Особенности углеводного обмена и секреции гормонов инкретинового ряда у пациентов с болезнью Иценко–Кушинга и акромегалией

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Цель. Анализ ритма и уровня секреции инкретинов у пациентов с акромегалией и болезнью Иценко–Кушинга (БИК) в зависимости от выявленных нарушений углеводного обмена.

Материалы и методы. В исследование были включены 62 пациента: 20 — с БИК, 21 — с акромегалией, 21 — контрольная группа. Контрольную группу составили лица без нарушений углеводного обмена, без БИК и акромегалии, сопоставимые по индексу массы тела (ИМТ) и возрасту с исследуемыми больными. Всем пациентам был проведен оральный глюкозотолерантный тест (ОГТТ) с 82,5 г моногидрата глюкозы с определением глюкозы плазмы крови исходно и на 120-й минуте теста; исходно, на 30-й и 120-й минуте производился забор крови для исследования гормонов инкретинового ряда (ГИП, ГПП-1), глюкагона и грелина.

Результаты. Частота встречаемости ранних нарушений углеводного обмена была выше в группе пациентов с БИК по сравнению с группой пациентов с акромегалией. Для пациентов с БИК и акромегалией было характерно отсутствие подавления глюкагона в ответ на ОГТТ. Уровни секреции инкретинов (ГИП и ГПП-1) у пациентов с БИК и акромегалией с нарушениями и без нарушений углеводного обмена не отличались между собой.

Заключение. Не получено убедительных данных о вкладе классических гормонов-инкретинов (ГИП и ГПП-1) в развитие нарушений углеводного обмена при БИК и акромегалии. Однако оба этих заболевания характеризуются высокой как базальной, так и стимулированной концентрацией грелина и глюкагона. Вероятно, эти два гормона в большей степени определяют нарушение углеводного обмена при БИК и акромегалии.

Ключевые слова: акромегалия; болезнь Иценко–Кушинга; нарушения углеводного обмена; инкретины, нейропептиды

Features of carbohydrate metabolism and incretin secretion in patients with Cushing disease and acromegaly

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Aim. This study aims to analyse the rhythm and levels of incretins and neuropeptides secretion in patients with Cushing disease (CD) and acromegaly, and thus specify the pathogenesis of carbohydrate metabolism disturbances.

Materials and methods. In this study, 42 patients (mean age, 37.5 years) with CD and acromegaly were enrolled. All patients were newly diagnosed with CD and acromegaly, and none had a history of previous drug therapy, radiotherapy or pituitary surgery. All patients underwent OGTT, during which glucose, glucagon, GLP-1, GLP-2, GIP and ghrelin were evaluated at 0, 30 and 120 min, respectively.

Results. During OGTT, glucose levels were not significantly different between the groups. The relevance of pre-diabetes was higher in patients with CD. In these patients, while glucagon levels were substantially higher at all cut-off points than those in controls (p = 0.001), GIP secretion was slightly lower. The acromegaly group was characterised by an inverse rhythm of GIP secretion with no peak level at 30 min. In addition, GLP-1 levels were significantly higher in patients with CD (p = 0.047). Similarly, GLP-2 levels were also significantly higher in patients with CD than in those with acromegaly and controls (p = 0.001). Finally, ghrelin levels were significantly higher in patients with CD (p = 0.013) and acromegaly (p = 0.023).

Conclusion. More pleiotropic actions of glucocorticoids can explain the higher relevance of carbohydrate metabolism disturbances in patients with CD. This can also be explained by higher levels of glucagon secretion, which do not depend on the type of carbohydrate metabolism disorder and are stimulated by a direct action of glucocorticoids on the glucagon receptor. GIP and GLP-1 secretion in patients with CD and acromegaly are characterised by the inverse rhythm with no peak levels, implying that these hormones do not play a crucial role in the development of carbohydrate disturbances in these patients. In contrast, GLP-2 and ghrelin seem to influence and potentially regulate glucose homeostasis in patients with CD and acromegaly.

