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Sodium-glucose cotransporter 2 (SGLT2) inhibitors: from renal glycosuria to the treatment of type 2 diabetes mellitus

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ABSTRACT

For centuries, the kidney has been considered primarily an organ of elimination and a regulator of salt and ion balance. Although once thought that the kidney was the structural cause of diabetes, which in recent years has been ignored as a regulator of glucose homeostasis, is now recognized as a major player in the field of metabolic regulation carbohydrate. During fasting, 55% of the glucose comes from gluconeogenesis. Only 2 organs have this capability: the liver and kidney. The latter is responsible for 20% of total glucose production and 40% of that produced by gluconeogenesis. Today we have a better understanding of the physiology of renal glucose transport via specific transporters, such as type 2 sodium-glucose cotransporter (SGLT2). A natural compound, phlorizin, was isolated in early 1800 and for decades played an important role in diabetes and renal physiology research. Finally, at the nexus of these findings mentioned above, recognized the effect of phlorizin-like compounds in the renal glucose transporter, which has offered a new mechanism to treat hyperglycemia. This has led to the development of several potentially effective treatment modalities for the treatment of diabetes.

Key words: *Type 2 diabetes mellitus. Familial renal glucosuria. SGLT2 inhibitors.*

Inhibidores del cotransportador sodio-glucosa tipo 2 (SGLT2): de la glucosuria renal familiar al tratamiento de la diabetes mellitus tipo 2

RESUMEN

Durante siglos, el riñón se ha considerado principalmente un órgano de eliminación y un regulador de la sal y del equilibrio iónico. A pesar de que una vez se pensó que era la causa estructural de la diabetes, y que en los últimos años ha sido ignorado como regulador de la homeostasis de la glucosa, actualmente es reconocido como un actor importante en el ámbito de la regulación del metabolismo glucídico. Durante el ayuno, el 55% de la glucosa proviene de la gluconeogénesis. Sólo 2 órganos tienen esta capacidad: el hígado y el riñón. Este último es responsable del 20% de la producción total de glucosa y del 40% de la producida por la gluconeogénesis. Hoy en día tenemos una mejor comprensión de la fisiología del transporte de glucosa renal a través de transportadores específicos, como el cotransportador sodio-glucosa tipo 2 (SGLT2 por sus siglas en inglés: Sodium Glucose Cotransporter). Un compuesto natural, floricina, se aisló a principios de 1800 y durante décadas desempeñó un papel importante en la diabetes y la investigación de la fisiología renal. Finalmente, en el nexo de estos descubrimientos antes mencionados, se reconoció el efecto de compuestos floricina-like en los transportadores de glucosa renal, lo que ha ofrecido un nuevo mecanismo para el tratamiento de la hiperglucemia. Esto ha llevado al desarrollo de varias modalidades terapéuticas potencialmente eficaces para el tratamiento de la diabetes.

Palabras clave: *Diabetes mellitus tipo 2. Glucosuria renal familiar. Inhibidores de SGLT2.*

INTRODUCTION

In 2009, De Fronzo[1] described the rapid advances in the knowledge of the various pathophysiological pathways related to the development of diabetes. This was explained by the change from the triumvirate to the ominous octet, referring to the important role seemed to be played in carbohydrate metabolism by the kidney[2-4] (increasing the reabsorption of glucose), the small intestine and alpha cells (decreasing the incretin effect and increasing the production of glucagon), and the dysfunction of neurotransmitters in the central nervous system, together with the classic insulin resistance

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components (decreased insulin production, increased hepatic glucose production, decreased glucose uptake by skeletal muscle and increased lipolysis).

THE KIDNEY AND GLUCOSE HOMEOSTASIS

The kidney was traditionally considered as one of the main organs responsible for glucose homeostasis. However, we now understand that it plays an important role in glucose homeostasis in two ways: *1)* gluconeogenesis, and *2)* glomerular filtration and reabsorption of glucose in the proximal convoluted tubules.

With a better understanding of the renal mechanisms responsible for glucose homeostasis and the ability to manipulate that system, the kidney has become a key component in the treatment of hyperglycaemia.

