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Sodium-Glucose Cotransporter-2 (SGLT-2) Inhibitors: Antidiabetics Medications for Treating Diabetes

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Abstract

Type 2 diabetes (T2D) is a progressive disease, and most patients need to treat with monotherapy and combinations of oral hypoglycaemic drugs. At present about 500 million people worldwide are suffering from T2D. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are a novel antidiabetic drug class that mediates epithelial glucose transport at the renal proximal tubules, inhibiting glucose absorption that result in glycosuria, modest weight loss and improve glycaemic control with a low risk of hypoglycaemia. These are used by T2D patients together with diet and exercise, either alone or in combination with other diabetes medicines. The main side-effects of SGLT-2 inhibitors are urinary tract and genital infections, as well as euglycemic diabetic ketoacidosis. Some other probable adverse effects are lower limb amputations, risk of bone fractures, Fournier gangrene, male bladder cancer, female breast cancer, orthostatic hypotension, and acute kidney injury. This mini review explains aspects of SGLT-2 inhibitors with treatment procedures and side-effects.

Keywords: SGLT-2 inhibitors, oral hypoglycaemic drugs, glycaemic control, cardiovascular disease, ketoacidosis

1. Introduction

Diabetes mellitus (DM) is a serious chronic disorder that significantly harms patients' lives, families, and societies. It is considered as a public healthcare problem with increasing incidence and prevalence worldwide (Santos et al., 2017; Mohajan & Mohajan, 2023b, c). In 2013, there are greater than 381 million and in 2017, there are more than 451 million people with DM worldwide, and the global healthcare expenditure is an estimated cost $850 billion for DM. By 2035 it is projected to reach to about 592 million. About 5 million deaths worldwide are attributable to DM (Cho et al., 2018; Mohajan & Mohajan, 2023a, d, e). To treat T2D patients, the use of Metformin as first-line therapy followed by the addition of a second oral agent, such as a sulfonylurea (SU), thiazolidinedione (TZD), dipeptidyl peptidase-4 (DPP-4) inhibitor, or sodium-glucose cotransporter-2 (SGLT-2) inhibitors, or by the addition of a glucagon-like peptide-1 (GLP-1) receptor agonist or basal insulin (Mohajan & Mohajan, 2023v-z).

At present there are a number of oral antidiabetics drugs in the global market. But the blood glucose level among remarkable diabetes patients worldwide remains out of controlled, and most of the patients are outside of the therapeutic goal range (Thaddanee et al., 2013). Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are the newest group of oral hypoglycaemic agents that have revolutionized for the treatment of type 2 diabetes (T2D). These mainly act by preventing the reabsorption of filtered glucose through the renal convoluted tubules. These are the first antidiabetic drugs that demonstrate impressive cardiovascular benefits apart from their

glucose-lowering effect. These reduce glycated hemoglobin (HbA1c) between 0.6%–1.0% by inhibiting the absorption of glucose from the proximal tubule of the kidney, causing glycosuria (Tentolouris et al., 2019).

Some SGLT-2 agents are Canagliflozin, Dapagliflozin, Sergliflozin, Remogliflozin, Ipragliflozin, Empagliflozin, Ertugliflozin, Luseogliflozin, Tofogliflozin, Sotagliflozin, and Desoxyrhaponticin. These inhibitors block receptor site, preventing activation of the glucose channel and glucose reabsorption, so the glucose remains in the renal filtrate and ultimately in the urine (Chao & Henry, 2010).

2. Literature Review

The literature review is an introductory section of a research that consults the works of previous researchers (Polit & Hungler, 2013). It assists all researchers to improve research questions and to move forward energetically in the current research (Creswell, 2007). Anastasios Tentolouris and his coauthors have discussed that SGLT-2 inhibitors are the latest class of antidiabetic medication that inhibit the absorption of glucose from the proximal tubule of the kidney and hence cause glycosuria. In their study they have found that SGLT-2 inhibitors reduce glycated hemoglobin by 0.5%–1.0% and have shown favorable effects on body weight, blood pressure, lipid profile, arterial stiffness and endothelial function (Tentolouris et al., 2019). Rekha Thaddanee and her coworkers have observed that SGLT-2 inhibition offers a unique target for achieving adequate control of diabetes among adults (Thaddanee et al., 2013).

