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DIABETES AND MODERN APPROACHES TO ITS TREATMENT

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Abstract

Diabetes needs to be reclassified as a "death illness" rather than just a glycemic control anomaly. A significant factor in the decline in life expectancy in diabetic individuals is macrovascular disease, particularly cardiovascular disease. Blood pressure, blood lipids, cholesterol, and glucose control should all be the focus of treatment for diabetic patients. The following treatment goals for type 2 diabetes are specified by the International Diabetes Federation European Policy Group: glycated hemoglobin 6.5%, blood pressure 140/85 mm Hg, low-density lipoprotein cholesterol 3.0 mmol/L (115 mg/dL), and triglycerides 1.7 mmol/L (150 mg/dL).

Keywords: diabetes, angiopathy, hypoglycemic effect, cholesterol, glucose

Introduction

As defined by experts from the World Health Organization: "Diabetes is a problem of all ages and all countries." Currently, diabetes mellitus (DM) ranks third among the immediate causes of death after cardiovascular and oncological diseases, so the solution of many issues related to this disease has been put in many countries of the world at the state, federal level [1].

According to the International Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (1997), diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or a combination of both.

Evidence has now accumulated around the world that effective control of diabetes can minimize or prevent many of the complications associated with it.

With regard to the effective management of diabetes, there is strong evidence that improved glycemic control can significantly reduce the risk of developing both micro- and macroangiopathy.

An analysis of the 10-year DCCT study (Control of Diabetes and its Complications) showed that for every percent decrease in glycated hemoglobin, the risk of developing microvascular complications (retinopathy, nephropathy) was reduced by 35%. In addition, the results of this study clearly demonstrate that aggressive glycemic control, along with normalization of blood pressure parameters, significantly reduces the risk of coronary heart disease, cerebrovascular disease, and peripheral angiopathy in patients with type 2 diabetes mellitus. Based on this, the main goal of the treatment of the disease is the fullest possible compensation of carbohydrate metabolism disorders. Only the use of complex and pathogenetically substantiated therapy, taking into account the chronic course of the disease, the heterogeneity of metabolic disorders, the progressive decrease in the mass of β-cells, the age of patients and the risk of hypoglycemia, as well as the need to restore impaired insulin secretion and achieving effective long-term glycemic control will achieve this goal.

To date, there is no cure for type 2 diabetes, but it can be well managed and lead a fulfilling life.

A type 2 diabetes management program includes the following main objectives:

- lifestyle changes (diet therapy, exercise, stress reduction);
- drug treatment (oral hypoglycemic drugs, incretin mimetics, insulin therapy).

Despite numerous recent publications on the management of type 2 diabetes, not all physicians are familiar with the treatment algorithm for this severe disease. Currently, a revised American Diabetes Association (ADA) and European Association for the

Study of Diabetes (EASD) Consensus Statement regarding the management of hyperglycemia in type 2 diabetes has been developed and published [4].
Table 1 presents various current anti-diabetic interventions, according to their effectiveness, advantages and disadvantages.

Purpose of the Research

A fundamentally important point is the objective digital criteria for compensating for type 2 diabetes mellitus. In 1999, Type 2 Diabetes Care Guidelines were published, which provide criteria for compensating the disease. It is important to pay special attention to the need for tighter control of not only carbohydrate metabolism, but also lipid metabolism, as well as blood pressure indicators through the prism of vascular risk, or the risk of developing fatal vascular complications of type 2 diabetes.

Materials and Methods

Choice of therapy and its role in the treatment of type 2 diabetes mellitus
Numerous studies around the world are focused on finding effective treatments for diabetes. However, do not forget that in addition to drug therapy, recommendations for lifestyle changes are no less important.
Basic principles of diet therapy
• fractional balanced meals 6 times a day, in small portions, at the same time, which helps to maintain weight within the normal range and prevents sharp postprandial changes in glycemia levels
• if overweight, a low-calorie diet (≤1800 kcal) is indicated
• restriction of simple, easily digestible carbohydrates (sugar and products containing it, honey, fruit juices)
• increased intake of fiber-rich foods (from 20 to 40 g per day)
• limiting the intake of saturated fats ‹ <10%, polyunsaturated fats ‹ <10%; preference should be given to monounsaturated fats
• the daily amount of protein in food should be 1.0–0.8 g/kg of body weight; in case of kidney pathology, this amount should be reduced (Fig.1),
• restriction of salt intake to 3 g per day, due to the high risk of arterial hypertension, nephropathy. It should be taken into account that the daily amount of unsalted foods already contains 1.5–2.0 g of salt,
• restriction of alcohol consumption, taking into account the high calorie content and the risk of developing hypoglycemia (<30 g per day),

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• the diet should be rich in vitamins and contain the necessary amount of trace elements. In winter and spring, it is recommended to take multivitamin tablets [1, 2, 3].