Filtration and the reabsorption of glucose

For a healthy adult, approximately 180g of glucose is filtered by the glomerulus every day.[5] Under normal circumstances, almost all of this glucose is reabsorbed with less than 1% being excreted in the urine.[6] Glucose reabsorption in the tubules is a multi-step process involving several transport mechanisms. Glucose is filtered through the tubule and then transported via the tubular epithelial cells through the basolateral membrane into the peritubular capillary. Under optimal conditions, when tubular glucose load is approximately 120mg/min or less, there is no glucose loss in urine. However, when the glucose load exceeds approximately 220mg/min (glucose threshold), glucose starts to appear in the urine.

The blood glucose level required to provide such a tubular load covers a range of values in humans. A study of this process reported that the blood glucose concentration required to exceed the tubular glucose threshold ranged between 130 and 300mg/dl.[7] In addition, the study found a relationship between age and increased threshold levels.

90% of filtered glucose is reabsorbed by the high absorption capacity of SGLT2 transporter in the convoluted segment of the proximal tubule, and the remaining 10% of filtered glucose is reabsorbed by the SGLT1 transporter in the straight segment of the descending proximal tubule.[2] As a result, no glucose appears in the urine.

The maximum renal capacity for tubular reabsorption (Tm) of glucose is greater in animal models with type 1 and type 2 diabetes.[8] In people with type 1 diabetes, Mogensen et al.[9] showed that the glucose Tm is increased. Conflicting results have been reported in patients with type 2 diabetes.

Clinically, the most common cause of glycosuria is diabetes. Patients do not excrete glucose in the urine until the concentration of blood glucose is over 180mg/dl, which does not normally occur in people without diabetes.

Role of the SGLT2 transporter

The first step in the reabsorption of urine glucose involves the transport of glucose from the tubules to peritubular capillaries via tubular epithelial cells.[10] This is accomplished with the family of sodium-glucose cotransporters (SGLT), see Figure 1. The SGLTs include a variety of membrane proteins that act on the transport of glucose, amino acids, vitamins, ions and osmolytes across the brush border membrane of the renal proximal tubules and the intestinal epithelium.[11] SGLT1 is a low capacity and high affinity carrier. It is found mainly in the gastrointestinal tract, but can also be found in the S3 segment of the renal proximal tubule. Although SGLT1 is the key transporter for glucose absorption in the gastrointestinal tract, its impact on the kidney is less important; representing about 10% of glucose reabsorption.

This has been of some pharmacological interest because blocking this transporter theoretically reduces the gastrointestinal absorption of glucose and may provide a method for inducing weight loss or reducing postprandial hyperglycaemia.

By contrast, SGLT2 transporter has a high capacity and low affinity, and is found mainly in the kidney. Table 1 compares the SGLT1 and SGLT2 transporters.

A third member of this family, SGLT3, is widely found in skeletal muscle and the nervous system. SGLT3 is not believed to be a glucose transporter, but acts as a sensor.[12]

Although other members of this family have been identified (SGLT4, SGLT5 and SGLT6), their role in humans is not known at this time (Table 2). The most prevalent and functionally most important transporter in the kidney is SGLT2. It is responsible for 90% of glucose reabsorption in the kidney, and has become the subject of much interest in the diabetes field.

This transporter is found in a relatively high proportion in the initial segment of the proximal tubule (S1). SGLT2 transports glucose by using the energy gradient of sodium reabsorption in the tubular filtration. This process is called secondary active transport and is driven by the electrochemical gradient of sodium in the tubular filtration.

