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The treatment of diabetes with new generation drugs

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Abstract

Introduction: Diabetes is a global problem, affecting nearly 422 million people around the world. Pathogenesis includes a defect in secretion or insulin activity. This results in an increase in the glucose level, which is associated with the development of complications. These include changes in peripheral vessels and nerves that lead to their damage. It is necessary to introduce appropriate treatment in the earliest stages of the disease to prevent these effects.

Materials and methods: The aim of this work is to present knowledge about the treatment based on the recommendations of the Polish Diabetes Association, American Diabetes Association, as well as a literature review and analysis of publications published on PubMed and Google Scholar platforms.

Results: Over the years, the recommendations and recommendations for treatment change. Recently, a greater role has been given to the latest antidiabetic drugs. This group includes SGLT-2 inhibitors as well as incremental drugs, the main representatives of which are GLP-1 analogues. These drugs affect the level of glycemia, but also have a beneficial effect on

weight reduction and reduce the risk of cardiovascular events. Recently, Poland has introduced reimbursement of some new generation antidiabetic drugs such as dapaglyphosin, empaglyphosin and canaglyphosin.
Conclusions: Dynamic development of diabetes treatment helps to slow down the course of the disease and postpones the introduction of insulin therapy as the final treatment method. Reimbursement of some antidiabetic drugs enables patients to have better access to drugs that have not been within their reach so far. The changes introduced are, in a way, groundbreaking in the treatment of diabetes.
Key words: diabetes, GLP-1 analogues, SGLT-2 inhibitors.

Introduction

Diabetes mellitus is a group of metabolic diseases characterized by hyperglycaemia resulting from a defect in secretion or insulin. About 422 million people worldwide suffer from this disease. [1] The causes of diabetes include defects in insulin secretion, insulin action or both, and disorders in the metabolism of carbohydrates, fats and proteins. Chronic hyperglycaemia causes damage, dysfunction and failure of various organs, especially eyes, kidneys, nerves, heart and blood vessels. [2] Diabetes mellitus is the main cause of blindness, kidney failure, heart attacks, stroke, and lower limb amputations. Early diagnosis of symptoms is essential for effective treatment. The most typical symptoms include polyuria, polydypsia, as well as drowsiness and fatigue, weight loss, dry skin. [3] Diabetes can be treated and its consequences can be avoided or delayed with diet, physical activity, medication and regular screening and treatment of complications. Diabetes can be recognized in 4 situations: when the adventitious glycemia is ≥11.1 mmol/l (200 mg/dl) and the typical symptoms of hyperglycemia occur; adventitious glycemia ≥11.1 mmol/l (200 mg/dl) without typical symptoms of hyperglycemia and once (on another day) fasting glycemia ≥7.0 mmol/l (126 mg/dl); twice (determined on other days) fasting glycemia ≥7.0 mmol/l (126 mg/dl); glycemia in 120. min OGTT ≥11.1 mmol/l (200 mg/dl). [4] The American Diabetes Association (ADA) additionally allows diagnosis of diabetes if HbA1c >6.5% (48 mmol/mol), subject to HPLC determination. [5] There are also two more pre-diabetes conditions: abnormal glucose tolerance and abnormal fasting glycemia. The first one is diagnosed when the glycemia at 120 min OGTT is between 7.8-11.0 mmol/l (140-199 mg/dL), while the second one when the fasting glycemia is between 5.6-6.9 mmol/l (100-125 mg/dL) [4] ADA additionally takes into account the pre-diabetic state based on HbA1c 5.7-6.4% (39-46 mmol/mol). In the diagnosed pre-diabetes or diabetes condition it is necessary to delay the development of the disease. Patients with pre-diabetes condition should receive recommendations for a healthy lifestyle (weight reduction and maintenance, physical activity, min. 150 min/week) and information on the effectiveness of such a procedure in the prevention of overt diabetes mellitus [2].

