Universidade de Lisboa

Faculdade de Farmácia

Therapeutic Advancements: The role of SGLT1 inhibitors in the current management of type 2 Diabetes

Carla Alexandra Guerreiro Pereira

Monografia orientada pelo Professor Doutor Bruno Miguel Nogueira Sepodes, Professor Associado com Agregação

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Trabalho Final de Mestrado Integrado em Ciências Farmacêuticas apresentado à Universidade de Lisboa através da Faculdade de Farmácia

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Resumo

Os co-transportadores de Na+-glucose, SGLT1 e SGLT2, transportam a glucose através das membranas epiteliais. A maior parte da captação intestinal da glucose proveniente da dieta é mediada pelos SGLT1, e como tal, os indivíduos com mutações neste gene apresentam má absorção de glucose/galactose. Ambos os transportadores, SGLT1 e SGLT2, estão presentes no rim, e estudos recentes indicam que os SGLT2 medeiam até 97% da reabsorção da glucose, pelo que humanos com mutações no gene SGLT2 têm glicosúria renal familiar. Surpreendentemente, o knock-out dos SGLT2 ou a terapia com inibidores seletivos dos SGLT2 resulta numa excreção fracionada de glucose de apenas 60%, um efeito mediado pela sobre regulação renal de SGLT1.

Como a inibição dos SGLT1 reduz os níveis de glucose no sangue através da inibição da absorção de glucose no intestino e a sua reabsorção renal, foi proposto que a inibição dupla SGLT1/2 poderia melhorar ainda mais o controle glicémico, tendo como alvo os órgãos que expressam SGLT1: o intestino e o rim.

Além disso, os fármacos que inibem o transporte de glucose mediado por SGLT1 podem proteger o tecido cardíaco, reduzindo a acumulação de glicogénio e a formação de espécies reativas de oxigénio. Porém, modelos genéticos mostram que a inibição dos SGLT1 pode ter um impacto negativo em vários órgãos. Esta abordagem pode causar diarreia, depleção de volume, interferir na correção da hipoglicemia pela administração oral de carbohidratos e predispor o desenvolvimento de cetoacidose diabética euglicémica. Como resultado, a inibição SGLT1 parece ser uma faca de dois gumes.

Vários inibidores seletivos SGLT2, assim como os inibidores seletivos SGLT1 e duplos SGLT1/2, foram desenvolvidos com base na estrutura da florizina, uma molécula natural que atua como um inibidor duplo do SGLT1/2.

Esta revisão irá abordar as manifestações clínicas e o diagnóstico de diabetes, a gestão farmacológica da glucose na diabetes tipo 2, com foco no racional para o desenvolvimento de inibidores seletivos SGLT1 e inibidores duplos SGLT1/2, enquanto avalia os potenciais benefícios em comparação com a inibição seletiva SGLT2, pesando a evidências sobre os efeitos benéficos versus prejudiciais que a inibição SGLT1 pode ter.

Palavras-chave: diabetes tipo 2; SGLT1; SGLT2; inibidor.

Abstract

Na+-glucose co-transporters, SGLT1 and SGLT2, transport glucose across epithelial membranes. The bulk of dietary glucose uptake in the intestine is mediated by SGLT1, and for that, individuals with SGLT1 gene mutations have glucose/galactose malabsorption. Both transporters, SGLT1 and SGLT2, are present in the kidney, and new research indicates that SGLT2 mediates up to 97% of glucose reabsorption, for that, humans with mutations in the SGLT2 gene have familial renal glucosuria. Surprisingly, SGLT2 knock-out or therapy with SGLT2 selective inhibitors only results in a fractional glucose excretion of 60%, an effect mediated by renal SGLT1 up-regulation.

Since inhibiting SGLT1 reduces blood glucose levels via inhibiting glucose absorption in the intestine and renal reabsorption, it was proposed that dual SGLT1/2 inhibition might enhance glycaemic control even further by targeting these separate organs that express SGLT1: the intestine and the kidney.

Furthermore, medications that inhibit SGLT1-mediated glucose transport may protect cardiac tissue by lowering glycogen accumulation and the generation of reactive oxygen species. Yet, genetic models of SGLT1 inactivation show that the failure of these transporters might have a negative impact on a variety of organs. This method may cause diarrhoea, volume depletion, interfere with the correction of hypoglycaemia by oral carbohydrate delivery, and predispose to the development of euglycemic diabetic ketoacidosis. As a result, SGLT1 inhibition appears to be a two-edged sword.

Several SGLT2 inhibitors, as well as SGLT1 and dual SGLT1/2 inhibitors, have been developed based on the structure of phlorizin, a natural molecule that acts as a dual SGLT1/2 inhibitor.

This review will address the clinical manifestations and diagnosis of diabetes, the pharmacological management of glucose in type 2 diabetes, focusing on the rationale for the development of SGLT1 and dual SGLT1/2 inhibitors, while evaluating potential benefits compared to sole SGLT2 inhibition and weighting evidence on the beneficial versus detrimental effects that SGLT1inhibition might have.

Keywords: type 2 diabetes; SGLT1; SGLT2; inhibitor.

List of Abbreviations

3p-MACE = three-point major adverse cardiovascular events

CKD = chronic kidney disease

CV = cardiovascular

CVD = cardiovascular disease

CVOT = cardiovascular outcome trial

DM = diabetes mellitus

DPP-4 = dipeptidyl peptidase-4

eGFR = estimated glomerular filtration rate

FGR = fractional glucose reabsorption

FPG = fasting plasma glucose

GGM = glucose-galactose malabsorption

GIP = glucose-dependent insulinotropic polypeptide

GLP-1 = glucagon-like peptide 1

GLP-1 RA = glucagon-like peptide 1 receptor agonist

HbA1c = glycated haemoglobin

HF = heart failure

MI = myocardial infarction

OGTT = oral glucose tolerance test

RPG = random plasma glucose

SCFA = short chain fatty acids

SGLT = sodium glucose co-transporter

SGLT1 = sodium glucose co-transporter 1

SGLT2 = sodium glucose co-transporter 2

T1DM = type 1 diabetes mellitus

T2DM = type 2 diabetes mellitus.

WHO = world health organisation

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1 Introduction

Diabetes describes a group of metabolic disorders with heterogeneous aetiologies characterized by chronic hyperglycaemia due to insufficient insulin secretion and/or insulin resistance involving consequent disturbances of carbohydrate, fat, and protein metabolism, leading to microvascular and macrovascular damage, which forefronts to retinopathy, nephropathy, neuropathy, heart, and skin damage over time.(1,2) There is also an increased risk of non-alcoholic fatty liver disease, cerebrovascular disease, erectile dysfunction and some infectious diseases, such as tuberculosis.(1,2) Diabetes is the most common cause of blindness in working-age people in high-income countries, the most common cause of end-stage kidney disease, and non-traumatic amputation.(3) However the leading cause of morbidity and mortality is cardiovascular (CV) complications, with about three out of four individuals with the disease dying from CV complications.(3) In addition, the risk of stroke is increased by four times, liver cirrhosis development is increased by three times, and epidemiological results also indicate a substantially increased risk of cancer, regardless of obesity.(3) It is also increasingly known that heart failure (HF) is a major comorbidity associated with diabetes.(3) On 20 December, 2006, the United Nations General Assembly declared diabetes an international public health issue and declared World Diabetes Day as a United Nations Day(4). The global Type 2 Diabetes Mellitus (T2DM) crisis has been propelled by multiple factors, including unhealthy lifestyles with an increased consumption of highly processed foods, sugar-sweetened beverages and reduced physical activity, consequently of rapid cultural, economic, and social changes, and ageing populations, it is a widespread and urgent global health issue.(1)

