



# Pharmacological Treatment in Diabetes Mellitus Type 1 – Insulin and What Else?

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## Abstract

The basis of treatment in autoimmune diabetes is insulin therapy; however, many clinical cases have proven that this method does not solve all problems. Trials of causal treatment including blocking the autoimmune processes and insulin-producing cells transplants were carried out. Those methods require more research to be concerned as efficient and safe ways of treatment in type 1 diabetes. The use of non-insulin adjunct treatment is a new trend. It has been successfully used in laboratories as well as clinical trials. Metformin is the most widely used drug, together with sodium-glucose co-transporters 2 (SGLT2) inhibitors, amylin analogues, glucagon-like peptide 1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) inhibitors. The results of administration of these medicaments give good outcomes in patients with diabetes mellitus type 1. Most likely, in the near future, they will progressively be used in both adult and adolescent patients with type 1 diabetes. Further multicenter, randomized studies are required to evaluate the efficacy of treatment and long term safety of these drugs.

**Keywords:** Type 1 Diabetes, Insulin Therapy, Non-Insulin Adjunct Therapy, Metformin, SGLT2: Sodium-Glucose Co-Transporters, Amylin Analogue, Glucagon-Like Peptide 1 (GLP-1) Receptor Agonists, Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

## 1. Introduction

The essence of type 1 diabetes is the lack of endogenous insulin secretion and autoimmune destruction of  $\beta$ -cells in the pancreas. This pathogenesis of the condition brings the necessity of external insulin supply. Insulin therapy itself is the basis in treatment of type 1 diabetes.

Recent years have brought multiple solutions in the implementation of the treatment. New types of insulin, modern glycaemia monitoring, and insulin administration techniques revolutionized the capabilities of contemporary insulin therapy.

Trials of causal treatment in this type of diabetes, including blocking the autoimmune processes and insulin-producing cells transplants are still carried out. Those methods require more research to be concerned as efficient and safe ways of treatment in type 1 diabetes (1-3).

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. These agents are meant to stimulate insulin secretion, increase insulin sensitivity, or inhibit the antagonists of the hormone. Up until now, those kind of studies included adults, mainly with type 2 diabetes. Nowa-

days, however, the increasing number of research focuses on type 1 diabetic patients.

In type 1 diabetes, insulin resistance is present in addition to the deficit of endogenous insulin. Validation of insulin resistance is one of the fundamentals in the discussion that considers the legitimacy of the currently existing division of type 1 and type 2 diabetes (4-6). Presently, the division created in 1995 still applies (7, 8).

We aimed to review the existing data on non-insulin treatments in type 1 diabetes.

## 2. Insulin Resistance in Type 1 Diabetes

Formerly, insulin resistance was considered to only be present in type 2 diabetes. Nowadays it is known to exist in a variety of conditions including type 1 diabetes mellitus (9).

Insulin resistance together, with reduced insulin secretion, may directly affect the accelerating manifestation of type 1 diabetes. Coexisting insulin resistance is in fact an additional factor interfering on the ability to maintain homeostasis of glucose. Nowadays, the increase in number of patients with type 1 diabetes who develop disorders in insulin sensitivity is observed (10-13). Insulin resistance

plays an important role in the development of angiopathy in patients with carbohydrate metabolism disturbances

Investigations of insulin resistance relationships with metabolic and inflammatory parameters were documented to the high risk of cardiovascular disease in patients with type 1 diabetes (14).

Insulin resistance is a feature of type 1 diabetes; however, further investigations are required for the assessment of its contribution to the progression of the disease, which can help optimize the treatment (15).

### 3. The Role of Obesity in Type 1 Diabetes

Excess weight is one of the crucial factors leading up to type 2 diabetes and it is not indifferent for patients with type 1 diabetes (16, 17).

The primary cause of type 1 diabetes is the autoimmune destruction of the  $\beta$ -cell of the pancreas. The base of the treatment is substitutive usage of insulin specimens. The increase of adipose tissue mass is a cause of insulin resistance. Being overweight in type 1 diabetes is often a result of over insulinization.