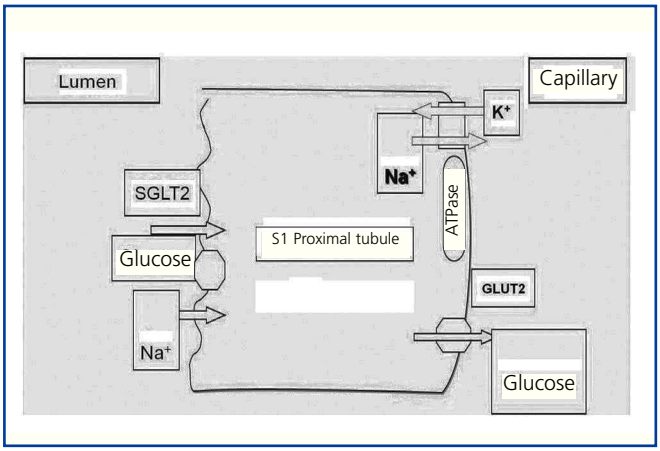

Figure 1. Mechanism of action of SGLT2
On the luminal side of the S1 segment of the proximal tubule, the absorption of sodium creates an energy gradient which allows glucose uptake via SGLT2 (sodium-glucose cotransporter type 2). On the other side of the cell, sodium is transported through the blood capillary basement membrane by the sodium-potassium ATPase pump. This phenomenon in turn creates another energy gradient and glucose is transported to capillary flow by glucose transporter 2 (GLUT210).

RENAL GLYCOSURIA: SGLT2 TRANSPORTER INHIBITION MODEL

Renal glycosuria is a genetic condition where the effects of the inhibition of SGLT2 transporter can be observed. Patients with this condition are asymptomatic, even though in most cases they have a SLC5A2 gene mutation (solute carrier family 5A), responsible for encoding SGLT2 transporter protein. Autosomal dominant and recessive inheritance patterns have been reported. As a result of this mutation, patients with renal glycosuria excrete in their urine more than 100g of glucose in 24 hours.

Santer et al.[13] conducted a genetic study on 23 families diagnosed with renal glycosuria and found 21 different mutations of the SLC5A2 gene. Fourteen out of the 21 families were homozygous and had glycosuria between 15 and 200g/day. Heterozygotes typically had glycosuria of under 4.4g/day, although some did not.

Two families diagnosed with renal glycosuria did not have the SLC5A gene mutation, but may have had mutations of the genes encoding GLUT2 (type 2 glucose transporter), HNF-1· (hepatic nuclear factor 1 alpha) which regulates the transcription of SGLT2 or genes related with SGLT1 or SGLT3.

Except for glycosuria, there were no other associated diseases. Plasma glucose was high or low, and blood volume remained essentially normal due to sodium reabsorption via other transporter channels. Renal and bladder function was normal, and this group of patients had no increased incidence of diabetes, kidney disease or urinary tract infections, compared with the general population.[14]

Figure 2 schematically shows the reabsorption of glucose in normal individuals and patients with renal glycosuria. As mentioned previously, the maximum renal capacity of tubular reabsorption (Tm) for glucose is variable, although for physiological studies (theoretical, continuous black line) it is about 198mg/dl (11mmol/l). The glucose Tm usually observed is below this figure (broken black line), and is saturated with glucose concentrations near 180mg/dl (10mmol/l[15]).

Renal glycosuria can be classified into two types.[13] Type A has a glucose Tm lower than in normal subjects (blue line).

Table 1. Comparison of SGLT1 and SGLT2 transporters

	SGLT1	SGLT2
Location	Small intestine and kidney	Kidney
Substrates	Glucose or galactose	Glucose
Glucose affinity	High	Low
Glucose transport capacity	Low	High
Function	- Intestinal absorption of glucose and galactose - Renal reabsorption of glucose	Renal reabsorption of glucose

In the kidney, SGLT2 transporter is responsible for 90% of tubular reabsorption of glucose, whereas SGLT1 is responsible for the remaining 10%. The low affinity for glucose and its high carrying capacity, make inhibition of SGLT2 a pharmacological mechanism for the treatment of type 2 diabetes mellitus.[14]

Table 2. Sodium-glucose cotransporter family

Transporter	Substrate	Tissue distribution
SGLT1	Glucose and galactose	**Kidney**, small intestine, heart and trachea
SGLT2	Glucose	**Kidney**
SGLT3	Glucose sensor	Small intestine, thyroid, testes, uterus and lung
SGLT4	Mannose, glucose, fructose, galactose and AG	**Kidney**, small intestine, liver, stomach and lung
SGLT5	Glucose and galactose	**Kidney**
SGLT6	Myo-inositol, glucose, xylose and chiro-inositol	**Kidney**, small intestine, spinal cord and brain

1,5 AG: 1,5-anhydro-D-glucitol[12]

These patients have decreased SGLT2 transporter activity as well as more significant glycosuria.

In type B renal glycosuria, the SGLT2 transporter has no affinity for glucose, resulting in a decrease in the reabsorption rate of glucose, but a normal glucose Tm (green line).