In 2019, the global prevalence of diabetes was projected to be 9.3%, rising to 10,2% by 2030 and 10,9% by 2045.(5) There are just under half a billion people worldwide living with diabetes and the figure is expected to rise by 25% in 2030 and 51% in 2045.(5) One in two (50.1%) individuals remain undiagnosed.(5) 90 to 95% of diabetes accounts for T2DM and evolves various degrees of β-cell dysfunction and insulin resistance, commonly associated with overweight and obesity.(2) It mainly affects adults, but the incidence is increasing in children and adolescents.(1) Since this disease affects many people in the workforce, it has an important and deleterious effect on both individual and national productivity.(6) The socio-economic effects of diabetes and its

complications could have a significant negative impact on developed and developing countries' economies.(6) Worlwide, in 2017, about 5 million deaths were related to diabetes, and US$850 billion was projected to be the global healthcare spending on the disease.(7) In the European Union, in 2017, about 32.7 million adults were diabetics, up from an estimated 18.2 million adults in 2000, additionally, the prevalence rate of diabetes among adults in European union countries nations was 6% on average and rates ranged from 9% or more in Portugal, Romania, and Malta to 4% or less in Ireland, Lithuania, and Estonia.(8) Diabetes prevalence rates have stabilized in several European countries in recent years, particularly in the Nordic countries, although they have increased somewhat in Southern Europe and Central and Eastern Europe.(8) In 2017, the European Union's health cost to treat diabetes and avoid complications was projected to be over EUR 150 billion, with the average spend per diabetic adult estimated to be around EUR 4 600 per year.(8) In Portugal, in 2018, the estimated prevalence of Diabetes in population aged between 20 and 79 years was 13.6%, this means that more than 1 million Portuguese in this age group have diabetes, furthermore, Diabetes direct cost expenses were estimated to be 1300-1550 million euros (0,6- 0,8% of Portuguese gross domestic product (GDP) and 7-8% of the total heath expenditure).(9)

According to «*Lifestyle Interventions for Patients with and at Risk for Type 2 Diabetes: A Systematic Review and Meta-analysis*», lifestyle interventions successfully decrease the incidence of T2DM in high-risk patients, however, there is no evidence of decreased all-cause mortality in patients who already have T2DM and insufficient evidence to indicate advantages for CV and microvascular outcomes.(10)

Pharmacological options for treatment of T2DM have improved rapidly during the last 10 years, allowing clinicians to target different pathophysiological defects. The most exciting achievement is the demonstration of CV benefits from two of these new classes, the glucagon-like peptide 1 receptor agonist (GLP-1 RA) and SGLT2 inhibitors.(11) The sodium glucose co-transporter (SGLT2) inhibitors and dual SGLT1/2 inhibitors are among the most recent additions to the antidiabetic armamentarium(12).This work pretends to review the role of sodium glucose co-transporter 1 (SGLT1) inhibition in the current management of the disease.

2 Clinical Manifestations and Diagnosis of T2DM

2.1 Clinical Manifestations of T2DM

For the first several years, T2DM can remain undiagnosed because hyperglycaemia is not serious enough to cause classic symptoms, clear signs, and clinical signs of chronic complications.(2) Ketoacidosis is rare in T2DM, but when observed, it usually occurs in combination with the stress of another disease, such as infection. Hyperosmolar coma, particularly in elderly individuals, may occur.(2,13)

Table Erro! Não existe nenhum texto com o estilo especificado no documento.**.1 Classic Symptoms, Signs, and Chronic Complications of T2DM**

<table>
<tr><th>Classic Symptoms (2)</th><th>Signs (2)</th><th>Chronic Complications (2)</th></tr>
<tr><td>Thirst</td><td>Unexplained weight loss</td><td>Acute Coronary Disease</td></tr>
<tr><td>Blurring of vision</td><td rowspan="6">Signs of acute metabolic deterioration (severe dehydration, Kussmaul’s respiration, vomiting, altered level of consciousness)</td><td>Stroke</td></tr>
<tr><td>Fadigue</td><td>Kidney Disease</td></tr>
<tr><td>Polydipsia</td><td>Vison loss</td></tr>
<tr><td>Plyuria</td><td rowspan="3">Diabetic Foot</td></tr>
<tr><td>Hyperphagia</td></tr>
<tr><td>Recurrent Urogenital Candidiasis</td></tr>
</table>

At a slow rate, hyperglycaemia worsens and is sufficient to cause pathological and functional changes that could occur long before a diagnosis is made, resulting in complications.(2) Hyperglycaemia is known to generate oxidative stress, which causes a chain reaction of events that culminates in the generation of reactive oxygen species, the creation of advanced glycated end products, and various other molecular processes

that create long-term complications(12) A large percentage of diabetes cases (30-80%) are reported to be undiagnosed.(2) The diagnosis criteria for diabetes mellitus (DM) are clear, and defined as result of the World Health Organisation (WHO) recommendations.(2,4,13,14)

2.2 Diagnosis of T2DM

Diabetes diagnosis is based on the following parameters for venous plasma:(2,4,13,14)

- Fasting plasma glucose (FPG) ≥ 126 mg/dl (≥ 7,0 mmol/l) or,
- Classic symptoms + random plasma glucose (RPG) ≥ 200 mg/dl (≥ 11,1 mmol/l) or,
- 2-hour post-load plasma glucose (2hPG) after a 75 g oral glucose tolerance test (OGTT) ≥ 200 mg/dl (≥ 11,1 mmol/l) or,
- Glycated haemoglobin (HbA1c) ≥ 6,5%.

Diagnosis of an asymptomatic person should not be made upon a single abnormal FPG value or HbA1c, as it should always be confirmed on a second evaluation, after one or two weeks.(2,4,13) DM should be investigated using FPG or HbA1c, and OGTT if still in doubt.(14) Individuals with established cardiovascular disease (CVD) should be screened using HbA1c and/or fasting glucose; an OGTT can be carried out if FPG and HbA1c are inconclusive.(14) If elevated values are observed in asymptomatic subjects, it is recommended to repeat evaluation, preferably with the same test, to confirm the diagnosis as soon as possible on a succeeding day.(2,4,13) WHO suggests that the use of HbA1C in the diagnosis of T2DM provides a convenient screening method.(4) HbA1c can be measured at any time of the day as it does not undergo variations during the day.(4) However, it is crucial to understand that the HbA1c value is contingent on the lifespan of erythrocytes, so, any condition which may increase their turnover (haemolysis or blood loss) will therefore lead to a false reduction of HbA1c, and any condition that decreases turnover (such as anaemia) will lead to a false elevation of HbA1c.(4) Furthermore, haemoglobinopathy or interfering haemoglobins can make HbA1c uninterpretable, and in this case, glucose tests should be used diagnostically.(4)

A diagnosis of diabetes has significant impacts for patients, not just for their health, but also because of the possible stigma that can be brought on by a diabetes diagnosis that can impact their jobs, health, and life insurance, driving status, social opportunities, and other cultural, ethical, and human rights implications.(1)

3 Pharmacological Management of Glucose in T2DM

DM management requires a multidisciplinary strategy that includes both behavioural changes, such as diet and exercise, as well as pharmacologic therapies as needed to achieve individualized glycaemic targets.(15)

For optimum glycaemic regulation, lifestyle changes must be paired with oral pharmacologic agents, especially as T2DM progresses with continued loss of pancreatic beta-cell function and insulin synthesis.(15) To reduce microvascular complications, it is recommended a glucose control that targets near-normal HbA1c values (<7.0% or <53 mmol/mol), aiming 6.0%-6.5% in younger patients without CVD, if possible, without significant hypoglycaemic episodes or other adverse effect of treatment. Elderly patients and those with severe complications or advanced CVD may be subjected to less rigorous targets (<8.0% or <64 mmol/mol) or (<9.0% or <75 mmol/mol), in this case a HbA1c target value to reduce macrovascular risk is less compelling. In conclusion, HbA1c targets should be personalized according to the duration of T2DM, comorbidities, and age of the patient.(14)

Therapeutic agents used to treat hyperglycaemia can be categorized into one of five types:(14)

- Insulin sensitizers (e.g., metformin and thiazolidinediones),
- Insulin providers (e.g., sulfonylureas and meglitinides),
- Gastrointestinal glucose absorption inhibitor (acarbose),
- Incretin-based therapies (e.g., GLP1-RA and DPP4 inhibitors), and
- SGLT inhibitors (SGLT2 inhibitors and dual SGLT1/2 inhibitors).