Masayuki Isaji has reviewed the structure and advancing profile of various SGLT-2 inhibitors, comparing their similarities and differences, and discusses the expected SGLT-2 inhibitors for an emerging category of antidiabetic drugs (Isaji, 2011). Umesh Dashora and his coauthors have realized that the rapid evolution of the SGLT-2 inhibitors in joining the pharmacological armamentarium have managed hyperglycaemia in T2D that have ensured the highest quality of care for people with diabetes (Dashora et al., 2023). Richard F. Arakaki examines the prevalence, recurrence rates, treatment options, and responses for the treatment of genital and urinary tract infections in patients with T2D receiving SGLT-2 inhibitors (Arakaki, 2016).

Oriana Hoi Yun Yu and her coauthors have aimed to compare the risk of below-knee amputation with SGLT-2 inhibitors versus dipeptidyl peptidase (DPP)-4 inhibitors among patients with T2D. In their observational study they have noticed that there was no association between SGLT-2 inhibitor use and incident below-knee amputations among patients with T2D, compared to DPP-4 inhibitor use (Yu et al., 2020). Devajit Mohajan and Haradhan Kumar Mohajan have studied overweight and obesity, and their related complications, such as diabetes mellitus, eating disorders, and various anthropometric indices. They have also studied on insulin and various oral medications for the treatment of T2D (Mohajan & Mohajan, 2023a-z).

3. Research Methodology

Research is a scholarly inquiry and investigation that aim for the discovery of new facts and findings (Adams et al., 2007). Methodology is a system of explicit rules and procedures in which research is based, and against which claims of knowledge are evaluated (Ojo, 2003). Research methodology is the systematic procedure adopted by researchers to solve a research problem (Kothari, 2008). In this study we have used secondary data sources to enrich this paper (Mohajan, 2017, 2020). To prepare this paper we consulted books of famous authors, handbooks, theses, national and international journals, e-journals, websites, etc. (Mohajan, 2018). We start our research with the discussion of historical background of SGLT-2 inhibitors. Then we have briefly consulted the functions and treatment with SGLT-2. Finally, we have highlighted on side-effects of SGLT-2.

4. Objective of the Study

The leading objective of this study is to discuss about the glucose lowering newest group of oral hypoglycaemic drug sodium-glucose cotransporter-2 (SGLT-2) inhibitors that have revolutionized for the treatment of type 2 diabetes (T2D). SGLT-2 inhibitors are also used to reduce cardiovascular events, particularly heart failure in cardiovascular outcome trials. Other trifling objectives of this study are as follows:

- to focus on historical background of SGLT-2,
- to highlight on functions and treatment with SGLT-2, and
- to make awareness on side-effects of SGLT-2.

5. Historical Background

In August 1960, American biochemist Robert Kellogg Crane (1919-2010), for the first time has presented the discovery of the sodium-glucose cotransport as the mechanism for intestinal glucose absorption (Wright & Turk, 2004). In the 1990s, seven facilitative (GLUT 1-7) and two active glucose transporters (SGLT-1 and SGLT-2) were identified. In the 1990s, the first orally active derivatives of phlorizin, the SGLT-2 were developed. In 1996, investigators at Kyoto University and Tanuba Seiygyu Co. in Japan developed phlorizin analogues, the first chemically engineered sodium glucose cotransporter-2 (SGLT-2) inhibitors (Tsujihara et al., 1996). In 2000, they

have developed T-1095 that is an SGLT-2, which reduce hyperglycaemia when given orally to diabetic rats and suggested that it could be useful in the management of persons with T2D (Adachi et al., 2000).

Between 2012 and 2015, the European Medicine Agency (EMA) and the US Food and Drug Administration (FDA) approved three SGLT-2 inhibitors; Dapagliflozin, Canagliflozin, and Empagliflozin, for reducing plasma glucose in persons with T2D. These are authorized as mono-component and as fixed dose combination with Metformin (Braunwald, 2022).

