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REVIEW OF THE COURSE AND TREATMENT OF DIABETES MELLITUS IN THE ELDERLY

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Abstract: Diabetes mellitus (DM) is becoming one of the most common problems among older people [5,8]. The prevalence of DM worldwide among people aged 65 years and older was 123 million in 2017 [2,6,12], and the number of such patients is expected to double in 2045. Over the past three decades, age-standardized prevalence of the disease has increased significantly in various countries, regardless of income level. According to experts, up to 40% of this increase is due to population growth and aging [1,3,9,15]. Diabetes mellitus is one of the most common health problems in older people, who form a heterogeneous and complex group, because it includes newly diagnosed elderly patients with DM and patients with a long course of the disease, onset in middle or young age [4,7,11]. This creates challenges for clinicians in the management of diabetes due to difficulties in defining individual glucose control goals, treatment options, comorbidities, multiple medications, and the risk of hypoglycemia. The objective of this review article is to consider the optimal glucose levels and treatment options for older adults with type II diabetes based on current global guidelines.

Key words: diabetes mellitus, features, course, diagnostics, elderly, treatment.

In the 21st century, the problem of diabetes mellitus (DM) has become a global epidemic affecting the population of all countries of the world, representatives of different nationalities and all ages. The number of patients with DM is growing especially rapidly among the elderly. According to the third revision of the US National Health Registry (NHANES III), the prevalence of type II DM is approximately 8% at the age of 60 years and reaches its maximum values (22-24%) at the age of over 80 years [10,15]. Such a significant increase in the prevalence of DM in the elderly is associated with a number of features characterizing physiological changes in carbohydrate metabolism during aging.

To understand the specifics of age-related changes in carbohydrate tolerance, it is necessary to find out which mechanism underlying the development of type II diabetes undergoes the greatest changes as the body ages.

Insulin sensitivity of tissues. Reduced tissue sensitivity to insulin (insulin resistance) is the main cause of carbohydrate metabolism disorders in overweight people. In elderly people, a hyperglycemic clamp was used to detect decreased sensitivity of peripheral tissues to insulin and, consequently, decreased glucose uptake by peripheral tissues. This deficiency is mainly seen in overweight elderly people. Old age brings with it many additional factors that aggravate existing insulin resistance. These include low physical activity, decreased muscle mass (the main peripheral tissue that utilizes glucose), and abdominal obesity (increases by the age of 70, then, as a rule, decreases). All these factors are closely interrelated.

Insulin secretion. Decreased insulin secretion is the main problem underlying the development of type II diabetes in people without obesity. As is known, insulin secretion in response to intravenous glucose administration occurs in two stages (two phases): the first phase is a rapid, intense insulin secretion that lasts for the first 10 minutes; the second phase is longer (up to 60-120 minutes) and less pronounced. The first phase of insulin secretion is necessary for effective control of post-lunch blood sugar levels. Most researchers have found a significant decrease in the first phase of insulin secretion in older people without excess weight. Perhaps this is the reason for such a noticeable increase in post-lunch blood sugar levels (by 0.5 mmol/l) every decade after the age of 50.

Glucose production by the liver. Numerous studies have shown that glucose production by the liver does not change significantly with age. The suppressive effect of insulin on glucose production by the liver also does not decrease. Therefore, changes in glucose metabolism in the liver cannot underlie the pronounced age-related changes in glucose tolerance. Indirect evidence of normal glucose production by the liver in the elderly is the fact that fasting glucose levels, which largely depend on the release of glucose by the liver at night, change very little with age. Therefore, in old age, glucose metabolism is determined by two main factors: tissue sensitivity to insulin and insulin production. The first factor, insulin resistance, is more pronounced in overweight elderly people. The second factor, reduced insulin production, predominates in non-obese elderly people. Understanding the main mechanisms of type II diabetes development allows for a differentiated approach to prescribing treatment in elderly patients.

