DM2 after a test breakfast was shown. In patients with genotype CA (Leu/Phe), a normal postprandial insulin level change was noted, unlike that
Fig. 1. Levels of hormones of the gastrointestinal tract (C-peptide, insulin, ghrelin and glucagon-like peptide [GLP-1]) in the groups under study. Data are presented as median and interquartile range (Me [Q1; Q3]).

Table 1. Serum glucose and HOMA-IR index

<table>
<thead>
<tr>
<th></th>
<th>Serum glucose, mmol/l</th>
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<tbody>
<tr>
<td></td>
<td>Group</td>
<td>Fasting</td>
<td>After breakfast</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy donors</td>
<td>(n = 92)</td>
<td>5.23 [4.90;5.45]</td>
<td>5.5 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Obese patients with DM2</td>
<td>(n = 82)</td>
<td>7.80 [6.64;10.39]</td>
<td>p &lt; 0.05*</td>
<td>11.03 ± 5.23</td>
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</tr>
</tbody>
</table>

* p < 0.05, Mann–Whitney test for independent samples.
Data are presented as median and interquartile range (Me [Q1; Q3]).

DM2, type 2 diabetes mellitus; GLP-1, glucagon-like peptide 1; HOMA-IR, homeostasis model assessment–insulin resistance.
in carriers of other genotypes of the Leu260Phe polymorphism of the GLP-1R gene (p < 0.05). In obese patients with DM2 who were carriers of the CC genotype (Leu/Leu), postprandial increases of 3.25 [1.83; 4.16] ng/ml in C-peptide levels and 3048 [1978; 4972] ng/ml in insulin levels were observed, compared with levels in carriers of the CA genotype (Leu/Phe).

Discussion of the primary result of the study

Despite the increases in postprandial levels of C-peptide and insulin compared with the fasted state, the postprandial content of GLP-1 in the plasma of obese patients with DM2 did not change from its level in the fasted state. This result may indicate a disruption of incretin production in obese patients with DM2, stimulated by the intake of nutrients. Incretins and ghrelin are connected with energy metabolism and regulation of food intake [11]. Ghrelin production reaches its maximum shortly before the usual mealtime, whereas GLP-1 is secreted after intake of nutrients [12]. In obese patients with DM2, the postprandial changes in the studied parameters were different from those in control subjects; there were no significant differences between fasting and postprandial plasma levels of ghrelin and GLP-1. Strong positive correlations between the fasting and postprandial levels of ghrelin and GLP-1 may indicate a disruption of the reciprocal relationship between these analytes in DM2 patients.

Previous studies have shown disruption of carbohydrate metabolism with the infusion of ghrelin in healthy patients [13]. Combined administration of ghrelin and the GLP-1 receptor antagonist exendin (9-39) resulted in more pronounced postprandial glycaemia compared with administration of ghrelin alone in healthy individuals [13]. This effect was due to impaired β-cell function and decreased glucose clearance [13]. In obese patients with DM2 in the present study, the basal level of GLP-1 was higher than that in conditionally healthy donors. It is known that GLP-1 inhibits the negative effect of ghrelin on glucose tolerance. Based on these results, the increase in the basal level of GLP-1 in obese patients with DM2 may be due to the action of a compensatory mechanism.

Changes in the production of insulin and C-peptide in obese patients with DM2 according to different genotypes of the Leu260Phe polymorphism of the GLP-1R gene did not depend on the plasma concentration of GLP-1. The functional role of the Leu260Phe polymorphism of the GLP-1R gene is not fully understood, but several authors have pointed out its role in changing cortisol production [10]. The data obtained in experimental animals and humans demonstrate pronounced insulinotropic and antihyperglycaemic effects of GLP-1R agonists [14, 15].