Keywords: acromegaly; Cushing disease; carbohydrate metabolism disturbances; incretins; neuropeptides
Acromegaly and itsenko–Cushing’s disease (ICD) are two of the most severe neuroendocrine disorders and are characterised by excessive secretion of somatotropic and adrenocorticotropic hormones by a pituitary tumour. The severity of acromegaly and ICD is attributed to multiple complications that hinder radical treatment and lead to disability or even death. In the Russian population, up to 56% and 50% of cases of acromegaly and endogenous hypercorticisim, respectively, present with glucose metabolism disorders [1]. Studying glucose metabolism in patients with acromegaly and ICD has a particular clinical significance due to the high frequency of glucose metabolism disorders in these patients as well as difficulties associated with selecting an appropriate antihyperglycaemic therapy [2]. The efficacy of hyperglycaemia control is usually low in these diseases owing to the immense difficulty in controlling the impact of the primary disease and also of specific therapies that trigger hyperglycaemia.

Recently, there has been an increasing research interest in incretin hormones (gastrointestinal hormones involved in the regulation of glucose metabolism) and their secretion in patients with various glucose metabolism disorders. However, to date, there have been no comprehensive studies on the functioning of the incretin system in patients with excessive glucose metabolism disorders and patients who have never received any therapy affecting glucose metabolism [3, 4]. The exclusion criteria were as follows: pregnancy or lactation, ectopic adrenocorticotropic hormone (ACTH) syndrome, acute or chronic pancreatitis or inflammatory bowel disease (Crohn’s disease, ulcerative colitis).

**STUDY DESIGN**

This cross-sectional study was conducted at the Endocrinology Research Centre. Patients were recruited for one year. A cross-sectional study design was used, with a single patient examination performed by a physician.

**METHODS**

**STUDY DESIGN**

This cross-sectional study was conducted at the Department of Neuroendocrinology and Osteopathy of the Endocrinology Research Centre. Patients were recruited between November 2014 and November 2015.

A total of 62 patients were enrolled: 20 of which had ICD, 21 had acromegaly and 21 comprised a control group.

The mean age of participants was 41.8 years. The sample included 20 males (32.26%) and 42 females (67.74%).

The control group comprised individuals without glucose metabolism disorders, ICD or acromegaly and were matched for age and body mass index (BMI).

**ELIGIBILITY CRITERIA**

Inclusion criteria were as follows: patients aged >18 years with newly diagnosed acromegaly or ICD who have never received any therapy affecting glucose metabolism (somatostatin analogues), patients with no diagnosis of glucose metabolism disorders and patients who have never received any oral hypoglycaemic agents.

The exclusion criteria were as follows: pregnancy or lactation, ectopic adrenocorticotropic hormone (ACTH) syndrome, acute or chronic pancreatitis or inflammatory bowel disease (Crohn’s disease, ulcerative colitis).

**STUDY CONDITIONS**

The study was conducted at the Endocrinology Research Centre.

**DURATION OF THE STUDY**

Patients were recruited for one year. A cross-sectional study design was used, with a single patient examination performed by a physician.

**DESCRIPTION OF MEDICAL INTERVENTION**

All patients underwent an oral glucose tolerance test (OGTT) with 82.5 g of glucose monohydrate. Blood specimens were collected at 0, 30 and 120 min after glucose load. Blood samples for the assessment of incretin hormones were drawn using aprotinin tubes. At time-point ‘0’, liver function tests were performed, and glycated haemoglobin and hormone levels (glucagon, GIP, GLP-1 and ghrelin) were measured. Samples taken at time-points 30 and 120 min were tested for glucose and selected hormones (glucagon, GIP, GLP-1 and ghrelin). Time-points were selected according to previous studies describing the secretion of incretin hormones in individuals without neuroendocrine disorders during an OGTT. These studies demonstrated that concentrations of GIP and GLP-1 peaked at a time-point of 30 min but returned to baseline after 120 min [12, 13].

**PRIMARY OUTCOME OF THE STUDY**

The main parameter assessed within the study was the level of incretin hormones (GIP and GLP-1). Evaluation of their secretion assisted in identifying the main features of glucose metabolism in patients with ICD and acromegaly.

**SECONDARY OUTCOMES OF THE STUDY**

Additionally, we assessed the secretion of ghrelin—a neuropeptide that affects glucose metabolism.

