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GESTATIONAL DIABETES: EVALUATION OF RISKS AND DIAGNOSIS STRATEGIES

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Abstract
The article discusses the pathogenesis of type 2 diabetes mellitus. Based on the above mechanisms, the pathogenetic validity of lifestyle modification in patients with type 2 diabetes mellitus, as well as the use of metformin (Siofor) and glimepiride (Oltar) is emphasized.

Keywords: Type 2 diabetes mellitus, pathogenesis, metformin, glimepiride.

Introduction

Pathogenesis of type 2 diabetes mellitus The most important triggering external factor (trigger) that implements the genetic propensity to type 2 diabetes is an eating disorder with excessive consumption of saturated fats, mainly omega-6 and omega-9 free fatty acids (FFA). At its core, type 2 diabetes is a disease that develops as a result of poor nutrition (lifestyle) against the background of a genetic predisposition. Today, a huge number of genes are known that encode type 2 diabetes (for example, HNFs, PPARG, IPF-1, IB1, TIEG2/KLF11) and determine the tendency to dyslipidemia [11]. Thus, HHEX controls the activity of pancreatic structures [12], SLC30A8 — zinc transport in islet cells; activation of FSADS1 and PPARG leads to changes in fat metabolism, IGF2BP2 and FTO - to obesity and insulin resistance [13], TCF7L2 — to a general decrease in secretory response; DGKB, FADS1, GCK, MTNR1B interfere with the implementation of Phase 1 of insulin secretion; WFS1 is responsible for apoptosis of T cells [14]. As stated in the most recent and important recommendations of 2012 ("The approved position of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EAID) on the strategy for the treatment of type 2 diabetes"), "the increase in glycemic levels is due to the predominance of glucose intake into the blood plasma over its release" [15]. At the same time, fasting hyperglycemia, especially in the morning, is caused by excessive glucose formation in the liver, and postprandial hyperglycemia is mainly due to

insufficient inhibition of glucose formation and a weak secretory response, i.e. dysfunction of pancreatic beta cells. Thus, type 2 diabetes is based on several important disorders, the main of which are: 1) excessive formation of glucose in the liver; 2) defect in insulin secretion (basal compensatory hyperinsulinemia and decreased insulin release after meals); 3) insulin resistance against hypertriglyceridemia. Other recently known mechanisms of impaired glucose utilization are: 1) an increase in the level of glucagon; 2) an increase in the level of glucose-dependent insulinotropic polypeptide; 3) postprandial deficiency of glucagon-like peptide (GLP-1), which also require drug correction.

Excessive glucose production by the liver and the role of lipids The production of glucose by the liver (gluconeogenesis) mainly occurs at night due to the fats eaten during the day — free fatty acids, their accumulation and oxidation in the liver. At the very beginning of the development of type 2 diabetes, FFA activates gluconeogenesis, then stimulates late insulin secretion, which inhibits endogenous glucose production. Compensatory mechanisms that restrain the effect of elevated FFA levels are hyperinsulinemia and, oddly enough, hyperglycemia itself, aimed at maintaining glucose utilization in insulin-sensitive tissues (muscles, liver, adipose tissue). It has been confirmed that FFA increases glucose-stimulated insulin secretion by 30-50%. However, the long-term existence of an excess of FFA leads to increased insulin resistance, depletion of the insulin response and, ultimately, to persistent hyperglycemia. Another effect mediated by FFA is the inhibition of carbohydrate oxidation, i.e. reducing glucose utilization and increasing its concentration in the blood. The only drug whose key mechanisms of action are suppression of nocturnal gluconeogenesis, reduction of lipid levels and insulin resistance is metformin, which is effectively used in the prevention and treatment of type 2 diabetes (the average decrease in HbA1c is 1.5%). In recent years, there has been evidence that metformin contributes to an increase in incretin levels, primarily GLP-1, blocks dipeptidyl peptidase-4 (DPP-4), which reduces glucagon secretion by alpha cells of the pancreas [16]. In Ukraine, metformin is represented by the drug Siofor.

