MODERN VIEW IN THE TREATMENT OF PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Annotation. *The incidence of type 2 diabetes mellitus (T2DM) is very high and continues to grow alarmingly, being the leading cause of mortality in the population. The medical and social significance of T2DM is determined primarily by its severe vascular and neurological complications, which lead to early disability and high mortality, reduced life expectancy and deterioration in its quality. T2DM is characterized by progressive dysfunction of pancreatic β-cells accompanied by the development of insulin resistance. The article discusses the mechanisms of action of hypoglycemic drugs from the group of peroxisome proliferator-activated receptor (PPARγ) agonists - pioglitazone and the group of dipeptidyl peptidase-4 inhibitors - alogliptin. Pioglitazone improves insulin sensitivity through increasing the expression of numerous genes encoding proteins or proteins that modulate glucose and fat metabolism. Alogliptin increases glucose-dependent activity of β-cells with a low risk of hypoglycemia, suppresses increased secretion of glucagon, and has cardiovascular safety. The feasibility of using a fixed combination of pioglitazone and alogliptin has been substantiated, which makes it possible to effectively and safely manage T2DM, simultaneously influencing 10 of 11 pathophysiological disorders that lead to the development of the disease.*

Keywords: *type 2 diabetes mellitus, insulin resistance, β-cells, dipeptidyl peptidase-4 inhibitor, thiacholidinedione, gliptin.*

Introduction. Type 2 diabetes mellitus (T2DM) is one of the most common diseases worldwide. Despite the large number of glucose-lowering drugs available, the number of patients achieving the target level of glycated hemoglobin (HbA1c) is small. According to the Russian register of patients with T2DM, 52.2% of patients have an HbA1c level <7%, and in some regions - 25.2% [1]. The progressive nature of the disease is associated with the complex pathogenesis of diabetes, in which the

development of complications is promoted not only by hyperglycemia, but also by other metabolic disorders. In addition to the main links in pathogenesis - insulin resistance (IR) and insufficiency of β-cell function, other pathophysiological mechanisms have been identified:

reduced incretin effect - impaired secretion of glucagon-like peptide (GLP-1), resistance of β-cells to the stimulating effect of GLP-1;

an increase in free fatty acids in the blood plasma, accumulation of toxic lipid metabolites in β-cells, hepatocytes and myocytes due to the resistance of adipocytes to the antilipolytic action of insulin;

increased secretion of glucagon by α-cells of the pancreas and increased sensitivity of liver cells to glucagon;

increased reabsorption of glucose by the kidneys;

increased appetite, weight gain, worsening insulin resistance in muscles and liver [2].

A key element in the pathogenesis of T2DM is IR, which over time leads to an increasing decrease in the function of pancreatic β-cells. Both disorders can be addressed by sensitizing hepatocytes, myocytes and adipocytes to insulin, as well as correcting incretin deficiency - GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) [3]. The used glucose-lowering drugs of certain classes cannot immediately affect all pathophysiological disorders present in T2DM, therefore, for optimal glycemic control, a combination of drugs from various groups is necessary, in particular glitazones with a dipeptidyl peptidase-4 inhibitor (DPP-4). In addition, since different groups of drugs reduce plasma glucose levels through different mechanisms, such combination therapy will have a net effect in reducing HbA1c compared with each drug alone [4].

Pioglitazone

Currently, pioglitazone is the only representative of the group of glucose-lowering drugs - thiazolidinediones (glitazones). These drugs are agonists of nuclear peroxisome proliferator-activated receptor γ (PPARγ), which is expressed predominantly in adipose tissue and induces transcription of genes involved in glucose and lipid metabolism.

The benefits of pioglitazone include:

fairly high glucose-lowering activity - the effectiveness of pioglitazone is comparable or superior to the effectiveness of DPP-4 inhibitors and sulfonylurea derivatives; the effect of drugs from this group is not associated with hypoglycemia

positive effect on the lipid spectrum: pioglitazone reduces triglyceride levels, increases the amount of high-density lipoproteins and increases the particle size of low-density lipoproteins while reducing their concentration due to activation of PPARα [2];

reducing the concentration of free fatty acids in the blood plasma, increasing the formation of nitric oxide and, thus, improving endothelial function [8];
stimulation of PPARα, increased secretion of adiponectin, which leads to increased tissue sensitivity to insulin and inhibition of atherogenesis [9].

