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Insufficient of Existing Drugs Used for Diabetes Ii Types and the Need to Improve Them

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Abstract: People with type I diabetes but type II diabetes are more susceptible to various diseases, such as nerve and eye damage, as well as heart attacks and strokes. Preventing this is the purpose of taking medications. Age and other factors determine whether medications are right for you, and if so, which ones. People with type II diabetes have high blood sugar levels, so it may seem reasonable to take medications to lower blood sugar levels. However, this is not always necessary. If other methods of regulating blood sugar fail, for example, by changing the diet or increasing physical activity, medications are necessary. Lowering blood sugar levels is not the only goal of treatment, and it depends on your age and general health. To mitigate complications and maintain a good quality of life, the treatment of type II diabetes requires an integrated approach, including pharmacological and behavioral methods. Monitoring glucose levels, weight, risk factors for cardiovascular disease, comorbidities and related complications, as well as lifestyle changes are part of the treatment. As a result, active targeting strategies, such as the functionalization of suitable ligands or combinatorial drug therapy using two or more antidiabetic drugs, can correctly control glucose levels for a longer period of time. Thanks to constant technological advances in nanotechnology, an effective therapy for lowering glucose levels may be developed in the foreseeable future.

Keywords: Type I diabetes, type II diabetes, hypoglycemia, sulfonylurea, insulin replacement therapy, hyperglycemia.

Introduction. Diabetes mellitus (DM) is a group of metabolic diseases characterized by a constant increase in blood sugar levels. This occurs in cases where the pancreas cannot produce enough insulin from beta cells or cannot bind to insulin receptors, which leads to an increase in blood glucose levels. According to recent studies, by 2025, the probability of developing diabetes among adults will increase from 4% in 1995 to more than 6%. The data was collected as a result of a recent survey. Pathological changes such as nephropathy, retinopathy and cardiovascular complications are inevitable when the disease progresses in the body. DM is mainly divided into two categories: type I DM and type II DM. For the treatment of DM I, insulin replacement therapy is usually used, and oral hypoglycemic drugs are used for the treatment of DM II. Currently, antidiabetic drugs such as metformin, sulfonylurea, thiazolidinedione or DPP-4 inhibitors are used to treat diabetes [1,2,3,4,5,6]. These medications are prescribed either as a separate therapy or in combination with other hypoglycemic drugs. The main disadvantages of using the above-mentioned traditional drugs are severe hypoglycemia, weight gain, decreased therapeutic efficacy due to improper or ineffective dosing regimen, low efficacy, altered side effects due to drug metabolism, lack of target specificity, problems with solubility and permeability [7,8,9].

New drugs for lowering blood glucose levels have appeared in the last ten years. These drugs do an excellent job with risk factors for cardiovascular diseases. These medications have shown a significant reduction in the incidence of cardiovascular complications in both diabetic and non-diabetic patients. Partly because these drugs have reduced the importance of maintaining near-normal blood glucose levels, the attention of cardiologists, nephrologists, and other healthcare professionals has shifted to

preventing heart and kidney disease. On the other hand, a number of significant studies have highlighted how important it is to maintain optimal blood glucose levels to prevent both microvascular and macrovascular complications. These studies raise the important question of whether 7% HbA1c levels are sufficient to achieve the goals or whether we should strive to normalize blood glucose levels [10,11,12,13].

Traditional treatments for hyperglycemia include increased insulin release from the islets of Langerhans; decreased glucose production in the liver; peroxisome proliferator-activated receptor agonists (PPARy), which increase the action of insulin; and α-glucosidase inhibitors. Despite the emergence of promising antihyperglycemic drugs, the main objectives of effective diabetes treatment are to optimize existing treatment methods to ensure optimal and balanced glucose concentration and reduce the risk of long-term complications associated with diabetes. Thus, nanoformulations have a stable history of overcoming potential problems with the use of conventional drugs. This review examines modern traditional drugs used to treat type 2 diabetes, as well as the limitations associated with these drugs, as well as the latest nanopreparations that are constantly being investigated to eliminate the disadvantages of traditional drugs [14,15,16,17].

It is recommended to take medications. The age at which type 2 diabetes begins is one of the factors determining whether medications are right for you to lower blood sugar levels. Many elderly people with type 2 diabetes have slightly higher blood sugar levels than normal. Nerve and blood vessel damage is rare when type 2 diabetes develops in old age. Other diseases, such as high blood pressure, often bring additional difficulties. If you have already been diagnosed with type 2 diabetes at the age of forty or fifty, the probability is that you will live quite a long time. Even low blood sugar levels can cause additional problems in the long run. Thus, maintaining low blood sugar levels is crucial for young people with type 2 diabetes [7,8,9,13,14]. The goal of treatment is to prevent the development of diabetes, which can lead to other health problems. High blood sugar levels can damage nerves and blood vessels. This can cause health problems with the kidneys, legs, and retina (the shell of the back of the eye). In addition, the risk of stroke or heart attack may increase. Blood sugar lowering drugs are used to prevent or delay these health problems [10,11,12,13].

