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Review

Considerations for Initiating a Sodium-Glucose Co-Transporter 2 Inhibitor in Individuals with Type 2 Diabetes Using Insulin

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ABSTRACT

In order to meet and maintain glycemic control, pharmacological management of individuals with type 2 diabetes typically begins with metformin followed by the introduction of other oral antihyperglycemic agents as needed. In some patients, the aggressive and progressive degeneration of pancreatic β cell activity means insulin therapy will become a given. The need to routinely monitor blood glucose levels coupled with the undesirable effects associated with insulin—primarily hypoglycemia and weight gain—commonly contribute to physician and patient inertia. The new β-cell-independent sodium-glucose co-transporter 2 (SGLT2) inhibitors are approved for combination use with all of the currently approved oral and injectable antihyperglycemic classes. The addition of SGLT2 inhibitors to background insulin therapy has the potential to afford many benefits and, in some cases, may reduce the incidence of insulin-associated side effects. This article reviews the available literature on SGLT2 inhibitor-insulin combination therapy and underscores the issues that should be considered prior to introducing SGLT2 inhibitors to individuals with type 2 diabetes who are already on insulin (with or without other antihyperglycemic agents) to ensure individualization of therapy.

Mots clés :
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RÉSUMÉ

Pour que les individus atteints du diabète de type 2 atteignent des valeurs glycémiques cibles et les maintiennent, la prise en charge pharmacologique commence généralement par la metformine, et se poursuit par l'introduction d'autres antihyperglycémiants oraux si nécessaire. Chez certains patients, la dégénération agressive et progressive de l'activité des cellules β du pancréas signifie que l'insulinothérapie sera inévitable. La nécessité de surveiller systématiquement les concentrations de la glycémie et les effets indésirables associés à l'insuline—principalement l'hypoglycémie et le gain de poids—contribue généralement à l'inertie du médecin et du patient. Les nouveaux inhibiteurs du cotransporteur sodium-glucose de type 2 (SGLT2) dont l'action est indépendante des cellules β sont approuvés pour une utilisation combinée avec toutes les classes d'antihyperglycémiants oraux et injectables actuellement approuvés. L'ajout des inhibiteurs du SGLT2 à l'insulinothérapie de fond a le potentiel d'offrir plusieurs avantages et, dans certains cas, peut réduire la fréquence des effets secondaires associés à l'insuline. Le présent article passe en revue la littérature actuelle sur le traitement combiné par insuline et inhibiteurs du SGLT2, et souligne les questions à considérer avant l'introduction des inhibiteurs du SGLT2 chez les individus atteints du diabète de type 2 qui prennent déjà de l'insuline (avec ou sans autres antihyperglycémiants) pour s'assurer de l'individualisation du traitement.

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Introduction

Most individuals with type 2 diabetes will experience deterioration of glycemic control over time and may eventually require insulin therapy (1, 2) to achieve and maintain the generally recommended glycated hemoglobin (A1C) target of <7.0% (3–7). Insulin is an effective glucose-lowering medication, and earlier use of insulin in the United Kingdom Prospective Diabetes Study was associated with a decrease in diabetes complications (8, 9). Despite this body of evidence, clinical inertia and reluctance around insulin use persist in part because of concerns around hypoglycemia and weight gain (10, 11). That said, data from the recent Diabetes Mellitus Status in Canada study suggest that some family physicians and patients with type 2 diabetes may be becoming more comfortable with using insulin (12). Notwithstanding the use of insulin and aggressive targets for glucose levels, many individuals initiating use of insulin do not achieve or maintain their A1C targets (13, 14).

The sodium-glucose co-transporter 2 (SGLT2) inhibitors are a newer class of antihyperglycemic agents that competitively inhibit SGLT2 in the proximal tubule, thereby reducing glucose reabsorption and promoting glucosuria (15, 16). Given their unique beta-cell–independent mechanism of action, SGLT2 inhibitors can be used along the entire type 2 diabetes continuum and may be combined with any of the currently approved oral and injectable antihyperglycemic classes (3–7).

This paper provides a review of the literature that has addressed the addition of SGLT2 inhibitors to individuals with type 2 diabetes already taking insulin, either alone or in combination with other antihyperglycemic agents. It also suggests potential issues to consider before introduction of SGLT2 inhibitors to insulin regimens to ensure appropriate personalization of therapy.

Rationale for the addition of an SGLT2 inhibitor to background insulin

The side effects of insulin are usually the reason it is often considered the “last resort” in glycemic control by many clinicians. However, the combination of an insulin with a non-insulin antihyperglycemic agent, such as an SGLT2 inhibitor, can afford several potential advantages without compromising glycemic efficacy (Table 1). Specifically, there is the potential to use fewer insulin injections and reduce insulin doses (17–19), improve glycemic control with a lower daily insulin requirement (18–28), produce weight loss or mitigate weight gain (17–21, 23–33), lower blood pressure (23–25, 28, 32, 33) and, in some cases, reduce the risk of hypoglycemia (23, 25, 29–31).