Such effects are directly associated with a decrease in IR, which, as shown in large prospective studies, is a strong independent predictor of cardiovascular disease, myocardial infarction (MI) and stroke [10, 11]. The PROactive trial, which included more than 5000 patients with T2DM, confirmed that pioglitazone reduced the primary secondary endpoint of all-cause mortality, nonfatal MI, and stroke by 16% compared with placebo [11, 12].

The PROactive study was a large, prospective, randomized, double-blind, secondary prevention trial that examined the effect of pioglitazone on macrovascular events in 5238 patients with T2DM and a history of cardiovascular disease. About 50% of patients included in this study had a history of MI, and 25% of patients had a history of stroke. Peripheral artery disease was diagnosed in 25% of patients. According to the study protocol, pioglitazone or placebo was prescribed in addition to standard diabetes treatment, which included hypoglycemic, antihypertensive, lipid-lowering, and antithrombotic drugs. The study results showed a statistically significant reduction in the risk of the composite endpoint of MACE by 18% (cardiovascular death, non-fatal MI and non-fatal stroke) (RR 0.82, 95% CI 0.70–0.97) [11, 13] . It should be especially noted that in patients with a history of myocardial infarction, pioglitazone significantly reduced the risk of recurrent myocardial infarction by 28% and the risk of developing acute coronary syndrome by 38% [14]. In patients with a history of stroke, pioglitazone reduced the risk of recurrent stroke by 47% [15].

Thiazolidinedione group drugs have demonstrated a beneficial effect on various biomarkers of atherosclerosis: studies have shown a decrease in the level of pro-inflammatory cytokines in patients with T2DM - C-reactive protein, interleukin 6, CD40L, monocyte chemoattractant protein-1 and metalloproteinase-9 [16], which resulted in improvement of endothelial function, reduction of intima-media thickness of the carotid artery [17].

IR is known to be associated with atrial fibrillation, and T2DM is one of the strongest independent risk factors for this disorder. In a meta-analysis, pioglitazone was associated with a lower risk of recurrent atrial fibrillation [18].

A significant advantage of pioglitazone is its protective effect on β-cells. Studies show that after an initial decrease in HbA1c, better glycemic control is achieved by maintaining β-cell function in patients with T2DM [19]. In the ACT NOW study, the risk of developing T2DM was reduced by 72% ($p<0.0001$). Along with this, there was an improvement in the insulin secretion index/IR (disposition) - the “gold standard”

for assessing β-cell function. This indicator is the strongest predictor of diabetes prevention [20].

Improvement in β-cell function under the influence of pioglitazone occurs, on the one hand, due to stimulation of nuclear receptors PPARγ on β-cells, and on the other, due to increased sensitivity of β-cells to glucose and reduced lipotoxicity [21].

Alogliptin

As already noted, in patients with T2DM, the incretin effect is reduced, and therefore the incretin hormones do not have the proper effect on insulin secretion by β-cells and the mechanism of the necessary suppression of glucagon secretion in response to food intake is disrupted.

Drugs of the DPP-4 group, which include alogliptin, prevent the physiological inactivation of GIP and GLP-1, resulting in elevated levels of these hormones in the blood plasma after meals.

As a result of this action, DPP-4 inhibitors reduce plasma glucose levels after meals and on an empty stomach. Features of the action of DPP-4 i also include a decrease in HbA1c levels with a low risk of hypoglycemia and the absence of weight gain [22]. Elevated levels of incretin hormones determine additional sensitivity to glucose in the α- and β-cells of the pancreas, which in hyperglycemia leads to increased insulin secretion and decreased glucagon secretion, and in hypoglycemia - to decreased insulin secretion and increased glucagon secretion [22, 23]. In addition, during treatment with DPP-4 i, additional effects are determined: a decrease in lipolysis and a decrease in the level of triacylglycerol-rich atherogenic lipoproteins after meals [24, 25].

The hypoglycemic effect of alogliptin has been proven in a large number of studies. When alogliptin was added to the treatment of patients with poorly controlled diabetes while taking sulfonylureas (HbA1c level 8.1%), HbA1c levels decreased by 0.39–0.53% compared with the control group [26]. In another study, in patients with a baseline HbA1c level of 7.9 ± 0.8% who did not receive treatment, the administration of alogliptin showed a good glucose-lowering effect. 50% of patients experienced a decrease in HbA1c levels by 0.5%, and in 29% by more than 1%. In addition, when taking alogliptin at a dose of 25 mg, a slight decrease in total cholesterol and triglyceride levels was observed [27, 28].

