Can J Diabetes 38 (2014) 356–363

Contents lists available at ScienceDirect

Canadian Journal of Diabetes

journal homepage: www.canadianjournalofdiabetes.com

Review

Sodium-Glucose Cotransporter 2 Inhibition in Type 1 Diabetes: Simultaneous Glucose Lowering and Renal Protection?

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ARTICLE INFO

Article history:
Received 4 March 2014
Received in revised form
30 April 2014
Accepted 9 May 2014

Keywords:
blood pressure
hemodynamic function
hyperfiltration
hyperglycemia
renin-angiotensin-aldosterone system
SGLT2 inhibition
tubuloglomerular feedback
type 1 diabetes

ABSTRACT

Diabetic nephropathy is the most common cause of end-stage renal disease requiring chronic dialysis or renal transplantation, resulting in high morbidity, mortality and societal costs to Canadians. Unfortunately, glycemic targets are often not achieved, and existing medications that block the renin-angiotensin-aldosterone system only offer partial protection against the development of renal and cardiovascular complications. As a consequence, in type 1 diabetes mellitus, 20% of patients treated with angiotensin-converting enzyme inhibition still have progressive nephropathy over 10 years. More recent work has suggested that blockade of renal sodium-glucose cotransport-2 (SGLT2) improves glycemic control and also reduces blood pressure, suggesting a potential for protective effects. Furthermore, in patients with type 1 diabetes, we have shown that SGLT2 inhibition reduces hyperfiltration, which is a risk factor for diabetic kidney disease and vascular dysfunction. Because primary prevention with renin-angiotensin-aldosterone system blockers have been ineffective in type 1 diabetes, early intervention studies that target alternative pathogenic mechanisms are of the utmost importance. SGLT2 inhibition may represent a safe, novel therapy that simultaneously reduces hyperglycemia, hyperfiltration and blood pressure, leading to renal and cardiovascular protection.

Mots clés :
pression artérielle
fonctionnement hémodynamique
hyperfiltration
hyperglycémie
système rénine-angiotensine-aldostérone
inhibition du SGLT2
rétroaction tubuloglomérulaire
diabète de type 1

RÉSUMÉ

La néphropathie diabétique, la cause la plus fréquente d'insuffisance rénale terminale, nécessite la dialyse à répétition ou la transplantation rénale entraînant une morbidité, une mortalité et des coûts sociaux élevés chez les Canadiens. Malheureusement, les cibles glycémiques sont rarement atteintes et les médicaments actuels qui bloquent le système rénine-angiotensine-aldostérone n'offrent seulement qu'une protection partielle contre l'apparition des complications rénales et cardiovasculaires. Par conséquent, lors de diabète sucré de type 1, 20 % des patients traités par l'inhibition de l'enzyme de conversion de l'angiotensine ont immuablement une néphropathie évolutive depuis plus de 10 ans. De plus récents travaux ont suggéré que le blocage du cotransporteur sodium glucose de type 2 (SGLT2) améliore la régulation glycémique et réduit également la pression artérielle, ce qui indique un potentiel d'effets protecteurs. De plus, chez les patients souffrant du diabète de type 1, nous avons montré que l'inhibition du SGLT2 réduit l'hyperfiltration, un facteur de risque de néphropathie diabétique et de dysfonctionnement vasculaire. Puisque la prévention primaire à l'aide des bloqueurs du système rénine-angiotensine-aldostérone ont été inefficaces lors de diabète de type 1, des études sur l'intervention précoce qui ciblent les autres mécanismes pathogéniques sont de la plus grande importance. L'inhibition du SGLT2, un nouveau traitement qui réduit simultanément l'hyperglycémie, l'hyperfiltration et la pression artérielle, s'avérerait sûre, et entraînerait une protection rénale et cardiovasculaire.

Introduction

In the effective management of type 1 diabetes mellitus, there exists a need to simultaneously meet glycemic targets while also targeting other factors that promote the development of complications. Intensive insulin therapy, the standard of care for glycemic control in type 1 diabetes, has profound beneficial effects on glycemia and complications risk that are marred by the amplification of weight gain and hypoglycemia. Novel consideration of adjunctive to insulin therapies—such as the coadministration of oral sodium-glucose cotransporter 2 (SGLT2) inhibitors—have the potential to improve glycemic control without dramatically

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1499-2671/$ – see front matter © 2014 Canadian Diabetes Association
http://dx.doi.org/10.1016/j.jcjd.2014.05.006

increasing hypoglycemia risk, while independently having salutary effects on weight, blood pressure and other metabolic parameters. Specifically, SGLT2 overactivity in diabetes has the problematic consequence of augmented glucose and sodium (Na) reabsorption by the nephron's proximal tubular epithelial cells, which has 2 fundamental pathological effects: first, it maintains systemic hyperglycemia as a mechanism against osmotic diuresis of glucose; and second, the consequent decrease in distal tubular epithelium sodium delivery promotes renal hemodynamic dysfunction. This review places into context the early research findings of SGLT2 inhibition specifically in type 1 diabetes by describing the rationale and key research findings for its role, first, in the management of glycemic control and, second, for its role in renal protection.

Physiology of SGLT2 in Health and Disease

The precursor compound of modern SGLT2 inhibitors, phlorizin, was isolated from the bark of apple trees by French chemists in 1835 (1). Investigators subsequently observed that, similar to the signs and symptoms of diabetes in humans, phlorizin induced polyuria, polydipsia, polyphagia and weight loss in animals (2). Subsequent human studies demonstrated that phlorizin increases glycosuria in healthy persons (3). However, phlorizin is a nonspecific inhibitor of both SGLT1 and SGLT2 (2). As a consequence of SGLT1 inhibition, phlorizin also blocks intestinal glucose absorption, causing carbohydrate malabsorption, bacterial fermentation, gas and abdominal pain, which prevented further use of phlorizin in humans (2).