**SUBGROUP ANALYSIS**

The study sample included 62 patients, of which 20 had ICD, 21 had acromegaly, and 21 comprised a control group.

ICD was diagnosed at a hospital using at least three tests confirming endogenous hypercorticisim: increased level of free cortisol in urine (reference value: 413 nmol/24 h),...
cortisol in saliva collected at 11 pm (reference range: 0.5–9.4 nmol/L) [5] and evening plasma cortisol (reference range: 46–270 nmol/L) and the absence of cortisol suppression under 50 nmol/L during a minor dexamethasone suppression test (DST). ACTH-dependent hypercorticism was diagnosed when the ACTH level > 10 pg/mL; further differential diagnostics were performed according to the Russian Clinical Guidelines on ICD [6] using a major DST (a 60% decline in morning cortisol level compared to baseline after the intake of 8 mg dexamethasone on the previous day at 11 pm), selective bilateral blood sampling from inferior petrosal sinuses after stimulation with corticoliberin and magnetic resonance imaging of the brain.

Acromegaly was diagnosed in a patient with increased IGF-1 levels in the absence of STH suppression under 1 ng/mL during the OGTT.

Various glucose metabolism disorders were diagnosed according to the 2013 WHO Guidelines as follows:

- Impaired glucose tolerance: fasting plasma glucose < 7.0 mmol/L and 2-h postprandial plasma glucose > 7.8 < 11.1 mmol/L.
- Impaired fasting glucose: fasting plasma glucose > 6.1 < 7.0 mmol/L and 2-h postprandial plasma glucose < 7.8 mmol/L.

Diabetes mellitus (DM): fasting plasma glucose > 7.0 mmol/L and 2-h postprandial plasma glucose > 11.1 mmol/L.

Due to the relatively low number of patients, participants with impaired glucose tolerance and impaired fasting glucose were pooled into one group titled ‘prediabetes’.

METHODS FOR OUTCOME REGISTRATION

Liver function tests were performed using a biochemical analyser Architect C4000 (Abbott Diagnostics, Abbotpark, IL, USA) with standard kits.

Glycated haemoglobin (HbA1c) was measured by high-performance liquid chromatography using the D10 Analyzer (BioRad).

Hormonal testing: Total GLP-1 (detection range: 0.206–50 ng/mL) and pancreatic glucagon (detection range: 0.05–10 ng/mL) were measured using enzyme-linked immunosorbent assay (ELISA) with BioVendor kits. Total GIP and total ghrelin were measured using ELISA with USCN kits (detection range: 0.0617–5 ng/mL) and RayBiotech kits (detection range: 0.1–1000 ng/mL), respectively.

ETHICAL REVIEW

The study was approved by the Ethics Committee of the Endocrinology Research Centre (Protocol No. 12 from 22.10.2014). Upon hospitalisation, patients were informed about the possible use of their data for research purposes. Patient data was anonymised prior to analysis.

STATISTICAL ANALYSIS

Sample size calculation: The sample size was not pre-calculated.

Statistical analysis: Statistical analysis was performed using Statistica 12 (StatSoft inc.) and SPSS 22 (IBM Corp.).

Data were presented as mean ± standard deviation (M ± SD). For non-normally distributed data, median and quartiles (Me [Q1; Q3]) were calculated. Continuous variables were compared using analysis of variance with subsequent pairwise comparisons (Scheffe’s post-hoc tests) for detecting significant differences. Non-normally distributed continuous variables were compared using the Kruskal–Wallis test and Dunn’s post-hoc test. Correlation analysis was performed using the Spearman’s correlation coefficient.

Absolute and relative values (%) were calculated for the analysis of categorical variables and compared using the Pearson’s chi-square test.

RESULTS

STUDY POPULATION

Patients groups are shown in Table 1.

MAIN FINDINGS AND DISCUSSION

We found that 40% of patients with ICD have some disorders of glucose metabolism (prediabetes) already in the early stages of ICD (Table 2). The prevalence of prediabetes was 24% among patients with acromegaly.