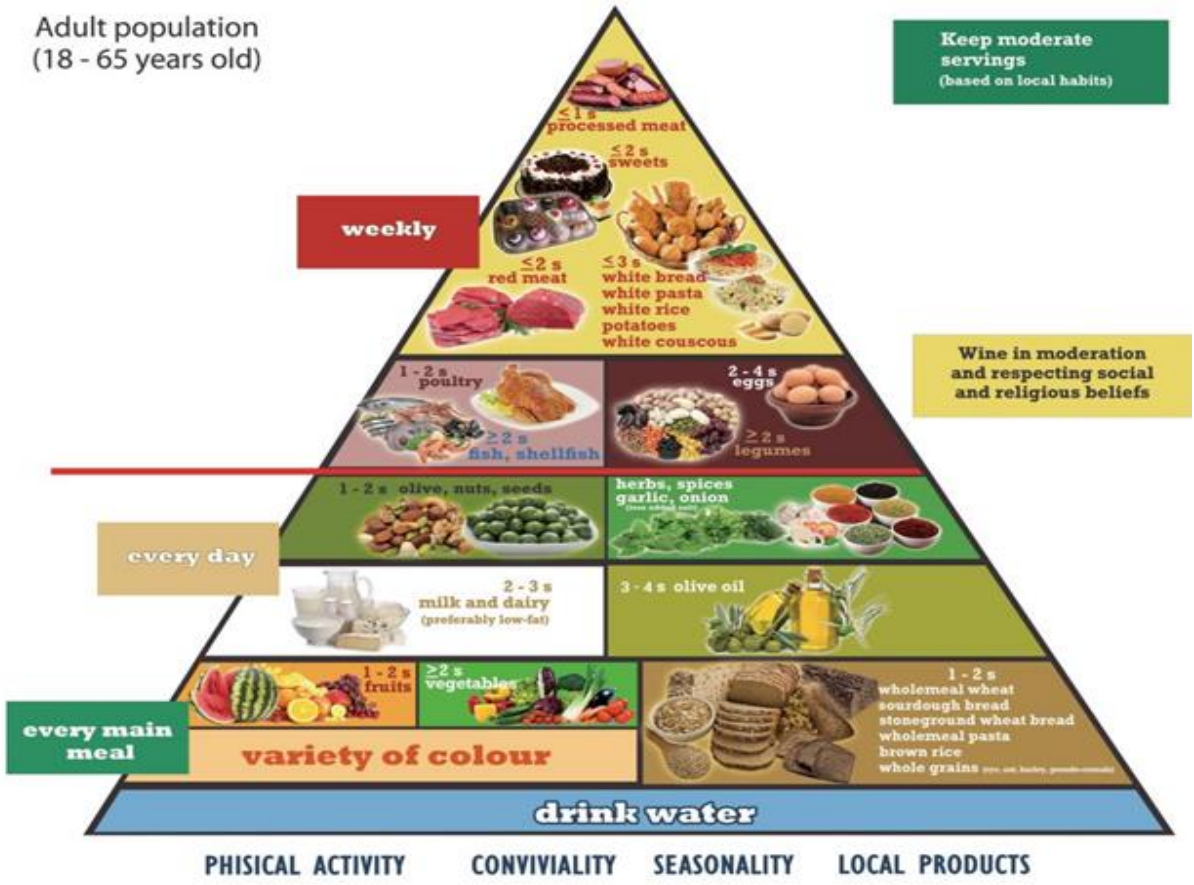

Fig.1. The pyramid of proper nutrition reflects the distribution of nutritional components of food during the day

Table 1. Goals of carbohydrate metabolism therapy [European Diabetes policy Group, 2018-2019]

Index	Low risk of angiopathy (target value)	Risk of macroangiopathy	Risk of microangiopathy
HbA_{1C} (%)	≤6,5	>6,5	>7,5
Fasting/pre-meal glycemia (mol/l) - in venous blood plasma	≤6,0	>6,0	>7,0
- whole capillary blood (self-control)	≤5,5	>5,5	>6,0
Postprandial glycemia (2 hours after eating) mmol/l - in venous blood plasma and whole capillary blood (self-monitoring)	<7,5	>7,5	>9,0

