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A CLINICAL CASE OF ASYMPTOMATIC PANCREATIC HYPERENZYMEMIA ON THE BACKGROUND OF TAKING A GLUCAGON-LIKE PEPTIDE-1 ANALOGUE (GLP-1)

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Key words: *asymptomatic pancreatic hyperenzymemia, glucagon-like peptide-1, type 2 diabetes*
Ключові слова: *безсимптомна панкреатична гіперферментемія, глюкагоноподібний пептид-1,цукровий діабет 2 типу*

Abstract. A clinical case of asymptomatic pancreatic hyperenzymemia on the background of taking a Glucagon-like peptide-1 analogue (GLP-1). Sanina N.A., Hondulenko N.O., Panina S.S., Shulha V.S. *According to current statistics, the incidence of type 2 diabetes has increased significantly over the past few years. The number of drugs prescribed to correct carbohydrate metabolism is also increasing, and new groups of hypoglycemic drugs are appearing. This prompts a more detailed study and analysis of the possible side effects of the prescribed therapy. One of the modern groups of medications f or treating type 2 diabetes are analogues of glucagon-like peptide-1 receptor agonists, which, in addition to correcting carbohydrate metabolism, have a beneficial effect on the risk of developing cardiovascular events. Despite this, there is evidence that their use may be associated with the development of undesirable adverse effects from the pancreas, particularly acute pancreatitis, pancreatopathy, or asymptomatic hyperenzymemia. The aim of our work was the analysis of a clinical case of an asymptomatic increase in the level of pancreatic enzymes (Gullo's syndrome) in a patient with type 2 diabetes, who used a glucagon-like peptide-1 receptor analogue for treatment according to the usual scheme (dulaglutide 0.75 mg subcutaneously once a week during 2 years). As a result, the patient developed a side effect that could be related to taking this medicine. This did not lead to the withdrawal of the drug but required a more thorough examination of the patient and regular further screening for the timely detection of the development of possible organic pathology of the pancreas in the future. So, after analyzing this clinical case, it is possible to see the possibility of developing asymptomatic pancreatic hyperenzymopathy during the treatment of type 2 diabetes mellitus with glucagon-like peptide-1 receptor agonist analogues, which should be taken into account when determining the treatment tactics.*

Реферат. Клінічний випадок безсимптомної гіперферментемії підшлункової залози на фоні прийому глюкагоноподібного аналога пептиду-1 (GLP-1). Саніна Н.А., Гондуленко Н.О., Паніна С.С., Шульга В.С. *Згідно із сучасними статистичними даними, захворюваність на цукровий діабет 2-го типу за останні кілька років значно зросла. Збільшується і кількість медикаментозних засобів, які призначаються для корекції вуглеводного обміну, з'являються нові групи гіпоглікемічних препаратів. Це спонукає до більш детального дослідження та аналізу терапії, яка призначається. Однією з сучасних груп препаратів для лікування цукрового діабету 2-го типу є аналоги агоністів рецепторів глюкагоноподібного пептиду-1, які, окрім корекції вуглеводного обміну, мають сприятливий вплив на ризик розвитку серцево-судинних подій. Незважаючи на це, існують дані про те, що їх застосування може бути пов'язане з розвитком небажаних побічних ефектів з боку підшлункової залози, зокрема панкреатитів, панкреатопатій або безсимптомних гіперферментемій. Метою нашої роботи був аналіз клінічного випадку безсимптомного підвищення рівня панкреатичних ферментів (синдром Гулло) у хворого на цукровий діабет 2-го типу, який застосовував для лікування аналог рецептора глюкагоноподібного пептиду-1 за звичайною схемою (дулаглутид 0,75 мг підшкірно один раз на тиждень упродовж 2 років). Як результат, у пацієнта розвинувся побічний ефект, який міг бути пов'язаний з прийомом цього лікарського засобу. Це не призвело до відміни препарату, однак потребувало більш ретельного обстеження хворого та регулярного подальшого скринінгу для своєчасного виявлення розвитку можливої органічної патології підшлункової залози в майбутньому. Отже, проаналізувавши цей клінічний випадок, можна побачити можливість розвитку безсимптомної панкреатичної гіперферментопатії при лікуванні цукрового діабету 2 типу препаратами – аналогами агоністів рецепторів глюкагоноподібного пептиду-1, що має бути взято до уваги і враховуватися при визначенні лікувальної тактики.*

Glucagon-like peptide-1 (GLP-1) is a hormone of the intestinal tract, produced mainly by cells of the mucous membrane of the small intestine (so-calledL-cells). Additional secretion of a small amount of the hormone takes place in the pancreas and the central nervous system [1]. GLP-1 is the basis of many modern drugs for the treatment of type 2 diabetes and obesity and the basis for the development of new effective drugs.

