Int J Endocrinol Metab. 2018 January; 16(1):e13008. doi: 10.5812/ijem.13008.

Published online 2017 November 20. **Review Article**

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

Ewa Otto-Buczkowska,[1,*] and Natalia Jainta[2]

[1]Medical Specialist Centre in Gliwice, Poland
[2]Medical University of Silesia in Katowice, Poland

[*]*Corresponding author*: Ewa Otto-Buczkowska MD PhD, Jasnogorska 16/2144-100 Gliwice, Poland. E-mail: em.buczkowski@pro.onet.pl

Received 2017 May 11; **Revised** 2017 September 18; **Accepted** 2017 October 31.

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 β-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 untill now, those kind of studies included adults, mainly with type 2 diabetes. Nowadays, 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 fundaments 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 diabete.

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 β-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 β 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 mas 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 β 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 β 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.

Ramkissoon 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 Weinzimer 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 β cells in addition to the protective effect on them. Agonists of GLP-1R stimulate the growth and differentiation of β cells, in-

fluence the process of differentiation of young pancreatic cells, and may be involved in the recreation of the β cells. Experimental studies indicate that GLP-1 may find use in gene therapy of diabetes and β 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(2)) (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 β-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 contrregulation 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 β-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.

References

1. Ludvigsson J. Combination therapy for preservation of beta cell function in Type 1 diabetes: new attitudes and strategies are needed!. *Immunol Lett*. 2014;**159**(1-2):30–5. doi: 10.1016/j.imlet.2014.02.006. [PubMed: 24576850].
2. Otto-Buczkowska E. Type 1 diabetes mellitus - what is news in the prevention and therapeutic strategies?. *Med Matabol*. 2013;**17**:84–90.
3. Pozzilli P, Maddaloni E, Buzzetti R. Combination immunotherapies for type 1 diabetes mellitus. *Nat Rev Endocrinol*. 2015;**11**(5):289–97. doi: 10.1038/nrendo.2015.8. [PubMed: 25688000].
4. Machnica L, Otto-Buczkowska E, Jarosz-Chobot P. *Handbook of Type 1 Diabetes Mellitus: Etiology, Diagnosis, and Treatment*. In: Aucoin L, Prideux T, editors. USA: Nova Science Publisher; 2010. The dilemmas in differential diagnosis of types of diabetes in adolescent patients; p. 467–79.
5. Otto-Buczkowska E, Jarosz-Chobot P, Machnica L. Diabetes mellitus type 1, type 2 or type 1.5–dilemmas in making proper diagnosis. *DDK/ECD*. 2008;**8**(3):91–4.
6. Pozzilli P, Guglielmi C. Double diabetes: a mixture of type 1 and type 2 diabetes in youth. *Endocr Dev*. 2009;**14**:151–66. doi: 10.1159/000207484. [PubMed: 19293582].