In 2018, the US Food and Drug Advisory Committee (FDA) and subsequent European Medicines Agency (EMA) recommended that all potential antihyperglycemic drugs be tested for CV safety using Cardiovascular Outcome Trials (CVOTs).(16) This came in response to questions over the use of rosiglitazone, which, while an efficient antihyperglycemic drug, seemed to increase CV events in some patients.(17). CVOTs are large, multicentre, double-blind, randomized control trials, the majority of which uses three-point major adverse CV events (3p-MACE) as their primary endpoint (nonfatal stroke, nonfatal myocardial infarction (MI), and CV death), with others even

including hospitalization for unstable angina, using four-point major adverse CV events (4p-MACE).(3) Hospitalization for HF, a common complication of T2DM that contributes to the disease's high mortality, is often included, usually as a secondary end point. Lately, there has been a shift in the focus of trials primarily evaluating renal outcomes.(3)

With all the treatment options currently available for T2DM, clinicians may require assistance in determining which pharmacotherapy is most appropriate for their patients. According to the *«2019 Guidelines on Diabetes, Pre-Diabetes and Cardiovascular Diseases»* the current treatment algorithm for patients with T2DM consists of metformin monotherapy, if not contraindicated, if the patient does NOT have concomitant atherosclerotic CVD, or high/very high CV risk. If HbA1c remains above target after 3 months on monotherapy the addition of a second agent such as dipeptidyl peptidase-4 (DPP-4) inhibitor, glucagon-like peptide 1 receptor agonist (GLP-1 RA), sodium glucose co-transporter 2 (SGLT2) inhibitor (if estimated glomerular filtration rate (eGFR) is adequate) or thiazolidinediones is considered. The selection of the drug should be based on the patient's specific risk/benefit profile to achieve optimal outcomes. On the other hand, the current treatment algorithm for patients with T2DM AND concomitant atherosclerotic CVD, or high/very high CV risk, consists of SGLT2 inhibitors or GLP-1 RA monotherapy, or in addition to metformin if the patient is already on metformin. If HbA1c remains above target after 3 months, it is recommended to consider adding metformin (if SGLT2 inhibitor or GLP-1 RA monotherapy) and if needed other classes with proven CV benefit (GLP-1 RA or SGLT2 inhibitor).(14). Two new classes, the GLP-1 RA and selective SGLT2 inhibitors have demonstrated CV benefits, exceeding expectations for the management of T2DM.(11) If weight loss, hypoglycaemia prevention, and CVD control are priorities, GLP-1 RA could be the best choice, according to the Korean Diabetes Association.(11) In the treatment of patients with T2D and CVD, there is growing consensus that GLP-1 RA and SGLT2 inhibitors can take precedence over conventional medications (e.g., metformin).(11) This customized approach is part of a broader definition of patient-centred care, which considers adverse medication effects, disease duration, life expectancy, identified vascular problems and/or other comorbidities, specific patient perceptions, and the patient services and support system.(11) When selecting a chronic medication, the cost of the treatment is also a major consideration,

since patients will struggle to obtain access to these new types of medications before treatment standards are uniformed and prescription prices are reduced.(11)

Data from several CVOTs indicates CV benefits from the use of glucose-lowering drugs in patients with CVD or at very high/high CV risk. These trials findings, which included both GLP1-RAs (LEADER, SUSTAIN-6, Harmony Outcomes, REWIND, and PIONEER 6) and SGLT2 inhibitors (EMPA-REG OUTCOME, CANVAS, DECLARE- TIMI 58, and CREDENCE), clearly conclude that these medications should be prescribed in patients with T2DM who have CVD or are at extremely high/high CV risk, such as those with target-organ damage or multiple CV risk factors, whether they are on metformin or not.(14)

GLP1-RAs benefits are most likely resulting from a decrease in arteriosclerosis-related events, whereas SGLT2 inhibitors seem to minimize HF-related endpoints.(14) As a result, SGLT2 inhibitors can be particularly beneficial in patients who have an elevated risk of HF.(14) The findings show that metformin has a beneficial role in primary prevention in subjects with newly diagnosed T2DM who do not have CVD and are at intermediate risk.(14) Furthermore, liraglutide is recommended in patients with prevalent CVD or very high/high CV risk, and empagliflozin is recommended in patients with prevalent CVD to minimize the risk of death, based on the mortality benefits shown in LEADER and EMPA-REG OUTCOME.(18)

T2DM management has never seen so many clinical trial-supported strategies. To have the best possible health outcomes, the decrease in CVD morbidity and mortality must be weighed when selecting a medication for each patient, however, further research into the mechanisms of action of newer therapies is needed.(11) Ongoing trials examining the use of some of these medications, especially SGLT2 inhibitors, in nondiabetic patients with CVD and HF will be enlightening. At the moment, clinical education on the benefits and risks of these medications, as well as providing patient access, are top priorities.(11)

3.1 Insulin Sensitizers

Insulin sensitizers include Biguanides (metformin) and Thiazolidinediones (rosiglitazone, pioglitazone).

Metformin is the first line antihyperglycemic for the management of T2DM in the absence of contraindications.(3) It has a good glycaemic efficacy (~1.0%–1.5% HbA1c reduction) achieved through the improvement of the hepatic adenosine monophosphate-activated protein kinase (AMPK) activity, while inhibiting hepatic gluconeogenesis, lipogenesis and increasing insulin-mediated glucose uptake peripherally, besides this, metformin also presents outstanding long-term safety profile.(15,19) It does not induce hypoglycaemia and promotes weight loss (approximately 1.1 kg).(20) The most frequent side effect is gastrointestinal irritation, which can be avoided by gradually increasing the dose and taking the medication with meals.(20) It is contraindicated in patients with eGFR<30 mL/min/1.73 m2, active liver disease, unstable HF or history of lactic acidosis while on metformin.(21)

Thiazolidinediones raise the amount of adiponectin, a fat tissue-secreted cytokine that raises not only the number of insulin-sensitive adipocytes but also induces fatty acid oxidation, while stimulating the nuclear receptor peroxisome proliferator-activated receptor gamma (PPAR- γ) in muscle, adipose tissue and liver, which increases insulin sensitivity and therefore peripheral glucose uptake.(15) They have comparable glycaemic efficacy to metformin, but their use is restricted due to side effects such as weight gain and fluid retention, which can aggravate HF and increased postmenopausal fractures in women.(3). Pioglitazone use was linked to an elevated risk of bladder cancer in T2DM patients, but this link was not established after a 10-year follow-up.(22) Rosiglitazone raises baseline LDL levels and was linked to a 43% increase in MI in a meta-analysis, it has been withdrawn from the market in Europe due to safety issues.(3,23)

3.2 Insulin Providers

Insulin providers include Sulfonylureas (glipizide, glyburide, gliclazide, glimepiride), Meglitinides (repaglinide) and Amino Acid D-Phenylalanine Derivatives (nataglinide).