In obese patients with DM2 with CC (Leu/Leu) and CA (Leu/Phe) genotypes, normal postprandial changes in insulin level were noted. In obese patients with DM2 with the CC (Leu/Leu) or CA (Leu/Phe) genotype, postprandial increases in insulin levels were detected compared with those in the fasted state (p < 0.05). In carriers of the AA genotype of the Leu260Phe polymorphism of the GLP-1R gene, no postprandial increase in insulin level was shown compared with that in the fasted state. In obese patients with DM2 who were carriers of the CC genotype (Leu/Leu), the increases in the postprandial levels of C-peptide and insulin were almost two times higher than those in carriers of the CA genotype (Leu/Phe) carriers.
Thus, we have observed significant disorders of the functional activity of GLP-1R in obese patients with DM2 who were carriers of the AA genotype of the Leu260Phe polymorphism of the GLP-1R gene. There is evidence for a decrease in the functional activity of incretin receptors in pancreatic β-cells with hyperglycaemia [8], which is consistent with our study results. Many studies have shown a loss of the insulinotropic effect of GLP-1 in DM2 patients through impaired incretin signal transmission [16, 17].

Ghrelin is a hunger hormone. Its concentration increases in the fasted state and decreases after meals [18]. This observation does not contradict the results of studies demonstrating a decrease in the level of circulating ghrelin in patients with abdominal obesity and an increase in patients after weight loss [18, 19].

In DM2 patients, regardless of the genotype of the Leu260Phe polymorphism of the GLP-1R gene, the postprandial level of ghrelin did not decrease relative to the fasting values, unlike the results in the control group. However, in obese patients with DM2 who were carriers of the CA genotype of the Leu260Phe polymorphism of the GLP-1R gene, this indicator was higher than that in carriers of the AA genotype and did not differ from that in carriers of the CC genotype (p < 0.05). This observation explains the eating disorder in obese patients in which the feeling of satiety after a meal does not develop.

The location of the Leu260Phe polymorphism within the GLP-1R gene indicates that it can influence the down-regulation of signal transmission from GLP-1 to its receptor, mediating changes in the mature translated protein.

### Table 3. Level of hormones of the gastrointestinal tract in the studied groups according to the variant of the Leu260Phe polymorphism of the GLP-1R gene

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Plasma C-peptide level, ng/ml</th>
<th>Fasting</th>
<th>After breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC (1)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Healthy donors (n = 64)</td>
<td>0.81 [0.79;0.86]</td>
<td>1.67 [1.55;2.45]</td>
<td>1.42 [0.85;2.15]</td>
</tr>
<tr>
<td>Obese patients with DM2 (n = 86)</td>
<td>2.18 [1.66;2.85]</td>
<td>3.25 [1.83;4.16]</td>
<td>2.21 [1.8;2.49]</td>
</tr>
<tr>
<td></td>
<td>CA (2)</td>
<td>0.88 [0.74;1.14]</td>
<td>1.42 [0.85;2.15]</td>
</tr>
<tr>
<td></td>
<td>AA (3)</td>
<td>0.67 [0.66;0.68]</td>
<td>1.03 [0.86;1.2]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Plasma insulin level, ng/ml</th>
<th>Fasting</th>
<th>After breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC (1)</td>
<td>1418 [1116;1688]</td>
<td>482 [473;776]</td>
</tr>
<tr>
<td>Healthy donors (n = 64)</td>
<td>592 [584;631]</td>
<td>1462 [1146;2304]</td>
<td>530 [449;611]</td>
</tr>
<tr>
<td>Obese patients with DM2 (n = 86)</td>
<td>1813 [985;2246]</td>
<td>3048 [1978;4972]</td>
<td>1951 [1264;2638]</td>
</tr>
<tr>
<td></td>
<td>CA (2)</td>
<td>477 [417;657]</td>
<td>1146 [2304]</td>
</tr>
<tr>
<td></td>
<td>AA (3)</td>
<td>460 [392;528]</td>
<td>1191 [2304]</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Plasma GLP-1 level, ng/ml</th>
<th>Fasting</th>
<th>After breakfast</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CC (1)</td>
<td>177 [170;185]</td>
<td>305 [302;319]</td>
</tr>
<tr>
<td>Healthy donors (n = 64)</td>
<td>68.95 [52.7;94.9]</td>
<td>55.5 [49.5;61.7]</td>
<td>66.3 [48.1;90]</td>
</tr>
<tr>
<td>Obese patients with DM2 (n = 86)</td>
<td>68.95 [55;96.9]</td>
<td>74.2 [68.95;61.7]</td>
<td>98 [86;109]</td>
</tr>
<tr>
<td></td>
<td>CA (2)</td>
<td>216 [202;239]</td>
<td>248 [234;252]</td>
</tr>
<tr>
<td></td>
<td>AA (3)</td>
<td>138 [123;154]</td>
<td>123</td>
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<table>
<thead>
<tr>
<th>Genotype</th>
<th>Plasma ghrelin level (ng/ml)</th>
<th>Fasting</th>
<th>After breakfast</th>
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<tbody>
<tr>
<td></td>
<td>CC (1)</td>
<td>68.95 [52.7;94.9]</td>
<td>55.5 [49.5;61.7]</td>
</tr>
<tr>
<td>Healthy donors (n = 64)</td>
<td>68.95 [55;96.9]</td>
<td>74.2 [68.95;61.7]</td>
<td>98 [86;109]</td>
</tr>
<tr>
<td>Obese patients with DM2 (n = 86)</td>
<td>74.9 [55;96.9]</td>
<td>112 [85;120]</td>
<td>98 [86;109]</td>
</tr>
<tr>
<td></td>
<td>CA (2)</td>
<td>84.8 [43.9;122.8]</td>
<td>65.2 [50.8;93.3]</td>
</tr>
<tr>
<td></td>
<td>AA (3)</td>
<td>78.6 [49.5;119]</td>
<td>66.3 [48.1;90]</td>
</tr>
</tbody>
</table>