The main clinical objectives of the hypoglycemic treatment of diabetes should be to free the patient from the ailment and to achieve a quality of life that ensures self-esteem and individual and social satisfaction. The goals also include effective prevention of acute and chronic complications of the disease, elimination of disability, increased efficiency and

normalization of lifestyle. The aim of the treatment is to achieve a life expectancy for diabetics corresponding to the average life expectancy of the general population to which they belong.

The pathophysiological goals of diabetes treatment are not only to maintain the glycemia in normal values, but also to equalize lipid metabolism and blood pressure. The Polish Diabetes Society presents a general objective for the treatment of diabetes which is HbA1c ≤ 7% (≤ 53 mmol/mol). Individual goals are also set for individual patient groups. The value of HbA1c≤6.5% (≤ 48 mmol/mol) in individuals with type 1 diabetes, whose goal is not associated with an increased risk of hypoglycaemia and deterioration of quality of life, also in individuals with short-term type 2 diabetes and children and adolescents regardless of type of disease. The goal of glycated haemoglobin ≤8.0% (≤ 64 mmol/mol) is set in patients with advanced age with long-term diabetes mellitus and complications. In women planning to become pregnant, the treatment target is set at < 6.5% (48 mmol/mol), and in the 2nd and 3rd trimester of pregnancy < 6.0% (42 mmol/mol), unless it is associated with an increased risk of hypoglycemia.

Targets are also set for the equalization of lipid metabolism. These are LDL cholesterol < 55 mg/dl or a reduction of at least 50% in patients with a very high cardiovascular risk. LDL-C < 70 mg/dl (1.8 mmol/l) or a reduction of at least 50% in patients at high cardiovascular risk, <100 mg/dl in patients with moderate risk. Non-HDL cholesterol levels are set to < 85 mg/dl for patients at very high cardiovascular risk and <100 mg/dl for patients at high risk. The HDL cholesterol fraction should be above 40 mg/dl for men and above 50 mg/dl for women. The triglyceride concentration should be < 150 mg/dl. It is recommended to maintain blood pressure values of < 130 mm Hg for systolic and < 80 mm Hg for diastolic. [2]

Results

Education is the basis for effective diabetes care and prevention. It is focused on the patient and his individual needs. The aim of patient education is to support the patient in self-management training and lifestyle modification, due to the recommended diet and physical activity.

Behavioral therapy has also found application in the prevention and treatment of diabetes. All patients should be under the care of an interdisciplinary team consisting of a doctor, a dietician, a diabetes nurse and a diabetes educator. They establish detailed and individual diet and lifestyle recommendations using various methods and techniques.[2]

The American Diabetes Prevention Program and the Finnish Diabetes Prevention Study prove that the use of behavioral therapy reduces the risk of developing diabetes in vulnerable groups by 58%. [6]

In many cases the basic method of treatment is to choose an appropriate diet. Over the years the recommendations and recommendations for diabetes diets change. Modern methods of diabetes treatment allow great flexibility in the choice of food products. The importance of limiting the supply of carbohydrates in individual meals and the entire diet is stressed, and a daily calorie deficit of 500-750 kcal is considered safe. [2]

Physical effort has multi-directional benefits. It has beneficial effects on insulin sensitivity, glycemic control, lipid profile and weight reduction. In order to achieve the optimal effect, physical effort should be undertaken regularly, at least every 2-3 days, and preferably daily.

The intensity of physical effort is determined by the doctor on the basis of the full clinical picture. [2]

In recent years the approach to the treatment of diabetes, especially type 2 diabetes, has changed significantly, which is mainly due to the introduction of new groups of antidiabetic drugs (sodium-glucose 2 cotransporter inhibitors and glucagonist peptide receptor agonists 1) and numerous publications of research results evaluating their effectiveness and safety. Pharmacological treatment may complement behavioural therapy. [14] In the document for 2020, PTD recommends that in people with diabetes, who despite the implementation of lifestyle modifications (weight reduction, increased physical activity up to 30-45 min/d) and the use of metformin, glycemia increases and the target percentage of HbA1c is not reached, another antidiabetic drug should be added, The choice of which should depend on the occurrence of coexisting diseases [2] In people with cardiovascular disease, SGLT-2 inhibitor or GLP-1 receptor agonist should be administered first, while in people with chronic kidney disease, treatment should be started with phosin, followed by GLP-1 receptor agonists. Phosphine is also used preferentially in coexisting heart failure. In patients struggling with obesity, drugs from the group of GLP-1 receptor agonists or SGLT-2 inhibitors should be preferred [14].