7. Otto-Buczkowska E. Diabetes - but what? Diagnostic and own observations. *Diabetologia po Dyplomie*. 2015;**12**:20–7.
8. Word Heath Organization. *Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO Consultation*. Geneva; 1999.
9. Kaul K, Apostolopoulou M, Roden M. Insulin resistance in type 1 diabetes mellitus. *Metabolism*. 2015;**64**(12):1629–39. doi: 10.1016/j.metabol.2015.09.002. [PubMed: 26455399].
10. Szadkowska A, Pietrzak I, Mianowska B, Markuszewski L, Bodalska-Lipinska J, Bodalski J. [Insulin resistance in type 1 diabetic children and adolescents - a simplified method of estimation]. *Endokrynol Diabetol Chor Przemiany Materii Wieku Rozw*. 2006;**12**(2):109–15. [PubMed: 16813715].
11. Szadkowska A, Pietrzak I, Mianowska B, Bodalska-Lipinska J, Keenan HA, Toporowska-Kowalska E, et al. Insulin sensitivity in Type 1 diabetic children and adolescents. *Diabet Med*. 2008;**25**(3):282–8. doi: 10.1111/j.1464-5491.2007.02357.x. [PubMed: 18279410].
12. Pietrzak I, Mianowska B, Gadzicka A, Mlynarski W, Szadkowska A. Blood pressure in children and adolescents with type 1 diabetes mellitus–the influence of body mass index and fat mass. *Pediatr Endocrinol Diabetes Metab*. 2009;**15**(4):240–5. [PubMed: 20455418].
13. van Vliet M, Van der Heyden JC, Diamant M, Von Rosenstiel IA, Schindhelm RK, Aanstoot HJ, et al. Overweight is highly prevalent in children with type 1 diabetes and associates with cardiometabolic risk. *J Pediatr*. 2010;**156**(6):923–9. doi: 10.1016/j.jpeds.2009.12.017. [PubMed: 20223481].
14. Bulum T, Duvnjak L. Insulin resistance in patients with type1 diabetes: relationship with metabolic and inflammatory parameters. *Acta Clin Croat*. 2013;**52**(1):43–51. [PubMed: 23837272].
15. Pozzilli P, Buzzetti R. A new expression of diabetes: double diabetes. *Trends Endocrinol Metab*. 2007;**18**(2):52–7. doi: 10.1016/j.tem.2006.12.003. [PubMed: 17208448].
16. Szadkowska A, Pietrzak I, Szlawska J, Kozera A, Gadzicka A, Mlynarski W. Abdominal obesity, metabolic syndrome in type 1 diabetic children and adolescents. *Pediatr Endocrinol Diabetes Metab*. 2009;**15**(4):233–9. [PubMed: 20455417].
17. Otto-Buczkowska E, Dryzalowski M. Metabolicsyndrome in youngpatients. *Pediatr Endocrinol Diabetes Metab*. 2015;**21**(1):32–6. doi: 10.18544/PEDM-21.01.0022. [PubMed: 26901043].
18. Luczynski W, Szypowska A, Bossowski A, Ramotowska A, Recko P, Rembinska M, et al. [Overweight, obesity and metabolic syndrome in children with type 1 diabetes melllitus]. *Pediatr Endocrinol Diabetes Metab*. 2010;**16**(2):83–8. [PubMed: 20813084].
19. Luczynski W, Szypowska A, Glowinska-Olszewska B, Bossowski A. Overweight, obesity and features of metabolic syndrome in children with diabetes treated with insulin pump therapy. *Eur J Pediatr*. 2011;**170**(7):891–8. doi: 10.1007/s00431-010-1372-7. [PubMed: 21140273].
20. Bode BW, Garg SK. The Emerging Role of Adjunctive Noninsulin Antihyperglycemic Therapy in the Management of Type 1 Diabetes. *Endocr Pract*. 2016;**22**(2):220–30. doi: 10.4158/EP15869.RA. [PubMed: 26484403].
21. Lebovitz HE. Adjunct therapy for type 1 diabetes mellitus. *Nat Rev Endocrinol*. 2010;**6**(6):326–34. doi: 10.1038/nrendo.2010.49. [PubMed: 20404854].
22. Otto-Buczkowska E, Machnica L. The perspectives of adjunctive drugs usage in the treatment of glucose metabolism disturbances in adolescent patients. *Pediatr Endocrinol Diabetes Metab*. 2009;**15**(4):260–5. [PubMed: 20455421].
23. Otto-Buczkowska E, Nowowiejska B, Jarosz-Chobot P, Stanczyk J. [Could oral antidiabetic agents be useful in the management of different types of diabetes and syndromes of insulin resistance in children and adolescents?]. *Przegl Lek*. 2009;**66**(7):388–93. [PubMed: 20043582].
24. Otto-Buczkowska E, Machnica L. The perspectives of adjunctive drugs usage in the treatment of glucose metabolism disturbances in adolescent patients. *Pediatr Endocrinol Diabetes Metab*. 2009;**15**(4):260–5.