The main purpose of this review is to briefly analyze existing drugs, their shortcomings and the need to create new promising drugs for the treatment of type 2 diabetes, which is now considered the main global health problem.

Methods of treatment of type 2 diabetes mellitus that are not related to insulin. Patients can take antidiabetic medications if changing their lifestyle does not help you lower blood sugar levels. If one medicine is not enough, you can use a combination with other pills to lower blood sugar levels. Studies have shown that lowering blood sugar levels reduces the risk of damage to small blood vessels, especially in the eyes. It is unclear how well antidiabetic drugs prevent complications such as heart attacks and strokes. There is almost no long-term research in this area. In addition, there is insufficient research on the interaction of different drugs (table 1). Sometimes any antidiabetic drugs can cause a severe decrease in blood sugar. Hypoglycemia is an excessively low blood sugar level [12,13,14,15].

Pharmaceutical therapy during pregnancy. In women with low blood sugar levels, early pregnancy is characterized by a marked increase in insulin sensitivity. However, as pregnancy progresses in the second and third trimesters, the opposite happens: insulin sensitivity decreases significantly. This change reduces glucose uptake by muscle and adipose tissues, as well as insulin-mediated lipolysis and beta oxidation. Together, these changes help meet the growing energy needs of the developing fetus [16,17,18,19]. In women with diabetes mellitus, these changes in glucose metabolism are more noticeable and can lead to a hyperglycemic condition, which increases the likelihood of pregnancy complications such as preeclampsia, premature birth and congenital malformations. In addition, almost half of women with diabetes have children who are large for their gestational age, which increases the risk of birth trauma and later development of metabolic syndrome, cardiovascular diseases and type 2 diabetes mellitus. Thus, for pregnant women with a history of diabetes, glucose control is crucial [15,19,20].

Future medicines and research. In a study on the molecular basis of insulin resistance, scientists discovered a tiny molecule, Co-insulin, that binds to insulin rather than the insulin receptor (IR). This molecule with a mass of 222 Da binds to a certain section of the insulin A-chain, which triggers the interaction between the A- and B-chains and activates the insulin receptor. Autophosphorylation of the insulin receptor, phosphorylation of IRS proteins and the action of insulin with "immediate" and "delayed" reactions are all the results of this activation. The "immediate" reaction includes the well-known effect of hypoglycemia mediated by Glut-4 and affecting the phosphorylated IRS molecule [17,18,19,20]. On the contrary, the "delayed" reaction involves the penetration of certain parts of the phosphorylated insulin receptor into the nucleus. Another phosphorylated IRS molecule may contribute to this. It is important to note that coinsulin acts only by activating insulin signaling processes. This innovative study examines whether these small molecules are able to control the action of other peptide hormones in the mammalian body. This study may help in the development of new drugs for the treatment of diabetes [19,21,22,23].

Table 1. Pharmacological properties of drugs used in diabetes mellitus.

№	Drug group	Specific drug	Effects	Adverse effects	Safety
1.	Biguanides	Metformin	Decrease HbA1c, Improvement/decrease Body weight, Decrease cancer, Improvement/decrease cardiovascular	Aggravation gastrointestinal disorders, Increase reversible vitamin B12 deficiency, Increase lactic Acidosis	None
2.	Glinides	Repaglinide Nateglinide	Decrease HbA1c, Increase body weight	Increase hypoglycemia, Aggravation headache, Increase upper respiratory tract infection	None
3.	Alpha-Glucosidase inhibitors	Acarbose	Decrease HbA1c, Improvement/decrease Body weight,	Aggravation gastrointestinal disorders, Increase serum transaminases (AST, ALT)	None
4.	Thiazolidineidiones	Pioglitazone	Decrease HbA1c, Decrease BP, Decrease nonalcoholic fatty liver disease, Decrease major adverse cardiovascular events,	Increase body weight, Increase peripheral edema, Increase anemia, Increase hospitalization for heart failure, Increase bone fracture in women	Cancer not confirmed
5.	Sulfonylurea	Glimepiride	Decrease HbA1c	Increase body	Glibenclamid

	s	Gliclazide Glibenclamide Glipizide		weight, Increase hypoglycemia, Absence of long-lasting impact	e Glipizide: Cardio-vascular events not confirmed
6.	Combination therapy	Tirzepatide Retatrutide	Quality of life for patients with heart failure, Decrease nonalcoholic fatty liver disease,	It has not any effects not confirmed yet	Not confirmed
7.	Dipeptidyl Peptidase-4 Inhibitors	Sitagliotin Saxagliptin Alogliptin	Decrease HbA1c,	Saxagliptin: Hospitalization for heart failure not confirmed	
8.	Glucagon-like Peptide-1 Receptor Agonists - GLP-1 RA	Liraglutide Dulaglutide Semaglutide Orforglipron	Clearly decrease HbA1c, Improvement/decrease Body weight, Improvement/decrease systolic BP, Decrease major adverse cardiovascular events,	Aggravation gastrointestinal disorders	Pancreatitis Bile stones Thyroid carcinoma
9.	Sodium-Glucose Cotransporter Inhibitors - SGLT-2i	Empagliflozin Dapagliflozin Canagliflozin	Decrease HbA1c, Improvement/decrease Body weight, Decrease major adverse cardiovascular events, Decrease hospitalization for heart failure,	Increase diabetic ketoacidosis, Increase genital infection, Increase urinary tract infection, Increase hypovolemia, Increase acute kidney injury	None

