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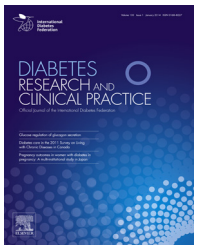

Invited review

SGLT2 inhibitors in the treatment of type 2 diabetes

Farhad M. Hasan [a,*], *Mazen Alsahli* [b], *John E. Gerich* [c]

[a] *University of Virginia School of Medicine, Charlottesville, VA, USA*
[b] *University of Toronto Faculty of Medicine, Toronto, Ontario, Canada*
[c] *University of Rochester School of Medicine, Rochester, NY, USA*

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ABSTRACT

The kidney plays an important role in glucose homeostasis via its production, utilization, and, most importantly, reabsorption of glucose from glomerular filtrate which is largely mediated via the sodium glucose co-transporter 2 (SGLT2). Pharmacological inhibition of SGLT2 increases urinary glucose excretion and decreases plasma glucose levels in an insulin-independent manner. Agents that inhibit SGLT2 represent a novel class of drugs, which has recently become available for treatment of type 2 diabetes. This article summarizes the rationale for use of these agents and reviews available clinical data on their efficacy, safety, and risks/benefits.

Contents

* *Corresponding author at*: 403 Woodcrest Road Wayne, PA 19087, USA. Tel.: +1 585 752 2860.
E-mail address: johngerich@compuserve.com (J.E. Gerich).

Abbreviations: HbA1c, hemoglobin A1c; FRG, familial renal glucosuria; GLUT, glucose transporter; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; SGLT, sodium–glucose co-transporter; T2DM, type 2 diabetes mellitus; UGE, urinary glucose excretion.

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1. Introduction

Management of type 2 diabetes (T2DM) continues to be challenging despite the numerous therapeutic options available. Metformin is currently recommended as the first choice agent [1–3]. However side effects, primarily gastrointestinal, are common and approximately 10% of patients cannot tolerate it at any dose [4]. T2DM is a progressive disease so that as β cell function deteriorates, most patients will require additional therapy [5]. Alternatives and additions to metformin also have problems, which limit their usefulness. Sulfonylureas, meglitinides, and insulin are associated with weight gain and risk of hypoglycemia [5,6]. Thiazolidinediones are associated with risk of weight gain, edema, heart failure, and fractures [6,7]. Dipeptidyl peptidase 4 (DPP-4) inhibitors have only modest glucose lowering effect and their long-term safety remains to be established [6,8]. Similarly, the long-term safety of glucagon-like peptide-1 (GLP-1) analogs is unknown, and their use is often associated with significant gastrointestinal side effects [6,8]. The use of alpha glucosidase inhibitors outside the orient and Germany is generally low due to their common gastrointestinal side effects and frequent dosing schedule [6,9]. Additionally, renal insufficiency places major restrictions on many of the above agents (e.g. metformin, sulfonylureas, GLP-1 analogs, and alpha glucosidase inhibitors) [10]. Thus there is a need for additional treatment options. The ideal antidiabetes drug would be one associated with a robust and sustained HbA1c reduction, is well tolerated, can be administered easily, has low or no risk of hypoglycemia, has good long term safety, and has added benefit such as a favorable impact on β cell function, blood pressure, weight, albuminuria etc.

The kidney plays an important role in glucose homeostasis and has recently become a target for treatment of diabetes. The majority of glucose reabsorption from glomerular filtrate is mediated via a transporter protein called sodium glucose co-transporter 2 (SGLT2) [11]. Pharmacological inhibition of SGLT2 increases urinary glucose excretion (UGE) and decreases plasma glucose levels in an insulin-independent manner [11]. SGLT2 inhibitors represent a novel class of drugs that has recently become available for treatment of T2DM. This article summarizes the rationale for use of these agents and reviews available clinical data on their efficacy, safety, and risks/benefits.

2. The kidneys and normal glucose homeostasis

The kidney is involved in the regulation of glucose homeostasis via three different mechanisms: release of glucose into the circulation (gluconeogenesis), uptake of glucose from the circulation for its energy needs, and most importantly, glucose reabsorption from glomerular filtrate.

2.1. *Renal gluconeogenesis*

After a 14–16 h overnight fast, approximately half of the glucose released into the circulation is from the breakdown of liver glycogen (glycogenolysis) stored in the liver and the other half is from the production of new glucose molecules (gluconeogenesis) by liver and kidneys [12–14]. In humans, only the liver and kidney contain significant amounts of the enzyme glucose-6-phosphatase and therefore are the only