25. Frandsen CS, Dejgaard TF, Madsbad S. Non-insulin drugs to treat hyperglycaemia in type 1 diabetes mellitus. *Lancet Diabetes Endocrinol*. 2016;**4**(9):766–80. doi: 10.1016/S2213-8587(16)00039-5. [PubMed: 26969516].
26. Gao YQ, Gao M, Xue Y. Treatment of diabetes in children. *Exp Ther Med*. 2016;**11**(4):1168–72. doi: 10.3892/etm.2016.3039. [PubMed: 27073417].
27. George P, McCrimmon RJ. Potential role of non-insulin adjunct therapy in Type 1 diabetes. *Diabet Med*. 2013;**30**(2):179–88. doi: 10.1111/j.1464-5491.2012.03744.x. [PubMed: 22804102].
28. Otto-Buczkowska E. Metformin addend to insulin therapy for type 1 diabetes mellitus - based on literature and own experience. *Medica Rev*. 2010;**8**:338–42.
29. Vella S, Buetow L, Royle P, Livingstone S, Colhoun HM, Petrie JR. The use of metformin in type 1 diabetes: a systematic review of efficacy. *Diabetologia*. 2010;**53**(5):809–20. doi: 10.1007/s00125-009-1636-9. [PubMed: 20057994].
30. Jacobsen IB, Henriksen JE, Beck-Nielsen H. The effect of metformin in overweight patients with type 1 diabetes and poor metabolic control. *Basic Clin Pharmacol Toxicol*. 2009;**105**(3):145–9. doi: 10.1111/j.1742-7843.2009.00380.x. [PubMed: 19496776].
31. Lund SS, Tarnow L, Astrup AS, Hovind P, Jacobsen PK, Alibegovic AC, et al. Effect of adjunct metformin treatment on levels of plasma lipids in patients with type 1 diabetes. *Diabetes Obes Metab*. 2009;**11**(10):966–77. doi: 10.1111/j.1463-1326.2009.01079.x. [PubMed: 19558610].
32. Abdelghaffar S, Attia AM. Metformin added to insulin therapy for type 1 diabetes mellitus in adolescents. *Cochrane Database Syst Rev*. 2009;(1). CD006691. doi: 10.1002/14651858.CD006691.pub2. [PubMed: 19160294].
33. Bacha F, Klinepeter Bartz S. Insulin resistance, role of metformin and other non-insulin therapies in pediatric type 1 diabetes. *Pediatr Diabetes*. 2016;**17**(8):545–58. doi: 10.1111/pedi.12337. [PubMed: 26592507].
34. Anderson J, Pena AS, Sullivan T, Gent R, D'Arcy B, Olds T, et al. Does metformin improve vascular health in children with type 1 diabetes? Protocol for a one year, double blind, randomised, placebo controlled trial. *BMC Pediatr*. 2013;**13**:108. doi: 10.1186/1471-2431-13-108. [PubMed: 23865839].
35. 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**:2241–50.
36. Ficek R, Chudek J, Wiecek A. *Cukrzyca w populacji wieku rozwojowego - co nowego?*. In: Otto-Buczkowska E, editor. Wroclaw; 2009. Blocking the re-absorption of glucose in the renal tubules as a new potential treatment for diabetes; p. 244–50.
37. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium-glucose transport: role in diabetes mellitus and potential clinical implications. *Kidney Int*. 2009;**75**(12):1272–7. doi: 10.1038/ki.2009.87. [PubMed: 19357717].
38. Bays H. From victim to ally: the kidney as an emerging target for the treatment of diabetes mellitus. *Curr Med Res Opin*. 2009;**25**(3):671–81. doi: 10.1185/03007990802710422. [PubMed: 19232040].
39. Idris I, Donnelly R. Sodium-glucose co-transporter-2 inhibitors: an emerging new class of oral antidiabetic drug. *Diabetes Obes Metab*. 2009;**11**(2):79–88. doi: 10.1111/j.1463-1326.2008.00982.x. [PubMed: 19125776].
40. Nair S, Wilding JP. Sodium glucose cotransporter 2 inhibitors as a new treatment for diabetes mellitus. *J Clin Endocrinol Metab*. 2010;**95**(1):34–42. doi: 10.1210/jc.2009-0473. [PubMed: 19892839].
41. Fioretto P, Giaccari A, Sesti G. Efficacy and safety of dapagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, in diabetes mellitus. *Cardiovasc Diabetol*. 2015;**14**:142. doi: 10.1186/s12933-015-0297-x. [PubMed: 26474563].
42. Henry RR, Rosenstock J, Edelman S, Mudaliar S, Chalamandaris AG, Kasichayanula S, et al. Exploring the potential of the SGLT2 inhibitor dapagliflozin in type 1 diabetes: a randomized, double-blind,