An innovative approach to treatment. The DPP-1 study involving patients with prediabetes showed how important normalization of blood glucose is. The study assessed whether a healthy lifestyle or metformin could reduce blood glucose levels in some study participants. Even temporary normalization of blood glucose levels can prevent the development of diabetes for several years. Recent studies have shown that there is a direct correlation between a decrease in HbA1c levels to less than 6.5% and a significant decrease in the number of complications of the micro- and macrovascular system [66]. If we combine these results and emphasize how important normalization of blood glucose levels is to prevent the development of diabetes and related risk factors, then our current goals should be to treat diabetes and reduce HbA1c levels below 5.7%, even if this effect lasts only a few years [4,5,14,17,19,21,23]. This method can significantly affect the results of treatment of patients with DM2, especially considering that most people experience this disease after the age of 50. With timely diagnosis of diabetes, new drugs that not only reduce glucose levels, but also reduce risk factors for cardiovascular diseases, reduce weight and reduce the amount of fat in the abdominal cavity can cure most patients. As a result, the treatment method should be significantly different from traditional methods. Patients with prediabetes or diabetes should be diagnosed as soon as possible. It is important that diabetic patients start receiving treatment with a healthy lifestyle and combination therapy as soon as possible, which includes at least one of these new drugs [20,21,22,23,24,25].

Discussion. More than 400 million people worldwide suffer from diabetes, which is a serious public health problem. Gradually, this metabolic disorder leads to chronic microvascular, macrovascular and neuropathic complications, which can be fatal. Either insufficient insulin secretion, damage to pancreatic β-cells, or insulin resistance caused by its use may be the cause of diabetes. A tendency to a sedentary lifestyle may be the main reason for the constant increase in the number of diabetic patients worldwide. It is expected that in 2030 there will be 366 million diabetic patients among the elderly over the age of 65 [4,5,11,12]. DM can cause various complications such as nephropathy, neuropathy, heart and kidney complications, retinopathy, nutritional problems, and others. Two types of diabetes mellitus are type I diabetes mellitus and type II diabetes mellitus. Type 2 diabetes is the result of a malfunction of the beta cells of the pancreas, which prevents the use of insulin. DM 1 is an autoimmune disease affecting pancreatic cells, which reduces or disrupts insulin production [12,13,14,15].

Treatment regimens vary depending on the treatment method, the type of drugs and their effects, as well as the degree of organ protection and weight loss achieved. Research is ongoing, and new treatments can reduce difficulties and improve the quality of life of people with type 2 diabetes. Modern methods of treating diabetes can only control its symptoms and slow its progression. However, they cannot completely cure the disease, and they can also cause various side effects. Researchers are constantly looking for new compounds that can become the basis for effective treatment of diabetes mellitus and its complications. They are also trying to find a method that will reduce the side effects. Insulin therapy, biguanides, sulfonylurea, glinides, thiazolidinediones, gliptins, α-glucosidase inhibitors, amylin analogues, SGLT-2, dopamine D-2 agonists are old methods of treating diabetes mellitus [22,23,24,25]. Not only can they eliminate symptoms and slow the progression of the disease as the main targets, but they can also cause many side effects such as weight gain, hypoglycemia, diarrhea, nausea, mitogenic effect, bladder cancer, etc., which is unfavorable for patients with these metabolic diseases. Researchers are constantly looking for new targets for diabetes treatment, and in recent decades, targets such as PPAR have been the focus of researchers' attention. However, despite the huge number of preclinical studies, clinical studies and market research, no results have been obtained. Because of this, we cannot rely on current diabetes treatments, and we must explore some new, innovative ones [26,27,28,29,30].

Conclusion. Currently, a large number of people suffer from a vulnerable disease known as diabetes, which has spread around the world. The goal of any diabetes treatment is to achieve an almost normal blood glucose level.

An increase in the number of diabetic patients as a result of an increase in the number of sedentary people and cases of obesity has led to a constant increase in the number of diabetic patients. This has led to a significant increase in demand for antidiabetic drugs, which has prompted companies to invest more money in research and development of targeted drugs.

Indications for initial therapy with a combination of three drugs include the patient having active cardiovascular disease or heart failure, proteinuria and impaired renal function, as well as lack of success in treatment with a combination of two drugs. The National Diabetes Council in Israel has developed a calculator that helps medical professionals choose the ideal combination of drugs for each patient. The calculator is based on the patient's BMI, HbA1c level and risk of heart failure, stroke, kidney failure and coronary heart disease.

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