Sulfonylureas induce the secretion of insulin from pancreatic beta cells.(3,15). Their low cost and potent glucose reducing properties (1%–1.5% HbA1c reduction) makes them appealing for use.(24,25) Sulfonylureas are more effective than moderate lifestyle changes alone in lowering CV risk, but they are less effective than metformin. Hypoglycaemia is a concern of sulfonylureas, and there has been a controversy about the CV protection of sulfonylureas since the 1960s.(24,25). When compared to older

agents, newer sulfonylureas can have a marginally better CV profile.(3) Sulfonylureas may also lose efficacy as a result of beta-cell failure.(3) The key reason reducing their use is hypoglycaemia, which can be serious in the elderly or the renally affected, and is much more common than for incretin-based therapy or metformin. Since sulfonylurea metabolites are excreted by the kidneys, the likelihood of hypoglycaemia is considerably greater in patients with chronic kidney disease (CKD), but it is less troublesome with shorter acting sulfonylureas with more inactive metabolites, such as glimepiride and gliclazide.(3)

Meglitinides work similarly to sulfonylureas by regulating adenosine triphosphate-sensitive potassium (K-ATP) channels in pancreatic beta cells, causing an increase in insulin secretion.(15)

3.3 Gastrointestinal Glucose Absorption Inhibitors

Alpha-glucosidase inhibitors (acarbose) compete with alpha-glucosidase enzymes in the intestinal brush border cells that digest dietary starch, preventing polysaccharide reabsorption and sucrose metabolism to glucose and fructose.(15)

3.4 Incretin Based Therapies

Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the main incretin hormones secreted by enteroendocrine cells in response to food consumption.(11) These two incretins stimulate insulin secretion from the beta cells of the pancreatic islets of Langerhans via a process that is dependent on (high) glucose levels and they also inhibit alpha cells from secreting glucagon.(11) Furthermore, since it slows gastric emptying and suppresses appetite, GLP-1 is linked to weight loss. Because of this, GLP-1 RA are an optimal therapeutic class for glucose and weight regulation, unlike natural GLP-1 which has a half-life of just around 2 minutes since it is quickly degraded by DPP-4 enzyme, limiting its therapeutic value.(11) Incretin based therapies work by increasing GLP-1 activity and for that they use different strategies: DPP-4 inhibition which inhibits GLP-1 enzymatic degradation, (sitagliptin, saxagliptin, vildagliptin, linagliptin, alogliptin), acting as GLP-1 RA (exenatide, lixisenatide, semaglutide) or GLP-1 Analogues, resistant to enzymatic degradation (liraglutide and dulaglutide).(15)

GLP1-RAs are DPP-4 enzyme resistant and reach major HbA1c reductions without the hazard of hypoglycaemia, they promote weight loss as well as lipid and blood pressure improvements.(3) They can be used in patients with an eGFR as low as 15 mL/min/1.73 m2.(3) GLP1-RAs have different mechanisms and durations of action, and the CVOTs including these agents differed in size and patient attributes, leaving the results inconclusive.(3) A meta-analysis of seven major trials (ELIXA, EXSCEL, LEADER, SUSTAIN-6, REWIND, PIONEER-6, and HARMONY) revealed a 12% reduction in 3p-MACE, with no heterogeneity within patient subgroups.(26) There is some variation among agents- e.g. exenatide and lixisenatide have not been shown to boost CV outcomes.(27,28) On the other hand, SUSTAIN 6 trial, associated semaglutide with higher rates of retinopathy, when compared to placebo, which was believed to be attributed to rapid HbA1c decreases in patients with pre-existing retinopathy.(29) The major HbA1C change can also be responsible for the observed CV impact.(30) Furthermore, GLP1-RAs boost several CV parameters, including a slight decrease in systolic blood pressure and weight loss, as well as having direct vascular and cardiac effects that may lead to the findings.(30)

GLP-1 analogues are safe in patients with stage 3 CKD. This class is well-known for their gastrointestinal adverse effects, which include nausea, vomiting, constipation, diarrhoea, and stomach discomfort.(11) In clinical trials, these signs have been identified as the primary cause for drug discontinuation.(11) These agents have been reported to induce hypoglycaemia on rare occasions by having an additive reaction with insulin.(11) Liraglutide was the first drug to demonstrate a benefit in both cardiovascular and mortality as per the LEADER trial, a large multicentre double-blind trial, where it decreased CV events by 13%, all-cause mortality by 15%, and CV death by 22%.(31)

DPP-4 inhibitors (gliptins) show modestly better glycaemic regulation but lower HbA1C reduction when compared to GLP1-RAs (0.8–1%). They are weight-neutral, have a low chance of hypoglycaemia, and few side effects, although have been associated with a small increase in risk of pancreatitis.(11) All CVOTs who studied DPP-4 inhibitors demonstrated CV safety but no CV protection.(3) DPP-4 inhibitors have little effect on gastric emptying or lodging despite increases in active GLP-1 concentrations.(11) CARMELINA is currently the only study investigating kidney outcomes of DPP-4 inhibitors in patients with T2DM who are at high cardiorenal

risk.(32) Regardless of the degree of renal dysfunction, linagliptin did not induce renal disease progression, although it did show lower rates of albuminuria progression (HR 0.86) relative to placebo.(32)

3.5 SGLT inhibitors

SGLT inhibitors (gliflozins) include **selective SGLT2 inhibitors** such as dapagliflozin, empagliflozin and tofogliflozin and **dual SGLT1/2 inhibitors** such as sotagliflozin and canagliflozin whom also have a mild or moderate intestinal and renal SGLT1 inhibitory effect because of their relatively weak selectivity for SGLT2 over SGLT1.(33) Sotagliflozin (also known as LX4211) is a dual SGLT1/SGLT2 inhibitor that is under development for clinical use and has a stronger inhibitory effect on SGLT1 compared with current SGLT2 inhibitors, including canagliflozin, although both canagliflozin and sotagliflozin increase circulating GLP-1 levels.(33)

These medications glucose-lowering efficacy is comparable to that of conventional anti-diabetic medications, and their administration is followed by a moderate reduction in body weight and blood pressure readings.(34) The bigger advantage of these compounds, however, is that both CVOTs and real-world data show that they lower CV and overall mortality as well as the incidence of hospitalization for HF.(34) Furthermore, SGLT2 inhibitors have renoprotective effects in both patients with pre-existing diabetic nephropathy and patients with normal renal function at baseline.(34) SGLT2 inhibitors have been proven to reduce the risk of MI, stroke, and CV death in patients with established atherosclerotic CVD but not in those with multiple risk factors.(34) They have also been proven to reduce the risk of hospitalization for HF and progression of renal disease in the presence or absence of atherosclerotic CVD or HF.(34) As a result, guidelines recommend that these agents be used as a second-line glucose-lowering treatment (after metformin) at the very least in patients with T2DM and established CVD.(35) Current guidelines recommend starting SGLT-2 inhibitors in T2DM only when eGFR is greater than 60 mL/min/1.73 m2 and discontinuing it when it falls below 45 mL/min/1.73 m2.(14) They are associated with a decrease in all-cause mortality, regardless of HbA1C, body weight, blood pressure, or serum uric acid decreases seen in tests, implying that the drugs' diuretic and natriuretic properties are to account.(36)

In the absence of insulin or sulfonylureas, the risk of hypoglycaemia is minimal.(37) Among the gliflozin-related side effects, euglycemic ketoacidosis is perhaps the most concerning and it is to note that glycosuria makes the urinary tract more prone to bacterial and fungal activity, raising the risk of urinary tract and vaginal yeast infections, fractures and possibly limb amputations (especially with canagliflozin).(35,38)

4 Targeting SGLTs for Glycaemic Control

Glucose is transported through epithelial membranes by Na+-glucose co-transporters (SGLTs), SGLT1 and SGLT2.(39) The basic premise behind targeting SGLTs for glycaemic regulation is to decrease glucose load by inhibiting dietary glucose absorption in the intestine (mediated by SGLT1) and excreting filtered glucose into the urine (mediated by SGLT2 and SGLT1) through the kidneys.(39) Their inhibition has emerged as an important therapeutic tool for the treatment of T2DM.(35)

