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STUDY OF THE INFLUENCE OF GLP-1 RECEPTOR AGONISTS ON THE METABOLIC ACTIVITY OF THE INTESTINAL MICROBIOTA IN PATIENTS WITH TYPE 2 DM

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The aim: *to investigate the peculiarities of the metabolic activity of the intestinal microbiota in patients with type 2 diabetes under the influence of glucagon-like peptide-1 receptor agonist therapy.*
Materials and methods*: 21 patients with type 2 diabetes mellitus were included in the study, the average age was 57.2±8.53 years (M±SD), the HbA1c level was 8.29±0.88 % (M±SD). Patients were prescribed raGLP-1 at the maximum tolerated dose for 6 months. Before and after the course of treatment, indicators of body composition were determined by the bioelectrical impedance method (TANITA BC-545N analyzer, Japan), characteristics of carbohydrate metabolism and the lipid spectrum of blood serum, as well as the concentration of GLP-1, trimethylamine-N-oxide (TMAO) by the immunoenzymatic method, of short-chain fatty acids (SCFA) by the method of chromatographic research.*
Results*. After 6 months of therapy with liraglutide against the background of a statistically significant decrease in fasting blood glucose and HbA1c levels ($p<0.05$), a decrease in body mass index and waist circumference ($p<0.05$), a decrease in the content of visceral ($p<0.05$) and total fat ($p<0.05$) in patients with type 2 diabetes, there was a decrease in the concentration of TMAO in blood serum ($p<0.05$) and an increase in the concentration of SCFA: acetic, propionic ($p<0.05$) in the coprofiltrate and a tendency to increase in the level of butyric acids. Data analysis also established an increase in the concentration of endogenous GLP-1 in the blood ($p<0.05$).*
Conclusions*. The detected changes in microbial metabolites may indicate a positive effect of raGLP-1 on the composition of the intestinal microbiota and its metabolic activity in patients with T2DM, which in turn contributes to the improvement of endogenous secretion of incretins*
Keywords: *diabetes, obesity, raGLP-1, intestinal microbiota, short-chain fatty acids, trimethylamine-N-oxide*

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1. Introduction

Given the fact that obesity and associated dysmetabolic diseases, such as type 2 diabetes mellitus, have today reached the scale of a "non-infectious epidemic", the development of effective preventive and therapeutic measures is of significant scientific and practical interest in the field of clinical endocrinology. It is known that type 2 diabetes is accompanied by multiple hormonal and metabolic disorders, in particular, the dysfunction of the enteroendocrine cells of the small intestine, which synthesize incretin hormones (glucagon-like peptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP)), which bind with their receptors on the surface of β-cells of the pancreas and stimulate the glucose-dependent release of insulin [1]. In addition to the insulinotropic effect, GLP-1 exerts a number of other pleiotropic effects: it stimulates the proliferation and inhibits apoptosis of β-cells, inhibits the secretion of glucagon, as well as affecting the activity of the renin-angiotensin-aldosterone system (inhibits), natriuresis and causing vasodilation, causing cardioprotective and nephroprotective effects on the body [2].

Recently, a lot of attention has been paid to the mechanisms of epigenetic regulation of the development of DM, in particular, the role of the intestinal microbiota and its metabolic products is being investigated [3]. Short-chain fatty acids (SCFA), namely propionic, acetic, butyric, isobutyric, isovaleric, valeric, isocaproic, and caproic acids, are important metabolites formed in the large intestine as a result of fermentation by predominantly anaerobic bacteria of dietary fibres [4, 5]. It has been established that SCFA through FFAR2 receptors in β-cells of the pancreas stimulate insulin secretion, have an anti-apoptotic effect on pancreatic islets, and are also important modulators of intestinal hormone secretion and lipogenesis [6, 7]. Their role in the prevention of cardio-

vascular complications in diabetes is due to a number of proven effects: SCFAs have a direct antioxidant effect, contributing to the neutralization of free radicals; inhibit the production of anti-inflammatory factors [8]; participate in the regulation of adipogenesis; affect the appetite, contributing to the feeling of satiety; increase tissue sensitivity to insulin; have a positive effect on the metabolism of lipids and glucose; maintain electrolyte balance; improve intestinal peristalsis [9, 10].

There is an opinion that the relationship between GLP-1 and SCFA is carried out through the activation of the latter's receptors on enterocytes, which leads to increased release of GLP-1 and, therefore, more effective regulation of blood glucose levels. However, the mechanisms of this process are still poorly understood [11].