The concept of combining SGLT2 inhibitors with insulin is particularly attractive, given that SGLT2 inhibitors work independently from insulin, do not stimulate insulin secretion from the beta-cells and, therefore, may be associated with fewer concerns around hypoglycemia or lack of efficacy during the later stages of the disease (34, 35). Meta-analyses and individual clinical trials with cohorts receiving background insulin have revealed that SGLT2 inhibitors may also exert other potential benefits, such as blood pressure lowering (23–25, 28, 32, 33) and weight loss (18, 19, 23–28, 32, 33) without appreciably increasing the risk of hypoglycemia (18, 19), a common feature of insulin intensification. Of note, in a meta-analysis of 5 SGLT2 inhibitor and 9 dipeptidyl peptidase-4 inhibitor randomized controlled trials, investigators reported that SGLT2 inhibitor–insulin regimens were associated with greater glycemic and weight benefits than dipeptidyl peptidase-4 inhibitor–insulin combinations (18). Given the results of the EMPAgliflozin Removal of Excess of Glucose OUTCOME trial (36), in which half of subjects were taking insulin, use of combination therapies that involve the pairing of insulin with an SGLT2 inhibitor is likely to increase among comparable populations in clinical practice.

Three SGLT2 inhibitors are currently approved for use in combination with insulin in Canada—canagliflozin, dapagliflozin and empagliflozin. The therapeutic potential of all 3 SGLT2 inhibitors for individuals who have type 2 diabetes that is inadequately managed with insulin has been studied and continues to be evaluated under different conditions (23–28, 32). The primary outcome measurement in these studies has generally been the change in A1C from baseline, and secondary outcomes have included temporal changes in A1C, fasting plasma glucose, body weight, blood pressure and lipids, as well as frequencies of hypoglycemic episodes, genitourinary events and fractures. Table 2 summarizes the key findings from completed studies on the efficacy and safety of SGLT2 inhibitors in individuals treated with insulin. Based on the results of these studies, the Canadian product monographs of all 3 SGLT2 inhibitors include labels for use in various insulin regimens (37–39).

Canagliflozin

The CANagliflozin CardioVascular Assessment Study (CANVAS) is a recently completed multinational, phase III, double-blind, placebo-controlled trial that evaluated the cardiovascular safety of canagliflozin (100 and 300 mg once daily [QD]) in individuals ≥30 years old with type 2 diabetes who are at high risk for cardiovascular disease and whose diabetes is inadequately managed (A1C ≥7.0% to ≤10.5%) with their current antihyperglycemic regimen (ClinicalTrials.gov NCT01032629) (40). The insulin substudy from CANVAS included 2072 individuals who at baseline were using ≥20 IU of insulin per day (24). During the first 18 weeks, insulin doses were maintained to ensure stable background therapy, and glycemic rescue was only permitted per prespecified criteria. At week 18, both doses of canagliflozin were associated with appreciable reductions in cardiometabolic risk factors (A1C, blood pressure, weight, high-density lipoprotein cholesterol), and these positive effects were sustained up to week 52 (Table 1). The insulin+metformin substudy of CANVAS, which evaluated 432 individuals who were using ≥30 IU or insulin per day and ≥2000 mg of metformin per day at baseline, recently demonstrated significant decreases in A1C, body weight and systolic blood pressure 18 weeks into the study (33). Of note, the incidence of hypoglycemia was balanced across the groups with low rates of severe hypoglycemia (46%/3%, 42%/1% and 47%/2% for total/severe hypoglycemia for placebo, canagliflozin 100 mg QD and canagliflozin 300 mg QD trial arms, respectively).

A recent 16-week study enrolled Japanese adults ≥20 years old with type 2 diabetes and A1C ≥7.5% to ≤10.5% while using a variety of insulin therapies (8 to 60 IU/day) (ClinicalTrials.gov NCT02220920) (32). Although the overall findings of this study echoed those of the CANVAS insulin substudy (Table 1), the change in A1C from baseline for the canagliflozin 100 mg QD group was nearly double that

Table 1
Potential reasons for the addition of an SGLT2 inhibitor to insulin treatment for an individual with type 2 diabetes

To improve glycemic control
To reduce the risk of cardiovascular disease and mortality
To reduce the risk of hospitalization for heart failure
To promote weight loss
To lower blood pressure
To discontinue 1 or more of the ongoing antihyperglycemic agents
To discontinue or decrease the number of insulin (basal or bolus) units and/or injections
To delay initiation of bolus insulin
To lower the risk of hypoglycemia
To reduce the risk of chronic kidney disease

SGLT2, β-cell-independent sodium-glucose co-transporter 2.
Note: There may be more than 1 reason, and reasons are not listed in any particular order.