Subsequent modification of the chemical structure of phlorizin to produce C-aryl glycosides resulted in the development of selective inhibitors, which act in the proximal renal tubule to competitively inhibit sodium-glucose cotransport (4). SGLT2 is a high-capacity, low-affinity transporter located in the S1 and S2 segments of the proximal tubule responsible for 90% of glucose reabsorption in the kidney, whereas SGLT1 is a low-capacity, high-affinity transporter responsible for the remaining 10% in the S3 segment (5).

As reviewed elsewhere, SGLT2 has been estimated to be responsible for only 5% of total renal Na^+ reabsorption under steady-state conditions in nondiabetes experimental models based on isolated renal micropuncture studies (6). However, in the context of hyperglycemia, the contribution of SGLT2 to renal Na^+ reabsorption has been shown to be enhanced. Specifically, mRNA expression of SGLT2 and SGLT1 was increased by >20% in experimental models (6). Consequently, SGLT1/2 activity accounts for as much as 14% of total renal Na^+ reabsorption in the setting of experimental diabetes (7), as compared with the 5% observed in controls. These findings were calculated based on the assumption that plasma Na^+ concentration is 140 mmol/L, and that the total proximal reabsorption of Na^+ (including that mediated by SGLT1/2, net Na^+ mass movement and Na^+-hydrogen exchange) is 75% of the filtered load in control rats and 85% in diabetic rats (8). This increased proximal reabsorption leads to 4 physiological consequences: 1) a marked reduction in distal Na^+ delivery to the macula densa; 2) downregulation of tubuloglomerular feedback; 3) vasodilation of afferent arterioles, and 4) the glomerular hyperfiltration characteristic of diabetes (8,9).

From a therapeutic perspective, because of the marked increase in SGLT2 activity in diabetes, SGLT2 inhibition results in profound glycosuric responses (80 to 110 g per day) in type 2 diabetes (10) and type 1 diabetes (11–14). Experimental and human studies have taken advantage of the insulin-independent mechanism of action of SGLT2 inhibition to improve glycemic control and induce weight loss, primarily in type 2 diabetes (10). Animal studies and our pilot study in humans have also demonstrated positive effects on glycemic control, weight and arterial stiffness in type 1 diabetes (12,14,15). In addition to effects on glucose control, SGLT2 inhibition lowers blood pressure in patients with type 1 diabetes and type 2 diabetes, possibly because of diuretic effects and improved arterial compliance (12,13), as will be discussed in detail.

Based on these effects, clinical studies with SGLT2 inhibition in type 2 diabetes have focused on blood pressure and glucose lowering. However, SGLT2 inhibition also has potential renal protective effects in diabetes, possibly through modulation of tubuloglomerular feedback, thereby causing afferent vasoconstriction and reduced hyperfiltration in animals and humans (13,16). Therefore, based on a unique, insulin-independent mechanism of action, SGLT2 inhibition has the potential to improve both renal and glycemic outcomes in type 1 diabetes.

Inhibition of SGLT2 Glycemic Control in Type 1 Diabetes

Urgent need to determine novel approaches to address the problem of long-term adherence to glycemic control

Despite clear beneficial advances in insulin formulation and delivery—such as the development of basal and bolus insulin analogues, continuous subcutaneous insulin infusion and continuous glucose monitoring systems—patients with type 1 diabetes commonly fail to achieve optimal metabolic targets for preventing risk of complications (17,18). Although several factors may explain this gap between clinical research and practice, the fundamental barriers to successful intensification of insulin therapy are the risk and fear of hypoglycemia and weight gain (17,19). It is of critical importance to develop new therapies that improve glycemic control in patients with type 1 diabetes while simultaneously addressing the risk of hypoglycemia and weight gain and their negative metabolic consequences.

Glycemic strategies using adjunctive-to-insulin therapy

A number of strategies have recently been tested—or are being tested—in randomized controlled trials of adjunctive-to-insulin therapies to help address this need (20). These include metformin therapy (21), thiazolidinediones (22), alpha-glucosidase inhibitors (23) and incretin therapies, which include amylin analogues (24,25) dipeptydil peptidase-4 (DPP-4) inhibitors (26) and glucagon-like peptide-1 (GLP-1) receptor agonists (27,28).

Substantial insulin dose reductions and putative effects on cardiovascular risk attributable to adjunctive-to-insulin metformin therapy have been observed in several studies and summarized in systematic review (21). Owing to these findings, the clinical impact of metformin is currently being pursued in a multicentre clinical trial (Reducing With Metformin Vascular Adverse Lesions in Type 1 Diabetes [REMOVAL], www.clinicaltrials.gov NCT01483560) investigating the effect of 3 years of metformin therapy on a cardiovascular disease surrogate, carotid intimal media thickness, in 500 overweight subjects. Alpha-glucosidase inhibitor trials have shown modest glycated hemoglobin (A1C) reductions in subjects with type 1 diabetes (23), whereas trials of insulin sensitization by way of thiazolidinediones have implied concerns over adverse effects such as edema, weight gain and possible accelerated decline of insulin production (22,29). Amylin analogue therapy with subcutaneously administered pramlintide has long been approved by the US regulatory authority. A 1-year double-blind, placebo-controlled, randomized clinical trial involving 480 subjects with type 1 diabetes demonstrated substantial benefits for glycemic control and weight reduction (24), but it should be noted that in postmarketing monitoring, hypoglycemia risk arose as a concern that may have limited its systematic adoption into clinical practice.

Although the effect on glycemic control by way of incretin-based therapy with the DPP-4 inhibitors may be modest, the effect in