Diagnosis of diabetes in the elderly. The diagnostic criteria for diabetes in the elderly do not differ from those adopted by WHO (1999) for the general population.

Diagnostic criteria for diabetes:

- ✓ fasting plasma glucose >7.0 mmol/l (126 mg%)
- ✓ fasting capillary blood glucose >6.1 mmol/l (110 mg%)
- ✓ plasma (capillary blood) glucose 2 hours after a meal (or a 75 g glucose load) >11.1 mmol/l (200 mg%)

The diagnosis of diabetes is made with double confirmation of the specified values. If fasting plasma glucose is between 6.1 and 6.9 mmol/l, fasting hyperglycemia is diagnosed. If glycemia is detected 2 hours after a glucose load between 7.8 and 11.1 mmol/l, impaired glucose tolerance is diagnosed.

DM in the elderly does not always have pronounced clinical symptoms (polyuria, polydipsia, etc.). Often, this disease is latent, asymptomatic and is not detected until late complications of DM come to the forefront in the clinical picture - visual impairment (retinopathy), kidney pathology (nephropathy), trophic ulcers or gangrene of the lower extremities (diabetic foot syndrome), heart attack or stroke. Therefore, DM II in the elderly must be actively identified, that is, regular screening for DM in high-risk groups.

Hypoglycemic therapy in the elderly. Therapy of elderly patients suffering from type II diabetes mellitus is often a very difficult task, as it is complicated by the presence of multiple concomitant diseases, the need to prescribe a large number of medications (polypharmacy), social factors (loneliness, helplessness, poverty), cognitive impairment, poor learning ability and lack of adherence to treatment.

Modern approaches to the treatment of type II diabetes mellitus in the elderly remain unchanged:

- ✓ diet and exercise;
- ✓ use of oral agents to lower blood sugar levels;
- ✓ use of insulin or combination therapy.

Diet. The basic nutritional rules for patients with type II diabetes mellitus in the elderly are similar to those recommended for young patients - restriction of caloric intake with the exclusion of easily digestible carbohydrates. However, if the patient cannot follow dietary recommendations due to age or social factors, then you should not insist on it.

Physical activity. Physical activity is an integral part of the treatment of patients with type II diabetes, as it increases the sensitivity of peripheral tissues to insulin, reduces insulin resistance, decreases serum atherogenicity, and lowers blood pressure. The physical activity regimen is selected individually for each patient, taking into account their concomitant diseases and the degree of development of diabetes complications. General recommendations include walking for 30 to 60 minutes daily or every other day. Longer periods of exercise are not recommended due to the risk of worsening cardiovascular disease or hypoglycemia.

Oral hypoglycemic agents. Below are five main groups of oral drugs for lowering blood sugar levels used in modern diabetology:

- ✓ Sulfonylureas (gliclazide, gliquidone, glipizide, glimepiride, glibenclamide);
- ✓ Meglitinides (repaglinide) and phenylalanine derivatives (nateglinide);
- ✓ Biguanides (metformin);
- ✓ Thiazolidinediones (pioglitazone, rosiglitazone);
- ✓ Alpha-glucosidase inhibitors (acarbose).

Sulfonylureas and meglitinides are stimulators of insulin secretion by the pancreas. Biguanides and thiazolidinediones eliminate insulin resistance: biguanides mainly at the liver level, blocking hepatic gluconeogenesis, thiazolidinediones mainly at the peripheral tissue level, increasing the sensitivity of muscle tissue to insulin. Alpha-glucosidase inhibitors prevent the absorption of glucose in the gastrointestinal tract (GIT) by blocking the enzyme involved in the breakdown of glucose in the intestine. When choosing a particular drug, it is important to understand which mechanism dominates in the development of type II diabetes in a particular patient.

The optimal hypoglycemic drug for elderly patients with type II diabetes must meet a number of requirements, the main one of which is "do no harm".