TYPE 2 DIABETES MELLITUS AND THE SGLT2 TRANSPORTER

Type 2 *diabetes mellitus* is associated with increased expression and activity of SGLT2.

In a study[16] of the SGLT2 transporter, human exfoliated proximal tubular epithelial cells (HEPTC) were used, which were obtained from urine samples. HEPTC were isolated from healthy individuals and diabetic patients, and were cultured in a hyperglycaemic medium.

As shown in Figure 3, the HEPTC of diabetic patients showed a statistically significant higher expression of SGLT2 and GLUT2 compared with non-diabetic individuals. They also determined the renal glucose uptake using methyl-α-D-[U^{14}C]-glucopyranoside (AMG), which is an analogue of glucose. More glucose uptake was also observed in diabetes patients? HEPTC than in individuals without diabetes.

These findings prove that the renal system noticeably contributes to the body's energy balance by regulating glucose uptake, and that diabetic patients appear to be poorly adapted to this mechanism. In diabetes, glucose reabsorption may be increased in absolute terms by an increase of glucose Tm.

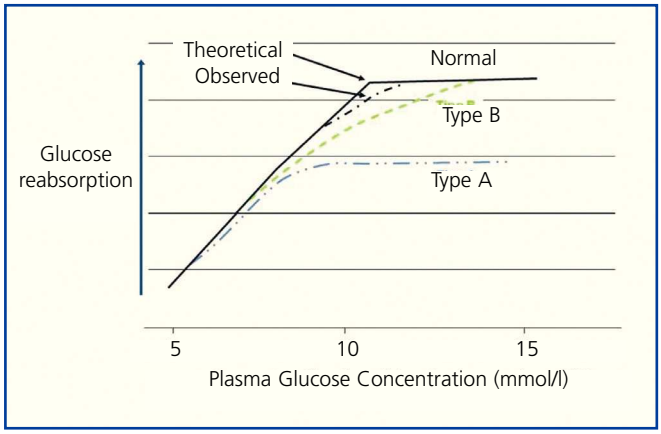

Figure 2. Comparison of the maximum tubular glucose reabsorption capacity (Tm)
The solid black line shows the theoretical glucose Tm, while the broken line shows the glucose Tm in healthy subjects. The glucose Tm in patients with type A renal glycosuria is shown by the blue line and type B in green.[13]

SGLT2 TRANSPORTER INHIBITORS FOR THE TREATMENT OF TYPE 2 *DIABETES MELLITUS*

In 1835, French chemists isolated a substance called phlorizin from the roots of apple trees. Although it was believed that phlorizin was a compound for treating fever, infectious diseases and malaria, it was not until 50 years after its discovery that it was found that high doses of phlorizin caused glycosuria.[17]

For several decades, phlorizin was used in the assessment of renal physiology. Then in 1970, it was discovered that glycosuria could be caused by phlorizin inhibiting an active transport system for tubular reabsorption of glucose. Between 1980 and 1990, the SGLT2 transporter was identified, and the inhibition of this transporter began to be profiled as a treatment for type 2 *diabetes mellitus*. Phlorizin was therefore the first known SGLT2 inhibitor.

However, phlorizin could not be used as a treatment for type 2 *diabetes mellitus* for several reasons. Firstly, because intestinal absorption is very poor and, secondly, because it

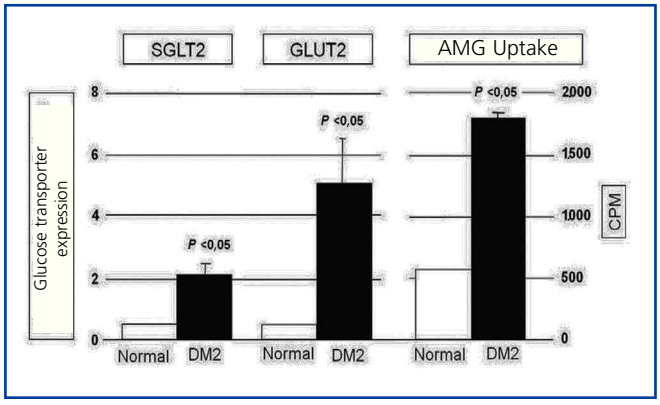

Figure 3. Comparison of the glucose tubular transporters in diabetics and non-diabetics.
Comparison of the expression of SGLT2 and GLUT2, and the methyl-α-D-[U14C]-glucopyranoside (AMG) uptake in human exfoliated proximal tubular epithelial cells (HEPTCs) in healthy individuals and diabetic patients[16] CPM: counts per minute.

does not just inhibit SGLT2, it is also capable of inhibiting SGLT1, causing osmotic diarrhoea in most cases.