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Table 2. Goals of lipid metabolism therapy. [European Diabetes policy Group, 2018-2019]				
Serum index	**target value**	**Low risk of angiopathy**	**Moderate risk of angiopathy**	**High risk of angiopathy**
Total cholesterol (mmol/l)	≤4,5	>4,8	4,8-6,0	>6,0
LDL cholesterol (mmol/l)	<2,5	<3,0	3,0-4,0	>4,0
HDL cholesterol (mmol/l)	-male>1,0 - female>1,2	>1,2	1,0-1,2	<1,0
Triglycerides (mmol/l)	<1,7	<1,7	1,7-2,2	>2,2

Note: target values of lipid metabolism indicators were proposed by NCEP III (USA), adopted by VNOK (Russia) (2004)

Table 3. Goals of blood pressure control therapy			
Blood pressure level	**Low risk of angiopathy (target values)**	**Moderate risk of angiopathy**	**High risk of angiopathy**
Blood pressure level, mm Hg.	≤130/80	>130/80-≤140/85	>140/85

Physical activity in the treatment of type 2 diabetes

Patients with type 2 diabetes are recommended daily dosed physical activity of the same type: walking in the fresh air, swimming, cycling, etc.

The type of physical activity, its intensity, duration and frequency should be individually selected for each patient, taking into account age, initial physical activity, the general condition of the patient, the presence of complications of diabetes and concomitant diseases (Fig.2).

Fig.2. Physical activity pyramid.

It is important to note that physical activity not only has a positive effect on glycemic indices, facilitating the utilization of glucose (and this effect persists for several hours after the end of physical exercise), but also improves lipid metabolism (reduces the level of triglycerides that contribute to the development of microangiopathy, and increases the level high-density lipoproteins that prevent the development of atherosclerosis), and also have a positive effect on the blood coagulation system (increase fibrinolytic activity and reduce blood viscosity, platelet aggregation and fibrinogen levels).

In addition, physical exercises have a beneficial effect on the cardiovascular system: they increase the efficiency of cardiac output, contribute to the electrical stability of the myocardium, reduce oxygen consumption by the heart muscle, reduce and stabilize blood pressure, and improve blood circulation in the muscles.

It is equally important that physical activity causes positive emotions and helps to resist stressful situations, lead to favorable hormonal changes: reduce the level of stress hormones, increase the level of “pleasure hormones” (endorphins) and testosterone, and, most importantly, lead to a decrease in insulin resistance and hyperinsulinemia.

It should be remembered that physical activity reduces blood sugar if the initial level of glycemia is less than 14 mmol / l. At blood glucose levels above 14 mmol / l, physical exercises are contraindicated, since they cause not a decrease, but an increase in blood sugar and enhance ketogenesis. Also, physical activity is contraindicated when the level of glycemia is below 5.0 mmol / l. Therefore, before, during and after exercise, it is necessary to control blood sugar levels, and in the presence of concomitant cardiovascular diseases, also blood pressure (BP) and heart rate (HR) [1].

Results and Discussion

Medical management of type 2 diabetes

The Consensus Statement of the American Diabetes Association and the European Association for the Study of Diabetes emphasized that in the "total" glycated hemoglobin, equal to 7%, is the starting point on the basis of which certain decisions are made. However, if we talk not about general, but about individual goals, then in this case, glycosylated hemoglobin should be as close as possible to 6%. Thus, the Agreed Resolution indicated that HbA1c≥7% should be considered as an indication for action to change therapy.

In this regard, it was noted that the positive effect of a lifestyle change program primarily aimed at weight loss and increased physical activity can be observed quite quickly, even before a significant decrease in body weight is recorded. However, the

limited long-term effect in relation to the reduction of glycemic levels on a long-term basis dictates the need for drug therapy in most patients. It was also emphasized that the choice of treatment goals and the drugs to be used to achieve them should be individualized for each patient, balancing between the potential decrease in glycated hemoglobin and the long-term positive impact on the risk of complications with side effects, tolerability of the drug and the cost of treatment.

