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Review

Are SGLT2 inhibitors joining the mainstream therapy for diabetes type 2?

Mortaza F. Hassanabad [a,*], Zahra F.H. Abad [b]

[a] Faculty of Science, 11455 Saskatchewan Drive, University of Alberta, Edmonton, Alberta, T6G 2E9, Canada
[b] Department of Internal Medicine, Emam-Zamaan Hospital, Mashhad, Iran

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ABSTRACT

Background: Conventional therapies to prevent type 2 diabetes mellitus (T2DM) complications are only partially effective. Therefore, new therapeutic approaches leading to additional risk reduction are required. While many anti-diabetic medications have been prescribed world-wide for controlling T2DM over the past half-century, sodium-glucose co-transporter-2 (SGLT2) inhibitors are relatively new. In addition to their plasma glucose lowering effect, SGLT2 inhibitors have been shown to reduce considerably cardiovascular mortality rate in patients with T2DM.
Aim: Since, a risk and benefit analysis of co-administration of SGLT2 inhibitors and other anti-diabetic agents in patients who suffer from hypertension, heart failure or renal deficiency is currently lacking, the main objective of this article is to review the recent literature and provide the health care professionals with evidence-based opinions on the subject.
Conclusion: SGLT2 inhibitors have relatively safe profiles and can efficiently decrease HbA1c as well as fasting and postprandial glucose levels. Furthermore, SGLT2 inhibitors administrations are not associated with significant hypoglycemic episodes or weight gain. Thus, combination of SGLT2 inhibitors and other less harmful anti-diabetic medicines could be considered if there is no any contraindication.

1. Introduction

Controlling hyperglycemia in patients with type 2 diabetes mellitus (T2DM) is still a challenging task for clinicians and patients, and the continuous rise in its prevalence has strained healthcare systems around the world and prompted the search for therapies that not only effectively treat hyperglycemia, but are also devoid of serious side effects associated with conventional anti-diabetic medications such as hypoglycemia, weight gain and cardiac toxicity. Although, majority of physicians may believe that lifestyle changes and metformin are the first steps to initiate lowering blood glucose levels, these interventions in some subjects may not be tolerated or efficacious. Now it is well established that among those who have initial success with metformin for reducing HbA1c, a high percentage eventually need add-on therapy to achieve the clinical objectives [1–3].

Sodium-glucose co-transporter-2 (SGLT2) inhibitors (e.g. canagliflozin, dapagliflozin and empagliflozin) are used to lower blood glucose level of patients suffering from T2DM by preventing its re-absorption in the renal proximal tubule leading to an increased urinary glucose excretion [4,5]. The most common side effect of these agents is urinary tract infection which is attributed to high glucose concentration in urine [6]. There is evidence supporting SGLT2-inhibitor therapy is associated with weight loss and decreasing blood pressure [7]. In particular, empagliflozin has been shown to decrease mortality in patients suffering from T2DM and cardiovascular disease [8,9]. On the other hand, many studies have shown that metformin is beneficial for obese patients [10,11]. Since hypertension is a common comorbidity in patients with obesity and T2DM, and is associated with higher mortality [12,13], over the past decades attempts have been made to establish protocols which can be used to avoid or at least to control and manage these pathological conditions [14,15]. A meta-analysis of 41 studies concluded that beneficial effect of metformin on high blood pressure was not significant [16]. Based on several clinical observations, it has been suggested that following a failure of a monotherapy with metformin, a SGLT2 inhibitor could be more suitable alternative to the add-on of a sulphonylurea, especially in diabetic patients at risk of

* Corresponding author.
E-mail addresses: mortaza@ualberta.ca, f_mortaza@yahoo.com (M.F. Hassanabad).

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hypoglycaemia [17–19]. In an obese patient suffering from hypertension or hyperuricaemia, antecedents of cardiovascular disease (especially heart failure), without advanced renal insufficiency or conditions related to dehydration such as hypotension, SGLT2 inhibitors seem to be of greater value [20].

In this review, current perspectives on clinical efficacy and safety in combination pharmacotherapy of SGLT2 inhibitors with other anti-diabetic agents will be presented.