SGLT2 inhibition can reduce plasma glucose levels by reducing the glucose Tm, resulting in increased urinary excretion of glucose.

In animals without diabetes, inhibition of SGLT2 has no effect on plasma glucose, because hepatic glucose production is increased to compensate for glycosuria. However, in diabetic animals, administration of SGLT2 inhibitors produces dose-dependent glycosuria and a significant reduction in plasma glucose.

SGLT2 inhibition essentially resets the maladaptive diabetic kidney by reducing the affinity of the transporter and increasing glycosuria, which decreases blood glucose and, therefore, glucotoxicity.[18]

Recently, phlorizin analogues selective for SGLT2 with better intestinal absorption have been developed. Table 3 shows some drugs in this group, including dapagliflozin and canagliflozin, which are currently in phase III clinical trials.

In addition, one laboratory is currently in phase I clinical trials[19] with a molecule called ISIS-388626 to reduce expression of SGLT2. This compound is an oligonucleotide that decreases transcription of the gene encoding the SGLT2 transporter. In murine and canine models, treatment with ISIS-388626 is highly selective, as it reduces the mRNA (messenger ribonucleic acid) of SGLT2 by 80% without modifying SGLT1. There was a significant reduction in fasting blood glucose, postprandial blood glucose and HbA_{1c} (glycated haemoglobin) in animal models, while no changes were observed in plasma and urine electrolyte concentrations.[20]

Of the SGLT2 inhibitors, the most developed is dapagliflozin.

Dapagliflozin is rapidly absorbed after oral administration in an average time of 1 hour (0.5hr-4.0hr) in patients with type 2 *diabetes mellitus*. A phase I study (in healthy volunteers) suggested that absorption was slower when given with meals, although this difference was minimal.[21] The half-life of dapagliflozin is approximately 16 hours. Glycosuria is dose-dependent.

Dapagliflozin renal clearance is minimal (3-6ml/min) and renal excretion is low (less than 2.5% in urine over 24h). *In vitro* studies have suggested that dapagliflozin is metabolised by metabolic inactivation of the enzyme glucuroniltransferase.[22]

Table 3. SGLT2 transporter inhibitor drugs and development phase

Active ingredient	Company	Clinical trials phase
Dapagliflozin	BMS/Astra Zeneca	III
Canagliflozin	Johnson & Johnson	II
Sergliflozin	GSK	Failed in phase I
Remogliflozin (KGT-1611)	Kiseei Pharmaceuticals	Failed in phase I
BI-10773	Boehringer Ingelheim	II
BI-44847	Boehringer Ingelheim	II
YM-543	Astellas	II
AVE-2268	Sanofi-Aventis	II

Information source: www.clinicaltrials.gov. BMS: Bristol Myers Squibb; GSK: GlaxoSmithKline.

Dapagliflozin has showed a hypoglycaemic effect at daily doses of 2.5mg, 5mg, 10mg, 20mg and 50mg in phase II clinical trials. Most of the ongoing phase III trials are evaluating the effects of daily doses of 2.5mg, 5mg and 10mg.

The randomised, double-blind, placebo-controlled phase II study on dapagliflozin assessed dose-dependent effects in patients with type 2 *diabetes mellitus*. A total of 389 type 2 diabetic patients without treatment and with HbA_{1c} higher than 7% were randomly assigned to a placebo group or a group treated with increasing doses of dapagliflozin for 12 weeks.[23] Metformin XR was the active comparator, although no statistical comparisons were made. Fasting blood glucose, postprandial blood glucose using prolonged oral glucose overload (3h) and HbA_{1c} were assessed.