The influence of intestinal microbiota on the cardiovascular system is not only through the effects of SCFA. As a result of intestinal microbial metabolism, trimethylamine (TMA) is produced from dietary phosphatidylcholine and L-carnitine, which is transported to the liver and transformed into trimethylamine-N-oxide (TMAO) with the participation of the enzyme FMO (hepatic flavin-containing monooxygenase). It has now been proven that TMAO is a proatherogenic and prothrombotic factor [12, 13].

It has been demonstrated that its plasma levels increase in individuals with diastolic dysfunction, heart failure, atherosclerosis, and peripheral artery disease [14].

In addition, the results of a recent clinical study proved that there is a positive correlation between TMAO levels and histological features of non-alcoholic fatty liver disease (NAFLD) in obese patients, mainly in the presence of type 2 diabetes [15].

Although the mechanisms by which this compound contributes to dysmetabolic disorders remain somewhat speculative and poorly understood, TMAO has been proposed by some researchers as a biomarker for predicting cardiometabolic and chronic kidney diseases [16].

Another important aspect of the treatment of patients with type 2 diabetes cannot be skipped. According to the literature, it was established that the metabolic and biological effects of oral antidiabetic drugs, as well as the variability of the therapeutic response to them and the development of gastrointestinal complications are also closely related to the activity of the intestinal microbiota [17]. Therefore, the study of the composition and functional activity of the latter, the development of methods for correcting the detected dysbiosis is one of the promising directions in creating effective schemes for the treatment of type 2 diabetes and preventing the development of its complications.

The aim of the work: to investigate the peculiarities of the metabolic activity of the intestinal microbiota under the influence of GLP-1 receptor agonist therapy in patients with type 2 diabetes.

2. Materials and methods

The prospective study included 21 patients diagnosed with type 2 diabetes, age 57.2±8.53 years (M±SD), disease duration 5.54±11.8 years (M±SD), who had unsatisfactory control of carbohydrate metabolism (HbA1c 8.29±0.88 % (M±SD)) against the background of previous hypoglycemic therapy.

The patients were observed in the department of geriatric endocrinology and clinical pharmacology of the State University "V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Sciences of Ukraine" during 2019–2024. The study was conducted in compliance with the main provisions on human rights and biomedicine of the Council of Europe Convention, the Helsinki Declaration of the World Medical Association (1964–2008), as well as the order of the Ministry of Health of Ukraine No. 690 from September 23, 2009. The research was approved by the ethics and deontology commission of the SU "V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Sciences of Ukraine", protocol No. 29/1-KE dated June 26, 2019.

Inclusion criteria: diagnosis of type 2 diabetes (duration of more than 6 months), taking stable oral glucose-lowering therapy for 6 months, which included metformin, sulfonylurea derivatives, NSAIDs, insulin. Exclusion criteria: taking analogues of human glucagon-like peptide-1 (GLP-1), the presence of active inflammatory processes, acute or chronic pancreatitis in the anamnesis, severe lesions of the liver and biliary tract (increased ALT, AST more than 2.5 times), gallstone disease, GFR below 30 ml/min; diabetic ketosis; arterial hypertension, not controlled by medication or endocrine genesis; myocardial infarction, stroke, hospitalization due to unstable or transient ischemic angina within 60 days before the day of inclusion in the study, heart failure III-IV FC according to NYHA; history of oncological diseases, in particular, family history of cases of medullary carcinoma or multiple endocrine neoplasia (including MEN-2); unstable diabetic retinopathy, maculopathy; pregnancy.

Patients were prescribed raGLP-1 (liraglutide at the maximum tolerated dose) for 6 months.

Patients were examined at the beginning of the study (visit 1) and after 6 months of taking raGLP-1 (visit 2). Anthropometric parameters were determined: height, weight, waist circumference (WC), body mass index (BMI) was calculated. 91 % of patients were diagnosed with general obesity according to WHO criteria (BMI ≥ 30 kg/m^2). Abdominal obesity (WC >80 cm for women and WC >95 cm for men) was observed in all subjects [18].

Body composition was assessed by the bioelectrical impedance method (TANITA BC-545N analyzer, Japan). The following parameters were determined: the percentage of total fat and water in the body, the level of visceral fat (VF), muscle and bone mass, indicators of metabolic age and basal metabolism.