2. Risks and Cautions

A recent clinical observation reported a case of advanced dehydration and acidosis in an elderly patient taking metformin and a SGLT2 inhibitor [21]. It has been suggested that occurrence of these conditions, namely, lactic acidosis and dehydration, could be due to decreased function of kidney and diarrhea in addition to glycosuria resulted from SGLT2 inhibitor administration in geriatric populations. These phenomena should be considered as major concerns when older patients are treated with a combination of a SGLTI and metformin [21].

Furthermore, mycotic genital infections are considered to be the most common adverse effect of SGLT2 inhibitors [22]. More importantly, although very rare but very serious cases of gangrene have been reported recently to be associated with use of empagliflozin [23,24].

Another important clinical point to consider is that all SGLT2 inhibitors are contraindicated when eGFR <45 mL/min/1.73 m^2. This means that administration of these medications in patients with T2DM and concomitant chronic kidney disease (CKD) should be decided with great care and close monitoring [25]. Nonetheless, several cohorts concluded that the SGLT2 inhibitors including canagliflozin and empagliflozin were potentially beneficial in reducing risk for some adverse renal and cardiovascular events [3,26,27].

3. Benefits

3.1. Lowering blood glucose

A clinical trial performed to evaluate the effects of canagliflozin on plasma volume, urinary glucose excretion (UGE), fasting plasma glucose (FPG) and glycated haemoglobin (HbA1c) demonstrated that 300 mg/day of this medication increased 24-h UGE and decreased both FPG and HbA1c along with a reduction in blood pressure. These effects of canagliflozin were significant compared to placebo effects [28]. All other clinically approved SGLT2 inhibitors share similar lowering blood glucose property [29].

Based on supportive clinical evidence, recently some experts suggested that in case of a monotherapy- or double treatment-resistant diabetes which resulted in a failure of achieving glycated haemoglobin target, a SGLT2 inhibitor might be considered as an add-on prior to prescription of injection of insulin [30].

3.2. Lowering blood pressure

Administration of SGLT2 inhibitors may provide modest reduction of hemoglobin A1C. There is accumulating evidence supporting the hypothesis of SGLT2 inhibitors would lower systolic and diastolic blood pressure. However, the mechanisms of actions by which these agents exert their beneficial effects on cardiovascular function are not understood. Although risk of volume depletion and acute kidney injury as adverse effects have been taken seriously, SGLT2 inhibitors are believed to be viable second-line glucose-lowering agents for people with T2DM [31,32].

A recent article reviewed data on the effect of SGLT2 inhibitors on blood pressure in patients with T2DM [33]. A recent meta-analysis also concluded that a decrease in 24-h ambulatory blood pressure induced by SGLT2 inhibitors was significant and attributed to all members of this group of medications [3,34].

It has been suggested that lowering blood pressure property of SGLT2 inhibitors could be linked to factors such as osmotic diuresis, SGLT2 inhibitor-associated reductions in body weight and less arterial rigidity. Some proposed that local inhibition of the renin-angiotensin-aldosterone system secondary to elevated sodium delivery to the juxtaglomerular apparatus during SGLT2 inhibition may also contribute to their blood pressure lowering effect. Based on this concept, it has been postulated that even subtle reduction in systolic and diastolic blood pressure could be considered as advantages of SGLT2 inhibitors for patients with T2DM [33].

3.3. Nephroprotection

Some recent studies suggest that SGLT2 inhibitors are potentially nephroprotective because of their glucose-lowering effects and also through their renal hemodynamic effects which mainly are glucose-independent phenomena [7,35,36].

Furthermore, since diabetic nephropathy is a significant cause of end-stage renal disease worldwide, and controlling blood glucose and blood pressure could reduce the risk of developing this complication, search for medicines with favorable profiles such as nephroprotection and lowering blood pressure has become a major theme in modern pharmaco-therapeutics. Some investigations demonstrated that SGLT2 inhibitors reduced glomerular hyperfiltration in T2DM patients, and transiently decreased glomerular filtration rate. However, this effect was followed by a progressive recovery and stabilization of renal function [35,37]. Moreover, some studies have shown a reduction in albuminuria in patients treated with SGLT2 inhibitors [9,38,39].

It is expected that prospective randomised long-term clinical trials on larger populations with T2DM, using robust renal end points, will elucidate whether SGLT2 inhibitors, in addition to their well-recognised effects of glycemia and attenuated blood pressure, provide beneficial effects manifested by prevention of the development and or slowing down progression of diabetic nephropathy.