Baseline HbA_{1c} ranged between 7.7% and 8.0% in all groups. In the dapagliflozin group, the decrease in HbA_{1c} was around 0.8%, while in the placebo group it was 0.2% ($P<.01$). Dapagliflozin patients had glycosuria between 52-85g/day, with a reduction in fasting blood glucose between 16-30mg/dl. A weight loss of 2.2kg-3.2kg was observed in the group treated with dapagliflozin, equivalent to an average weight loss of 2.5%-3.4%. An increase in urine volume from 107 to 470ml/day was also observed.

Regarding adverse effects, there was a slight increase in the incidence of urinary tract infections, although this was not statistically significant. There were no differences in the frequency of episodes of hypoglycaemia and hypotension between the groups.

Dapagliflozin is currently in advanced development for use alone or in combination with other hypoglycaemic agents. The drug was well tolerated in early stages, with the following as the most common side effects: urinary tract infections, dizziness, headache, fatigue, backache, and nasopharyngitis.[24] Phase III studies include monotherapy in patients with type 2 *diabetes mellitus* not controlled with diet and exercise, and in combination therapy with metformin, sulphonylureas, thiazolidinediones and insulin.[25-29]

SGLT2 inhibitors are a novel group of drugs that appear to provide several advantages in the treatment of type 2 *diabetes mellitus*:

1. Weight: SGLT2 inhibitors promote weight loss by increasing glycosuria (1g of glucose is equivalent to 4kcal), which lowers plasma glucose levels and stimulates lipolysis.
2. It corrects a defective mechanism in type 2 *diabetes mellitus*: Increased tubular reabsorption of glucose has been shown in diabetic patients.
3. Adverse effects: Hypoglycaemia is usually a barrier when considering strategies for optimal glycaemic control. As inhibition of SGLT2 is completely independent of insulin secretion, there is no increased risk of hypoglycaemia.
4. Treatment of hyperglycaemia: The unique mechanism of SGLT2 inhibitors means they can probably be used alongside other hypoglycaemic treatments.

The main concerns regarding inhibition of SGLT2 are the risk of urinary tract infections, reduced intravascular volume secondary to osmotic diuresis, electrolyte imbalance, nephrotoxicity due to the accumulation of advanced glycation end products, nocturia and drug interactions. Long-term studies are required to address these concerns, although the evidence obtained so far is sufficient to consider SGLT2 inhibitors as safe drugs.

SGLT2 inhibitors may not be effective in patients with renal failure due to a reduced glomerular filtration rate, although this is currently under investigation. Studies are underway to identify the glomerular filtration rate cut-off point to contraindicate SGLT2 inhibitors.

CONCLUSION

Inhibition of the SGLT2 glucose transporter is a new therapeutic approach to type 2 *diabetes mellitus*. Studies in experimental models for diabetes have shown that induction of glycosuria reverts glucotoxicity, restores normoglycaemia and improves beta cell function and insulin sensitivity.

The fact that there are genetic mutations of the SGLT2 glucose transporter, as occurs in renal glycosuria, supports the long-term inhibition of this transporter in humans. Preliminary results with dapagliflozin provide evidence of the efficacy of SGLT2 inhibitors in reducing fasting and postprandial blood glucose and decreasing HbA_{1c} in diabetic patients.

Understanding the pathophysiology of type 2 diabetes is a dynamic process: When new pathophysiological concepts arise, new potential therapeutic tools are found. The optimal treatment of type 2 *diabetes mellitus* requires a multiple approach to different defects in glucose homeostasis.

KEY CONCEPTS

1. 55% of glucose production comes from gluconeogenesis. The kidney is responsible for 40% of the glucose produced in gluconeogenesis, which is equivalent to about 20% of total glucose production.
2. In the kidney, the main carrier for tubular reabsorption of glucose is SGLT2.
3. In renal glycosuria there is a mutation of the SCL5A2 gene, which encodes SGLT2. In these patients, there is no increase in the incidence of diabetes or kidney disease. The only finding in most cases is asymptomatic glycosuria.
4. An increase in SGLT2 transporter activity has been observed in diabetic patients, resulting in increased tubular reabsorption of glucose.
5. SGLT2 inhibitors are emerging as a treatment for type 2 diabetes mellitus, due to inducing glycosuria and thus lowering plasma glucose and glucotoxicity.

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