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SCIENCE BOX

POSTBARIATRIC HYPOGLYCEMIA: THE VIEW OF AN ENDOCRINOLOGIST

Xudoyorova Dilnoza Rizoyevna
Department of Internal Medicine and Endocrinology Bukhara State Medical Institute

Annotation: *The obesity epidemic has led to an increase in the number of bariatric surgeries performed as the most effective method of treating obesity and the expansion of indications for their implementation; in this regard, endocrinologists are increasingly faced with late complications, including post-bariatric hypoglycemia. Postbariatric hypoglycemia is a rare but severe disorder of carbohydrate metabolism that occurs months or years after surgery on the upper gastrointestinal tract. Postbariatric hypoglycemia can be accompanied by severe clinical symptoms and lead to a decrease in the quality of life and disability of patients. It is difficult to assess the prevalence of hypoglycemia after bariatric surgery due to the lack of clear diagnostic criteria, the often hidden clinical picture, and the lack of awareness of doctors and patients about this complication. Hypoglycemia in this case is postprandial hyperinsulinemic in nature. The mechanisms of development of this complication have recently been actively discussed, and the production of incretins and dysregulation of insulin secretion are the subject of constant research in this area. Understanding the mechanisms of development of this condition allows us to develop optimal diagnostic and treatment methods. This review will discuss the pathophysiology, basic principles of diagnosis and treatment methods for postbariatric hypoglycemia.*

In recent decades, increasing attention has been focused on the problem of obesity due to the progressive prevalence of this disease among both adults and children. According to WHO, almost a quarter of the Russian adult population was obese in 2016 [1]. Due to the increased risk of obesity-related diseases, as well as the impact on quality and life expectancy, this disease requires effective treatment strategies. As is known, in morbid obesity the effectiveness of conservative therapy does not exceed 5–10% [2]. Therefore, for patients with high degrees of obesity, especially in combination with serious concomitant diseases (such as type 2 diabetes mellitus, atherogenic dyslipidemia, obstructive sleep apnea syndrome, etc.), when conservative therapy is ineffective, bariatric surgery is the method of choice. Its main goal is to influence the course of diseases comorbid with obesity through a significant reduction in body weight, as well as improve the quality of life of patients. In recent decades, there has been a worldwide trend towards both an increase in the number of operations performed and an expansion in the number of countries where bariatric surgery is becoming more widespread.

For morbid obesity, bariatric surgery has proven effectiveness and advantages over conservative treatment methods [3].In parallel with this, in connection with the expansion to bariatric surgery and the growing number of interventions performed for obesity, the number of publications on perioperative, postoperative and late complications, in particular postbariatric hypoglycemia, which occurs in 25–30% of those operated on during some types of operations, is naturally increasing [4] [5] and can cause the development of life-threatening situations associated with neuroglycopenic conditions (injuries, car accidents, decreased performance) and disability of patients [6]. The risk

associated with hypoglycemia determines the urgent need to obtain more accurate information about the true incidence of this complication. This review provides information on the incidence of development depending on the type of bariatric surgery, pathogenetic mechanisms, diagnostic criteria, and treatment methods for this complication. To collect information, full-text and abstract-bibliographic databases were used: Pub Med, scientific electronic librarieseLIBRARY.RUAndcyberleninka.ru, the literature review was carried out over the past 20 years. Springer and Elsevier websites were used to access the full text of articles. The search for sources of primary information was carried out using the following keywords (in English-language databases - with appropriate translation): postbariatric hypoglycemia, incretins, pathogenesis of obesity, hypoglycemia after gastric bypass, bariatric surgery, GLP-1 and GIP, insulin secretion, insulin receptors, mechanism of hypoglycemia , daily glycemic monitoring, hyperinsulinemic hypoglycemia, dumping syndrome, treatment of hypoglycemia, diagnosis of hypoglycemia. To increase the specificity and sensitivity of the search, logical operators (AND OR) and filters were used: types of articles - books, clinical and original studies, clinical cases, systematic reviews, meta-analyses.It is possible to predict the effectiveness and safety of any bariatric surgery only with careful preoperative selection of candidates by a multidisciplinary team of specialists (including an endocrinologist, bariatric surgeon, therapist, cardiologist, psychiatrist, etc.) in accordance with established indications and contraindications, guided by the criteria of the International Federation of Obesity Surgery and metabolic disorders (IFSO)[7], European Interdisciplinary Guidelines for Metabolic and Bariatric Surgery[8], Russian clinical guidelines for the treatment of obesity in adults[9, 10]. The choice of surgery depends on body mass index (BMI), concomitant metabolic disorders and diseases, the nature of eating disorders, etc. Most researchers tend to conclude that this is a joint decision between the patient and the surgeon.[8–9][eleven]. Depending on their effect on the anatomy of the gastrointestinal tract, all bariatric surgeries can be divided into the following groups: restrictive and combined (restrictive and bypass). Restrictive (gastro-restrictive) operations are aimed at reducing the size of the stomach. Among them, two are currently most widely used: sleeve gastrectomy, from the English sleeve - sleeve, in which it is vertically stitched from the prepyloric region to the angle of His with staplers, as a result of which the stomach takes the shape of a tube, or sleeve (hence the name), with a capacity of about 100 ml, in which most of the stomach is cut off, and adjustable gastric banding, in which a special silicone cuff (band) is put on the cardia area, dividing the stomach into smaller and larger parts, a port connected by a catheter is placed subcutaneously with a cuff, which allows you to adjust the diameter of the bandage by introducing saline into the port and thereby influence the amount of food the patient eats. The mechanism of action of restrictive bariatric surgery is based on a reduction in gastric volume and, accordingly, nutrient intake; low-calorie diet of patients in the early postoperative period; reduction of fat mass, incl. visceral, which helps reduce insulin resistance; in the case of longitudinal gastrectomy - removal of the ghrelin-producing zone of the fundus of the stomach, which helps suppress the feeling of hunger and reduce appetite; increased levels of glucagon-like peptide-1 (GLP-1) due to accelerated food evacuation and the early influence of chyme on ileal L cells.