The lack of glycosuria under normal conditions is due to SGLTs reabsorbing the filtered glucose load. Of them, SGLT2, a protein located predominantly in the proximal convoluted tubule, reabsorbs the most.(35) As a result, SGLT2 inhibitors block glucose from being reabsorbed proximally by the kidneys, inducing glycosuria in diabetics and effectively reducing glucose levels in the bloodstream.(15) The bulk of dietary glucose uptake in the intestine is regulated by SGLT1, and humans with SGLT1 gene mutations experience glucose galactose malabsorption (GGM).(39) Both transporters, SGLT1 and SGLT2, are expressed in the kidney, and recent research has shown that SGLT2 mediates up to 97 percent of glucose reabsorption. Humans with SGLT2 gene mutations have familial renal glucosuria.(39) Surprisingly, SGLT2 knock-out or therapy with SGLT2 selective inhibitors only results in a fractional glucose excretion of 60%, an outcome induced by renal SGLT1 up-regulation. SGLT1/2 double knockout mice have no renal glucose reabsorption.(39)

Based on these results, it was proposed that dual SGLT1/2 inhibition could enhance glycaemic regulation even more by targeting two distinct organs that express SGLT1: the intestine and the kidney. Several SGLT2 inhibitors, as well as SGLT1 and dual SGLT1/2 inhibitors, have been developed based on the structure of phlorizin, a natural compound that acts as an SGLT1/2 inhibitor. Multiple SGLT2 inhibitors and one dual SGLT1/2 inhibitor have now been approved by the regulatory agencies.(39)

4.1 Glucose transport in the kidney

In healthy adult kidneys, all filtered glucose (180 g/dL) is reabsorbed by the proximal tubule. The brush boundary membranes of the early and late proximal tubule segments include SGLT2 and SGLT1, respectively.(40) The proximal tubule requires a

secondary active transport mechanism that relies on basolateral Na+/K+-ATPase activity to generate the driving force for apical glucose uptake through SGLTs.(40)

Under normoglycemia, SGLT2 accounts for 97 % of fractional glucose reabsorption (FGR), while SGLT1 accounts for 3 % of FGR. As a result, in normoglycemia, all transporters, SGLT1 and SGLT2, are responsible for all renal glucose reabsorption.(39)

As blood glucose levels exceed 200 mg/dL, the renal transport limit of glucose is reached, so glucose cannot be fully reabsorbed and is excreted in the urine. Because of this process, the human body is able to prevent prolonged stages of hyperglycaemia.(41) Under diabetic conditions, the renal transport maximum may increase, causing more glucose to be reabsorbed and leading to long-term hyperglycaemia. It is still unknown why diabetes causes a rise in renal transport maximum for glucose, although there are many (mal)adaptive pathways in the kidney that may play a role, more research is needed to understand these adjustments that occur in diabetes.(42) Evidence from SGLT2 inhibitors show that in the absence of SGLT2, the kidneys' reabsorptive ability for glucose drops to the residual capacity of SGLT1, resulting in a FGR of 40% or 80 g/dL. These results are supported by experiments in SGLT1−/− mice, which, when treated with an SGLT2 inhibitor, have no renal glucose reabsorption.(43) Inhibition of SGLT2 or hyperglycaemia reveals a significant capability of SGLT1 for glucose reabsorption in the late proximal tubule.(39)

Renal glycosuria is known to be caused by about 50 mutations, the majority of which are in the gene encoding SGLT2.(44) The disease is known as hereditary renal glucosuria and it is usually considered mild, it may cause symptoms such as polydipsia, polyuria, urogenital infections (including candida), and postprandial hypoglycaemia.(44) So far, no long-term complications in patients with SGLT2 mutations have been found, which suggested that designing SGLT2 inhibitors may be a theoretically safe therapeutic path to lowering glucose levels.(44)

Because SGLT2 receptors are glucose-dependent, a higher glycaemic index enhances the effect of SGLT2 inhibitors and potentiates glucose lowering independent of insulin action, consequently, there is no correlation between SGLT2 inhibitor activity and pancreatic beta-cell function.(11) SGLT2 inhibitors have also been identified as possible weight-loss agents and have shown blood-pressure-lowering effects by

osmotic diuresis with subsequent inhibition of the renin-angiotensin system, in addition to being hypoglycaemic agents. (11)

SGLT-2 inhibition has resulted in a considerable improvement in composite renal outcomes, which was more pronounced in patients with better renal function at baseline. This included decreases in albuminuria worsening, deteriorating renal function, progression of ESRF, and death from a renal cause.(34) Canagliflozin was shown to be the only antihyperglycemic agent successful in lowering cardiorenal outcomes in primary prevention groups with T2D and CKD as in CREDENCE trial. It also displays cardiorenal effectiveness in all levels of CKD, with the greatest efficacy in eGFR groups of 45–60 mL/min/1.73 m2 and urinary albumin to creatinine ratio >1000 mg/mL(45)

4.2 Glucose transport in the intestine

Seeing as postprandial hyperglycaemia is linked to an increased risk of diabetes complications, such as CVD, interventions aimed at avoiding such can also be used to treat CVD.(46)

The small intestine is the primary site of dietary glucose absorption, which is mediated mainly by SGLT1 on the brush border membrane. Facilitative glucose transporter, GLUT2, transports glucose into the bloodstream on the basolateral side. In addition to glucose uptake, intestinal SGLT1 controls the release of intestinal hormones involved in glucose balance, such as GIP and GLP-1.(47–50)

SGLT1 genetic mutations in humans cause GGM. Patients have symptoms in early childhood and have chronic watery diarrhoea, which is fatal if untreated. The signs are relieved by removing the harmful sugars (glucose, galactose, and lactose).(39,50)

Diabetes has an unclear effect on SGLT1 expression in the intestine.(39,51) According to the studies, hyperleptinemic mice, a well-established mouse model of T2DM, have slightly lower intestinal SGLT1 expression than aleptinemic mice, another T2DM model, which have no differences in SGLT1 expression.(39,51) As a result, hyperleptinemic mice had lower blood glucose rise in response to oral glucose tolerance tests, and treatment with the SGLT1/2 inhibitor phlorizin did not decrease blood glucose rise anymore.(39,51) The activation of the leptin receptor isoform A is one possible explanation for the decreased expression of SGLT1 in hyperleptinemic mice

(LEPRa).(39) More research is required to determine the possible benefits of intestinal SGLT1 inhibition in hyperleptinemic obese patients.(39)

5 Development of SGLT inhibitors

SGLT inhibition cause significant reductions in blood glucose level, HbA1c, body weight, blood pressure, reduced triglyceride. Because these parameters are prevalent co-morbidities in T2DM, lowering them altogether would lessen DM consequences. Hyperglycaemia is a significant cause of oxidative stress. It is generally understood that oxidative stress causes protein glycation, which leads to the dysfunction of essential enzymes in the body.(12)

Based on the logic presented above, inhibiting renal glucose reabsorption and/or intestinal glucose absorption has been presented as a promising approach to treating hyperglycaemia.(39) Dual SGLT1/2 inhibition may minimize postprandial glucose excursion, enhance insulin release/ inhibit glucagon release, and increase renal glucose excretion.(39)

Side effects of SGLT1 and 2 inhibitors may include polyuria, infections of the urinary and genital tracts, hypotension when combined with loop diuretics, hypoglycaemia when combined with insulin or sulfonylureas, lower limb amputation (hypovolemia leading to blood viscosity and venous thromboembolism)- this is probably not a class effect because a meta-analysis of 27 random controlled trials showed that although the risk of peripheral artery disease increased with SGLT2 inhibitors, it was only significant for patients taking canagliflozin, increased risk of bone fracture and acute kidney injury. (12) As a result, on February 24, 2017, the European Medicines Agency (EMA) warned patients taking the SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin about the potential increased risk of lower limb amputation (mostly affecting the toes), reminding them to check their feet regularly and follow their doctor's advice on routine preventative foot care.(52) Other side effects reported for SGLT2 inhibitors include nausea, polydipsia, arthralgia, angioedema, perineal necrotizing fasciitis, Fournier gangrene, diabetic ketoacidosis and hyperkalaemia(12). On February 25, 2016, the European Medicines Agency (EMA) emitted recommendations to reduce the risk of diabetic ketoacidosis, updating product information to include diabetic ketoacidosis as a rare adverse reaction and alerting for diabetic ketoacidosis symptoms.(53) EMA also cautioned healthcare professionals that SGLT2 inhibitors are not approved for the treatment of type 1 diabetes mellitus (T1DM), adding that incidences of ketoacidosis

have occurred during off-label usage and clinical studies in T1DM. In the treatment of T2DM, the advantages of these medications continue to exceed the dangers.(53)