Patients try to maintain a normal glucose profile by increasing the dose of insulin. This creates the vicious circle. Increasing doses of insulin without limiting the supply of calories leads to a growth of adipose tissue mass, which enhances insulin resistance. This increased insulin resistance causes the need to accelerate the dose of insulin etc. Breaking this vicious circle requires radical changes in nutrition and lifestyle. Limitations in calories supply and higher energy expenditure due to physical activity are needed (18, 19).

Increasingly, there is the use of adjuvant drugs to lower insulin resistance and lower the insulin dose while maintaining metabolic control.

### 4. Adjunctive Treatment in Insulin Therapy

The trials of supporting insulin therapy with the use of oral noninsulin medicaments have been carried out for many years (20, 21). Such attempts are also undertaken in juvenile patients (22-24).

In addition to biguanides - the first noninsulin medications used in adjunctive therapy - the efforts of using other classes of drugs, such as thiazolidinediones, amylin analogues, sodium-glucose co-transporter 2 inhibitors, incretin-based agents as glucagon-like peptide-1 (GLP-1) receptor agonists, and dipeptidyl peptidase-4 (DPP-4) are reported (25-27).

### 5. Biguanides

A currently used derivative is metformin, one of the first drugs found to be useful in adjunctive therapy. Its effects are considered to be pleiotropic. In the clinical practice it is mostly used as a medicament that decreases insulin resistance. However, more and more reports of its other activities, including its protective effect on  $\beta$  cells, are being published.

Metformin is a long-known drug. The attempts of using its specimens in type 1 diabetes have quite a long history. In the case of insulin resistance in patients with type 1 diabetes, manifesting as high endogenous insulin requirement and difficulties in obtaining metabolic control, it is assumed that it may be beneficial to include the metformin formulation (28, 29).

A positive impact of metformin, as an addition to intensive insulin therapy with decrease of insulin requirement and lowering the body mass was confirmed (30). It was also found that metformin improves the metabolism of lipids (31).

The research on the influence of metformin on improving diabetes control in juvenile patients with type 1 diabetes is being conducted (32, 33). Australian researchers undertook a randomized study on the effects of metformin added to insulin therapy in the function of the cardiovascular system in a group of 76 adolescent patients with type 1 diabetes (34). The authors believe that metformin, used as adjunctive therapy with insulin, may be useful in the prevention of cardiovascular complications in adolescent patients with type 1 diabetes.

Not all authors confirm the usefulness of metformin to improve control in overweight juvenile patients with type 1 diabetes (35). Further studies are necessary.

### 6. Sodium-Glucose Co-Transporter 2 Inhibitors (SGLT-2 Inhibitors)

Kidneys play a crucial role in glycaemia regulation. The essential part of the excretion of glucose in the urine and consequently in maintaining the glucose homeostasis is the sodium-glucose co-transporters system (36).

Currently, the pharmaceutical market is rich of a number of new formulations, which are used mainly in type 2 diabetes treatment, however, the attempts to use them in autoimmune diabetes (type 1 and LADA) as adjunctive treatment are also undertaken.

Among these drugs, a particularly great deal of research relates to the use of sodium-glucose co-transporter 2 (SGLT-2) inhibitors. The modulation of the activity of

sodium-glucose co-transporter is one of the proposed therapeutic methods. The trials of therapeutic use of SGLT-2 inhibitors in the treatment of diabetes mellitus aims to block reabsorption of glucose in the kidney tubules (37-40).

The formulations of this group decrease the blood glucose level by increasing urinary excretion (41-44). In addition to the improvement of glucose metabolism, SGLT-2 inhibitors have a positive effect on the lipid profile (45).

The beneficial effect of these drugs in type 1 diabetes is confirmed by experimental studies (46).

