Adjunctive Treatment in Insulin Therapy in Autoimmune-Mediated Diabetes (Type 1 and Type LADA Diabetes)

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Abstract: Tightening of the diabetes control criteria in the last few years induces searches for adjunctive drugs to reinforce the basic treatment typical for the specific type of the disease. Disorders of glucose homeostasis may be the result of a deficiency of insulin resulting from the destruction of β cells. Formerly it was thought that this is the only factor in the pathogenesis of autoimmune diabetes. Currently, it is already known that insulin resistance is also present in these forms of diabetes, as well as impaired secretion and the action of other hormones. This diversity of mechanisms leading to the manifestation of diabetes causes that in addition to the drugs considered to be basic for a specific type of diabetes, supplementary drugs are needed to improve metabolic disorders. Metformin is traditionally used among these medicines. Currently, however, more modern drug groups are being used more and more often. There are many indications that they have a beneficial effect not only as drugs that reduce insulin resistance, but also may play a role in immunization processes and promote the protective function of β cells. Among these new drug groups, GLP-1R receptor agonists stimulate the growth and differentiation of β cells, and also affect the process of differentiation of young pancreatic cells and can participate in the reproduction of β-cells of the pancreas. Experimental studies also indicate that GLP-1 may be used in gene therapy of diabetes and in the culture of β cells for their use in transplantation. Role dipeptidyl peptidase-4 (DPP-4) inhibitors in autoimmune diabetes require further research. In the group of patients with LADA-type diabetes improved glycemic control was observed. The beneficial effect of DPP-4 inhibitors in combination with vitamin D3 observed in new-onset type 1 diabetes and in LADA in preserving the residual function of β cells.

Keywords: type 1 diabetes, type 2 diabetes, adjunctive treatment, metformin, amylin, SGLT-2 Inhibitors, GLP-1 agonists, DPP-4 inhibitors

1. Introduction

Recent years bring an ever wider range of drugs affecting the regulation of glucose metabolism. These drugs are mainly used in the treatment of type 2 diabetes. Increasingly, however, attempts are being made to use them as supportive drugs in the treatment of type 1 diabetes. The essence of this type of diabetes is the destruction of β cells as a result of autoimmune processes. In this situation, the basis of treatment is the supply of exogenous insulin to the body. In this area, there are also more and more new products in the field of insulin preparations and ways of its delivery to the body [1]. However, insulin deficiency is the basic but not the only cause of glucose homeostasis disorders in type 1 diabetes, hence there is an increasing number of attempts to improve the efficiency of delivering of insulin [2,3,4]. The basis for the treatment of autoimmune diabetes is insulin therapy. However, more and more trials of causal treatment are being undertaken. Drugs supporting the mechanisms of an insulin action are also being introduced more and more widely [5]. There is a need for randomized trials to assess the effectiveness and long-term safety of such treatment.

2. Metformin

Metformin has been used for a long time as a booster for this drug [6,7,8]. This is especially related with the overweight patients [9]. Metformin as an insulin-boosting treatment reduces insulin resistance and allows insulin doses to be reduced in patients with type 1 diabetes and with an excessive amount of adipose tissue [10]. Similar observations were also made by Priya and Kalra, who pointed out that metformin has been shown to reduce maximal carotid intima media thickness and therefore may extend cardioprotective benefits in type 1 diabetes [11]. Chinese authors have recently presented the results of a literature analysis in which it has been shown that metformin use in type 1 diabetes and lower BMI reduces insulin requirement [12]. However, negative outcomes, such as gastrointestinal adverse effects and severe hypoglycaemia may also occur in these patients. Recently, the results of studies on the effect of metformin on insulin resistance in patients with type 1 diabetes were presented by Sheriba et al. [13] The authors concluded that metformin reduced the level of fetuin-A. Fetuins are blood proteins that are made in the liver and secreted into the bloodstream. Fetuin-A has been demonstrated to play an important role in free fatty acid induced insulin resistance in the liver. Increased fetuin-A in patients with pre-diabetes is associated with increased progression to diabetes and decreased reversal to normoglycaemia. The role of fetuin-A in insulin resistance was also emphasized by other authors [14]. On the basis of the analysis of the literature they also demonstrated its usefulness as a biomarker for liver dysfunction, cardiovascular diseases and disorders associated with metabolic syndrome. Siraz et al carried out the evaluation of fetuin-A levels in 80 juvenile patients who had diabetes [15]. The authors stated that fetuin-A is a reliable parameter in the prediction of complications and poor glycemic control in patients with type 1 diabetes. These observations evidence
that the use of metformin, which lowers fetuin levels, may be useful in reducing insulin resistance in patients with type 1 diabetes. Other drugs have also been used to support insulin therapy in type 1 diabetes. These drugs are of basic application in type 2 diabetes therapy, but more and more often they are also used as insulin-booster in patients with type 1 diabetes [4]. These drugs are also used in pediatric patients [16]. In the authors’ opinion, supportive therapies may also be preserving beta-cell function in type 1 diabetic patients. As supportive drugs, in addition to metformin, SGLT-2 Inhibitors (Sodium-Glucose Co-Transporter 2 Inhibitors), GLP-1 (glucagon-like peptide-1 receptor agonists), DPP-4 (dipeptidyl peptidase-4 inhibitors) [4,17,18,19] Amylin