Although glucocorticoids (GC) and STH are known to exhibit anti-insulin activity, the effect of GC on glucose metabolism is primarily associated with their pleiotropic activity. It is well known that excessive amounts of glucocorticoids trigger the development of insulin resistance in the skeletal muscle and adipose tissues, stimulate gluconeogenesis and suppress the activity of beta-cells, thereby reducing insulin secretion [7], which explains the high prevalence of glucose metabolism disorders in patients with ICD.

DM was diagnosed with an equal frequency (approximately 15%) in both groups (Table 2).

Glucagon secretion

Pronounced suppression of glucagon secretion was observed in healthy individuals at 30 min after oral glucose load (Figure 1). This was considered a normal reaction, as glucagon secretion is suppressed in response to increased

<table>
<thead>
<tr>
<th>General characteristics of patients</th>
<th>ICD (n = 20) M ± SD</th>
<th>Acromegaly (n = 21) M ± SD</th>
<th>Controls (n = 21) M ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>37.50±13.83</td>
<td>43.71±14.02</td>
<td>44.14±14.56</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.63±5.01</td>
<td>29.03±5.78</td>
<td>26.13±4.43</td>
</tr>
<tr>
<td>The time between the onset of clinical symptoms and diagnosis, years</td>
<td>3±2</td>
<td>3±1</td>
<td></td>
</tr>
</tbody>
</table>

Note: BMI: body mass index.
Insulin secretion, which has been confirmed in previous studies [12].

During the OGTT, all patients with ICD had a significant increase in glucagon levels at all three time-points compared with those of the controls (p = 0.001).

One of the main four mechanisms underlying the effect of GC on glucose metabolism is the stimulation of gluconeogenesis after the interaction of GC and glucagon receptors followed by hypersecretion of glucagon [8]. This hypothesis was confirmed in our study. It is important to note that the increase in glucagon concentration was independent of the severity of glucose metabolism disorders. Hyperglucagonaemia may be an independent characteristic of patients with ICD.

Glucagon secretion in patients with acromegaly did not significantly differ from that in controls at time-points 0 and 120 min. However, at 30 min, patients with acromegaly showed no suppression of glucagon secretion in contrast to the control group. Several studies have shown that excessive amounts of IGF-1 have no direct stimulating effect on glucagon production. Nevertheless, IGF-1 can indirectly facilitate glycogenolysis [9,10], although it does not lead to a significant increase in glucagon concentration.

Our findings suggest that, in patients with ICD and acromegaly, glucagon secretion in response to a glucose load is not suppressed (as observed in controls) but is rather increased. This effect is likely to cause the development of glucose metabolism disorders and DM in this patient population.

**GIP secretion**

A significant increase in GIP secretion was observed during the OGTT in healthy individuals with a peak at 30 min and a subsequent reduction at the last time-point (120 min). Patients with ICD had no peak increase in GIP secretion during the OGTT. The production of this incretin hormone remained at the same level in patients with ICD and acromegaly (Fig. 2).

Very few studies have evaluated the effect of GC on the secretion of incretin hormones, particularly GIP. Mazzochi et al. conducted a study using animal models and demonstrated that the adrenal cortex has GIP receptors, and GIP itself can stimulate the secretion of GC by affecting the synthesis of cyclic adenosine monophosphate (cAMP). Elevated plasma levels of GC suppress GIP secretion through a negative feedback mechanism [11].

In the present study, both healthy individuals and patients with acromegaly had similar levels of GIP secretion at time-point 0 min (Figure 2). We also did not observe a peak of GIP secretion at 30 min, which was typical of healthy controls. GIP hypersecretion in acromegaly has been previously described [13] and attributed to STH-induced hyperglycaemia.

**GLP-1 secretion**

In the control group, the GLP-1 secretion pattern during the OGTT was similar to that described above: a peak at 30 min after a glucose load and subsequent gradual decrease at the end of the test [12].