Dapagliflozin was approved by the EU in 2012. Canagliflozin was approved in March 2013 for use in the USA. Empagliflozin was approved in the USA in August 2014. Tofogliflozin was approved in Japan in March 2014 (Poole & Prossler, 2014). Luseogliflozin was approved in Japan in March 2014. Luseogliflozin was approved in Japan March 2014 under the brand name Lusefi and was developed by Taisho Pharmaceutical. Ertugliflozin was approved in the USA under the brand name Steglatro in December 2017 (Santos et al., 2017). Remogliflozin was commercially launched first in India by Glenmark in May 2019. Bexagliflozin was approved in the USA under the brand name Brenzavvy in January 2023 (Santos et al., 2017; Dashora et al., 2023).

6. Functions and Treatment with SGLT-2

The SGLT-2 inhibitors are necessary who are at risk of hypoglycaemia, overweight, or with cardiovascular disease, and cannot tolerate Sulfonylureas. These enhance renal glucose excretion by inhibiting renal glucose reabsorption and reduce plasma glucose insulin independently and improve insulin resistance in diabetes (Isaji, 2011). These are proteins which encourage glucose reabsorption in the proximal tubule in the kidney. These may provide an attractive, insulin independent target for increasing glucose excretion. These reduce renal glucose reabsorption resulting in increased glucose excretion equivalent to a net loss of 200-300 kcal per day. These may also reverse β-cell dysfunction and insulin resistance in T2D. These lower HbA1c up to 0.6–1.0% by inhibiting the absorption of glucose from the proximal tubule of the kidney, causing glycosuria, and also lower both body weight and blood pressure, and may benefit those who are overweight or obese. On the other hand, these do not cause hypoglycaemia (Thaddanee et al., 2013).

SGLT-2 inhibitors are expressed in the proximal renal tubules and are responsible for the majority of the reabsorption of filtered glucose from the tubular lumen. These act to decrease blood glucose by preventing reabsorption of glucose, mainly from proximal renal tubule in the kidney (Garber et al., 2019). These may induce urinary glucose excretion via the inhibition of renal glucose reabsorption; improve glycaemic control, and lower body weight (Cai et al., 2018).

SGLT-2 inhibitors block reabsorption of glucose in the kidney. These also improve cardiovascular and renal outcomes, including reduced cardiovascular mortality and fewer hospitalizations for heart failure (Keller et al., 2022). These decrease renal glucose reabsorption, resulting in glucosuria, alleviation of hyperglycaemia, and modest weight loss and are associated with a low risk of hypoglycaemia (Arakaki, 2016). Due to the cardiovascular and renal benefits, SGLT-2 inhibitors are recommended as one of the preferred second-line agents for patients who have high risk factors of cardiovascular disease, heart failure, and chronic renal disease. As a result, the use of SGLT-2 inhibitors has increased substantially among patients with T2D (Wu et al., 2020).

7. Side-Effects of SGLT-2

SGLT-2 inhibitors increase the risk of euglycemic diabetic ketoacidosis (DKA), urinary and genital tract infections, candidal vulvovaginitis, and hypoglycaemia (Arakaki, 2016). Some more adverse effects of these agents are lower limb amputations (LLA), Fournier gangrene, bone fractures, female breast cancer, male bladder cancer, orthostatic hypotension, and acute kidney injury (AKI) (Nadkarni et al., 2017; Szalat et al., 2018). Rare side-effects, such as pain, redness, swelling or discomfort in perineal or genital area are seen among some patients (Dashora et al., 2023). Sometimes life-threatening cases of diabetic ketoacidosis in patients under the treatment with SGLT-2-inhibitors are happened, and majority of them require hospitalization (Zinman et al., 2015).

8. Conclusions

From this study we have observed that SGLT-2 inhibitors are effective antidiabetic therapies for the T2D patients that are associated with better glycaemic control. At present these are using for the treatment and prevention of diabetic kidney disease and its progression, major pharmacological advances in cardiovascular and chronic heart failure. SGLT-2 inhibitors have been proven effective in the treatment of T2D, various forms of heart failure, and kidney failure and represent one of the major pharmacological advances in cardiovascular medicine. SGLT-2 inhibitors should be used very carefully and must stop immediately if one or more severe side-effects appeared.

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