According to the experts who took part in the development of the Agreed Resolution, due to the fact that lifestyle changes do not allow maintaining metabolic control for a long time, metformin should be prescribed at the first stage at the same time, almost at the stage of establishing the diagnosis. In their opinion, metformin is recommended at the initial stages of pharmacological treatment, in the absence of special contraindications, due to its effect on the level of glycemia, lack of weight gain and / or hypoglycemia, usually with a low level of side effects, good tolerability and relatively low cost. (scheme 1) [5].

Biguanides

It should be noted that biguanides began to be used in the treatment of type 2 diabetes more than 50 years ago. However, due to the frequent occurrence of lactic acidosis when taking phenformin and buformin, guanidine derivatives were practically excluded from the treatment of diabetic patients. It is known that the incidence of this complication in different drugs is not the same. Metformin is the only drug approved for use in many countries.

The hypoglycemic effect of metformin is due to several mechanisms of action unrelated to insulin secretion by β-cells. Firstly, metformin in the presence of insulin suppresses the production of glucose by the liver by increasing the sensitivity of hepatocytes to insulin, reducing gluconeogenesis, activating lactate metabolism, increasing glycogen synthesis and reducing glycogenolysis. Secondly, it reduces insulin resistance at the level of peripheral tissues (fat and muscle) and the liver by enhancing and potentiating the action of insulin, increasing the affinity of insulin receptors, restoring impaired post-receptor signal transduction links, and increasing the number of insulin receptors in target cells. Thirdly, metformin increases the utilization of glucose as a result of anaerobic glycolysis. Fourth, metformin somewhat slows down the absorption of glucose in the intestine, which in turn leads to a smoothing of postprandial glycemic peaks. Perhaps this is due to a decrease in the rate of gastric emptying and the motility of the small intestine. Fifth, when taking metformin, there is an increase in the anaerobic utilization of glucose in the intestine. Thus, taking into account the listed main mechanisms of action of this drug, it is more

correct to speak not about a truly hypoglycemic (hyperglycemic), but about an antihyperglycemic effect that prevents an increase in blood sugar.

In experimental and clinical studies, metformin has been shown to have a beneficial effect on the lipid spectrum and on the blood coagulation system. It reduces the concentration of triglycerides in plasma by an average of 10-20%. A significant decrease in the concentration of total cholesterol and LDL cholesterol probably occurs due to a decrease in their biosynthesis in the intestine and liver. Metformin reduces concentrations of chylomicrons and chylomicron residues after meals and slightly increases HDL cholesterol concentrations [6].

The drug enhances the processes of fibrinolysis, as a result of which the risk of thrombosis and vascular complications of diabetes is reduced.

In addition, metformin has a weak anorexigenic effect.

The BIGRO study (BIGyanides and Prevention of the Risk of Obesity) showed that the use of metformin in 324 patients with abdominal obesity was accompanied by a more pronounced decrease in body weight, plasma insulin, total cholesterol and fibrinolysis compared to placebo.

In general, the drug is well tolerated in most patients. Among the side effects of metformin, it should be noted diarrhea and other phenomena from the gastrointestinal tract (metallic taste in the mouth, anorexia, nausea, vomiting), which at the beginning of therapy are observed in almost 20% of patients, and then disappear on their own within a few days. Apparently, these disorders are associated with the effect of metformin on slowing the absorption of glucose in the small intestine. Accumulating in the gastrointestinal tract, carbohydrates cause fermentation processes, flatulence, which can create some inconvenience for the patient. Prevention or reduction of the negative effect of the drug on the gastrointestinal tract is ensured by the appointment of minimal doses of the drug with gradual titration with an interval of several days.

It was recommended to start metformin therapy with low doses of 500 mg taken 1 or 2 times a day with meals (breakfast and/or dinner). After 5-7 days, if there are no side effects from the gastrointestinal tract, the dose of metformin can be increased to 850 mg or 1000 mg after breakfast and after dinner. If side effects develop in response to an increase in dose, then the dose is reduced to the original, with subsequent attempts to increase the dose later.

It has been noted that the maximum effective dose of metformin is usually 850 mg twice daily, with moderately higher efficacy when the dose is increased to 3000 mg. However, side effects may limit the use of higher doses.

In general, paying due attention to the presented Agreed Resolution, it should be noted that despite the presence of metformin adherents both in our country and abroad, there is another point of view indicating the need to take into account that defects in insulin secretion play an important role in the development and progression of diabetes mellitus type 2, and therefore the role of other drugs for the treatment of type 2 diabetes should be properly evaluated.