Lowering the blood glucose level is not the only effect of this group of drugs. Interesting results of 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  $\beta$  cells in type 1 diabetes (47). Some data indicates a potential role of SGLT-2 inhibitors in protecting kidney functions in diabetic patients (48-50). Those observations are confirmed by experimental research (51, 52).

SGLT-2 inhibitors are also responsible for weight reduction, which can be a desirable outcome, especially in the increasing number of overweight patients with type 1 diabetes. The beneficial effect was also noted in lowering high blood pressure (53).

The possibility of higher risk of ketoacidosis is being pointed out (54). The prevailing view, however, is that the benefits of SGLT-2 inhibitor therapy outweigh the risks (55).

Lately, efforts of using new drugs from this group have been made, however, additional research needs to be conducted (56).

American authors who presented the results of the trial where a group of 33 patients with type 1 diabetes who underwent a treatment using a dual composition drug containing SGLT-1 and SGLT-2 inhibitor - sotagliflozin (57).

Recently, Biester et al. reported the results of a randomized study adjunctive treatment of dapagliflozin (DAPA) in adolescent patients with type 1 diabetes (58). The insulin dose was reduced by 13.6%. An improvement in glycemic control and significant reduction in HbA1c levels, as well as lower requirement of insulin and weight loss were achieved.

## 7. Amylin (Islet Amyloid Polypeptide IAPP)

Amylin is a peptide hormone produced by the  $\beta$  cells of Langerhans islets. Its deficit may increase the risk of severe post-insuline hypoglycemia. Amylin is involved in regulating the secretion of insulin and glucagon and is considered an anorectic hormone (59), in type 1 diabetes, a parallel deficit of insulin and amylin occurs (60). This fact was a motive for the trials of using amylin analogue in type 1

diabetes treatment. Pramlindite is the analogue of amylin used in a combined therapy together with insulin that provides more physiological conditions in the process (61-63).

A significant improvement in diabetes control, in adults with long-term type 1 diabetes, was presented by Huffman et al. (64). The authors carried out pilot study of 11 patients with type 1 diabetes using insulin pumps. Subcutaneous pramlintide infusion (CSPI) was safe and well tolerated. The 16-week observation of the group showed a decrease HbA1c levels, body mass, and insulin requirements. The beneficial effect of this therapy in patients with type 1 diabetes, including juveniles, was demonstrated by other authors (65-67).

The suitability of pramlintide usage in therapy was pointed out by Herrmann et al. who conducted a multicenter randomized study in patients with type 1 diabetes treated with continuous subcutaneous insulin infusion (CSII) therapy with the addition of pramlintide (68).

The authors found that adding pramlintide to CSII provided better glycemic control in patients with type 1 diabetes.

These authors also reported beneficial effects of pramlintide in patients with patients with longer duration type 1 diabetes (69). This analysis demonstrated that mealtime pramlintide added to insulin was effective in reducing HbA1c levels and body weight in patients who have optimized the use of insulin but have still not reached therapeutic goal.

Ramkissoo et al. presented proposals for optimizing the dosage model of pramlintide and insulin for glycemic control (70).

The effect of pramlintide on prandial glycemic excursions during closed-loop (CL) control in adolescents and young adults with type 1 diabetes were presented by Weinzier et al. (71).

Young et al. presented a review of the data on pramlintidine application in patients with both type 1 and type 2 diabetes (72). The authors pointed that in addition to the decrease of HbA1c levels, these drugs also have a significant impact on weight loss.

## 8. Incretin-Based Agents

That group of drugs is represented by glucagon-like peptide 1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors (73, 74).

Glucagon-like polypeptide 1 (GLP-1) is one of the most active incretin hormones. It has an ability to stimulate insulin secretion and blocking the production of glucagon. GLP-1 inhibits the apoptosis of pancreatic  $\beta$  cells in addition to the protective effect on them. Agonists of GLP-1R stimulate the growth and differentiation of  $\beta$  cells, in-

fluence the process of differentiation of young pancreatic cells, and may be involved in the recreation of the  $\beta$  cells. Experimental studies indicate that GLP-1 may find use in gene therapy of diabetes and  $\beta$  cells culture for its use in transplants. Attempts are being made using the incretin-like action of this class of drugs in adolescent patients with early onset type 2 DM, as well as in some forms of monogenic diabetes.

