

Recent advances in the drug therapy of type 2 diabetes mellitus with overweight

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This letter summarizes an update of the review [1] with special reference to recent developments and perspectives of the treatment of Type 2 Diabetes Mellitus (T2DM) with excessive body weight. Early in the course of T2DM with overweight is usually prescribed metformin, which reduces the demand for insulin, improving the sensitivity of peripheral tissues and inhibiting hepatic glucose production. Metformin does not stimulate insulin secretion by pancreatic beta cells, therefore it does not induce hypoglycaemia [2–8]. Metformin is indicated for the treatment of T2DM with obesity but is efficient also in patients with a normal body weight. Among beneficial effects of metformin is the appetite suppression, which contributes to the body weight loss. However, not all studies confirm the weight reduction after a prolonged intake of metformin; some authors classify metformin as neutral in regard to the weight gain [2,6,8]. The main contraindication to the metformin use is a reduction of the Glomerular Filtration Rate (GFR) because of the risk of lactate-acidosis. Further contraindications include conditions associated with hypoxia and a risk of metabolic acidosis (hunger) as well as severe liver disease [4]. In case of contraindications for the intake of metformin or its intolerance other drugs are administered. Sulfonylureas have been used for decades. Among their drawbacks is the risk of hypoglycemia, especially in aged patients with comorbidity, as well as the weight gain. A dysfunction of beta cells may occur after a prolonged stimulation by sulfonylureas [9]. The effect of glinides (e.g. repaglinide) is shorter than that of sulfonylureas. The action mechanism of both drug groups is similar, both contributing to the weight gain. Glinides are taken with meals and allow more liberal diets. Repaglinide can be used in conditions of renal insufficiency. The thiazolidinediones (e.g. pioglitazone) exhibit potent insulin-sensitizing properties. The intake of pioglitazone is accompanied by a low risk of hypoglycemia. Pioglitazone can be used in renal insufficiency. The drawback is a weight gain and retention of fluid, which is undesirable, in particular, in heart failure [4,10].

Dipeptidyl peptidase 4 (DPP-4) inhibitors (gliptins) inhibit the degradation of Glucagon-Like Peptide 1 (GLP-1), which stimulates the insulin secretion and suppresses the synthesis of glucagon. DPP-4 inhibitors do not enhance the risk of hypoglycemia and have no impact on the body weight. The hypoglycemic effect of GLP-1 receptor agonists is more pronounced than that of DPP-4 inhibitors. Apart from the stimulation of insulin secretion, these drugs slow down the gastric emptying, suppress the appetite and contribute to the weight loss [9–11]. The delayed gastric emptying may be associated with eructation [12,13] and regurgitation, which may be disturbing, in particular, for older patients. Semaglutid was reported to be the most efficient anti-diabetic drug among those proposed in the period 2013–2017; its efficiency in obese T2DM patients was pointed out [14,15]. There are experimental data about proliferation of beta cells and reduction of apoptosis under the influence of GLP-1 receptor agonists; however,

direct evidence in humans is lacking [11,16]. At the same time, an exhaustion of beta cells as a result of the stimulation by GLP-1 receptor agonists is not excluded [17]. A disadvantage is the delivery by injection as well as the relatively high price. An oral preparation of semaglutid is currently being evaluated. A combination of GLP-1 receptor agonists with metformin is efficient, associated with a low hypoglycemia risk and contributes to the weight loss [4].

The inhibitors of intestinal alpha-glucosidase (acarbose) prevent digestion of carbohydrates, lower the postprandial hyperglycemia and, secondarily, hyperinsulinemia, while hypoglycemia is not provoked. The side effects include meteorism and other intestinal symptoms [18]. According to one meta-analysis, acarbose does not influence the body weight [19], according to another one it significantly contributes to the weight loss [20] especially in T2DM patients with obesity [21]. In experiments, acarbose reduced the body weight of animals [18].

The Sodium-Glucose Co-Transporter-2 (SGLT-2) inhibitors (gliflozins) inhibit the renal reabsorption of glucose and induce glycosuria associated with a risk of urogenital infections. The osmotic diuresis lowers blood pressure thereby reducing the risk of cardiovascular complications. Glycosuria with a loss of calories reduces the potential glucotoxicity and hence the risk of beta cell failure [22]. Thanks to the insulin-independent action mechanism, SGLT-2 inhibitors can be combined with other anti-diabetic drugs and insulin [9,23,24]. In particular, a combination of SGLT-2 inhibitors with GLP-1 receptor agonists was reported to be favorable for T2DM patients with obesity [25]. Furthermore, a ketogenic effect of SGLT-2 inhibitors, in consequence of the switching from carbohydrates to lipids as a source of energy, should be pointed out [26,27]. A similar effect has the Low Carbohydrate - High Fat Diet (LCHF), which at the carbohydrate content ≤ 50 g/day is referred to as ketogenic diet [28,29]. Under the impact of such diet the amount of glucose taken up from food is insufficient to maintain glycogen stores in the liver and muscles. This results in a lowering of glucose and insulin levels in blood, reduction of glycogen stores and burning of fatty acids with production of ketones. These ketones are then used by the brain and muscles as a source of energy. The literature shows that diet studies with LCHF in patients with T2DM and obesity do induce favorable effects on weight loss, blood glucose and insulin. However, there is a lack of data supporting a long-term efficacy, safety and health benefits of LCHF [28,29]. Further studies are obviously needed. The action