Receptor agonists and analogues of glucagon-like peptide-1, together with inhibitors of dipeptidyl peptidase-4, belong to the class of antidiabetic incretins (incretin mimetics). The beneficial effect of this group of drugs on the risk of cardiovascular events (liraglutide, semaglutide, albiglutide, dulaglutide), slowing down the progression of diabetic nephropathy, and microangiopathic complications (especially liraglutide and semaglutide) was noted in the randomized clinical trials. GLP-1 receptor agonists are characterized by resistance to destruction by specific dipeptidyl peptidase-4, due towhich they act much longer than endogenous GLP-1 [5].

Dulaglutide is a GLP-1 agonist of prolonged action, which was achieved thanks to the modification of the human GLP-1 molecule using DNA recombination technology,is injected subcutaneously into the thigh or abdomen at a dose of 0.75 mg (monotherapy) or 1.5 mg (with combined treatment with other antidiabetic drugs) once a week [6].

Despite the benefits of using agonists of the GLP-1 receptor, their admission can lead to some undesirable effects, and among them gastrointestinal symptoms are the most common ones and the main reason for drug discontinuation [8].

One of the side effects that occur in patients during treatment with drugs from the group of GLP-1 agonists can also be asymptomatic pancreatichyperenzymemia. According to literature data, such cases can theoretically beregistered during treatment with GLP-1 agonists, although this side effect is quite rare. The works of P. Mehta et al. are known, in which they emphasize the need for dynamic monitoring of such patients to rule out organic pathology of the pancreas [9]. Nevertheless, descriptions of the clinical cases of benign pancreatichyperenzymemia during treatment with GLP-1 agonists are sporadic.

The aim of our work is to describe a clinical case of increased pancreatic enzymes in a patient with type 2 diabetes, who was treated with an analogue of the glucagon-like peptide-1 receptor Trulicity (dulaglutide).

The study was conducted by the principles of bioethics set forth in the Declaration of Helsinki "Ethical Principles of Medical Research Involving Human Subjects", the "Universal Declaration of Bioethics and Human Rights (UNESCO)", GCP principles and approved by the Bioethics Commission of Dnipro State Medical University (extract from the meeting of the bioethical commission No. 6 from 15.02.2023). The patient gave the informed consent to the examination, asked all the questions that interested him, received comprehensive answers, and all measures to ensure the patient's anonymity were taken.

Male patient X., 61 years old, was admitted to the clinic with the following diagnosis: diabetes mellitus type 2, of moderate severity (diabetic angiopathy of the lower extremities, diabetic nephropathy, diabetic polyneuropathy of the lower extremities, diabetic encephalopathy of the II stage), compensated (HbA1c 6,6%). CAD: diffuse cardiosclerosis. Supraventricular and ventricularextrasystole. Heart failure NYHA I. Arterial hypertension II stage (concentric hypertrophy of the left ventricle, atherosclerotic stenosis of the main arteries of the head up to 67%), stage 1, risk 4.

He has had type 2 diabetes since 2017, for treatment he receives metformin 1000 mg 2 BID, and since October 2020, dulaglutide 0.75 mg subcutaneously oncea week. During the period of taking dulaglutide, the patient noted a significant positive trend in the course of his diabetes – blood glucose decreased to 6.3 mmol/l, body weight decreased from the initial 93.0 to 83.5 kg, body mass index from 33.3 to 29.4 kg/m^2, waist circumference from 111 to 107 cm.

The patient follows a proper diet. Eats regularly. The patient has no current eating disorders. There was no significant change in body weight during the observation period. There was no history of acute or chronic pancreatitis.

The patient does not use, and has never used drugs and alcohol, does notsmoke, and has never smoked.

For the treatment of concomitant pathology, the patient receives carvedilol 25 mg/day, ramipril 5 mg, eplerenone 25 mg, ivabradine 7.5 mg, acetylsalicylic acid 100 mg, rosuvastatin 20 mg.

A complete clinical examination of the patient was carried out.