* p < 0.05, Mann–Whitney test for independent samples.

Data are presented as median and interquartile range (Me [Q1; Q3]).

DM2, type 2 diabetes mellitus; GLP-1, glucagon-like peptide 1.
The aspects of the parameters of carbohydrate metabolism in obesity and their relationship with the Leu260Phe polymorphism of the GLP-1R gene, as shown in this study, may be of interest for practical health care and be used to develop new pathogenetic approaches to the prevention, diagnosis, treatment and monitoring of treatment of DM2 with obesity.

**ADDITIONAL INFORMATION**

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**Conflict of interest**

The authors declare no obvious or potential conflicts of interest related to the publication of this article.

**Authors’ contributions**

D. A. Skuratovskaya analysed the data, wrote the text, processed the materials and performed genotyping by PCR; M. A. Wulf was involved in the formation of patient databases and the analysis of anthropometric and biochemical indicators; E. V. Kirienkova analysed the data and determined the hormone levels; N. I. Mironyuk performed the enrolment and exclusion of patients included in the study and diagnosed the presence of type 2 diabetes; P. A. Zatolokin collected biomaterial during planned laparoscopic surgeries; L. S. Litvinova analysed the data and wrote the text.

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**CONCLUSION**

In obese patients with DM2 with the genotype Leu/Leu (CC) or Leu/Phe (CA) of the Leu260Phe polymorphism of the GLP-1 receptor gene, increases in postprandial plasma levels of C-peptide and insulin were observed, which were more pronounced in carriers of the CC genotype. In obese patients with DM2 who were carriers of the CA genotype of the Leu260Phe polymorphism of the GLP-1R gene, an increased level of ghrelin was observed compared with that in carriers of the AA genotype; a disruption of the reciprocal relationship between plasma ghrelin and GLP-1 in this group of patients may indicate the involvement of these hormones in eating disorders. On the basis of the results, we suggest that the most pronounced effect during therapy with GLP-1R agonists can be expected in DM2 patients with the Leu/Leu (CC) genotype of the Leu260Phe polymorphism of the GLP-1R gene.

**Limitations of the study**

A limitation of this study is the small number of participants.

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