The main requirements for hypoglycemic drugs for elderly patients with type II diabetes include:

- ✓ Minimal risk of hypoglycemia;
- ✓ No nephrotoxicity;
- ✓ No hepatotoxicity;
- ✓ No cardiotoxicity;

Sulfonylurea drugs. The main principle of these drugs is to stimulate the secretion of their own insulin by beta cells of the pancreas. Five main drugs of the sulfonylurea class are registered and used in Russia, each of which has its own characteristics and area of application. The most serious side effect of sulfonylurea drugs for elderly patients is the development of hypoglycemia. The risk of developing hypoglycemic conditions depends on the duration of the drug's action and the characteristics of its metabolism. The longer the half-life of the drug, the higher the risk of developing hypoglycemia. Sulfonylurea drugs that are either metabolized primarily by the liver (gliquidone) or excreted by the kidneys as inactive metabolites (gliclazide) have a lower risk of developing hypoglycemic conditions. This type of metabolism does not create a threat of accumulation of the hypoglycemic effect of the drug and, consequently, the development of hypoglycemia even with a moderate decrease in the filtration function of the kidneys. Therefore, the drugs "Gliclazide" and "Glicvidone" can be used in elderly patients even with moderate renal failure (serum creatinine level up to 300 μmol/l).

A new drug - gliclazide-MV (long-acting) has received additional advantages in elderly patients. Having the same pharmacokinetic characteristics as regular gliclazide (half-life, metabolism features), gliclazide-MV, due to a special hydrophilic filler of the drug shell, is slowly released and absorbed into the blood over 24 hours, maintaining a stable concentration of the drug in the blood during the day. Therefore, such a drug can be taken only once a day, without fear of developing hypoglycemic reactions. A multicenter double-blind study of gliclazide-MV, in which this drug was taken by about one and a half thousand patients with type II diabetes mellitus for 10 months, showed the absolute safety and high efficiency of gliclazide-MV in elderly patients. The incidence of hypoglycemic conditions in patients over 75 years of age did not exceed 0.9 cases per 100 patients per month (P. Drouin, 2000). In addition, a single dose of the drug during the day increases the adherence (compliance) of elderly patients with diabetes mellitus to treatment.

Meglitinides. This is a relatively new group of drugs that are insulin secretagogues. This group includes benzoic acid derivatives - repaglinide and a derivative of the amino acid phenylalanine -

nateglinide. The main pharmacokinetic characteristics of these drugs are an extremely rapid onset of action (within the first minutes after administration), a short half-life (30-60 minutes) and a short duration of action (up to 1.5 hours). In terms of the strength of the hypoglycemic effect, they are comparable to sulfonylurea drugs. The main focus of their action is to eliminate postprandial peaks of hyperglycemia, which is why another name for this group is prandial glycemic regulators. Such a rapid onset and short duration of action of these drugs require that they be taken immediately before or during meals, and the frequency of their administration corresponds to the frequency of meals. Given the clinical features of type II diabetes in elderly patients, namely the prevalence of increased glucose levels after meals, which leads to a high risk of cardiovascular complications and death, the use of drugs in this group is especially appropriate for elderly patients. However, the patient receiving treatment with these drugs should be well educated and have intact cognitive functions to avoid errors in the use of these drugs.