Sulfonylureas

The main mechanism of action of sulfonylurea (SM) drugs is to stimulate insulin secretion. SM preparations act on β-cells of the pancreas, in particular, binding and closing K-ATP-dependent channels of the cell membrane. This results in depolarization of the cell membrane, opening of Ca2+ channels, influx of Ca2+, and exocytosis of insulin from the granules.

It is important to note that ATP-dependent K+ channels are found not only in the pancreas, but also in the myocardium, smooth muscles, neurons, and epithelial cells. Therefore, an extremely important characteristic for SM preparations is the specificity of binding to receptors located precisely on the surface of pancreatic β-cells. Extrapancreatic effects of SM preparations have not been convincingly proven, most likely they are associated with a decrease in glucose toxicity due to insulin stimulation. Treatment with SM preparations, as a rule, begins with the lowest possible doses, if necessary, gradually increasing once every 5-7 days until the desired level of glycemia is obtained. For patients with severe glucose toxicity, treatment can be started immediately with the maximum dose, further, if necessary, reducing it as the blood glucose level decreases (Table 4).

Table 4. Treatment regimen for sulfonylurea drugs

Drugs	Initial dose (mg)	Multiplicity of reception	Daily dose (mg)
Glibenclamide	2,5	1-2 times a day	20
Glibenclamide micronized	1,75	1-2 times a day	14
Glimepiride	1	1 time per day	8
Gliclazide MB	30	1 time per day	120
Glipizide	2,5	1-2 times a day	30
Gliquidone	30	1-3 times a day	120

Side effects of SM drugs include hypoglycemia, weight gain, skin rash, pruritus, gastrointestinal disturbances, blood disorders, hyponatremia, and hepatotoxicity.

Thiazolidinediones (glitazones)

The drugs in this group belong to a new class of oral hypoglycemic agents acting at the level of peroxisome proliferation-activated receptors (PPARs). These receptors are found mainly in the nuclei of adipose and muscle cells. PPAR-γ activation increases insulin sensitivity by increasing the expression of numerous genes encoding proteins responsible for glucose and free fatty acid (FFA) metabolism. As a result, insulin sensitivity at the level of the liver, muscle and adipose tissue improves.

Thiazolidinediones reduce insulin resistance by increasing the number of glucose transporters (GLUT-1, GLUT-4) and improving the conditions for glucose utilization by tissues, reducing the level of FFA and triglycerides in the blood, enhancing insulin peptide, suppressing glucose production by the liver, reducing tumor necrosis factor and remodeling adipose tissue.

In Russia, 2 drugs from the glitazone group are registered and approved for clinical use: rosiglitazone and pioglitazone (Table 5).

Table 5. Scheme of application of thiazolidinediones

Drugs	Initial dose (mg)	Multiplicity of reception	Daily dose (mg)
Pioglitazone	30	1 times a day	45
Rosiglitazone	4	1-2 times a day	8

Thiazolidinediones are contraindicated in patients with type 2 diabetes mellitus and NYHA class III-IV heart failure, with an increase in hepatic transaminases> 3 times the upper limit of normal, during pregnancy and lactation.

The results of international studies show that glitazones are effective for the treatment of type 2 diabetes. The use of rosiglitazone at a dose of 4 and 8 mg per day was accompanied by a statistically significant decrease in both the level of fasting glycemia by 0.9–2.1 mmol/l and by 2–3 mmol/l, respectively, and postprandially, glycated hemoglobin decreased by 0.3 % and 0.6–0.7%, respectively [7]. In addition, it has been demonstrated that with thiazolidinediones, cases of heart failure occur with the same frequency as in the placebo group (‹1%), in combination with insulin therapy - 1-3%, while with insulin therapy alone - 1% [8].

Prandial regulators (glinides)

Prandial regulators are short-acting drugs that realize their hypoglycemic properties by acute stimulation of insulin secretion, which allows you to effectively control the level of glycemia after a meal.

The mechanism of action of this group of drugs is to close the ATP-sensitive K + channels in the cells of the pancreas, which contributes to the depolarization and

opening of Ca2 + channels, and therefore increases the flow of calcium into β-cells, which, in turn, leads to insulin secretion.

It is important to note that the effect of glinides on ATP-sensitive K+ channels in the β-cell is comparable in strength to SM drugs, but these two groups of drugs realize this effect through different binding sites on the surface of the β-cell.