Still used in our country, sulfonyl urea derivatives are recommended to be attached to metformin in patients with low financial possibilities. At further stages of treatment, it is recommended to use tricotide therapy with metformin (always) and 2 other non-insulin drugs with different mechanisms of action. The next step in the progressing disease is to start insulin therapy. [2]

An update of the ADA guidelines published in January 2020, and even more strongly than the PTD recommendations, recommends the use of phosin and GLP-1 receptor agonists. [5] The latter protect against cardiac complications most effectively in the case of atherosclerosis and should be used not only in patients with already diagnosed cardiovascular disease or renal failure, but also in those with risk factors of these diseases: age >55 years, left ventricular hypertrophy, estimated glomerular filtration rate (eGFR) <60 ml/min/1.73 m2, proteinuria. In individuals who have no cardiovascular disease but heart failure and/or an eGFR <60 ml/min/1.73 m2 or an albumin/creatinine excretion ratio (UACR) >30 mg/g, SGLT-2 inhibitors are more beneficial in reducing cardiac risk [14].

Sodium ion-dependent glucose (SGLT-2) cotransporter 2 glucose (SGLT-2) inhibitors, commonly known as phlosin, have found use in the treatment of diabetes and pre-diabetes conditions. The mechanism of their action is based on inhibiting SGLT-2 activity, thus reducing renal glucose absorption. As a result, glucose is excreted in urine and its concentration in blood is reduced. Among the group of phosin approved for use in the USA and Europe are: canaglyphosine, dapaglyphosine, empaglyphosine and ertuglyphosine. [7]

Phosphinates also show other effects. They cause weight loss due to glucosuria. The degree of weight loss varies slightly depending on the agent and the dose used. A meta-analysis of randomized controlled trials involving participants treated with canaglyphosin 300 mg, empaglyphosin 25 mg or dapaglyphosin 10 mg per day showed weight loss of 2.66 kg, 1.81 kg and 1.80 kg respectively compared to placebo [8].

It has also been shown that SGLT-2 inhibitors, empaglyphosine and canaglyphosine significantly reduce cardiovascular events in people with Covert Cardiovascular Disease

(CVD).[9] The EMPA-REG OUTCOME study showed that the addition of empaglyphosine to the standard treatment of type 2 diabetes patients with high cardiovascular risk allows for a statistically significant 38% reduction in cardiovascular death. Empaglyphosine is the first hypoglycaemic drug to have a protective effect against death. The use of the drug saves the life of 1 patient in every 39 treated. [10]

The EMPA-REG OUTCOME study also studied the long-term effects of empaglyphosine on kidneys. The complex renal outcome included an incident or deterioration of nephropathy (progression to microalbuminuria, doubling of serum creatinine levels, initiation of renal replacement therapy, death from kidney disease). Empaglyphosine was associated with a slower management of kidney disease and a lower percentage of clinically significant renal events than placebo when added to standard care. The incident or deterioration of nephropathy occurred in 12.7% of participants in the emphaglyzine group compared to 18.8% in the placebo group (HR 0.61 [95% CI 0.53, 0.70]; p <0.001). There was no significant difference between the groups in the frequency of albuminuria. [11]

Taking in floats is also associated with side effects. Serious side effects are rare. Episodes of severe hypoglycaemia associated with dapaglyphosin are sporadic, most often during combined treatment. Most often the effects of SGLT-2 inhibition are inextricably linked to their mechanism of action, resulting in the occurrence of urogenital infections with a mild clinical course. [12]