Alogliptin is a highly selective DPP-4 i. The selectivity of alogliptin for DPP-4 is more than 10,000 times higher than for other types of DPPs, which is higher than that of other members of the iDPP-4 class. Therapeutic doses of alogliptin inhibit plasma DPP-4 by more than 80%, maintaining the effect for 24 hours, and increase the concentration of GLP-1 by 2-3 times [29].

The EXAMINE study, which included 5380 patients with type 2 diabetes and acute myocardial infarction or unstable angina, did not reveal the cardioprotective effect of alogliptin, but demonstrated its safety: after a mean follow-up period of 18 months. There were no significant differences in the incidence of myocardial infarction, stroke, cardiovascular mortality, or all-cause mortality between patients receiving alogliptin and those receiving placebo [30]. However, a study conducted in Japan showed that the use of alogliptin in patients with type 2 diabetes and hypertension not only improved glycemic control (after 3, 6 and 12 months, the HbA1c level decreased from 7.0 ± 0.97% to 6. 4±0.61%, 6.3±0.58% and 6.3±0.75%, respectively, $p<0.01$), but also reduced systolic blood pressure from 137±18 mm Hg. Art. up to 127±13, 125±15 and 120±17 mmHg. Art. accordingly ($p<0.01$), diastolic blood pressure - c 79±13 mm Hg. Art. up to 74±8, 74±10 and 70±8 mmHg. Art. respectively ($p<0.01$) [31].

Based on the results of a subanalysis of the EXAMINE study, JP Ferreira et al. [32] noted in a subgroup of patients with GFR≥60 ml/min/1.73 m2 treated with alogliptin, a statistically significant reduction in the risk of developing a composite endpoint of MACE, including death due to cardiovascular causes, non-fatal stroke and non-fatal myocardial infarction, by 19 % (RR 0.81, 95% CI 0.65–0.99, $p=0.014$) compared with those receiving placebo [32]. At the same time, the risk of cardiovascular mortality decreased by 39% ($p=0.013$), the risk of non-fatal MI - by 14% ($p=0.013$).

Combination of pioglitazone and alogliptin

Combination therapy with thiazolidinedione and DPP-4 inhibitors primarily showed a good glucose-lowering effect. Thus, in a 26-week study among naive patients [27] on a fixed combination of pioglitazone and alogliptin (Incresink®), 63% of patients achieved an HbA1c level of <7%, and in patients with an initial HbA1c level of >8.5% on the combination drug, a decrease in HbA1c the average was 2.1%. The combination of drugs provided a greater improvement in glycemic control than monotherapy with pioglitazone and alogliptin.

In another 26-week study, alogliptin alone or in combination with pioglitazone was added to metformin-treated patients with poor glycemic control. Changes in HbA1c levels from baseline, changes in fasting plasma glucose levels, and β-cell function were assessed. As a result, combination therapy resulted in a significant reduction in HbA1c and fasting glucose levels. The results of the study showed an improvement in β-cell function (as assessed by the homeostasis model of β-cell function) [28].

Conclusion. Thus, the fixed combination of pioglitazone and alogliptin appears to be clinically effective, since it immediately affects several links in the pathogenesis of diabetes mellitus: it reduces IR, increasing glucose uptake in muscle tissue and reducing glucose production in the liver, as well as reducing lipolysis in adipocytes, enhances the incretin effect, insulin secretion, reduces glucagon secretion. The drugs used complement each other according to their mechanism of action. Pioglitazone reduces the progression of atherosclerosis by improving endothelial function and reducing the risk of cardiovascular events. However, its side effects cannot be ignored: weight gain of 1–2 kg and fluid retention in 2–4% of patients. Alogliptin showed safety in terms of cardiovascular events and good hypoglycemic effect. The use of drugs in combination allows the use of lower doses of pioglitazone, minimizing side effects. The fixed dose of the drug and ease of administration make the drug attractive for use in patients with a short duration of diabetes or newly diagnosed diabetes, with intolerance to metformin or possible side effects when increasing the dose of metformin, as well as in patients with additional cardiovascular risk factors.

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