International Journal of Science and Research (IJSR)
ISSN: 2319-7064
Index Copernicus Value (2016): 79.57 | Impact Factor (2017): 7.296

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

Chwalba A[1], Otto-Buczkowska E[2]

[1]Medical University of Silesia in Katowice, Poland

[2]Medical Specialist Centre in Gliwice Poland

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 normoglycemia . 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-boosters in patients with type 1 diabetes [4]. These drugs are also used in pediatric patients [16]. In the authors' opinion, adjunctive 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

[1] Ang KH, Sherr JL. Moving beyond subcutaneous insulin: the application of adjunctive therapies to the treatment of type 1 diabetes. Expert Opin Drug Deliv. 2017;14:1113-1131. Doi: 10. 1080/17425247. 2017. 1360862e:

[2] Ludvigsson J. Combination therapy for preservation of beta cell function in Type 1 diabetes: new attitudes and strategies are needed! Immunol Lett. 2014;159:30–35. doi: 10.1016/j.imlet.2014.02.006.

[3] Otto-Buczkowska E. Type 1 diabetes mellitus - what is news in the prevention and therapeutic strategies?. Med Matabol. 2013;17:84–90.

[4] Otto-Buczkowska E, Jainta N. Pharmacological treatment in diabetes mellitus type 1 - Insulin and what else? Int J Endocrinol Metab. 2017;16:e13008. doi: 10.5812/ijem.13008.

[5] Pozzilli P, Maddaloni E, Buzzetti R. Combination immunotherapies for type 1 diabetes mellitus. Nat Rev Endocrinol. 2015;11:289–297. doi: 10.1038/nrendo.

[6] Bacha F, Klinepeter Bartz S. Insulin resistance, role of metformin and other non-insulin therapies in pediatric type 1 diabetes. Pediatr Diabetes. 2016;17:545–558. doi: 10.1111/pedi.12337.

[7] Libman IM, Miller KM, DiMeglio LA. T1D Exchange Clinic Network Metformin RCT Study Group. Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial. JAMA. 2015;314:2241–2250. doi: 10.1001/jama.2015.16174.

[8] Otto-Buczkowska E. Metformin addend to insulin therapy for type 1 diabetes mellitus - based on literature and own experience. Medica Rev. 2010;8:338–342.

[9] Zawada A, Naskręt D, Burchardt P. et al. Metformin added to intensive insulin therapy improves metabolic control in patients with type 1 diabetes and excess body fat. Pol Arch Intern Med. 2018;128:294-300. doi: 10.20452/pamw.4241.

[10] Beysel S, Unsal IO, Kizilgul M. et al. The effects of metformin in type 1 diabetes mellitus. BMC Endocr Disord. 2018 Jan 16;18:1. doi: 10.1186/s12902-017-0228-9 .

[11] Priya G, Kalra S. A Review of Insulin Resistance in Type 1 Diabetes: Is There a Place for Adjunctive Metformin? Diabetes Ther. 2018;9:349-361. doi: 10.1007/s13300-017-0333-9

[12] Meng H, Zhang A, Liang Y. et al. Effect of metformin on glycaemic control in patients with type 1 diabetes: A meta-analysis of randomized controlled trials. Diabetes Metab Res Rev. 2018;34:e2983. doi: 10.1002/dmrr.2983.

[13] Sheriba NA, Ahmed IZ, Abdelsalam MM. et al. Effect of Metformin Therapy on Serum Fetuin Levels in Insulin Resistant Type 1 Diabetics. Curr Diabetes Rev. 2018;14:291-297. doi: 10.2174/1573399813666170112151108

[14] Dabrowska AM, Tarach JS, Wojtysiak-Duma B, Duma D. Fetuin-A (AHSG) and its usefulness in clinical practice. Review of the literature. Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub. 2015;159:352-359. doi: 10.5507/bp.2015.018.

[15] Şiraz ÜG, Doğan M, Hatipoğlu N. et al. Can Fetuin-A Be a Marker for Insulin Resistance and Poor Glycemic Control in Children with Type 1 Diabetes Mellitus? J Clin Res Pediatr Endocrinol. 2017;9:293-299. doi: 10.4274/jcrpe.4532.

[16] Naciu AM, Pozzilli P. Novel blood glucose lowering therapies for managing type 1 diabetes in paediatric patients. Expert Opin Pharmacother. 2018;19:355-364. doi: 10.1080/14656566. 2018.1441288.

[17] Chamberlain JJ, Kalyani RR, Leal S. et al. Treatment of Type 1 Diabetes: Synopsis of the 2017 American Diabetes Association Standards of Medical Care in Diabetes. Ann Intern Med. 2017;167:493-498. doi: 10.7326/M17-1259.

[18] Frandsen CS, Dejgaard TF, Madsbad S, Holst JJ. Non-insulin pharmacological therapies for treating type 1 diabetes. Expert Opin Pharmacother. 2018;19:947-960. doi: 10.1080/14656566. 2018.1483339.

[19] Harris K, Boland C, Meade L, Battise D. Adjunctive therapy for glucose control in patients with type 1 diabetes. Diabetes Metab Syndr Obes. 2018;11:159-173. doi: 10.2147/DMSO.S141700. eCollection 2018.

[20] Mietlicki-Baase EG. Amylin-mediated control of glycemia, energy balance, and cognition. Physiol Behav. 2016;162:130–140. doi: 10.1016/ j.physbeh.2016.02.034.