The general condition is satisfactory. Consciousness is clear. The nature of the deposition of subcutaneous fat is uniform. The skin and visible mucous membranes are clean, and of normal physiological colour. His body temperature is 36.6ºC. Height 167 cm, body weight 83.5 kg. Body mass index – 29.9 kg/m_2.

Anatomical and functional changes were not detected during the head examination. The head is symmetrical, of the correct shape, without deformations.

The ears are located symmetrically, of the correct shape, without deformations. There are no anatomical changes in the nasal cavity and pharynx. The nose is straight, without deformations, breathing through the nose is free. The mouth is symmetrical. The tongue is moist and clean. No visible pathological changes on the part of the teeth were found. The throat is clean, not hyperaemic, free of plaque, the tonsils are not enlarged, and the posterior wall of the pharynx is clean, not hyperaemic.

The neck is symmetrical; movements are not limited. The thyroid gland is not enlarged, has a soft-elastic consistency, nodules are not palpable, and there are no signs of thyroid gland dysfunction. Peripheral lymph nodes are not enlarged.

The thorax is symmetrical and of regular shape. Auxiliary muscles do not participate in the act of breathing. Percussively pulmonary sound is over the chest. Breathing is vesicular, no wheezes.

Limits of relative cardiac dullness: the right and upper are not shifted, andthe left is shifted 1.0 cm laterally from l. mediaclavicularis sin. Tones of the heart are muffled and rhythmic. There are no accents or noises.

The abdomen is of normal shape and increased in size due to an excessively developed subcutaneous fat layer, soft and painless on palpation. The liver is not palpable. Kerr's and Ortner's symptoms are negative. The spleen is not enlarged. Palpation of the large intestine showed no abnormalities.

The kidneys are not palpable. Costovertebral angle is not tender on both sides. Urination is normal.

The spine has no visible pathological abnormalities; the joints are not changed. The muscular system is without visible disorders.

The nervous system is without visible pathology.

Leg skin: normal colour. The feet are warm. There is no peripheral edema.

There are no varicose veins. Pulsation in the arteries of the feet is preserved.

Laboratory tests taken during the visit revealed an increase in the level of pancreatic enzymes: blood lipase up to 326 u/l (normal 0-120 u/l) and blood amylase up to 151 u/l (normal 3-46 u/l). This exceeds the referent ranges more thanthree times, and such a situation, according to international standards, should be analyzed for the presence of acute pancreatitis.

After receiving the tests, the patient was again invited to the clinic to clarify the complaints. During a detailed examination the patient complained of a feeling of fullness in the stomach, occuring periodically after food intake, sometimes of nausea (1-2 times a month), periodic weakening of bowel movements (unformed stool after 1-2 bowel movements once a day). The patient does not have abdominal pain, these symptoms do not bother the patient very much, and they can be associated with the patient's intake of analogue of glucagon-like peptide-1 (GLP-1) receptors (dulaglutide), its mechanism of action, the slowing down of gastric emptying. In general, the patient feels satisfactory and notes an improvement in well-being since the beginning of receiving dulaglutide.

The patient underwent an ultrasound examination of the pancreas, gall bladder, and liver. According to the conclusion of the examination and the description of the ultrasound picture: the pancreas is not enlarged. Its capsule is not compacted, not thickened. The contours are clear and even. The structure is diffusely heterogeneous and granular, echogenicity is increased with areas of infiltration. Virsung's duct is not expanded, not compacted. There are no focal changes. According to this conclusion, the patient has no signs of acute pancreatitis.

GLP-1 in the human body performs several important functions, in particular, it enhances the production and release of insulin during meals and restrains the release of glucagon, which limits fluctuations in the level of postprandial glycemia; increases the volume of cells of the pancreas that produce insulin (beta cells); suppresses intestinal peristalsis, increasing the time between bowel movements; enhances the feeling of satiety during and between meals by affecting appetite centres in the brain [1, 2].

Receptor agonists and analogues of glucagon-like peptide-1 are divided into two groups: short-acting – exenatide (Byetta) and lixisenatide (Adlyxin) and long-acting – long-acting exenatide (Bydureon), albiglutide (Eperzan, Tanzeum), dulaglutide (Trulicity), liraglutide (Victoza, Saxenda), semaglutide (Ozempic, Wegovy, Rybelsus), which is determined by their pharmacokinetic properties. Almost all drugs in this group, except for semaglutide, are injectable and administered subcutaneously. So far, semaglutide is the only medication that, in addition to the injection form, is available in tablet formulation (Rybelsus) [3].