Patients with ICD had no changes in GLP-1 secretion in response to oral glucose load (Figure 3), although baseline secretion levels were significantly higher in patients with ICD than in controls (p = 0.049). Our results are somewhat contradictory to those of vanRaalte et al. [14], who described a negative effect of GC on GLP-1 secretion. These discrepancies may be attributed to the absence of

<table>
<thead>
<tr>
<th>Frequency of glucose metabolism disorders (%)</th>
<th>ICD (n = 20)</th>
<th>Acromegaly (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose metabolism</td>
<td>(45.00)</td>
<td>(61.90)</td>
</tr>
<tr>
<td>Prediabetes</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>DM</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>(15.00)</td>
<td>(14.29)</td>
</tr>
</tbody>
</table>

Table 2

Figure 1. Glucagon secretion in the groups

Figure 2. GIP secretion in the groups
The long exposure of the incretin system to GC as patients with ICD were examined at early stages of the disease.

Unlike the controls, patients with acromegaly had no peak of GLP-1 secretion at 30 min after glucose load. However, their baseline secretion of GLP-1 was slightly higher than that observed in healthy individuals.

To date, there have been no studies evaluating the association between STH hypersecretion and GLP-1 concentration.

Thus, no peaks of GIP and GLP-1 secretion at 30 min were observed, which indicated that patients in both groups did not have a normal reaction to hyperglycaemia, similar to that in the control group.

Secretion of glucagon and incretins depending on the glucose metabolism status.

We observed no significant differences in the levels of glucagon and incretins secretion depending on the glucose metabolism status (p > 0.05) (Table 3).

ADDITIONAL FINDINGS AND DISCUSSION

Ghrelin secretion

Ghrelin is a polypeptide predominantly synthesised by the cells of gastric mucosa; however there is evidence of its production in the hypothalamic-pituitary axis. Ghrelin is a ligand for the SHTH secretagogue receptor [5].

Patients with prediabetes and DM without neuroendocrine disorders had significantly decreased ghrelin concentrations, which was associated with an elevated insulin level and pronounced insulin resistance [15].

A significant suppression in ghrelin secretion (with a peak at 30 min) was observed in controls during the OGTT (Fig. 4).

Patients with ICD had significantly higher ghrelin concentrations at all time-points compared with those of controls (p = 0.013) (Fig. 4). These patients are known to have some STH secretagogue receptors produced by the adenoma tissue, which leads to a paradoxical increase in ghrelin concentration. All patients with ICD are characterized by ghrelin hypersecretion [5]; however, the mechanisms involved remain unclear.

Table 3

<table>
<thead>
<tr>
<th>Disease</th>
<th>OGTT (min)</th>
<th>Normal glucose metabolism</th>
<th>Prediabetes + DM</th>
<th>Acromegaly, Me [Q1; Q3]</th>
<th>Prediabetes + DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose metabolism (n = 9)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>191.8 [176.5; 210.7]</td>
<td>227.3 [193.2; 256.9]</td>
<td>130.4 [115.3; 146.9]</td>
<td>145.8 [127.6; 154.1]</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>184.5 [153.4; 225.3]</td>
<td>223.7 [175.3; 240.1]</td>
<td>113.6 [89.7; 131.2]</td>
<td>136.3 [119.7; 167]</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>154.7 [147.8; 168.3]</td>
<td>187 [170.3; 264.2]</td>
<td>116.7 [93.4; 128.5]</td>
<td>117.1 [76.5; 124.3]</td>
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Table 4

<table>
<thead>
<tr>
<th>Disease</th>
<th>OGTT (min)</th>
<th>Normal glucose metabolism</th>
<th>Prediabetes + DM</th>
<th>Acromegaly, Me [Q1; Q3]</th>
<th>Prediabetes + DM</th>
</tr>
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<tbody>
<tr>
<td>Normal glucose metabolism (n = 11)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>153.4 [138.2; 169.6]</td>
<td>154.5 [125.7; 203.4]</td>
<td>130.4 [115.3; 146.9]</td>
<td>196.4 [157.3; 264.7]</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>139.8 [127.4; 186.5]</td>
<td>152.5 [143.2; 179.8]</td>
<td>187.8 [175.4; 210.6]</td>
<td>142.5 [134.1; 168.3]</td>
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<tr>
<td>120</td>
<td>129 [101.3; 176.5]</td>
<td>150.4 [137.1; 169.4]</td>
<td>178.2 [137.1; 209]</td>
<td>147.2 [125.2; 173.6]</td>
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</table>