Two drugs of this group are registered in our country: repaglinide and nateglinide (Table 6).

Table 6. Scheme of application of glinides

Drugs	Initial dose (mg)	Multiplicity of reception	Daily dose (mg)
Repaglinide	0.5-1 (before each meal)	3-4 times a day	4 (before each meal)
Nateglinide	120 (before each meal)	3-4 times a day	120 (before each meal)

α-glucosidase inhibitors

This group of drugs includes drugs that compete with dietary carbohydrates for the binding centers of enzymes of the gastrointestinal tract involved in the breakdown and absorption of carbohydrates, that is, they are competitive inhibitors.

Only one drug from this group, acarbose, is registered in our country.

Under the action of acarbose, the amount of absorbed carbohydrates does not decrease, but their absorption slows down significantly, thereby reliably preventing a sharp increase in blood sugar after eating. At the same time, the drug itself practically does not break down and is not absorbed into the blood.

Acarbose does not stimulate the secretion of insulin from β-cells of the pancreas, therefore, does not lead to hyperinsulinemia, does not cause hypoglycemia. Slowing down the absorption of glucose into the blood under the influence of this drug facilitates the functioning of the pancreas and protects it from overexertion and exhaustion. Acarbose has been shown to reduce insulin resistance. With prolonged use, it leads to the alignment of the daily glycemic curve, a decrease in the average daily level of glycemia, a decrease in the level of fasting glycemia, as well as a decrease and normalization of the level of glycated hemoglobin, which contributes to the prevention of late complications of diabetes mellitus [1]. Treatment with acarbose begins with 50 mg during dinner, gradually increasing the dose to 300 mg per day (100 mg 3 times a day).

Finally, it should be noted the results of the use of acarbose to prevent type 2 diabetes mellitus - Stop NIDDM. As part of this study, it was demonstrated that the use of acarbose in patients with impaired glucose tolerance reduced the risk of developing type 2 diabetes by 37% [9].

Incretinomimetics (glucagon-like polypeptide-1 receptor agonists)

The first incretin mimetic approved by the US FDA for the treatment of patients with type 2 diabetes is exenatide (BYETTA). The mechanism of action of this drug is closely related to the main biological effects of the hormones of the gastrointestinal tract - incretins. It is known that food intake stimulates the formation of many hormones of the gastrointestinal tract involved in the regulation of gastric juice secretion, pancreatic enzymes, causes contraction of the gallbladder and ensures the absorption of nutrients (Fig. 3).

The most popular and most studied at present is glucagon-like polypeptide-1 (GLP-1). GLP-1 is produced by entero-endocrine L-cells of the small intestine, and the regulation of its secretion from the endocrine cells of the gastrointestinal tract is carried out using several intracellular signals, including protein kinase A, protein kinase C and calcium. Numerous experimental works have demonstrated that GLP-1 secretion is controlled by nutrients, as well as by nervous and endocrine signals. In studies by Kieffer T.Y., 1999, Drucker D.J., 1998, Massimo S.P., 1998, it was shown that GLP-1 is secreted in response to the intake of mixed food and such individual components as glucose, fatty acids and dietary fiber. Thus, oral administration of glucose in humans led to a two-phase increase in plasma GLP-1, while intravenous glucose infusions had a minimal effect [Hermann C., 1995]. The half-life of circulating, biologically active GLP-1 is less than 2 minutes. This short plasma half-life of GLP-1 is due to the protease activity of the enzyme dipeptidyl peptidase IV (DPP-IV). Given the role of gastrointestinal hormones in the regulation of carbohydrate metabolism, two new classes of drugs have been proposed: incretin mimetics and DPP-IV inhibitors.

Under the action of exenatide, there is a glucose-dependent increase in insulin secretion, restoration of the first phase of insulin secretion, suppression of the secretion of glucagon and FFA, slowing down gastric emptying and a decrease in food intake [10-12].

Various international studies have demonstrated that the effects of exenatide are independent of the duration and severity of type 2 diabetes mellitus [13,14].

Starting dose of exenatide 5 mcg twice daily for 60 minutes before breakfast and before dinner. After 1 month from the start of therapy, the dose can be increased to 10 mcg twice a day.

The main side effect is nausea of mild or moderate severity, passing after 1-2 weeks.

Thus, this fundamentally new class of drugs is indicated for the treatment of patients with type 2 diabetes mellitus as adjunctive therapy to metformin, sulfonylurea derivatives, or a combination of both to improve glycemic control.

