

Diabetes Mellitus And Effective Treatments

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Diabetes Mellitus and the Rationale for Treatment

Diabetes mellitus (DM) is a widespread disease throughout the world. Due to its epidemic nature, the high incidence of vascular complications, and the high mortality rate, the UN adopted a resolution to combat it. The International Diabetes Federation's 2025 Diabetes Atlas estimates that 589 million adults aged 20–79 were living with diabetes in 2024 and projects 853 million by 2050. About 85–90% of those patients have [type 2 diabetes](#) (Kalra, Bharti, Yashdeep Gupta, and Sanjay Kalra 1134–6). Type 2 diabetes increases the risk of coronary heart disease (CHD), stroke, as well as cardiovascular mortality (McCarthy 2339–2350). A satisfactory state of health of patients at the beginning of the disease delayed the diagnosis and the beginning of drug therapy in many patients with type 2 diabetes. In almost one-third of patients, micro-vascular and macro-vascular complications are detected simultaneously with the diagnosis of diabetes (Jean, Myriam et al. 138–149). The main pathophysiological mechanisms for the development of type 2 diabetes include insulin resistance (IR) and pancreatic β -cell dysfunction. At the initial stages of the disease, IR causes a compensatory increase in the increment of insulin. However, as MI (Matsuda index) progresses and the development of hyperglycemia becomes more prominent, the concentration of insulin in the plasma decreases (Kalra et al., 1134–6). In the manifestation of type 2 diabetes, the increment of insulin is reduced by 50%, and insulin sensitivity is reduced by 70 % (Wallia, Amisha, and Mark E Molitch 2315–2325).

The development of tissue precedes diabetes and depends on both genetic factors and environmental factors. A large number of mutations determining the development of MI (Matsuda index) have been identified; however, the frequency of their occurrence in the population is low. Most likely, sensitivity to insulin is determined by the effect of many genes. The acquired factors that affect insulin sensitivity include age, nutritional quality, physical activity, obesity and the type of fat distribution. IR is diagnosed in almost 90% of patients with type 2 diabetes (McCarthy 2339–2350).

Violation of the secretion of insulin can be associated with the MI of the β -cells themselves.

Metformin and Insulin Resistance in Type 2 Diabetes

Thus, the main strategic direction of treatment of type 2 diabetes should be the impact on MI as the underlying pathophysiological mechanism of the disease. With an increase in sensitivity to insulin, the load on the incremental apparatus of the pancreas decreases, the negative effect of hyperinsulinemia on the state of the cardiovascular system is leveled, and also leads to an increase in appetite and an

increase in body weight (Kalra, Gupta, and Kalra). For medical treatment of IR (Insulin resistance) with type 2 diabetes, oral hypoglycemic preparations of biguanides and thiazolidinediones (glitazones) are used (Kalra et al., 1134–6). The history of the application of biguanides originated from the Middle Ages when a guanidine-containing extract was used to treat diabetes (Herder et al., 679–692). Chemical synthesis of biguanides was first carried out in the 1920s, and they entered the practice of treatment in the late 1950s (Wallia and Molitch).

Metformin is a drug of the biguanide group, which has been on the international pharmaceutical market for more than 40 years. The end of the twentieth century can be described as the “second birth” of this drug. Metformin-induced lethality decreased by 42%, total mortality by 36%, and complication rate by 32% compared to the group of patients who were only on diet therapy (Herder et al., 679–692). In the groups of patients who did not receive Metformin, these indicators were significantly worse. In the last decade, numerous trials of Metformin were conducted not only to evaluate the therapeutic significance and confirm a positive effect on preventing the development of cardiovascular complications of diabetes but also to extend the range of indications for prescribing the drug. An observational study conducted by J. Evans et al. (2005) suggested that Metformin has a protective effect on certain cancers.

In the consensus of the ADA / EASD adopted in 2006, Metformin is recommended as the first choice drug, which is administered immediately after the diagnosis of diabetes, in parallel with lifestyle changes, without waiting for several months until a lifestyle change leads to an improvement in the glycemic profile. Metformin improves the utilization of glucose by peripheral tissues due to the increased activity of transmembrane glucose transporters GLUT-1, GLUT-3, and GLUT-4 (Wallia et al., 2315–2325). Also, Metformin delays the absorption of glucose in the intestine, which helps reduce the peaks of postprandial glycemia. The anorexigenic effect of the drug due to its direct contact with the mucosa of the gastrointestinal tract is important (McCarthy). Additional beneficial effects of this drug include weight loss (mainly due to fat reduction), improvement of the lipid profile and fibrinolytic activity of the blood, which determines the cardioprotective effect of Metformin (McCarthy 2339–2350). Reducing the concentration of free fatty acids (by 10–17%), Metformin not only improves insulin sensitivity but also contributes to the restoration of impaired secretion of insulin (Kalra et al., 1134–6).