Combinedcombine restrictive and shunting components. Their mechanism of action is aimed at reducing the volume of food consumed by reducing the volume of the stomach (restrictive component) and bypassing various parts of the small intestine, which reduces food absorption. Classic options for combined operations are gastric bypass (GSH, Roux-en-Y gastric bypass, and Mini-Gastric Bypass) and biliopancreatic bypass (BPS, Biliopancreatic Diversion). With GSH, most of the stomach, duodenum and the initial part of the small intestine are excluded from the transit of food; with BPS, most of the stomach is removed, and the duodenum and almost the entire jejunum are excluded from the passage of food.

In addition to the restrictive mechanisms described above, the following occur during combined operations: firstly, malabsorption of fats and carbohydrates, more pronounced in BPS; secondly, the exclusion of the duodenum and the initial parts of the small intestine from contact with the food mass promotes the inhibition of anti-incretins (possible candidates are glucose-dependent insulinotropic polypeptide (GIP) and glucagon), which are released in the proximal part of the small intestine in response to the entry of chyme into it and counteract the production or the action of insulin; thirdly, the accelerated intake of food into the distal part of the small intestine promotes the rapid release of GLP-1 from L-cells of the ileum, which has a glucose-dependent insulinotropic effect, which contributes to the so-called “incretin effect” and its most striking clinical manifestation - dumping syndrome; fourthly, GLP-1 suppresses the secretion of glucagon and accelerates satiety by acting on the corresponding centers of the brain; fifthly, changes occur in the intestinal microflora, the content of bile acids increases and their entry into the distal parts of the small intestine accelerates; In addition, with BPS, there is a selective reduction in ectopic lipid deposition in skeletal muscle and liver, resulting in improved insulin sensitivity. Glucose homeostasis in the body is the result of the interaction of a complex system, including both classical hormones and incretin hormones. On the one hand, maintaining glycemic levels within the physiological range is ensured by the secretion of insulin, which, being the only hormone in the human body that reduces blood glucose levels, enhances the absorption of glucose by tissues, stimulates glycolysis and glycogen synthesis, and suppresses glycogenolysis and gluconeogenesis. On the other hand, the maintenance of normoglycemia is ensured by counter-insular hormones (glucagon, adrenaline, cortisol, somatotropic hormone), which increase glucose levels due to the activation of glycogenolysis and gluconeogenesis[24]. The pancreas plays a key role in glucose metabolism: its α-cells secrete glucagon; β-cells - insulin, amylin, C-peptide; γ-cells - pancreatic polypeptide; δ-cells - somatostatin and ε-cells - ghrelin[2]. In addition to the pancreas, other organs/tissues are also involved in glucose metabolism: the central nervous system, liver, intestines (synthesis of GLP-1 and GIP), as well as adipose and muscle tissue. In addition to the pancreas, other organs/tissues are also involved in glucose metabolism: the central nervous system, liver, intestines (synthesis of GLP-1 and GIP), as well as adipose and muscle tissue. Normally, the postprandial increase in serum glucose concentration depends on the rate of evacuation of food from the stomach, as well as on the uptake of glucose by the liver and tissues. In patients after some types of bariatric surgery, the movement of food from the stomach into the intestine is accelerated, which leads to a higher level of postprandial glycemia and subsequently to a sharp decrease due to increased tissue uptake due to overcoming insulin resistance[6]. The mechanisms of development of postbariatric hypoglycemia are multifactorial and not fully understood. In Figure 1 you can see the currently known mechanisms of their development. It is assumed that β-cell hypertrophy and hyperplasia, which occurred before bariatric surgery and were compensatory in nature to overcome insulin resistance, after bariatric surgery, as insulin resistance gradually decreases, contributes to hypoglycemic conditions.