The O-glucosides phlorizin and T-1095 were the first SGLT inhibitors discovered/developed. In 1835, chemists identified phlorizin, a compound derived from the apple tree's root bark, leaves, shoots, and fruit. It was reported that phlorizin increased urinary glucose excretion.(54) Subcutaneous administration of phlorizin normalized plasma glucose profiles and insulin sensitivity in insulin resistant diabetic rats. (55,56) Despite this, phlorizin was not a candidate for clinical development due to its poor solubility, low bioavailability (10%), and only a 6-fold higher selectivity for SGLT2 vs SGLT1.(57) T-1095, a prodrug that serves as an SGLT1 inhibitor in the intestine, mitigated some of these drawbacks. As T-1095 enters the bloodstream, it is converted into the active drug (T-1095A), which inhibits renal SGLT2, causing glucosuria.(57) T-1095, however, was never developed as a clinical drug due to its non-selective nature and safety issues.(54)

Further research led to the development of the selective SGLT2 inhibitors dapagliflozin, canagliflozin, empagliflozin and ertugliflozin, all of which containing C-glucoside linkage in lieu of O-glucoside linkage, rendering resistant to hydrolysis by β-glucosidase and increasing their half-life. The selectivity of C-glucoside-containing SGLT2 inhibitors for SGLT2 over SGLT1 varies, but their potency, protein binding, and half-life are all comparable.(39)

Recently, several attempts have been made to produce dual SGLT1/2 inhibitors and selective SGLT1 inhibitors. The European Medicines Agency has authorised sotagliflozin (Zynquista) as a dual SGLT1/2 inhibitor, however, sotagliflozin only has a 20-fold higher potency for SGLT2 vs SGLT1.(58) LIK066 (licogliflozin) is a dual SGLT1/2 inhibitor that improves metabolic hormone profiles by increasing GLP-1, while decreasing GIP, insulin, and blood glucose levels. Furthermore, licogliflozin treatment resulted in a 6% decrease in body weight in dysglycemic obese patients relative to placebo. Licogliflozin is currently being studied in phase II clinical trials for metabolic diseases such as obesity (NCT03100058) and polycystic ovary syndrome in obese people (NCT03152591).(39,59)

Several compounds for selective SGLT1 inhibition have been developed. Mizagliflozin, the most selective SGLT1 inhibitor currently available, is 300 times

more selective for SGLT1 than SGLT2. Mizagliflozin is a non-absorbable intestinal SGLT1-specific inhibitor with very poor bioavailability (F = 0.02 %) and no significant accumulation in tissues.(60) Present clinical trials are looking into mizagliflozin as a potential treatment for functional constipation (since mizagliflozin increases luminal glucose and water content). LX276123 and TP043883625 are two recently discovered non-absorbable SGLT1 inhibitors. Both compounds greatly decreased blood glucose excursions in rats after oral glucose tolerance studies. (61,62)

When using a medication to reduce blood glucose levels in T2DM, one must acknowledge the possibility of hypoglycaemia, since hypoglycaemia may hinder cardioprotective effects, which are induced in part by sympathetic nervous system activation. Apart from patients who are either taking sulfonylureas or insulin, the likelihood of hypoglycaemia during SGLT2 inhibitor therapy is minimal.(37,63)

Major clinical trials have been conducted to assess the efficacy of the selective SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin in the treatment of T2DM.(39) The incidence of heart failure was decreased by 35% with canagliflozin and empagliflozin, exceeding the necessary safety criteria. When opposed to placebo, dapagliflozin has little impact on the risk of major coronary injuries, although it did result in a reduced rate of cardiovascular mortality and heart failure hospitalization.(39) Gliflozins have diuretic and natriuretic effects in addition to their glucosuric function, which can help to relieve volume overload, blood pressure, and body weight, resulting in cardioprotective mechanisms.(39,64) Additional renal benefits included reduced albuminuria and a slower drop in eGFR. Because of the decreased absolute filtered glucose load in diabetic patients with CKD, the increase in glycaemic regulation in response to SGLT2 inhibition is diminished. Despite this, SGLT2 inhibitors' cardioprotective and blood pressure-lowering properties are maintained in patients with CKD and low eGFR.(39,65)

5.1 Renal SGLT1 inhibition

The role of renal SGLT1 in healthy individuals is quantitatively insignificant. However, in patients with uncontrolled T2DM (where the resorptive capacity of SGLT2 is exceeded) and in patients receiving medicines that limit SGLT2-mediated glucose absorption, the role of SGLT1 transporters becomes more important.(35)

Renal SGLT1 contributes 3% of FGR under normoglycemic conditions.(39) Notably, as more glucose is supplied to the late proximal tubule under hyperglycaemia conditions or through SGLT2 inhibition, this contribution will increase significantly (up to 40%-50%).(39,43) Although SGLT2 usually leads to more than 90% of FGR, pharmacologic or genetic inhibition of SGLT2 in patients decreased FGR to 40 to 50%.(39,43) This is due to SGLT1's compensatory function in the late proximal tubule.(39,43) In a non-diabetic mouse kidney, the basal overall glucose reabsorption capacities of SGLT2 vs SGLT1 is in the spectrum of 3:1 to 5:1.(39)

Based on this, it appears that blocking both SGLT1 and SGLT2 in the kidney at the same time could be more effective than just inhibiting SGLT2. Inhibiting SGLT1 would have a significant influence on intestinal glucose absorption, and the renal effects would be predicted to be additive to the intestinal effects.(39,66) The anticipated stronger diuretic effect may put patients at greater risk of hypotension, pre-renal failure, and complications from haemoconcentration and diabetic ketoacidosis.(39) Preliminary evidence in a mouse model of acute kidney injury revealed that SGLT1 deficiency increased kidney regeneration, elucidating SGLT1's function in outer medullary integrity. As a result, at least in terms of SGLT2 inhibitor-induced acute kidney injury, concomitant SGLT1 inhibition can mitigate this risk.(39,67)

5.2 Intestinal SGLT1 inhibition

It has proved challenging to obtain a level of selective SGLT1 inhibition in the intestine that decreases and delays glucose absorption while increasing downstream intestinal hormone production, without interfering with intestinal homeostasis, as it can increase glucose and Na levels in the large intestine, being linked to adverse GI effects.(68) Furthermore, it is unclear how an increase in colonic glucose may negatively influence the microbiota, if at all.(68,69)

In healthy individuals and diabetic rodents, selective SGLT1 inhibition has been demonstrated to delay post-prandial intestinal glucose absorption and increase plasma levels of GLP-1 and GIP. Because GLP-1 receptor agonists are an authorized therapy for T2DM, it is significant that SGLT1 inhibition results in elevated GLP-1 levels.(70–72) GLP-1 is advantageous in diabetes because it stimulates pancreatic β-cells to boost insulin secretion while decreasing glucagon secretion, also, in preclinical studies, GLP-

1 lowered hunger and increased β-cell mass. SGLT1 appears to be required for normal pancreatic β-and α-cell function.(39,50,73)

A recent randomized trial in T2DM patients found that taking canagliflozin before meals enhanced plasma GLP-1 levels.(74) Despite being more selective for SGLT2 than SGLT1, canagliflozin was shown to limit intestinal glucose absorption because concentrations in the intestinal lumen approached 10 times the IC50 of SGLT1.(72) Therefore, at high dosages, canagliflozin may act as a dual SGLT1/2 inhibitor, with both direct and indirect effects linked to SGLT1 inhibition in the intestine. Canagliflozin boosted up caecal short chain fatty acids (SCFA) in CKD mice, indicating enhanced bacterial carbohydrate fermentation in the intestine.(75) It is worth noting that canagliflozin's SGLT1 inhibitory activity may extend beyond the gut. In diabetic mice and T2DM patients, canagliflozin, unlike dapagliflozin (a selective SGLT2 inhibitor), was observed to suppress glucagon secretion.(39)

Blocking glucose transport in the upper small intestine will result in increased glucose delivery to distal segments of the small intestine and colon.(70,72) The gut microbiome may metabolize glucose in the colon to generate SCFA, which bind to free fatty acid receptors (FFAR2/3) on distal small intestine L cells and may induce sustained GLP-1 secretion. A recent research showed that colonic GLP-1 can be produced in response to SCFA without activating FFAR2/3.(76) It would be expected that changes in distal intestinal luminal glucose concentration because of SGLT1 inhibition might alter the gut microbiome. Paradoxically, in diabetic rats, therapy with a dual SGLT1/2 inhibitor showed no effect on the relative abundance of bacterial orders or bacteria of interest.(77) Canagliflozin therapy for two weeks, on the other hand, drastically affected the microbiota composition in CKD mice.(75) More research is needed to better achieve a better understanding of SGLT1 and/or 2 inhibition in gut microbiota.