placebo-controlled pilot study. *Diabetes Care*. 2015;**38**(3):412–9. doi: 10.2337/dc13-2955. [PubMed: 25271207].
43. Lamos EM, Younk LM, Davis SN. Empagliflozin, a sodium glucose cotransporter 2 inhibitor, in the treatment of type 1 diabetes. *Expert Opin Investig Drugs*. 2014;**23**(6):875–82. doi: 10.1517/13543784.2014.909407. [PubMed: 24746173].
44. Pieber TR, Famulla S, Eilbracht J, Cescutti J, Soleymanlou N, Johansen OE, et al. Empagliflozin as adjunct to insulin in patients with type 1 diabetes: a 4-week, randomized, placebo-controlled trial (EASE-1). *Diabetes Obes Metab*. 2015;**17**(10):928–35. doi: 10.1111/dom.12494. [PubMed: 26080652].
45. Tamez HE, Tamez AL, Garza LA, Hernandez MI, Polanco AC. Dapagliflozin as an adjunct therapy to insulin in the treatment of patients with type 1 diabetes mellitus. *J Diabetes Metab Disord*. 2015;**14**:78. doi: 10.1186/s40200-015-0210-x. [PubMed: 26457255].
46. Tahara A, Kurosaki E, Yokono M, Yamajuku D, Kihara R, Hayashizaki Y, et al. Effects of sodium-glucose cotransporter 2 selective inhibitor ipragliflozin on hyperglycaemia, oxidative stress, inflammation and liver injury in streptozotocin-induced type 1 diabetic rats. *J Pharm Pharmacol*. 2014;**66**(7):975–87. doi: 10.1111/jphp.12223. [PubMed: 24533859].
47. 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**(1). e0147391. doi: 10.1371/journal.pone.0147391. [PubMed: 26807719].
48. Cherney DZ, Perkins BA. Sodium-glucose cotransporter 2 inhibition in type 1 diabetes: simultaneous glucose lowering and renal protection?. *Can J Diabetes*. 2014;**38**(5):356–63. doi: 10.1016/j.jcjd.2014.05.006. [PubMed: 25192954].
49. Cherney DZ, Perkins BA, Soleymanlou N, Maione M, Lai V, Lee A, et al. Renal hemodynamic effect of sodium-glucose cotransporter 2 inhibition in patients with type 1 diabetes mellitus. *Circulation*. 2014;**129**(5):587–97. doi: 10.1161/CIRCULATIONAHA.113.005081. [PubMed: 24334175].
50. Skrtic M, Cherney DZ. Sodium-glucose cotransporter-2 inhibition and the potential for renal protection in diabetic nephropathy. *Curr Opin Nephrol Hypertens*. 2015;**24**(1):96–103. doi: 10.1097/MNH.0000000000000084. [PubMed: 25470017].
51. Kitada K, Nakano D, Ohsaki H, Hitomi H, Minamino T, Yatabe J, et al. Hyperglycemia causes cellular senescence via a SGLT2- and p21-dependent pathway in proximal tubules in the early stage of diabetic nephropathy. *J Diabetes Complications*. 2014;**28**(5):604–11. doi: 10.1016/j.jdiacomp.2014.05.010. [PubMed: 24996978].
52. Vallon V, Gerasimova M, Rose MA, Masuda T, Satriano J, Mayoux E, et al. SGLT2 inhibitor empagliflozin reduces renal growth and albuminuria in proportion to hyperglycemia and prevents glomerular hyperfiltration in diabetic Akita mice. *Am J Physiol Renal Physiol*. 2014;**306**(2):F194–204. doi: 10.1152/ajprenal.00520.2013. [PubMed: 24226524].
53. Cherney DZ, Perkins BA, Soleymanlou N, Har R, Fagan N, Johansen OE, et al. The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc Diabetol*. 2014;**13**:28. doi: 10.1186/1475-2840-13-28. [PubMed: 24475922].
54. Peters AL, Buschur EO, Buse JB, Cohan P, Diner JC, Hirsch IB. Euglycemic Diabetic Ketoacidosis: A Potential Complication of Treatment With Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care*. 2015;**38**(9):1687–93. doi: 10.2337/dc15-0843. [PubMed: 26078479].
55. Handelsman Y, Henry RR, Bloomgarden ZT, Dagogo-Jack S, DeFronzo RA, Einhorn D, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Position Statement on the Association of Sglt-2 Inhibitors and Diabetic Ketoacidosis. *Endocr Pract*. 2016;**22**(6):753–62. doi: 10.4158/EP161292.PS. [PubMed: 27082665].
56. Mikhail N. Remogliflozin etabonate: a novel SGLT2 inhibitor for treatment of diabetes mellitus. *Expert Opin Investig Drugs*. 2015;**24**(10):1381–7. doi: 10.1517/13543784.2015.1061501. [PubMed: 26288025].