Defect in insulin secretion

Pancreatic T-cell dysfunction is an important and complex feature of type 2 diabetes. In the early stages of the disease, the formation of proinsulin, insulin and C-peptide formed from it is not impaired or even increased. At the same time, two processes are observed — basal hyperinsulinemia (due to excess FFA) and a weak insulin response to food stimulants, both the first (fast) phase of insulin secretion and the second (late) are disrupted. It is known that at the time of diagnosis of type 2 diabetes, the

effectiveness of stimulated insulin secretion has already been reduced by 50%, but it should not be confused with a decrease in the number of T cells due to destruction observed in type 1 diabetes and other specific types of diabetes. Recently, there has been evidence that T-cell dysfunction is also based on an initial genetic defect. Following a strict fat-restricted diet (i.e. FFA) gradually improves the stimulated insulin response, helps to reduce basal insulin levels, which means it improves tissue sensitivity to it, contributes to an effective reduction of glycemia before and after meals. Today, an important emphasis is being placed on the fact that islet cell dysfunction is usually reversible [16]. The secretory insulin defect increases both due to the toxic effect of free fatty acids (lipotoxicity) on pancreatic T cells and due to the development of hyperglycemia (glucose toxicity), therefore, the correction of such disorders contributes to the effective restoration or preservation of endocrine function of the pancreas [17]. In those patients who do not sufficiently limit the amount of fat in their diet or have a long-term course of the disease, treatment must be supplemented with metformin, as well as the use of medications that enhance the insulin response to glucose. The most studied drugs that restore the stimulated secretion of pancreatic T cells include sulfonylurea derivatives. Sooner or later, in the treatment of type 2 diabetes, doctors have to use combination therapy, including metformin in combination with other hypoglycemic drugs, of which sulfonylurea derivatives remain the most commonly used and effective (the average decrease in HbA1c is 1.5%). They improve postprandial (stimulated) and basal insulin release. This is true for all their modern forms — glibenclamide, glimepiride and gliclazide. If we compare the hypoglycemic activity of sulfonyluretics, then glimepiride has a higher activity than gliclazide MR. One of the main advantages of glimepiride over other sulfonylurea derivatives is that it not only stimulates insulin secretion by closing the CATP-dependent channels of pancreatic T cells, but also has pronounced extra-pancreatic effects, which leads to minimal stimulation of such T cells in comparison with other representatives of this group of drugs, causes a less pronounced increase in the level of insulin and, as a result, a more rare development of undesirable effects. Glimepiride suppresses lipolysis and increases the sensitivity of liver and muscle tissues to insulin, which reduces insulin resistance [18]. To date, among all sulfonylurea derivatives, glimepiride has the most powerful hypoglycemic effect, while causing the mildest, gentle dose-dependent stimulation of BETA cells. The frequency of administration of glimepiride does not affect the time to reach the maximum concentration of the drug in the blood. Glimepiride effectively normalizes postprandial insulin release throughout the day. In Ukraine, glimepiride is available in the form of the drug Oltar.

The role of endocrine secretion disorders

Up to 70% of insulin secretion after eating in healthy people is due to the effects of incretins, which are produced in the intestine. In patients with type 2 diabetes, this effect, aimed at glucose utilization, is significantly reduced. Currently, endocrinologists have new inherently revolutionary groups of hypoglycemic drugs in their arsenal, which are the result of scientific achievements in the field of physiology, pathophysiology, molecular biology and clinical pharmacology. Their creation is associated with advances in the knowledge of new hormones and regulatory mechanisms [19]. These drugs will be useful in the treatment of diabetes, however, it is already known that they all have lower efficacy (average reduction of HbA1c less than 1%) than metformin and sulfonylurea derivatives, their safety remains questionable, and the high cost does not correspond to effectiveness. Perhaps such disadvantages of new hypoglycemic agents (GPP-1, DPP-4 inhibitors, etc.) will disappear in the future after the development of new generations, but for now these are experimental drugs with currently unknown features of use and limited effectiveness. All existing recommendations recommend the use of DPP-4 inhibitors only in combination with metformin. Thus, despite modern achievements in understanding the mechanisms of development of type 2 diabetes, the basis for effective pathogenetic treatment of patients remains lifestyle modification (diet therapy and feasible physical activity) and classical oral hypoglycemic therapy with metformin drugs both in the form of monotherapy and in combination with sulfonylurea derivatives (fixed or separate combination).

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