Hyperinsulinemia, present in both conditions, promoted pancreatic cell proliferation through its effects on insulin-like growth factor-1 receptors.[26]. Resection of the pancreas, performed after appropriate additional examination for hypoglycemic syndrome, in some postbariatric patients actually made it possible to reduce the frequency and severity of hypoglycemia, but later this type of treatment was abandoned due to the development of severe complications and low effectiveness in the long term.[18]. Other studies did not support this theory, in particular, Meier JJ, together with colleagues, did not find differences in pancreatic β-cell hyperplasia among patients after HS compared with a group of obese and normal weight patients: in obese and normal weight patients body, the average nuclear diameter of β-cells correlated with BMI ($r(2)=0.79$, $p<0.001$); in postbariatric patients with hypoglycemia, the nuclear diameter of β-cells was increased ($p<0.001$) compared with that for BMI in controls subjects, possibly indicating their increased functional activity, but consistent with

preoperative BMI. The authors concluded that postprandial hypoglycemia after HS is most likely due to dumping syndrome and increased insulin secretion[27]. Thus, hypertrophy and hyperplasia of pancreatic β-cells cannot be considered as the sole or main causes of postprandial postbariatric hypoglycemia.

Conservative treatment methods

*Non-medicinal.*Basic dietary recommendations for patients with postbariatric hypoglycemia involve limiting carbohydrates in main (less than 30 g) and additional (less than 15 g) meals [53], and patients with late dumping syndrome are advised to delay fluid intake for at least 30 minutes after meals [43]. Studies have demonstrated that high carbohydrate, low protein meals lead to severe hyperinsulinemia and subsequent hypoglycemia. Restricting the diet to 30 g of solid or 28 g of liquid carbohydrates with a low glycemic index prevented the development of hypoglycemia in patients after bariatric surgery [16]. Consumption of foods with a low glycemic index is not accompanied by such a pronounced and rapid postprandial rise in blood glucose and, therefore, reduces the likelihood of postprandial hypoglycemia. It is recommended to consume mixed foods consisting of proteins (at least 0.9 g per kg of body weight) and healthy fats (nuts, avocados, olives, most vegetable oils, fish oil), since they are a source of calories and do not cause insulin secretion.

Breaks between meals should be no more than 3-4 hours, for this you can have snacks. Drinks should be taken at least half an hour after meals, since it is believed that the simultaneous intake of food and liquid leads to an even faster evacuation of food into the intestines. Patients are advised to avoid alcohol and caffeine consumption. Metabolization of alcohol is accompanied by a decrease in glucose synthesis by the liver, which increases the risk of hypoglycemia. Diet therapy is effective in the vast majority of cases[14]. If diet therapy is ineffective, drugs that act on various stages of pathogenesis can be used.

*Medication.*The first drug used in the treatment of postbariatric hypoglycemia was acarbose, which slows and reduces glucose absorption by inhibiting intestinal α-glucosidase, which breaks down carbohydrates into monosaccharides, thereby reducing postprandial excursions in glycemia. Acarbose may be used to treat symptoms of late dumping syndrome [15]. However, the high incidence of adverse events (flatulence, malabsorption) limits the use of acarbose in postbariatric patients [20]. Diazoxide activates ATP-sensitive potassium channels and inhibits calcium-induced insulin secretion by pancreatic β-cells. The drug has been used in the treatment of severe hyperinsulinemic hypoglycemia of newborns, insulinoma and non-insulinoma pancreatogenic hypoglycemia syndrome. In one study published in 2006, diazoxide reduced the number and severity of hypoglycemic events in 3 out of 6 patients[5]. Glucagon is used to treat severe hypoglycemia with the development of neuroglycopenic symptoms, it is administered subcutaneously, the main mechanism of action is to stimulate the release of glucose from the liver. Somatostatin analogues are also used, which reduce the secretion of insulin and GLP-1 by binding to somatostatin receptor subtypes 2 and 5. These drugs are the preferred treatment option for patients with established dumping syndrome who do not respond to initial dietary changes with or without acarbose treatment. The glucose tolerance test provided evidence of the effectiveness of octreotide and pasireotide in the treatment of late dumping syndrome[43]. For the treatment of hypoglycemia, octreotide 25–50 mcg is usually administered subcutaneously before meals, and if it is effective and well tolerated, long-acting agents administered intramuscularly can be used.

Another group of drugs that have shown effectiveness in treating hyperinsulinemic hypoglycemia are calcium channel blockers (nifedipine and verapamil), they block insulin secretion by inhibiting voltage-gated calcium channels of pancreatic β-cells. Several clinical cases of successful use of drugs in patients with hypoglycemia after bariatric interventions have been described.

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