57. Sands AT, Zambrowicz BP, Rosenstock J, Lapuerta P, Bode BW, Garg SK, et al. Sotagliflozin, a Dual SGLT1 and SGLT2 Inhibitor, as Adjunct Therapy to Insulin in Type 1 Diabetes. *Diabetes Care*. 2015;**38**(7):1181–8. doi: 10.2337/dc14-2806. [PubMed: 26049551].
58. Biester T, Aschemeier B, Fath M, Frey M, Scheerer MF, Kordonouri O, 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**(11):1635–9. doi: 10.1111/dom.12975. [PubMed: 28417527].
59. Mietlicki-Baase EG. Amylin-mediated control of glycemia, energy balance, and cognition. *Physiol Behav*. 2016;**162**:130–40. doi: 10.1016/j.physbeh.2016.02.034. [PubMed: 26922873].
60. 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. *Diabetologia Doswiadczalna i Kliniczna*. 2009;**9**(2):41–0.
61. Edelman SV. Optimizing diabetes treatment using an amylin analogue. *Diabetes Educ*. 2008;**34 Suppl 1**:4S–10S. doi: 10.1177/0145721707313939. [PubMed: 18268000].
62. Otto-Buczkowska E, Mazur-Dworzecka U, Dworzecki T. [Role of amylin in glucose homeostasis and its perspective use in diabetes management]. *Przegl Lek*. 2008;**65**(3):135–9. [PubMed: 18624122].
63. Riddle MC, Yuen KC, de Bruin TW, Herrmann K, Xu J, Ohman P, et al. Fixed ratio dosing of pramlintide with regular insulin before a standard meal in patients with type 1 diabetes. *Diabetes Obes Metab*. 2015;**17**(9):904–7. doi: 10.1111/dom.12504. [PubMed: 26040429].
64. Huffman DM, McLean GW, Seagrove MA. Continuous subcutaneous pramlintide infusion therapy in patients with type 1 diabetes: observations from a pilot study. *Endocr Pract*. 2009;**15**(7):689–95. doi: 10.4158/EP09044.ORR1. [PubMed: 19546056].
65. Chase HP, Lutz K, Pencek R, Zhang B, Porter L. Pramlintide lowered glucose excursions and was well-tolerated in adolescents with type 1 diabetes: results from a randomized, single-blind, placebo-controlled, crossover study. *J Pediatr*. 2009;**155**(3):369–73. doi: 10.1016/j.jpeds.2009.03.012. [PubMed: 19464026].
66. Hassan K, Heptulla RA. Reducing postprandial hyperglycemia with adjuvant premeal pramlintide and postmeal insulin in children with type 1 diabetes mellitus. *Pediatr Diabetes*. 2009;**10**(4):264–8. doi: 10.1111/j.1399-5448.2008.00490.x. [PubMed: 19140902].
67. Kishiyama CM, Burdick PL, Cobry EC, Gage VL, Messer LH, McFann K, et al. A pilot trial of pramlintide home usage in adolescents with type 1 diabetes. *Pediatrics*. 2009;**124**(5):1344–7. doi: 10.1542/peds.2008-3750. [PubMed: 19858155].
68. Herrmann K, Frias JP, Edelman SV, Lutz K, Shan K, Chen S, et al. Pramlintide improved measures of glycemic control and body weight in patients with type 1 diabetes mellitus undergoing continuous subcutaneous insulin infusion therapy. *Postgrad Med*. 2013;**125**(3):136–44. doi: 10.3810/pgm.2013.05.2635. [PubMed: 23748514].
69. Herrmann K, Brunell SC, Li Y, Zhou M, Maggs DG. Impact of Disease Duration on the Effects of Pramlintide in Type 1 Diabetes: A Post Hoc Analysis of Three Clinical Trials. *Adv Ther*. 2016;**33**(5):848–61. doi: 10.1007/s12325-016-0326-5. [PubMed: 27071768].
70. Ramkissoon CM, Aufderheide B, Bequette BW, Palerm CC. A model of glucose-insulin-pramlintide pharmacokinetics and pharmacodynamics in type I diabetes. *J Diabetes Sci Technol*. 2014;**8**(3):529–42. doi: 10.1177/1932296813517323. [PubMed: 24876617].
71. Weinzimer SA, Sherr JL, Cengiz E, Kim G, Ruiz JL, Carria L, et al. Effect of pramlintide on prandial glycemic excursions during closed-loop control in adolescents and young adults with type 1 diabetes. *Diabetes Care*. 2012;**35**(10):1994–9. doi: 10.2337/dc12-0330. [PubMed: 22815298].
72. Younk LM, Mikeladze M, Davis SN. Pramlintide and the treatment of diabetes: a review of the data since its introduction. *Expert Opin Pharmacother*. 2011;**12**(9):1439–51. doi: 10.1517/14656566.2011.581663. [PubMed: 21564002].