Table 5

<table>
<thead>
<tr>
<th>Disease</th>
<th>OGTT (min)</th>
<th>Normal glucose metabolism</th>
<th>Prediabetes + DM</th>
<th>Acromegaly, Me [Q1; Q3]</th>
<th>Prediabetes + DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose metabolism (n = 13)</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>2.16 [1.8; 2.9]</td>
<td>2.52 [2.3; 2.9]</td>
<td>1.82 [1.72; 1.94]</td>
<td>1.81 [1.6; 2.2]</td>
<td></td>
</tr>
<tr>
<td>30</td>
<td>2.19 [1.7; 2.27]</td>
<td>2.58 [2.27; 3.08]</td>
<td>1.8 [1.67; 2.01]</td>
<td>1.5 [1.37; 1.68]</td>
<td></td>
</tr>
<tr>
<td>120</td>
<td>2.04 [1.94; 2.2]</td>
<td>2.21 [1.91; 2.5]</td>
<td>1.8 [1.53; 1.95]</td>
<td>1.55 [1.34; 1.81]</td>
<td></td>
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</tbody>
</table>
There were no significant differences in ghrelin secretion among patients with acromegaly (Fig. 4), although its concentration was high at all time-points. The exposure to high STH levels may have disrupted the feedback control leading to increased ghrelin levels. Several studies have suggested that ghrelin is involved in regulating STH secretion in the adenohypophysis [16]; this is achieved via the activation of the STH secretagogue receptors type 1 by ghrelin, which is partly produced by the adenohypophysis [17, 18].

ADVERSE EVENTS

No patient experienced any adverse events during the study.

CONCLUSION

The prevalence of early-stage glucose metabolism disorders was higher among patients with ICD than in patients with acromegaly, which may be attributed to a more pronounced effect of GC on glucose metabolism compared to STH and GLP-1. Patients with ICD and acromegaly have no suppression of postprandial glucagon release, which normally occurs in healthy individuals. Such an effect may be associated with one of the mechanisms underlying glucose metabolism disorders in these patients. The levels of incretins (GIP and GLP-1) secretion are similar in patients with ICD and acromegaly, regardless of their glucose metabolism status. Therefore, these hormones do not play any significant role in the development of glucose metabolism disorders in patients with ICD and acromegaly. Thus, the administration of incretin mimetic drugs appears to be unsuitable in such patients, and preference should be given to insulin sensitizers. Both hypercorticism and STH hypersecretion are associated with increased ghrelin concentrations. This neuropeptide may be involved in the development of glucose metabolism disorders in patients with ICD and acromegaly. Further investigation of its secretion and interaction with STH receptors may improve our understanding of its impact on glucose metabolism in patients with neuroendocrine diseases.

Investigations of the functioning of the incretin system; interactions among cortisol, STH/IGF-1 and the main incretin hormones and the clarification of the role of ghrelin in the development of ICD and acromegaly are very important. These future investigations will provide a deeper understanding of mechanisms underlying glucose metabolism disorders and assist in improving therapeutic approaches to hyperglycaemia correction in these patients. Further studies are required to confirm the results obtained within our study.

ADDITIONAL INFORMATION

FUNDING

The study was funded by a grant from the Russian Science Foundation No. 14-35-00026 (investigation of glucagon, ghrelin, GIP and GLP-1) and a grant No. MD-3204.2017.7 (assessment of the hormonal profile for the diagnosis of ICD and acromegaly)

CONFLICT OF INTERESTS

The authors declare no conflict of interest related to this manuscript.

AUTHORS’ CONTRIBUTION

Macheikha L.B. collected the data, performed statistical analysis and drafted the manuscript; Shestakova E.A. drafted the manuscript; Belaya Zh.E. edited the manuscript; Astafyeva L.I. edited the manuscript; Nikankina L.V. performed laboratory testing and edited the manuscript and Shestakova M.V. developed the study design and edited the manuscript.
<table>
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<th>References</th>
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Цитировать:

To cite this article: