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Pharmacologic adjunctive to insulin therapies in type 1 diabetes: The journey has just begun

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Abstract

Treatment of type 1 diabetes (T1D) is currently based exclusively on insulin replacement therapy. However, there is a need for better glycemic control, lower hypoglycemia rates, more effective weight management, and further reduction of cardiovascular risk in people with T1D. In this context, agents from the pharmaceutical quiver of type 2 diabetes are being tested in clinical trials, as adjunctive to insulin therapies for T1D patients. Despite the limited amount of relevant evidence and the inter-class variability, it can be said that these agents have a role in optimizing metabolic control, assisting weight management and reducing glycemic variability in people with T1D. Specific safety issues, including the increased risk of hypoglycemia and diabetic ketoacidosis, as well as the effects of these treatments on major cardiovascular outcomes should be further assessed by future studies, before these therapeutic choices become widely available for T1D management.

Key words: Type 1 diabetes; Insulin; Adjunctive therapies; Cardiovascular risk

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Core tip: Adjunctive to insulin therapies in type 1 diabetes (T1D) may have a role in optimizing metabolic control, assisting weight management and reducing glycemic variability. Specific safety issues should be further assessed by future studies, before these therapeutic choices become widely available for T1D management.

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INTRODUCTION

Treatment of type 1 diabetes (T1D) is currently based exclusively on insulin replacement therapy, either by multiple daily injections (MDI) or *via* continuous subcutaneous insulin infusion ("insulin pumps") and closed-loop (also known as "artificial pancreas") insulin delivery systems. Whole pancreas and islet cell transplantations are alternative therapeutic options for carefully selected patients meeting specific eligibility criteria; still, these procedures are available only in a few number of specialized centers around the world, thus, being unavailable for the vast majority of people living with T1D^[1].

The idea of using agents from the pharmaceutical quiver of type 2 diabetes (T2D) as adjunctive to insulin therapies in T1D is not recent; back in 1985, Gin *et al*^[2], published their research on the effects of metformin on insulin sensitivity in patients with T1D and since then, a number of agents from different therapeutic classes have been tested in clinical trials. In the present article, we aim to discuss the rationale behind the use of adjunctive therapies in T1D, strengths and limitations of such an approach, as well as gaps in existing knowledge that deserve further evaluation by future research.

WHY IS THERE A NEED FOR ADJUNCTIVE THERAPIES IN T1D?

We live in the era of long- and short-acting insulin analogues (and the very recently introduced ultra-fast acting insulin analogues), which mimic physiological insulin release in a more effective way than human insulin, resulting in better metabolic control and lower hypoglycemia rates, as compared to the latter^[3]. Hence, what would adjunctive to insulin treatments contribute more to T1D management in everyday, clinical practice?

First, despite the progress been made during the past years, there is still an imperative need for better glycemic control in people with T1D. Results from a multi-centre, observational, cross-sectional study from Central and Eastern Europe (DEPAC Survey), involving more than 10000 individuals, proved that only 13.1% of T1D patients had glycated hemoglobin A_{1c} (HbA_{1c}) levels within target (< 6.5% / 47.5 mmol/mol)^[4]. Mean HbA_{1c} concentration among participants was 8.2% (66.1 mmol/mol), ranging from 7.7% (60.7 mmol/mol) to 9.8% (83.6 mmol/mol) among different countries.

Secondly, it is well established that people with T1D are in a greater risk of developing atherosclerotic disease, compared to the general population^[5]. Data from the United Kingdom General Practice Research Database (UK GPRD), indicate a hazard ratio for major cardiovascular disease (CVD) event (myocardial infarction, acute coronary heart disease death, coronary revascularizations, or stroke) of 3.6 (95%CI: 2.9-4.5) in men with T1D and of 7.7 (95%CI: 5.5-10.7) in women with T1D, compared to people without diabetes^[6]. Considering the impressive cardioprotective effects that specific agents used in T2D management have demonstrated in recent, randomized clinical trials^[7], it is reasonable to consider that these outcomes could be also applicable in T1D populations; however, this is something that remains to be proven by future research.

Thirdly, insulin resistance and adipose tissue inflammation as a result of increased body weight, are key components of T2D pathogenesis^[8]. A number of novel agents for T2D management, including glucagon-like peptide-1 (GLP-1) agonists and sodium-glucose co-transporter 2 (SGLT-2) inhibitors, exert optimal effects on body weight, through a variety of acting mechanisms^[9]. However, obesity is being increasingly recognized as a major health problem among people with T1D, as well. Results from a prospective study from the United States, where participants with T1D were being followed for a median of 18 years, demonstrated that overweight increased by 47% and the prevalence of obesity increased 7-fold during the above period, with 22.7% of people with T1D having body mass index (BMI) equal or greater to 30 kg/m²^[10], at the end of the study. In the same study, only seven percent of patients were on intensive insulin therapy (three or more daily insulin injections) at baseline (1986-1988), in contrast with the end of the follow-up period (2004-2007),

when this percentage reached 82%. Therefore, the aforementioned results could be attributed to the increasing rate of the adoption of a “Western” dietary model combined with poor physical activity by a significant proportion of the population worldwide, along with the intensification of insulin therapy during the last decades, which is known to positively correlate with weight gain^[11]. It is also known that weight, insulin resistance and CVD risk significantly interplay in people with diabetes. In a prospective cohort study following 603 patients with T1D for 10 years, classic insulin resistance-related factors, including dyslipidemia and waist-to-hip ratio, were found to predict future coronary artery disease events^[12], suggesting a strong need for effective management of traditional CVD risk factors, apart from T2D, in T1D as well.

There is data suggesting limitations in insulin availability and affordability in specific areas of the world, particularly for low-income patients^[13]. Reduction of insulin dose as a result of adjunctive therapies may prove helpful for those who consider insulin cost as a significant barrier to treatment adherence. Finally, there is no doubt that intensive compared to conventional glycemic control results in lower rates of both micro- and macro-vascular complications in individuals with T1D^[14]. However, this can be only achieved at a cost of increased incidence of hypoglycemia^[15], which is known to be related with cardiac dysrhythmias, CVD events and death^[16]. As a result, clinicians are often required to navigate “through stormy waters” and balance their clinical practice between intensive metabolic control and hypoglycemia, in a way that is not always easy.

AN OVERVIEW OF AVAILABLE EVIDENCE

Considering the above, there is an increasing amount of evidence suggesting that adjunctive to insulin treatments may assist glycemic control and weight management in T1D. Metformin has been shown to manifest optimal effects on BMI, total and low-density lipoprotein cholesterol concentrations, and total daily insulin dose (TDD), still not on HbA_{1c} which following a transient reduction during the first months of therapy, returns to its baseline values^[17]. The REMOVAL trial aimed to explore the effects of metformin on carotid intima media thickness (cIMT) in a sample of 428 T1D patients with multiple cardiovascular risk factors, aged over 40 years^[18]. Progression of mean cIMT was not significantly reduced with metformin, although maximal cIMT was significantly lower in the metformin group, as compared to placebo. Furthermore, metformin use has been linked to an increasing trend of the incidence of hypoglycemia^[19], a clue that requires further assessment by additional studies, particularly with the use of Continuous Glucose Monitoring systems. Overall, existing data do not support that metformin may improve glycemic control, though it might have a wider role in reducing CVD risk in people with T1D.

Dipeptidyl peptidase-4 (DPP-4) inhibitors have been tested in a very small numbers of trials and safe conclusions regarding these agents cannot be drawn. Their impact on glycemic control, seems to be non-significant^[20]; nevertheless, there is preliminary data indicating that sitagliptin might lower postprandial glucose levels in patients treated with a closed-loop system^[21] and preserve beta-cell function in individuals with slowly progressive T1D^[22]. In addition, DPP-4 inhibitors probably exert some important immunoregulatory actions^[23], thus, deserving further evaluation as adjunctive treatments in T1D or other autoimmune types of diabetes [Latent Autoimmune Diabetes in Adults (LADA), for example].

GLP-1 agonists have been demonstrated to significantly reduce HbA_{1c}, body weight and TDD (particularly bolus doses), when used in people with T1D^[24]. However, some studies raised concerns regarding their safety. In ADJUNCT ONE trial, 1398 patients with T1D were randomized to receive either liraglutide at varying doses or placebo, on top of insulin whose dose was adjusted according to a treat-to-target protocol over 52 wk^[25]. Symptomatic hypoglycemia was increased in all liraglutide groups as compared to placebo. Hyperglycemia with ketosis was more frequent in the group of patients receiving liraglutide at 1.8 mg, probably due to nausea related to its use and concomitant reduction of insulin dose. Similar reductions in HbA_{1c}, BMI and insulin dose have been observed with pramlintide, an injectable synthetic amylin analogue, being the only drug approved by the United States Food and Drug Administration, as an adjunctive to insulin therapy in T1D^[26]. Its use in everyday practice is limited by the fact that it should be subcutaneously administered three to four times a day before meals, being nonpractical for patients already on MDI regimens.

Probably, the most promising results in the field are coming from studies conducted with SGLT-2 inhibitors. These agents seem to contribute to better glycemic

control, lower body weight and insulin dose and most importantly, without increasing hypoglycemia rates^[27]. In addition, preliminary evidence suggests that they reduce glycemic variability^[28], a parameter that is being increasingly recognized to be related to the development of diabetic complications^[29]. On the other hand, a systematic review and meta-analysis of ten studies using SGLT-2 inhibitors on top of insulin in T1D, pointed towards an increased risk of diabetic ketoacidosis (DKA) in patients treated with these agents versus placebo^[27]. The review identified 16 incidents of both hyperglycemic and normoglycemic DKA in a total of 581 patients. Similar to the clinical experience from the use of SGLT-2 inhibitors in people with T2D, a consistent increase in the incidence of genital tract infections, particularly among females, has been documented in individuals with T1D, as well^[30]. As a result, gains and risks should be carefully balanced prior to the use of these drugs in everyday practice. **Table 1** summarizes the main advantages and pitfalls of the use of various therapeutic classes as adjunctive treatments in T1D.

A CRITICAL APPRAISAL OF RELEVANT STUDIES

The aforementioned results should be interpreted with caution, given that relevant data manifest specific weaknesses. First, the number of studies and patients involved is limited, rendering the extraction of definite conclusions challenging. Secondly, most of relevant studies have been designed to explore “conventional” outcomes, such as changes in HbA_{1c}, body weight and insulin dose. Data on glycemic variability, insulin resistance and oxidative stress markers are scarce, being inversely proportional to the significance that these parameters are gradually gaining, regarding their contribution to the development of diabetes complications.

Moreover, all of these studies are considering people with T1D as an homogenous group of patients, who will overall get - or not get - benefit from adjunctive therapies^[31]. It is well established that some people with autoimmune diabetes (either long-term T1D or LADA) share common pathophysiological and phenotypic features with T2D, thus, being difficult to draw the borderline between distinct diabetes types, in these cases^[32]. The need for individualized treatment approaches is emphatically highlighted by the paradigm of thiazolidinedione use in T1D; when pioglitazone was added on insulin in lean adolescents with T1D, it had no remarkable effect on glycemic control. In contrast, it resulted in a significant weight gain (+ 3.8 kg), as compared to placebo^[33]. Differently, rosiglitazone significantly decreased both HbA_{1c} and TDD, when it was administered in overweight subjects with T1D, where insulin resistance had an apparently important pathogenetic role in the development of metabolic disarrangement^[34].