SGLT1 deficiency causes GGM, which is characterized by osmotic diarrhoea, dehydration, and metabolic acidosis, so therapy with SGLT1 and dual SGLT1/2 inhibitors would be expected to elicit gastrointestinal side effects such as those. With this said, both the selective SGLT1 inhibitor mizagliflozin and the dual SGLT1/2 inhibitor sotagliflozin were found to be able to be administered orally at dosages that significantly reduce intestinal glucose absorption while causing no severe gastrointestinal side effects.(39,70,78) The increase in luminal glucose and water caused by SGLT1 inhibition, on the other hand, may be sufficient to loosen stools and

alleviate constipation. As previously stated, clinical trials are now being conducted to investigate the use of mizagliflozin for the treatment of functional constipation. Mizagliflozin has also been reported to alleviate abdominal discomfort, showing a potential in individuals with irritable bowel syndrome with constipation, that needs to be further investigated.(61,62)

SGLT1 inhibition in the intestine impacts glucose homeostasis directly by reducing glucose transport and indirectly by generating a sustained rise in GLP-1 and perhaps GIP release.(39) With this said, SGLT1 inhibition may be used to increase the effects of SGLT2 inhibitors or may have its own indications for the treatment of various disorders such as constipation, obesity, or polycystic ovarian syndrome.(39) Long-term studies are still required to properly assess the intestinal side effects and safety.(39) Compounds that inhibit SGLT1 must balance the modulation of mechanisms contributing to positive metabolic and negative intestinal effects to achieve therapeutic efficacy for metabolic diseases.(68)

5.3 SGLT1 inhibition beyond the kidney and intestine

In contrast to SGLT2 transporters that are exclusively expressed in renal proximal tubular cells, SGLT1 transporters exhibit a wider tissue distribution. Expression of these transporters has been observed in intestinal cells (where they participate in intestinal glucose absorption), heart (although it is not clear whether the expression involves myocardial or vascular endothelial cells), central nervous system cells, salivary glands, liver, pancreatic alpha cells, lung, and skeletal muscle. The pathophysiological role of SGLT1 transporters and the consequences of the inhibition are not well understood yet.(35,49)

Even though cardiac dysfunction is the leading cause of mortality in people with T2DM, lowering plasma glucose levels has minimal effect on CVD risk.(79) In vitro and in vivo investigations have shown that SGLT inhibitors are a potential therapeutic strategy for these pathological conditions.(79) Several clinical trials have indicated the effectiveness of SGLT inhibitors as a new and robust anti-diabetic medication that, in addition to antihyperglycemic action, can successfully treat the accompanying cardiac abnormalities.(79)

SGLT1 inhibition, according to a new study, should reduce the incidence of HF.(80) Several mechanisms have been proposed to contribute to the involvement of cardiac

SGLT1 in cardiac physiology and pathophysiology, it is known that SGLT1 is up regulated in cardiac ischaemia and hypertrophy(81,82).

Inhibiting or downregulating SGLT1 in the brain has been demonstrated to be useful for the early treatment of traumatic brain injury.(83)

Canagliflozin was linked to an increased incidence of below-knee amputations, which was first reported in the CANVAS study.(84) Udell et al. reported a 2-fold increase in amputation risk when the SGLT2 inhibitor cohort contained canagliflozin, empagliflozin, and dapagliflozin.(85) The cause of the increased amputation risk is uncertain, however it might be due to a direct SGLT2 inhibitory action or an off-target impact. Both may increase vulnerability to damage due to neuropathy, macro- and microvascular dysfunction-induced ischaemia, infection, and/or delayed wound healing. Another major adverse effect recently observed in individuals treated with SGLT2 inhibitors was the development of Fournier's gangrene.(86)

Data suggests a novel mechanism for the regulation of glucagon secretion through SGLT1 in pancreatic alfa cells, this could possibly explained the distinct effects of dapagliflozin and canagliflozin on plasma glucagon levels in mice(87)

Although SGLT1 inhibition warrants consideration for its therapeutic potential in diabetes and other pathologies (heart and brain), a better mechanistic insight of its function and the possible negative effects associated with SGLT1 inhibition is required.

5.4 Dual SGLT1/2 inhibitors

Dual SGLT1/2 inhibitors, such as sotagliflozin and licogliflozin, can block glucose uptake from the brush border of the small intestine in addition to preventing glucose absorption from the first, initial, segment of the proximal convoluted tubule.(12) This characteristic of dual SGLT1/2 inhibitors provides additional agonistic impact in hyperglycaemia treatment. The use of dual SGLT1/2 inhibitors has benefits and drawbacks.(12) This dual inhibition lowers postprandial glucose spike, increases GLP-1 release from the cecum, inhibits DPP-4, thereby extending GLP-1's longevity but it also causes adverse GI effects such as diarrhoea, increases the risk of diabetic ketoacidosis, and raises the risk of hypoglycaemia.(12)

Sotagliflozin (LX4211) is the first dual SGLT1/SGLT2 inhibitor of its kind.(58,88) The results of phase 1 and 2 clinical trials show results in postprandial glucose reduction,

stimulated GLP-1 and PYY secretion and increased urinary glucose excretion, resulting in substantial HbA1C reductions in patients with T2DM when combined with metformin, as well as in patients with T2DM and CKD.(73,88) Despite having a weaker effect on urinary glucose excretion than specific SGLT2 inhibitors, sotagliflozin is equally effective on HbA1C reduction as SGLT2 inhibitors, with a similar safety profile in short-term studies.(88)

6 Perspectives for SGLT1 inhibition in T2DM

Although SGLT2 does reduce blood glucose levels in diabetic individuals without inducing hypoglycaemia, it only inhibits glucose reabsorption by 50% and is thus ineffective as a monotherapy.(40) Given the large reserve capacity of SGLT1 in the late proximal tubule, dual SGLT1/2 inhibitors may be more successful in regulating renal glucose excretion.(40) Given the importance of the SGLT1 in renal glucose reabsorption and intestinal glucose absorption, it has been proposed that SGLT1 inhibition might be exploited to treat diabetic patients.(40) As a result, several dual SGLT1/2 and selective SGLT1 inhibitors are being evaluated as hypoglycaemic medicines. The long-term efficiency and safety of these therapies, unfortunately, is uncertain. Although SGLT2 inhibitors have the same problem, the benign course of hereditary glycosuria is comforting. Mutations linked with faulty SGLT1 transporters, on the other hand, cause severe osmotic diarrhoea, nephrocalcinosis, and proximal tubular dysfunction (as in GGM syndrome). As a result, the clinical effects of SGLT1 inhibition remain unknown.(35)