In Poland, only dapaglyphosine, empaglyphosine and canaglyphosine are approved among SGLT-2 inhibitors. In recent years their use has been limited by the high cost of monthly therapy. Recently, these drugs have been partially reimbursed. The level of payment is 30%. Invokana (canaglyphosine), Jardiance (empaglyphosine), Forxiga (dapaglyphosine) are reimbursed in patients with type 2 diabetes mellitus before insulin is included, treated with at least two oral hypoglycemic drugs for at least 6 months, with HbA1c ≥ 8% and a very high cardiovascular risk. [13]

Glucagon-like type 1 peptide receptor analogues (GLP-1) belong to the group of incremental drugs. They mimic the action of type 1 glucagon-like peptide - an intestinal hormone that regulates blood glucose levels by increasing insulin secretion by pancreatic β cells in a glucose-dependent mechanism. It also inhibits the secretion of glucagon, slows down the emptying of the stomach and inhibits appetite.

In the 2012 systematic review the authors asked the question what are the effects of GLP-1 analogues compared to other antidiabetics or placebo drugs in type 2 diabetes patients. 6899 patients with GLP-1 analogues compared to control were included in the analysis. All patients received metformin and/or sulfonyl urea derivative. The observation period was 8-30 weeks. GLP-1 analogues were found to reduce the percentage of HbA1c by about 1 percentage point compared to placebo. Compared to some drugs, they have a similar or more beneficial effect on body weight, plasma lipid profile and blood pressure. Their use is associated with a higher risk of side effects, mainly from the gastrointestinal tract. [15]

The actions of GLP-1 analogues have a positive effect on weight reduction. In a study by DeFronzo et al. the eenatide resulted in a dose-dependent weight loss of -2.8 ± 0.5 kg (10 mcg) and -1.6 ± 0.4 kg (5 mcg); p < 0.001 compared to placebo, respectively.[16] In a similar study by Kendall et al. the eenatide resulted in a significant weight loss from the beginning of the

study of each arm, i.e. the arm: -1.6 ± 0.2 kg, -0.9 ± 0.2 kg vs placebo; p < or = 0.01. It should be noted that patients were not recommended a low calorie diet. [17]
In the case of liraglutide, based on a meta-analysis of 5 studies (LEAD 1-5) carried out by Blonde and Russell-Jones , where patients taking metformin and glimepiride were randomly assigned to the placebo-taking group, Glargine or liraglutide insulin, weight loss in patients treated with liraglutide was higher than in the group with placebo (Δ 1.4 kg, p = 0.0001) or with glargine insulin (Δ 3.4 kg, p < 0.0001). [18]
From 1 January 2020, 2 preparations of GLP-1 receptor agonists for use once a week are reimbursed (30% list): Trulicity (dulagglutide) and Ozempic (semagglutide). The reimbursement indications are very similar to those of SGLT-2 inhibitors, with one difference - they apply only to patients with significant obesity, i.e. body mass index (BMI) >35 kg/m2. [13,14]

Conclusion

For several years we have been witnessing dynamic changes in the treatment of diabetes. The latest recommendations of ADA and PTD are based on the increasingly frequent and widespread use of incretinated drugs and SGLT-2 inhibitors. The design of reimbursement indications introduced recently increases the chance of these drugs being included before the start of insulin therapy and undoubtedly allows this moment to be postponed. What is most important, it enables access to new drugs that reduce cardiovascular risk to a much wider group of patients than before. What is important is that all doctors can prescribe these drugs, not only diabetologists, as long as they follow the indications for their use and reimbursement recommendations. The message that these modern drugs can already be used for reimbursement should be reinforced, so that knowledge about them becomes widespread. It can be stated that the past months have become a breakthrough for Polish patients with type 2 diabetes, not only because of the slightly changed rules of its treatment, but also because of the improved availability of modern anti-diabetes drugs in our country.

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