Finally, trials with “hard” CVD end points in T1D populations are currently lacking, being necessary to clarify whether the remarkable effects of specific agents on CVD morbidity and mortality in people with T2D, can be translated to respective CVD benefits in people with T1D. **Table 2** summarizes the main limitations of available evidence on the use of various drugs as adjunctive treatments in T1D.

FUTURE CLINICAL RESEARCH STUDIES

Despite the initial enthusiasm for potential clinical implications of immunotherapy in T1D, research in the field has so far failed to prevent the onset or to reverse autoimmune diabetes^[35]. Stem cell therapies, immune ablation and standard immunosuppressants have been tested in several studies, nevertheless not being able to confirm the expectations derived from animal models, at least for the moment. Immune prevention strategies have tested low insulin doses and alternative administration routes (*e.g.*, oral insulin) to prevent diabetes in individuals at high risk of T1D, still showed no remarkable benefit^[36]. Studies using non-antigen specific immunosuppressive drugs demonstrated encouraging results in prolonging remission of T1D; however, at a cost of toxicity and side effects^[37]. Leptin might prove useful in suppressing glucagon concentrations^[38], but clinical benefits of its use in T1D should be further evaluated by clinical trials. As a result, safety and efficacy of these treatments in T1D remain an area for forthcoming studies.

CONCLUSION

In conclusion, despite the limitations of available evidence and the inter-class variability, adjunctive to insulin therapies may have a role in optimizing metabolic

Table 1 Advantages and pitfalls of the use of various therapeutic classes as adjunctive treatments in type 1 diabetes

Therapeutic class	Advantages	Pitfalls
Biguanides (metformin)	Optimal effects on body weight, lipid concentrations and insulin dose	Effect on HbA _{1c} not sustainable over time. Potentially greater risk of hypoglycemia
DPP-4 inhibitors	Immunoregulatory actions. Potential role in preserving beta-cell function. Good safety profile	Non-significant effect on HbA _{1c}
GLP-1 agonists	Significant reductions in HbA _{1c} , body weight and insulin dose (particularly bolus doses)	Greater risk of hypoglycemia and DKA
Amylin analogues (pramlintide)	FDA approved. Significant reductions in HbA _{1c} , body weight and insulin dose (particularly bolus doses)	It should be subcutaneously administered 3-4 times/d
SGLT-2 inhibitors	Optimal effects on HbA _{1c} , body weight, insulin dose and glycemic variability. They do not increase risk of hypoglycemia	Increased risk of DKA and genital tract infections
Thiazolidinediones	Reduction in HbA _{1c} and insulin dose in insulin-resistant T1D patients	Weight gain. Not effective in lean patients

HbA_{1c}: Glycated hemoglobin A_{1c}; DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; FDA: United States Food and Drug Administration; SGLT-2: Sodium-glucose co-transporter 2; T1D: Type 1 diabetes; DKA: Diabetic ketoacidosis.

control, assisting weight management and reducing glycemic variability in people with T1D. Specific safety issues, including the increased risk of hypoglycemia and DKA, as well as the effects of these treatments on major cardiovascular outcomes should be further assessed by future studies, before these therapeutic choices become widely available for T1D management. It seems that for both physicians and people with T1D, a fascinating journey to the land of pharmacologic adjunctive to insulin therapies has just begun.

Table 2 Main limitations of available evidence on the use of various drugs as adjunctive treatments in type 1 diabetes

Limitations of clinical trials	Small number of studies and patients involved
	Heterogeneity in study designs and explored outcomes
	“Conventional” outcomes explored: changes in HbA _{1c} , body weight and insulin dose. Data on glycemic variability, IR and OS markers are scarce
	Not taking into account the clinical heterogeneity of patients with T1D
	Trials exploring the effects of adjunctive treatments on “hard” CVD end points in T1D patients are currently unavailable

HbA_{1c}: Glycated hemoglobin A_{1c}; T1D: Type 1 diabetes; CVD: Cardiovascular disease; IR: Insulin resistance; OS: Oxidative stress.

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