Vascular Protection and Metabolic Effects of Metformin

Vasoprotective effects of Metformin are due to the normalization of the cycle of contraction-relaxation of arterioles, a decrease in the permeability of the vascular wall and inhibition of neoangiogenesis (Jean, Myriam et al. 138–149). The mechanism of fibrinolysis activation is due to a decrease in the concentration and activity of the tissue plasminogen-1 activator inhibitor (PAI-1).

Metformin also possesses Angio-Sidan NO_y activity due to the inhibition of cellular oxidative reactions,

including oxidative glycosylation of proteins (Kalra et al., 1134-6). Treatment with the drug starts with a dose of 500-850 mg taken during supper, eventually increasing the dose by 500-850 mg every 1-2 weeks (Jean, Myriam et al. 138-149). The optimal daily dose at which the glycemic control closest to the target is observed is 2000 mg. Metformin does not stimulate the production of insulin β -cells, so the risk of developing hypoglycemia against the background of its intake is almost absent (McCarthy 2339-2350).

When Metformin is prescribed, some patients develop unwanted drug reactions such as diarrhea, flatulence, and metallic taste in the mouth. To avoid the appearance of such symptoms, you should gradually increase the dose of the drug and, in some cases – temporarily reduce it. Contraindications for the appointment of Metformin include impaired renal function (decreased keratinize clearance below 50 ml/min or increased keratinize concentration in the blood above 130-150 $\mu\text{mol} / \text{l}$), pregnancy, lactation, alcohol abuse, hypoxic conditions of any nature (due to the possibility of development Lactic acidosis) (Jean, Myriam et al. 138-149). Compliance with the rules for Metformin eliminates the risk of lactic acidosis.

Combination Therapy and Glycemic Control

Failure to achieve post-prandial glycemic targets against Metformin treatment indicates a significant incremental defect in β -cells and the need for a combination therapy, which is based on complementary mechanisms of drug action. Glucovans is a balanced combination of metformin 500 mg and glibenclamide in a dose of 2.5 mg or 5 mg in one tablet (Jean, Myriam et al. 138-149). This is the only combined preparation in which glibenclamide is presented in the form of a micronized form. Glucovans production technology is unique: glibenclamide is used in the form of particles of a strictly defined size and evenly distributed in the soluble matrix of Metformin (Herder and Roden).

Micronized forms of glibenclamide are characterized by much better bioavailability when used; the peak concentration of the active drug in the blood plasma occurs earlier than in un-micronized forms (Jean, Myriam et al. 138-149). When Glucovans is taken, these features make it possible to more effectively control the concentration of glucose in the blood plasma after eating and reduce HbA1c compared to monotherapy with its components. Micronized form of glibenclamide in the composition of Glucovans ensures the safety of the drug at high efficiency. The drug has less effect on β -cells, does not increase the concentration of insulin in blood plasma on an empty stomach, and reduces the risk of hypoglycemia.

Several retrospective studies have evaluated the effects of transferring patients from the combined use of Metformin and Glibenclamide to Glucovans. One of them analyzed data on 72 patients who received a combination of Metformin and Glibenclamide for at least six months before taking the test and then receiving Glucovans in daily doses up to 2000/20 mg on average for 196 days (Wallia and Molitch).

As a result of Glucovans intake, the concentration of HbA1c decreased among all patients by an average of 0.6% and among patients who initially had HbA1c > 8% – by 1.3%. After transferring patients to Glucovans, the mean daily dose of melamine increased significantly ($p = 0.02$), and the dose of glibenclamide decreased ($p = 0.007$) (Herder and Roden).

Glucovans, Treatment Efficiency, and Patient Compliance

The higher efficiency of Glucovans compared to the combination of Metformin and Glibenclamide may be due to better compliance and faster absorption of Glibenclamide in the unique Glucovans structure. Patients with type 2 diabetes often take several drugs at the same time. The combination of drugs in a single tablet simplifies the scheme of oral hypoglycemic therapy and ensures good adherence to patients' prescribed treatment.

The main indication for the appointment of Glucovans remains type 2 diabetes in adults, with the ineffectiveness of previous therapy with Metformin and (or) Glibenclamide. Contraindications to the appointment of Glucovans are composed of known contraindications to the appointment of metformin and glibenclamide (Wallia and Molitch).

Thus, Glucovans is a unique, modern treatment that affects the two main pathophysiological links of the pathogenesis of type 2 diabetes. This is the only combined preparation containing a micronized form of glibenclamide. The choice of dosages allows titration of the dose. Glucovans are highly effective in small doses, and convenient reception of the drug provides good compliance.

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