The level of visceral fat (VF) was estimated in the range from 1 to 59 units; each unit corresponds to 10 cm^2 of fat on the surface of internal organs; a normal level is between 1 and 12 units of fat.

Physical type (body structure) was evaluated on a scale from 1 to 9 points (hidden fullness – 1, full – 2, strong build – 3, trained – 4, normal – 5, standard–muscular – 6, thin – 7, thin and muscular – 8, very muscular – 9).

Fasting blood glucose concentration was measured using certified diagnostic strips and a One Touch glucometer (LifeScan Inc, Switzerland).

The level of glycated hemoglobin (HbA1c) was determined by the immunoturbodimetric method on the Cobas 6000 analyzer (Roche Diagnostics (Switzerland) in certified laboratories with the assignment of laboratory numbers to each sample.

GLP-1 concentration indicators were determined by enzyme-linked immunosorbent assay using a Glucagon-Like Peptide-1 (7–36) active ELISA kit (IBL International GmbH, Germany) on a StatFax 3200 analyzer, Awareness Technology (USA), reference values 0.5–3.1 pmol/l. TMAO was determined using the ELISA method using the Human Trimethylamine-N-Oxide ELISA Kit (BTlab, China) on the StatFax 3200 analyzer, Awareness Technology (USA). The measurement range of the TMAO kit for humans was from 0.2 ng/ml to 60 ng/ml, and the sensitivity was 0.119 ng/ml, the reference values were 7.13–12.8 ng/ml. The indicators were studied on the basis of the SU "V. P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Sciences of Ukraine".

Determination of SCFA indicators was studied at the SU "V.P. Komisarenko Institute of Endocrinology and Metabolism of the National Academy of Sciences of Ukraine", Dnipro, in the coprofiltrate of patients using the hardware and software complex for medical research based on the Chromatek-Crystal gas chromatograph. which was equipped with a RESTEK Rtx-2330 capillary column (60 m length × 0.25 mm diameter × 0.2 μm film) with a flame ionization detector (220 C°), with nitrogen as the carrier gas, with a flow rate of 0, 4 ml/min and a pressure of 97.74 kPa. Additional parameters of the technique were: hydrogen consumption – 20 ml/min, air consumption – 200 ml/min, column temperature 140 C°, evaporator temperature 230 C°. Areas under the peaks were calculated using Chromatek hardware and software connected to the gas chromatograph. Isolation of SCFA from coprofiltrate was performed according to the method of Guohua Zhao [19]. Stool samples were collected into a sterile test tube, 1 g of stool was homogenized in 3 ml of distilled water, 2 ml of 1 N hydrochloric acid solution was added to the homogenate, mixed and centrifuged at 7000 rpm for 10 min. Using a microsyringe, 5 μl of the supernatant liquid was injected into the evaporator of the chromatograph. Identification of each acid was carried out by comparing their retention time with that of their respective reference standard from Rastek, USA.

Statistical analysis was performed using the analysis packages Microsoft Excel 2019 16.0 and MedStat v. 5.2 (Free access). For quantitative signs, average values of indicators (M), standard deviation (SD) were calculated. The normality of the distribution was checked by the D'Agostino-Pearson test. To compare indicators in dynamics, a paired t-test for related samples, the Wilcoxon test, was used.

3. Research results

Against the background of raGLP-1 treatment, a significant decrease in BMI, WC, % of total and visceral fat was found (Table 1). The decrease in the amount of fat after treatment was accompanied by a significant increase in the content of total water (intracellular and extracellular) in the body and the skeletal-visceral index.

Table 1

Changes in anthropometric parameters and body composition in patients with type 2 diabetes after 6 months of liraglutide therapy

Parameters and statistical indicators		Visit 1	Visit 2	p
BMI, kg/m^2	M±SD	36.86±5.07	32.10±5.62*	p<0.01
WC, cm	M±SD	118.94±9.88	108.42±11.52*	p<0.01
% of total fat	M±SD	38.87±8.55	33.75±8.80*	p<0.01
VF level, unit	M±SD	16.44±4.45	13.28±4.39*	p<0.01
% of water	M±SD	44.92±5.40	48.04±5.79*	p<0.01
Muscle mass, kg	M±SD	63.39±12.12	59.39±12.33*	p<0.01
SVI (skeletal and visceral index)	M±SD	4.09±1.19	4.70±1.31*	p<0.01
Metabolic age, years	M±SD	66.67±8.94	63.15±8.47	p>0.05
Assessment of body structure (points)	M±SD	3.17±1.10	3.14±1.15	p>0.05
Basal metabolism, kcal	M±SD	2027.53±383.55	1787.65±348.72*	p<0.01

Note: p // — reliability of the difference between indicators before and after treatment, p <0.05 (paired t-test for related samples), M is the arithmetic mean; SD is the standard deviation*

After 6 months of raGLP-1 treatment, a decrease in fasting glucose concentration and HbA1c was detected in the blood serum of patients (p<0.05) (Fig. 1).