Dipeptidyl peptidase-IV inhibitor

Last year, a new class of oral drugs for the treatment of type 2 diabetes mellitus, the DPP-IV inhibitor, appeared on the global pharmaceutical market. The first and only member of this class recommended by the FDA is sitagliptin. The mechanism of action of this drug, as well as the action of exenatide, is closely related to the main biological effects of the hormones of the gastrointestinal tract. Sitagliptin is a powerful, fully reversible inhibitor of the DPP-4 enzyme, thereby leading to an increase in the level of active forms of incretins. The action of sitagliptin is to enhance the glucose-dependent insulin response and the simultaneous suppression of glucose-dependent secretion of glucagon against the background of an increase in blood glucose levels. Based on the results of numerous international studies of sitagliptin, the following data were obtained:

• significant and sustained reduction in fasting plasma glucose levels;
• a significant reduction in postprandial fluctuations in plasma glucose levels;
• a significant decrease in the level of glycated hemoglobin;
• improvement of b-cell function.

The frequency of hypoglycemia in the studies was low and equal to that observed when taking placebo. Sitagliptin does not affect body weight, which is also important in the treatment of patients with type 2 diabetes and obesity. This drug has a long duration of action, so it is taken 1 time per day.

Insulin therapy

Despite the large selection on the pharmaceutical market of various groups of oral hypoglycemic drugs that modulate various pathophysiological aspects of type 2 diabetes, it is rarely possible to achieve and maintain target glycemic values for a long time. A UKPDS study confirmed that prior addition of insulin therapy to oral antidiabetic therapy can safely maintain HbA1c close to 7% in the first 6 years after diagnosis. Thus, switching to insulin therapy in type 2 diabetes mellitus to compensate for β-cell function is a logical therapeutic approach to achieve optimal glycemic control [15].

Experts who participated in the Agreed Statement of the American Diabetes Association and the European Association for the Study of Diabetes propose the following scheme for initiating insulin therapy in patients with type 2 diabetes mellitus (Scheme 2) [5].

Thus, insulin therapy is indicated when the diet and maximum doses of hypoglycemic drugs are ineffective (HbA1c>7.5%, fasting glycemia>8.0 mmol/l with BMI<25 kg/m2), in the presence of ketoacidosis, temporary transfer to insulin therapy is indicated for surgical intervention.

Combination Therapy

For many patients with type 2 diabetes, monotherapy is usually insufficient to achieve and maintain long-term glycemic targets.

The UKPDS study demonstrated a progressive course of type 2 diabetes. It is known that β-cell function deteriorates at a rate of approximately 5% per year from the time of diagnosis. This explains the decrease in the effectiveness of monotherapy, identified when assessing the number of patients who had a glycated hemoglobin level of less than 7% after 3.6 and 9 years from the start of observation. Thus, in order to maintain glycemic control and prevent the development of complications of diabetes, it is necessary to constantly increase hypoglycemic therapy [16]. Therefore, the use of combination therapy in the early and subsequent stages of the disease is considered quite justified. It should be noted that combinations of oral hypoglycemic drugs that act on both pathophysiological defects of type 2 diabetes mellitus (for example, metformin in combination with a sulfonylurea, sulfonylurea in combination with exenatide) are most preferred. The most effective combination is insulin in combination with metformin. It is important to note that the combined therapy of insulin and thiazolidinediones is currently not approved in the EU countries.

An important role in the treatment of patients is played by the degree of implementation of the recommendations prescribed by the doctor (compliance). Obviously, the greater the number of drugs, the lower the compliance. In this regard, pharmaceutical companies have developed fixed combination drugs. Such therapy provides maximum efficiency in achieving almost normal glycemic control: it is possible to minimize the side effects of the components of the combination due to the low dosage. All this leads to an improvement in the quality of life of patients and increases adherence to treatment.

Conclusion

In conclusion, we would like to once again note the importance of achieving and maintaining target glycemic values for a long time. Most patients at the first stage should be given metformin at the same time with recommendations on nutrition and physical activity, almost at the stage of diagnosis. If it is impossible to achieve or maintain "near-normal" glycemic values with the help of one group of drugs, combination therapy is indicated. Taking into account the results of international studies, it is recommended to prescribe insulin therapy earlier in patients who have not reached the target glycemic values using oral hypoglycemic drugs.

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