Selective SGLT1 and dual SGLT1/2 inhibitors have already been shown to have protective effects in T2DM, however heir efficacy will need to be validated in large clinical outcome trials. However, the increased prevalence of diabetic ketoacidosis is alarming. These inhibitors are being studied in CKD and HF patients since they do not require a diabetic state to reveal their impact on GFR and the body's volume homeostasis.(39,89)

Recent evidence indicates that SGLT2 inhibitors with low SGLT2/SGLT1 selectivity, such as canagliflozin and sotagliflozin, increase circulation GLP-1, an incretin hormone that increases insulin release in pancreatic β cells.(33) This impact is most likely caused by the inhibition of intestinal SGLT1, and the increase in active GLP-1 levels is more noticeable when these treatments are combined with DPP4 inhibitors.(33) These data imply that combining canagliflozin or sotagliflozin with a DPP4 inhibitor can offer a favourable impact linked with an increase in circulation active GLP-1 and may be used as a treatment for patients with T2DM. (33) However, empagliflozin, a highly selective SGLT2 inhibitor, has recently been found to raise circulating GLP-1, albeit in a minor way. (33) This shows that the processes driving canagliflozin or sotagliflozin-induced

circulation GLP-1 increase are complicated, and that numerous mechanisms, including those independent of SGLT1 inhibition, may be implicated.(33)

The potential of SGLT1 and 2 inhibitors to effectively lower hyperglycaemia, HbA1c, body weight, and blood pressure is a considerable advantage over many other anti-diabetic medication classes. This is since these factors are known to induce a wide range of disorders, including CV events, cancer, and many others. Preclinical and clinical trials are presently investigating new techniques to improve the efficacy of SGLT inhibition and raise the benefit-to-risk ratio of this therapy method.(35) This may involve the following:

- Development of more potent and more specific SGLT1 and 2 inhibitors. Dual SGLT1/2 inhibitors may help in the reduction of SGLT2-induced adverse effects, such as urinary tract infection, hypotension (in patients taking loop diuretics), increased risk of bone fracture.(12) On the other hand, dual SGLT1/2 inhibitors are responsible for other side effects such as diarrhoea, diabetic acidosis and hypoglycaemia. A reduction in the dosage could probably reduce these side effects, since dual SGLT inhibitors have been shown to also inhibit DPP-4 (increasing GLP-1 lifespan) and stimulate incretins, such as GIP and GLP-1, which reduces hyperglycaemia by stimulating insulin release.(12)
- Combination with existing drugs such as metformin, GLP-1 agonists, sulfonylureas, and many others will facilitate agonistic mechanisms and can help in the reduction of the effective therapeutic dose.(12) SGLT2 inhibitors when combined with GLP-1 RA have been reported to be more potent in the reduction of HbA1c, glucose level, body weight and blood pressure than when each of the drugs were given alone.(12)

Much more safety data from clinical trials is required to demonstrate dual SGLT1/2 inhibitors preventive function in diabetes-related CV events and to develop selective SGLT1 inhibitors.(79) Drugs that inhibit SGLT1-mediated glucose transport may preserve cardiac tissue by lowering glycogen build-up and the formation of reactive oxygen species. On the other hand, this approach may cause diarrhoea and volume depletion, may interfere with the correction of hypoglycaemia by oral carbohydrate delivery, and may predispose to the development of euglycemic diabetic ketoacidosis. As a result, SGLT1 inhibition appears to be a two-edged sword for the time being.(35)

6.1 Potential beneficial effects of SGLT1 inhibition

Glucose-lowering impact- Inhibiting SGLT1 results in lower glucose absorption in the intestine, exacerbated glucosuria and augmented GLP-1 secretion by intestinal L-cells. (35,43,72) SGLT2 inhibitors with low SGLT2 selectivity (canagliflozin or sotagliflozin) have been shown to also raise GLP-1 levels.(33) This increase is more noticeable with concomitant use of DPP-4 inhibitors. (33) So, this combination may be useful for patients with T2DM.(35)

Reduced risk of SGLT2 inhibitor-mediated acute kidney injury- Increased downstream glucose reabsorption by SGLT1 has been linked to SGLT2 inhibitor-associated nephrotoxicity. So, concomitant inhibition of SGLT1 may be beneficial.(35)

6.2 Potentially detrimental effects of SGLT1 inhibition

Increased risk of hypoglycaemia- An increased risk of hypoglycaemia-related manifestations is anticipated in patients treated with SGLT1 inhibitors, which is low when used as monotherapy or concomitantly with metformin is low, but it can be higher in those already treated with other drugs known to increase the rate of hypoglycaemia (such as insulin or sulfonylureas) or in case of limited carbohydrate intake. (35)

Increased risk of diarrhoea- It was observed an increased risk of osmotic diarrhoea in T1DM patient treated with sotagliflozin or canagliflozin, most cases were mild to moderate and transient.(12,35)

Increased risk of diabetic ketoacidosis- This side effect is well recognized for SGLT2 inhibitors.(88) Canagliflozin and sotagliflozin treated patients vs placebo had an increased rate of this detrimental side effect which may be related to an augmented reabsorption of ketone body in the distal tubules mediated by the volume depletion, which may further increase the magnitude of ketonemia noticed during SGLT2 inhibition.(12,35)

Increased risk of lower extremity amputations- The greater volume depletion observed during dual SGLT1/2 inhibition, and the resulting haemoconcentration could be the explanation of the higher risk of lower extremity amputations found in the CANVAS trial in patients treated with canagliflozin.(39,84,90) On the other hand, the risk for limb amputations was not affected by the administration of empagliflozin in the EMPA-REG OUTCOME trial.(35)

In addition, it has been hypothesized that SGLT1 inhibition may be problematic in enteric inflammatory conditions, since SGLT1 has been proposed as a novel immunological player in the intestinal mucosa.(35)

7 Conclusion

Despite advances in technology, current knowledge, and the numerous medicines accessible to the patients, the prevalence of T2DM continues to increase. In addition to this, diabetes complications continue to have a severe influence on patients' quality of life and place an even greater pressure on the healthcare system. The UKPDS study showed that earlier intervention for glycaemic control after onset of T2DM can prevent progression of both micro- and macrovascular complications. New T2DM therapies allows to treat each patient as an individual, tailoring therapy to their preferences, complications, and comorbidities. The beneficial effects of newer therapies such as GLP-1 RA and SGLT2 inhibitors on additional diseases such as obesity, blood pressure, CVD, and renal disease, as well as the lack of hypoglycaemia, implies that these newer agents should be higher on the therapy pathway for many patients.

Given the large reserve capacity of SGLT1 in the late proximal tubule, dual SGLT1/2 inhibitors and selective SGLT1 inhibitors may be successful in regulating renal glucose excretion. An intestinal-restricted SGLT1 inhibitor may meet the needs of metabolic disease patients in a manner like other locally acting non absorbed drugs, such as alfa glucosidase inhibitors. SGLT1 inhibition, either alone or in conjunction with SGLT2 inhibition, improves glycaemic control, however, further research is needed to determine the long-term efficacy and safety of SGLT1-targeted treatments. Combination therapy with dual SGLT1/2 inhibitors, such as canagliflozin and sotagliflozin, and a DPP4 inhibitor enhances elevation of circulating active GLP-1 compared with DPP4 inhibitor monotherapy. This may serve as a new strategy for treatment of patients with T2DM, although several issues remain to be clarified. The difficulty in achieving the correct "balance" of SGLT1 inhibition may contribute to the few dual SGLT1/2 or selective SGLT1 inhibitors that have advanced through clinical trials for T2DM.

In conclusion, for T2DM it is unlikely that selective SGLT1 inhibition could match the efficacy or the safety profile of dual SGLT1/2 inhibitors, since marketed dual SGLT1/2 inhibitors, such as canagliflozin, have a selectivity profile that includes intestinal and renal SGLT1 inhibition and still show good overall efficacy, without the additional concerns about GI tolerability. It seems challenging and unplausible to mitigate

selective SGLT1 inhibition concerns for minimal additional benefit over dual SGLT1/2 inhibitors.

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