According to the obtained data presented in the Table 2, in the examined patients, at 6 months of treatment, an increase in the concentration of acetic and propionic coprofiltrate (p<0.05) and a tendency to increase in butyric acids were found, which may indicate an improvement in the function/composition of the intestinal microbiota, namely SCFA-producing bacteria.

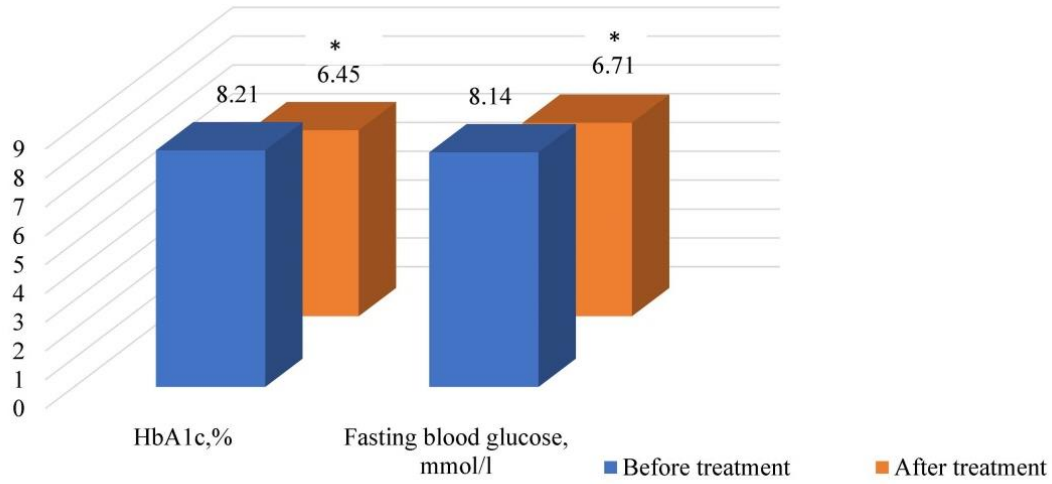

Fig. 1. Changes in indicators of carbohydrate metabolism after 6 months of liraglutide treatment in patients with type 2 diabetes: p /*/ — reliability of the difference between indicators before and after treatment, p<0.05

Table 2

Influence of liraglutide on SCFA content in coprofiltrate of patients with type 2 diabetes after 6 months of therapy

Parameters and statistical indicators			Visit 1	Visit 2	p
SCFA, μg/ml	Acetic acid	M±SD	1179.62±454.18	1272.86±727.99*	p<0.05
	Propionic acid	M±SD	533.36±319.45	927.12±504.41*	p<0.05
	Butyric acid	M±SD	484.72±290.82	538.20±349.07	p>0.05

Note: p // is the reliability of the difference between indicators before and after treatment, p<0.05 (Wilcoxon test), M is the arithmetic mean; SD is the standard deviation*

Against the background of the use of liraglutide, an increase in the level of endogenous GLP-1 was found (p<0.05), which may be associated with a change in the composition of the intestinal microbiota and the content of microbial metabolites. At the same time, a decrease in the concentration in blood serum of the marker of oxidative stress and endothelial dysfunction – TMAO (p<0.05) was observed, which may indicate a decrease in production by intestinal bacteria and the penetration of its precursor – TMA (trimethylamine) into the blood (Table 3).