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mechanisms of both LCHF and SGLT-2 inhibitors are analogous (decreased availability of glucose), so that their combination would be probably efficient for the purpose of weight loss. However, caution is needed because of the risk of euglycemic ketoacidosis developing rarely in the course of the treatment by SGLT-2 inhibitors (incidence <0.2% in canagliflozin studies) [22], more frequently in type 1 diabetes, e.g. after alcoholic excesses, surgeries or intercurrent illnesses [24–27,30]. A combination of SGLT-2 inhibitors with a strict LCHF is regarded to be contraindicated [31]. Considering that a prolonged adherence to LCHF is difficult for patients, the compliance being poor, a combination of LCHF with SGLT-2 inhibitors might contribute to the catabolism of fat depots causing less discomfort by the same effect than a strict LCHF alone. Such an experimental therapy would require a tight clinical control. Further studies are needed.

One of the most important questions is the price of drugs. According to an estimation in Russia for the year 2014, the annual costs of monotherapy in rubles (in brackets - converted to US dollars according to the course for 29 September 2018: 1 dollar = 65.59 rubles) were as follows: glibenclamide - 1256 (19.29), metformin - 4396 (67.02), pioglitazone - 6077 (92.65), sitagliptin - 38,873 (592.67), liraglutide - 149,504 (2,279.37) [32]; canagliflozin, according to https://medi.ru/instrukciya/invokana_6939/cena/ (29 September 2018) - 28000-49000 (\$426–747). It is not always clear how far advantages of certain drugs justify the price differences. This question is related to the topic of scientific integrity, conflicts of interest and reliability of publications. It seems to be evident for a reviewer of scientific literature that the quality of argumentation in some areas of medical and biological research has deteriorated during last decades. Certain publication series have been continued without making references to the published criticism [33–35]. A tendency of T2DM hypertherapy has been noticed, especially of older patients [36,37], which may be economically motivated. A tight glycemic control is hard to maintain for long time without undesirable side effects, whereas a benefit from such control is not always evident [38–40]. The polypragmasia elevates the risk especially in older patients [10]. On the contrary to some earlier studies, the large randomized clinical trials (ACCORD, ADVANCE, VADT) lasting 3.5–5.6 years have found that intensive glycemic control either has no impact on cardiovascular outcomes or even worsens them [7,41,42]. Admittedly, the intensive glycemic control improved some nephropathy-related outcomes in ADVANCE and slowed the progression of albuminuria in VADT [43,44]. However, given the relatively small number of cases with end-stage renal disease, the benefits were recommended to be interpreted with caution [43]. Apparently, intensive glucose control had minimal effects on hard microvascular complications (severe renal changes, decreased GFR, laser treatment, cataract extraction, vitrectomy, and new neuropathy) during a period of 5 to 6 years [44]. There is a well-founded opinion that the tight glycemic control may be beneficial in primary prevention of cardiovascular complications in younger T2DM patients, but in older patients with established or subclinical cardiovascular disease it is potentially deleterious [42].

Conclusion

It is important for the treatment of T2DM with overweight to use the drugs that contribute to the weight loss. Along with the widely used metformin, the following medication classes should be mentioned. The GLP-1 receptor agonists stimulate insulin secretion, slow down the gastric emptying, contributing to a weight loss. The SGLT-2 inhibitors lessen the renal glucose reabsorption, lower the blood pressure and contribute to a body weight reduction. A similar effect on the body weight should be awaited from the inhibitors of intestinal alpha-glucosidase (acarbose); however, its efficiency depends on the

carbohydrate contents of the diet. Importantly, hypoglycemic effects of the two latter drug classes are unrelated to the stimulation of the insulin secretion by beta cells. It is known that the secretory function of pancreatic islets can be exhausted by stimulation [45]. On the contrary, keeping insulin secretion at rest prevents the beta-cells exhaustion [46]. Detrimental effects of some anti-diabetic drugs can be mediated by excess insulin, which in itself contributes to the weight gain [47,48]. Conversely, the reduction of insulin hypersecretion is a method of weight loss [49]. An experimental blockade of hyperinsulinemia in mice prevents obesity [50]. This indicates that drugs acting without stimulation of the insulin secretion are preferable, other things being equal. In conclusion, the goals of glycemic control need to be individualized based on the age, prognosis, presence of macrovascular disease, and risk of hypoglycemia [42].

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