Positive results of the application of GLP-1RA, as adjunctive therapy with insulin, were also reported in patients with type 1 diabetes (75, 76).

Intensive insulin therapy in type 1 diabetes allows to keep a near normalized glycaemic control; however, it is associated with the side effects such as weight gain and risk of hypoglycaemia (77). The authors added to insulin therapy glucagon-like peptide-1 receptor agonist. Dejgaard et al. presented results of randomized studies in patients with type 1 diabetes with insufficient metabolic control (HbA1c > 8% [64 mmol/mol]), and overweight (BMI > 25 kg/m<sup>2</sup>) (78). The authors conclude that the addition of liraglutide (GLP-1RA) as a supportive therapy for insulin is associated with reductions in hypoglycaemic events, bolus and total insulin dose, as well as body weight.

Recent attempts are also made to evaluate the effects of these drugs for cardiovascular protection in patients with type 1 diabetes (79).

Dipeptidyl Peptidase-4 (DPP-4) inhibitors are commonly used in therapy of type 2 diabetes. Increasingly, however, attempts are made to their use in the treatment of type 1 diabetes.

Recently a number of reports on the use of these drugs in type 1 diabetes in laboratory animals were published.

DPP-4 inhibitors are proven to be beneficial in the prevention of diabetic kidney disease (DKD) in mice with type 1 diabetes (80). The authors claim that the results suggest the possible protective effect in DKD prevention in type 1 DM. The trial with STZ-induced diabetic rats confirmed a beneficial outcome of DPP-4 inhibitors in improvement in vascular endothelial function, which may be advantageous in type 1 diabetes (81). Attempts of usage DPP-4 inhibitors in humans are also undertaken.

The research on the influence of DPP-4 inhibitors on weakening of the immune processes and improvement of  $\beta$ -cell function based on experimental studies have an interesting outcome. Clinical trials are being carried out as well (82). Italian researchers presented the evaluation of DPP-4 inhibitors efficacy in a group of 25 patients with long-term type 1 diabetes (83). A significant weight loss, decrease in LDL levels, and insulin requirement were reported. The authors point out that the use of DPP4 inhibitors may be effective in patients with type 1 diabetes, however, further long-term studies are necessary.

Underland et al. (84), presented an attempt to use sitagliptin (dipeptidyl peptidase-4 inhibitors) for reduction of postprandial glucose concentrations in young patients with type 1 diabetes. The authors stated that sitagliptin may be considered as an adjunct therapy in a closed-loop setting.

Schopman et al. evaluated the change in mechanisms of counterregulation in hypoglycemia due to DPP-4 in patients with type 1 diabetes (85). The authors reported significantly increased active levels of glucose-dependent insulinotropic polypeptide and glucagon-like peptide-1. No significant differences were observed for glucagon or adrenergic counter-regulatory responses, however, it attenuates the growth hormone response during late hypoglycaemia.

## 9. Conclusions

In conclusion, there is a need to develop recommendations for the use of adjunctive therapy with insulin in patients with type 1 diabetes.

Insulin is the basic treatment in autoimmune diabetes; however, it does not solve all the problems in the control of this type of disease. An important task of this therapy is to protect pancreatic  $\beta$ -cells and to slow down autoimmune processes, to ensure amylin supply, and to regulate the secretion of glucagon. The aim of adjuvant therapy is not only to improve glycemic control, but also to protect vascular endothelium, to provide nephroprotection, and weight control due to the metabolic syndrome characteristics, frequently observed in these patients. Currently, attempts of the usage of adjuvant drugs are being made. Their results are promising, however, further multicenter, randomized clinical trials are necessary.

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