Table 3

Changes in the concentration of TMAO and GLP-1 in the blood of patients with type 2 diabetes after treatment with liraglutide

Parameters and statistical indicators		Visit 1	Visit 2	p
TMAO, ng/ml	M±SD	8.32±3.39	7.26 ±2.87*	p<0.05
GLP-1, pmol/l	M±SD	1.26±1.00	3.07±2.17*	p<0.05

Note: p // is the reliability of the difference between indicators before and after treatment, p<0.05 (Wilcoxon test), M is the arithmetic mean; SD is the standard deviation*

4. Discussion of research results

The results of the study demonstrated that when using the GLP-1 receptor agonist – liraglutide for 6 months, there is an improvement in carbohydrate metabolism. A decrease in the degree of general and abdominal obesity (according to BMI and WC) was also noted. The use of the non-invasive method of bioelectrical impedance made it possible to reveal the peculiarities of changes in the composition of the body, namely: a decrease in the percentage of total and visceral fat, which was accompanied by an increase in the relative water content in the body. It is worth noting that raGLP-1 treatment contributed to an increase in the skeletal-to-visceral ratio (SVR), which is used as a marker of sarcopenic obesity [20, 21].

As is known, in patients with type 2 diabetes, there is a decrease in endogenous GLP-1 content, which reflects insufficient secretion of incretin hormones by enteroendocrine L-cells of the intestinal mucosa. It has been demonstrated that the enzymatic action of the microbiota in the large intestine has a positive effect on the number of enteroendocrine cells and their secretory function [22, 23]. In particular, it was established that the binding of butyrate to G protein receptors (GPR) in the intestine leads to an increase in the secretion of endogenous incretins – GLP-1 and GLP-2 and the peptide PYY by enteroendocrine L-cells in the colon [24]. The work revealed a statistically significant increase in the concentration of acetic and propionic acids and a tendency towards an increase in the content of butyric acids, which may indicate an improvement in the functional activity of SCFA-producing intestinal bacteria. The latter are known to include such commensal bacteria as *Akkermansia muciniphilia, Prevotella spp., Ruminococus spp., Copro-*

coccus sp., Faecalibacterium prausnitzii, Eubacterium rectale and *Roseburia spp.* Therefore, it can be assumed that the use of supraphysiological doses of raGLP-1 (liraglutide), affecting the composition of the intestinal microbiota and its metabolic activity, leads to an improvement in the synthesis of one's own endogenous GLP-1, which is confirmed by the analysis of the data of the work carried out.

Considering that SCFAs play an important role in regulating the accumulation and function of adipose tissue and maintaining the sensitivity of peripheral tissues to insulin [5, 25], it is thought that the use of raGLP-1 preparations against the background of restoring the proper level of SCFAs may have an additive effect in reducing the degree of adiposity.

After 6 months of treatment with liraglutide, a decrease in TMAO levels was established [26]. To date, several assumptions have been made regarding the mechanisms by which the latter increases the risk of CVD mediated by the intestinal microbiota [27, 28], namely: it affects the lipid spectrum of the blood, changes the composition and transport of bile acids, induces the production of C-reactive protein, promotes endothelial dysfunction and increases serum levels of the proinflammatory endotoxin lipopolysaccharide (LPS), causes a prothrombotic effect, promotes platelet aggregation by activating Toll-like receptor (TLR) pathways [29]. Considering the above, the detected changes in the serum concentration of the toxic metabolite TMAO certainly have a positive value as a sign of reducing cardiometabolic risks in patients with type 2 DM.

Therefore, liraglutide therapy has a positive effect on the functional state of the intestinal microbiota, as evidenced by the detected changes in the concentration of microbial metabolites: a decrease in the level of the endotheliotoxic metabolite TMAO in the blood serum and an increase in the concentration of SCFA in the coprofiltrate.

Study limitations. A limitation of the study is the insufficient base of literary data on the topic of the study.

Prospects for further research. The data obtained in the work prove the feasibility of conducting further studies of the composition and functional activity of the intestinal microbiota as a factor influencing body composition, the level of endogenous GLP-1, and improving the cardiovascular prognosis in patients with type 2 diabetes in general.

5. Conclusions

1. A decrease in the concentration of the toxic metabolite TMAO in the blood serum and an increase in the concentration of acetic and propionic acid in the coprofiltrate ($p<0.05$), as well as a trend towards an increase in the content of butyric acid, were revealed. The indicated changes in SCFA may indicate a positive effect of raGLP-1 on the composition of the intestinal microbiota and its metabolic activity in patients with T2 DM, which in turn contributes to an increase in the endogenous secretion of incretins.

2. Liraglutide therapy for 6 months contributes to a decrease in BMI, WC, changes in body composition indicators, namely: a decrease in the content of total and visceral fat, an increase in % water, skeletal-visceral ratio.

Conflict of interests

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

The data cannot be provided for the reasons stated in the data availability statement.

Use of artificial intelligence technologies

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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