Similar mechanisms of action are characteristic of all representatives of this group of drugs: a decrease of glucose level in the blood due to the activation of the GLP-1 receptor, as a result of which glucose-dependent stimulation of insulin secretion occurs; glucose-dependent inhibition of glucagon secretion and reduction of glucose production by the liver; slowing of the gastric passage, which reduces the variability of glycaemic indicators after a meal. Agonists of the GLP-1 receptor also affect receptors located in the brain, contributing to a decrease in appetite, a decrease in food intake, and a decrease in body weight [4].

When using agonists of the GLP-1 receptor, the following undesirable effects can be observed: hypoglycemia (during combined treatment with

sulfonylurea derivatives, metformin or without it), usually mild or moderate; nausea (mild or moderate, depending on the dose, resolves during treatment), abdominal pain, bloating, vomiting, diarrhea, complaints related to the gallbladder (especially semaglutide); usually mild reactions at the injection site; acute pancreatitis is a very rare complication that may be associated with taking incretin drugs; kidney failure – medicines of this group are contraindicated for patients with severe kidney failure [7]. Among the widely used GLP-1 receptor agonists, semaglutide has the highest rates of gastrointestinal side effects, such as nausea and vomiting, followed by dulaglutide, liraglutide, and exenatide with an elongatedrelease [8].

Therefore, the clinical case analyzed in this study can be considered asymptomatic pancreatic hyperenzymemia, which is a negative side effect of the drug but is not a reason to stop dulaglutide therapy. It was recommended to repeat the pancreatic enzymes in one month.

Asymptomatic pancreatic hyperenzymemia, or Gullo's syndrome, is known since 1978 when A. Warshaw and K. Lee [10] described 17 cases of chronic hyperamylasemia without clinical manifestations and other signs of pancreatic diseases. In 1996, L. Gullo described a series of 18 cases of increased activity of pancreatic enzymes (isolated or combined increase in the content of lipase, total amylase, pancreatic amylase, and trypsin) in clinically healthy individuals. Accidentally detected hyperenzymemia became the reason for an in-depth examination, however, with a detailed anamnesis, thorough physical and laboratory-instrumental examination, which included ultrasound and computer tomography of the abdominal cavity, as well as the performance of endoscopic retrograde cholangiopancreatography (ERCP), the pathology that explains the increase in the activity of pancreatic enzymes could not be detected [11]. Professor Gullo continued to follow most of these patients from 1987 to 2006 and noted that during this period hyperenzymemia persisted in the absence of overt pancreatic disease or other known causes. The author concluded that the increase in the activity of pancreatic enzymes in these patients is of a benign nature, in connection with which he called the described anomaly chronic non-pathological pancreatic hyperenzymemia, or benign pancreatic hyperenzymemia, or Gullo's syndrome [12]. In most cases, with this syndrome, the level of at least two pancreatic enzymes is elevated, which was observed in our patient; in the remaining cases, an isolated increase in the activity of amylase or lipase is noted, more often by 1.5-4 times [13].

For such patients, it is recommended to observe and monitor the level of pancreatic enzymes for at least 1.5-2 years, since in some patients, a pathological morphological substrate of hyperenzymemia may be detected in the future [14].

As for our patient, a month later he was re-examined for blood lipase and amylase levels. Pancreatic enzymes remained slightly elevated (lipase 132 U/l,with a reference value of 0-120 U/l; amylase 63 U/l, with a reference value of 3-46 U/l). The patient did not complain, well-being is satisfactory. Further use of dulaglutide and monitoring of blood pancreatic enzymes is recommended.

CONCLUSIONS

1. When treating type 2 diabetes with drugs from the group of GLP-1 agonists, certain adverse effects may occur from the pancreas, which require careful examination of patients and the adoption of appropriate measures.
2. One of the infrequent side effects is asymptomatic pancreatic hyperenzymemia (Gullo's syndrome), which consists of a significant increase in pancreatic enzymes level without clinical manifestations.
3. Patients who receive GLP-1 agonist drugs should be screened for the level of lipase, total and pancreatic amylase, and blood trypsin for the purpose of timely detection of side effects and adequate treatment.

Contributors:

Sanina N.A. – conceptualization, methodology, research, writing (initial draft, review and editing);

Hondulenko N.O. – formal analysis, writing (initial draft);

Panina S.S. – methodology, research, resources;

Shulha V.S. – writing (review and editing).

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