73. Meier JJ, Nauck MA. Incretin-based therapies: where will we be 50 years from now?. *Diabetologia*. 2015;**58**(8):1745–50. doi: 10.1007/s00125-015-3608-6. [PubMed: 25994073].
74. Otto-Buczkowska E. *Cukrzyca w populacji wieku rozwojowego - co nowego?*. In: Otto-Buczkowska E, editor. 2009. Incretin action of certain hormones axis entero-pancreatic and their role in the metabolism of glucose; p. 61–8.
75. Hari Kumar KV, Shaikh A, Prusty P. Addition of exenatide or sitagliptin to insulin in new onset type 1 diabetes: a randomized, open label study. *Diabetes Res Clin Pract*. 2013;**100**(2):e55–8. doi: 10.1016/j.diabres.2013.01.020. [PubMed: 23490599].
76. Renukuntla VS, Ramchandani N, Trast J, Cantwell M, Heptulla RA. Role of glucagon-like peptide-1 analogue versus amylin as an adjuvant therapy in type 1 diabetes in a closed loop setting with ePID algorithm. *J Diabetes Sci Technol*. 2014;**8**(5):1011–7. doi: 10.1177/1932296814542153. [PubMed: 25030181].
77. Dejgaard TF, Knop FK, Tarnow L, Frandsen CS, Hansen TS, Almdal T, 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, placebo-controlled study: the Lira-1 study. *BMJ Open*. 2015;**5**(4). e007791. doi: 10.1136/bmjopen-2015-007791. [PubMed: 25838513].
78. Dejgaard TF, Frandsen CS, Hansen TS, Almdal T, Urhammer S, Pedersen-Bjergaard U, 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**(3):221–32. doi: 10.1016/S2213-8587(15)00436-2. [PubMed: 26656289].
79. Rizzo M, Rizvi AA, Sesti G. Cardiovascular effects of glucagon-like peptide-1 receptor agonist therapies in patients with type 1 diabetes. *Diabetes Obes Metab*. 2017;**19**(5):613–4. doi: 10.1111/dom.12883. [PubMed: 28098425].
80. Jung GS, Jeon JH, Choe MS, Kim SW, Lee IK, Kim MK, et al. Renoprotective Effect of Gemigliptin, a Dipeptidyl Peptidase-4 Inhibitor, in Streptozotocin-Induced Type 1 Diabetic Mice. *Diabetes Metab J*. 2016;**40**(3):211–21. doi: 10.4093/dmj.2016.40.3.211. [PubMed: 27098503].
81. Salheen SM, Panchapakesan U, Pollock CA, Woodman OL. The Dipeptidyl Peptidase-4 Inhibitor Linagliptin Preserves Endothelial Function in Mesenteric Arteries from Type 1 Diabetic Rats without Decreasing Plasma Glucose. *PLoS One*. 2015;**10**(11). e0143941. doi: 10.1371/journal.pone.0143941. [PubMed: 26618855].
82. Zhao Y, Yang L, Wang X, Zhou Z. The new insights from DPP-4 inhibitors: their potential immune modulatory function in autoimmune diabetes. *Diabetes Metab Res Rev*. 2014;**30**(8):646–53. doi: 10.1002/dmrr.2530. [PubMed: 24446278].
83. Giampietro O, Giampietro C, Bartola LD, Masoni MC, Matteucci E. Sitagliptin as add-on therapy in insulin deficiency: biomarkers of therapeutic efficacy respond differently in type 1 and type 2 diabetes. *Drug Des Devel Ther*. 2013;**7**:99–104. doi: 10.2147/DDDT.S38346. [PubMed: 23439744].
84. Underland LJ, Ilkowitz JT, Katikaneni R, Dowd A, Heptulla RA. Use of Sitagliptin With Closed-Loop Technology to Decrease Postprandial Blood Glucose in Type 1 Diabetes. *J Diabetes Sci Technol*. 2017;**11**(3):602–10. doi: 10.1177/1932296817699847. [PubMed: 28349708].
85. Schopman JE, Hoekstra JB, Frier BM, Ackermans MT, de Sonnaville JJ, Stades AM, et al. Effects of sitagliptin on counter-regulatory and incretin hormones during acute hypoglycaemia in patients with type 1 diabetes: a randomized double-blind placebo-controlled crossover study. *Diabetes Obes Metab*. 2015;**17**(6):546–53. doi: 10.1111/dom.12453. [PubMed: 25694217].