Among the drugs that support insulin therapy in type 1 diabetes, pramlintide, an amylin analogue should be also mentioned. Amylin is co-secreted with insulin by the pancreatic β-cells. Patients with type 1 diabetes have a deficiency of insulin and amylin [20, 21]. Amylin is physiologically relevant for glycemic and energy balance control. Amylin receptor agonists reduce postprandial blood glucose levels, feeding and body weight [22]. In type 1 diabetes levels of amylin are low in the plasma due to the destruction of β cells. Patients with type 1 diabetes have a deficiency of insulin and amylin [23]. The beneficial effect of pramlintide, a synthetic amylin analogue, as an adjunct to insulin therapy lies in significant reductions in A1C in patients with diabetes, with favourable effects on body weight.

However, adverse symptoms of such therapy as increased risk of hypoglycemia, nausea, vomiting, anorexia, reduced appetite, and headache must be underlined here. The authors draw attention to the necessity of very careful education of patients, who are offered such therapies. The beneficial effect of adjunctive treatment with pramlintide in the regulation of post-meal hyperglycemia in type 1 diabetes was presented by Galderisi et al. [24].

Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT-2 Inhibitors)

In the adjunctive therapy of insulin treatment in type 1 diabetes, more attention is paid to SGLT-2 Inhibitors. The use of SGLT-2 inhibitors in adjunctive therapy is aimed at block reabsorption of glucose in the kidney tubules [25, 26]. In experimental studies in laboratory animals have shown that the use of preparations of this group may have a beneficial impact on the protection and regeneration of β cells in type 1 diabetes by the reduction of oxidative stress within β-cell [27]. In patients undergoing this therapy, education in the prevention of ketoacidosis is indicated. [28]. Due to the increased risk of increase β-hydroxybutyrate levels reduction total daily insulin dose on 24-hour should not exceed 20% [29]

Recently the information about use of first dual SGLT1 / SGLT2 inhibitor in type 1 diabetic patients has been released [30]. A beneficial effect of the drug on glycemic control was found with a reduced risk of hypoglycaemia, however an increased risk of ketoacidosis was observed (DKA). According to the author, further research is necessary in this question.

GLP-1 agonists and GLP-1 receptor agonists

Attempts are also being made to apply GLP-1 agonists and GLP-1 receptor agonists as an insulin therapy adjuvant in patients with type 1 diabetes. The effect of GLP-1 on reducing blood glucose is the result of a number of processes including the effect on gastric emptying, food intake and production and / or glucose consumption as well as the impact on the secretion of pancreatic hormones. These extensive GLP-1 activities have led to attempts to use it in the treatment of diabetes. Based on recent literature Wang et al. presented the results of the use of glucagon-like peptide-1 receptor agonists therapy with insulin therapy [31]. Studies have demonstrated the beneficial effect of combination therapy with GLP-1 and insulin in patients with type 1 diabetes. A comprehensive discussion of 52 weeks follow-up in a group of 1,398 adults patients with type 1 diabetes was presented by Mathieu et al. [32]. These patients used injections of liraglutide as insulin therapy. The authors stated that liraglutide added to insulin therapy reduced HbA1c levels, total insulin dose, and body weight. As the unfavourable symptoms, they found increased rates of symptomatic hypoglycemia and hyperglycemia with ketosis, which constituted some limitation in the use of the drug in this group of patients. Dejgaard et al presented the results of tests carried out in overweight patients with type 1 diabetes, in whom GLP-1 was used in poorly balanced type 1 diabetes with overweight [33]. In this group reduction in insulin doses was observed as well as reduction of the frequency of hypoglycaemia and overweight. Similar positive results have been obtained after combination therapy with insulin and GLP-1RA [glucagon-like peptide-1 receptor agonist] in patients with type 1 diabetes [34].

Dipeptidyl peptidase-4 inhibitors (DPP-4)

Another group of drugs that have been used as insulin-boosting drugs in autoimmune diabetes are dipeptidyl peptidase-4 (DPP-4) inhibitors. However, according to Wang et al the results are not conclusive and require further research [35]. Although in the studies conducted in the group of patients with LADA-type diabetes, a change in the T cell phenotype and improved glycemic control was observed [36]. The beneficial effect of DPP-4 inhibitors in combination with vitamin D3 in preserving the residual function of β cells in new-onset type 1 diabetes and in LADA diabetes was found by Pinheiro et al [37].

3. Conclusions

The drug groups discussed earlier are quite commonly used in the treatment of type 2 diabetes. Their use in patients with type 1 diabetes is currently in the interest of clinical trials. So far there are no official recommendations of scientific societies. It seems, however, that based on the observations already carried out, they may prove to be very useful as drugs supporting insulin therapy. There are many indications that they have a beneficial effect not only as drugs that reduce insulin resistance, which can reduce the daily dose of insulin and reduce body weight- there are many indications that they may also play a role in immunization processes and
promote the protection of β-cell function. Because they can also cause adverse effects such as for example increasing the occurrence of ketosis -further observations are necessary.

References