[21] Otto-Buczkowska E, Jarosz-Chobot P, Machnica L. The role of amylin in glucose homeostasis regulation and possible future usage in adolescents with type 1 diabetes. . DDK/ECD 2009;9:91-94. ISSN 1643-3165

[22] Hay DL, Chen S, Lutz TA. et al. Amylin: Pharmacology, Physiology, and Clinical Potential. Pharmacol Rev. 2015;67:564-600. doi: 10.1124/pr.115.010629

[23] Hieronymus L, Griffin S. Role of Amylin in Type 1 and Type 2 Diabetes. Diabetes Educ. 2015;41(1 Suppl):47S-56S. doi: 10.1177/ 0145721715607642.

[24] Galderisi A, Sherr J, VanName M. et al. Pramlintide but Not Liraglutide Suppresses Meal-Stimulated Glucagon Responses in Type 1 Diabetes. J Clin Endocrinol Metab. 2018;103:1088-1094. doi: 10.1210/jc.2017-02265.

[25] Biester T, Aschemeier B, Fath M. et al. Effects of dapagliflozin on insulin-requirement, glucose excretion and ss-hydroxybutyrate levels are not related to baseline HbA1c in youth with type 1 diabetes. Diabetes Obes Metab. 2017;19: 1635–1639.doi: 10.1111/dom.12975. [PubMed: 28417527].

[26] Sands AT, Zambrowicz BP, Rosenstock J. et al. Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes. Diabetes Care. 2015;38:1181–1188. doi: 10.2337/dc14-2806. [PubMed: 26049551].

[27] Cheng ST, Chen L, Li SY, Mayoux E, Leung PS. The Effects of Empagliflozin, an SGLT2 Inhibitor, on Pancreatic beta-Cell Mass and Glucose Homeostasis in Type 1 Diabetes. PLoS One. 2016;11. e0147391. doi:10.1371/journal.pone.0147391.

[28] Van den Mooter L, Caerels S, Mathieu C. Efficacy of dapagliflozin as an adjunct therapy in patients with inadequately controlled type 1 diabetes mellitus. Expert Opin Pharmacother. 2018;19:617-622. doi: 10.1080/14656566.2018.1450387.
[29] Henry RR, Dandona P, Pettus J. et al. Dapagliflozin in patients with type 1 diabetes: A post hoc analysis of the effect of insulin dose adjustments on 24-hour continuously monitored mean glucose and fasting β-hydroxybutyrate levels in a phase IIa Diabetes Obes Metab. 2017;19:814-821. doi: 10.1111/dom.12882.
[30] Rendell MS. Efficacy and safety of sotagliflozin in treating diabetes type 1. Expert Opin Pharmacother. 2018;19:307-315. doi: 10.1080/14656566.2017.1414801.
[31] Wang W, Liu H, Xiao S. et al. Effects of Insulin Plus Glucagon-Like Peptide-1 Receptor Agonists (GLP-1RAs) in Treating Type 1 Diabetes Mellitus: A Systematic Review and Meta-Analysis. Diabetes Ther. 2017;8:727-738. doi: 10.1007/s13300-017-0282-3.
[32] Mathieu C, Zinman B, Hemmingsson JU. et al; ADJUNCT ONE Investigators. Efficacy and Safety of Liraglutide Added to Insulin Treatment in Type 1 Diabetes: The ADJUNCT ONE Treat-To-Target Randomized Trial. Diabetes Care. 2016;39:1702-1710. doi: 10.2337/dc16-0691.
[33] Dejgaard TF, Frandsen CS, Hansen TS. et al. Efficacy and safety of liraglutide for overweight adult patients with type 1 diabetes and insufficient glycaemic control (Lira-1): a randomised, double-blind, placebo-controlled trial. Lancet Diabetes Endocrinol. 2016;4:221–232. doi: 10.1016/S2213- 8587(15)00436-2.
[34] Dejgaard TF, Knop FK, Tarnow L. et al. Efficacy and safety of the glucagon-like peptide-1 receptor agonist liraglutide added to insulin therapy in poorly regulated patients with type 1 diabetes–a protocol for a randomised, double-blind, placebocontrolled study: the Lira-1 study. BMJ Open. 2015;5. e007791. Doi: 10.1136/bmjopen-2015-007791. [PubMed: 25838513].
[35] Wang X, Zheng P, Huang G, Yang L, Zhou Z. Dipeptidyl peptidase-4(DPP-4) inhibitors: promising new agents for autoimmune diabetes. Clin Exp Med. 2018 Jul 17. doi: 10.1007/s10238-018-0519-0. [Epub ahead of print]
[36] Wang X, Yang L, Cheng Y. et al. Altered T-cell Subsets and Transcription Factors in Latent Autoimmune Diabetes in Adults with Sitagliptin, a Dipeptidyl Peptidase-4 Inhibitor: A One-year Open-Label Randomized Controlled Trial. J Diabetes Investig. 2018 Jun 8. doi: 10.1111/jdi.12873. [Epub ahead of print]
[37] Pinheiro MM, Pinheiro FMM, Trabachin ML Dipeptidyl peptidase-4 inhibitors (DPP-4i) combined with vitamin D3: An exploration to treat new-onset type 1 diabetes mellitus and latent autoimmune diabetes in adults in the future. Int Immunopharmacol. 2018;57:11-17. doi: 10.1016/j.intimp.2018.02.003.