3.4. More favorable in heart failure

It is generally accepted that T2DM and heart failure (HF), either with reduced or preserved ejection fraction, occur together frequently (30–40% of patients) and the combination of these pathologic conditions is associated with a higher risk of hospitalization, all-cause and cardiovascular mortality. The European Society of Cardiology recently have made a position statement concluding that neither glucagon-like preptide-1 (GLP-1) receptor agonists, nor dipeptidyl peptidase-4 (DPP4) inhibitors reduce the risk for HF hospitalization [40].

Considering the fact that use of some dipeptidyl peptidase-4 (DPP4) inhibitors such as saxagliptin, has been associated with a higher risk of HF hospitalization, SGLT2 inhibitors, including empagliflozin and canagliflozin, are becoming attractive add-on therapy for T2DM patients with established cardiovascular disease or at risk of cardiovascular disease [40,41].

Although thiazolidinediones are associated with lowering blood pressure, but are contraindicated in patients with heart failure [32,40,42]. Sulfonylureas are known to be cardiotoxic and could elevate blood pressure [16,43]. Thus, SGLT2 inhibitors seem to be preferable medications to be combined with metformin and GLP-1 receptor agonists [3,44,45].

In an attempt to evaluate the magnitude of effect of SGLT2 inhibitors on specific cardiovascular and renal outcomes, a meta-analysis of randomised, placebo-controlled, cardiovascular

outcome trials of these medications in patients with type 2 diabetes has been performed very recently [46]. Based on their findings, the authors of this systematic review concluded that SGLT2 inhibitors administrations provided moderate protection against major adverse cardiovascular events that appeared to be restricted to patients with established atherosclerotic cardiovascular disease. Nonetheless, SGLT2 inhibitors were found to exert robust effects on deceasing hospitalization rate for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure [47]. Several other cohort investigations suggest a similar net protection of SGLT2 inhibitors against cardiovascular outcomes and death [16,47–52]. Although the efficacy results have been driven by findings for empagliflozin (the only SGLT2 inhibitor for which a dedicated long-term cardiovascular safety trial has been undertaken [53–55]), results for the other drugs in the class did not seem clearly different [56–63]. More double-blind and controlled prospective clinical observations are required to confirm these findings across the drug class. Nevertheless, current information provide a strong rationale for expecting advantageous effects from SGLT2 inhibitors in patients with type 2 diabetes at higher risks of cardiovascular complications.

4. CONCLUSION

Since T2DM is a progressive disease, the necessity of combination treatment over time seems unavoidable, encouraging search for therapies with complementary mechanisms of action. Thus far, therapeutic interventions using a combination of various antidiabetic medications for preventing cardiovascular and renal complications have been largely unsuccessful in T2DM populations. Overall, canagliflozin, dapagliflozin and empagliflozin, the three approved SGLT2 inhibitors, have relatively safe profiles and can efficiently decrease HbA1c, fasting and postprandial glucose levels. Their uses have not been associated with significant hypoglycemic episodes or weight gain. Based on the fact that the caloric losses related to renal glucose wasting induced by these agents may be a plausible cause for a net weight loss. In addition to this advantage, cardiovascular protective effects of SGLT2 inhibitors have been well accepted. On the other hand, the current available data have amply established the significance of cardiovascular complication in T2DM patients. The arguments in favor of preventing these complications rather than treating only hyperglycemia are irrefutable. As mentioned earlier in this review, the blood pressure lowering effect of SGLT2 inhibitors has been generally accepted. What is not known is to what extent the benefit of blood pressure reduction resulted from SGLT2 inhibitors administration can contribute to overall decrease in morbidity and mortality rate in type 2 diabetic populations. Despite the good efficacy on hypertension as a well recognised risk factor in patients with T2DM, it is unlikely that the beneficial effects of SGLT2 inhibitors on cardiovascular function and prevention of heart failure could be solely attributed to their blood pressure lowering property, because other stronger antihypertensive agents lack such a remarkable protection. In other words, so far, among all glucose-lowering agents only SGLT2 inhibitors have been shown in a robust clinical trial (the EMPA-REG OUTCOME) to decrease adverse cardiovascular events in patients with type 2 diabetes. Taking all currently available information and the encouraging conclusions derived from several robust cohort studies into account, it seems very likely to see SGLT2 inhibitors as one of the major components of pharmacotherapy of T2DM in near future.

Declarations of interest

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