Biguanides. Metformin is the only drug from the biguanide group that is approved for use in clinical practice. The main mechanism of action of this drug is to reduce the intensity of gluconeogenesis in the liver, which leads to a decrease in the release of glucose by the liver (especially at night). Metformin is primarily indicated for overweight patients who have a significant increase in fasting glucose. Metformin is not metabolized by the liver and is excreted unchanged by the kidneys. In elderly patients, metformin metabolism slows down due to age-related decline in renal function. Metformin does not cause hypoglycemic reactions, which is its advantage over drugs that stimulate insulin secretion. The main danger associated with the use of metformin is the possibility of developing lactic acidosis. Therefore, all conditions accompanied by increased lactate formation (unstable angina, heart failure, renal and hepatic failure, respiratory failure, severe anemia, acute infectious disease, alcohol abuse) are contraindications for the use of metformin. In elderly people over 70 years of age, due to age-related decline in renal function, the use of metformin is not recommended. Thiazolidinediones (glitazones). This is a new group of drugs, the mechanism of action of which is aimed at eliminating peripheral insulin resistance and, in particular, increasing the sensitivity of muscle and adipose tissue to insulin. Currently, two drugs from this group are approved for clinical use - pioglitazone and rosiglitazone. Thiazolidinediones do not stimulate insulin secretion by the pancreas, therefore they do not cause hypoglycemic conditions. The effectiveness of these drugs is demonstrated only in patients with obvious signs of insulin resistance and preserved insulin secretion. An additional advantage of glitazone therapy is the reduction of serum atherogenicity due to a decrease in triglyceride levels and an increase in high-density lipoprotein cholesterol.

Alpha-glucosidase inhibitors. The mechanism of action of these drugs is to block the alpha-glucosidase enzyme in the gastrointestinal tract, which prevents the breakdown of polysaccharides from food into monosaccharides. In the form of polysaccharides, carbohydrates cannot be absorbed in the small intestine, so they enter the large intestine and are excreted undigested. This prevents an increase in glucose levels after meals. Drugs in this group include acarbose and miglitol. The drugs are prescribed several times a day with meals, since they do not work on an "empty stomach". The advantages of drugs in this group include the relative safety of their use - the absence of hypoglycemia, toxic effects on the liver and kidneys. However, most patients experience poor tolerance of long-term treatment with these drugs. Patients are bothered by flatulence, diarrhea and other symptoms of gastrointestinal discomfort caused by the non-physiological flow of undigested carbohydrates into the large intestine. The effectiveness of this group of drugs is not very high when used as monotherapy. Thus, the poor tolerability of a-glucosidase inhibitors and the need for multiple doses do not allow these drugs to be considered the optimal choice for the treatment of elderly patients with type II diabetes.

Insulin therapy. If therapy with oral hypoglycemic drugs is ineffective, it is necessary to prescribe insulin - either as monotherapy or in combination with tablets.

Insulin therapy regimens may vary:

- A single injection of medium-acting insulin before bedtime - with severe hyperglycemia on an empty stomach;

- Two injections of medium-acting insulin - before breakfast and before bedtime;
- Double injections of mixed insulins containing fixed mixtures of short-acting and medium-acting insulin in ratios of 30:70 or 50:50;
- A regimen of multiple injections of short-acting insulin before main meals and medium-acting insulin before bedtime - in case of severe hyperglycemia on an empty stomach;
- Double injections of medium-acting insulin - before breakfast and before bedtime;
- Double injections of mixed insulins containing fixed mixtures of short-acting and medium-acting insulin in ratios of 30:70 or 50:50;
- A regimen of multiple injections of short-acting insulin before main meals and medium-acting insulin before bedtime.

The latter regimen is permissible only if the elderly patient's cognitive functions are , after training in the basic rules of insulin therapy and self-monitoring of glycemia levels.

In elderly patients with preserved residual secretion of endogenous insulin (normal C-peptide), but ineffective monotherapy with tablets, it is advisable to prescribe a combination of insulin with oral hypoglycemic agents.

Conclusion. Elderly people with diabetes mellitus represent a complex and diverse age group. Management of diabetes mellitus in the elderly remains an important clinical task for physicians at all stages of medical care, both primary and specialized. It is necessary to choose an individual, patient-oriented glycemic control goal that allows achieving glucose control without dangerous hypo- and hyperglycemic episodes. When diagnosing diabetes mellitus in the elderly, it is necessary to conduct a comprehensive geriatric assessment to determine the degree of functional impairment. When choosing a treatment strategy for diabetes mellitus, preference should be given to drugs with proven tolerability, safety and minimal risk of hypoglycemia. Treatment regimens for diabetes in older adults should be simple, sustainable and safe to better meet patients' preferences, wishes and needs.

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