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Renal Protection with Inhibitors of SGTL-2

João Pedro Rodrigues de Proença

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Orientadora: Dra. Catarina Cecília Pinheiro Reis dos Santos

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Resumo

A diabetes mellitus tipo 2 é uma patologia endócrina com complicações micro e macrovasculares. Dessas, a nefropatia diabética envolve um imenso esforço a nível mundial para controlar e tratar, sendo que ainda assim a maioria de casos de necessidade de terapia de substituição renal são devido à diabetes.

Os inibidores do cotransportador de sódio-glucose são uma classe de antidiabéticos orais que têm vindo a ser cada vez mais utilizados devido a resultados favoráveis na insuficiência cardíaca. Estudos mais recentes sugeriram um efeito positivo noutras condições, para lá do controlo glicémico, nomeadamente no atrasar da progressão da nefropatia diabética.

Esta revisão visa clarificar o estado da arte no que concerne ao efeito na função renal da utilização de inibidores da SGLT2, bem como no racional de inclusão desta classe no tratamento da doença renal crónica, mesmo em estadios avançados. Para o efeito, a presente revisão irá focar-se na fisiopatologia da nefropatia diabética, nos fatores que são alvo das terapias atuais e na discussão do papel que os inibidores da SGLT2 poderão ter no processo de doença.

Palavras-chave

“Nefropatia diabética”; “Doença renal diabética”; “Função renal”; “Inibidores da SGLT2”; “Diabetes mellitus tipo 2”

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Resumo alargado

A diabetes mellitus tipo 2 é uma patologia endócrina com implicações sistémicas que vão para além apenas da hiperglicemia e resistência à insulina. Trata-se de uma patologia que promove, a longo prazo, complicações macro e, particularmente, microvasculares como retinopatia, neuropatia e, de particular interesse para efeitos deste trabalho de revisão, nefropatia.

Apesar de existirem várias causas de doença renal crónica, a nefropatia diabética é comumente considerada a causa mais frequente de necessidade de terapia de substituição renal. O desenvolvimento de doença renal crónica num paciente diabético é também o principal preditor de mortalidade na diabetes mellitus.

Associado a isto, a incidência de nefropatia diabética tem aumentado ao longo dos anos, fruto quer da própria incidência e prevalência elevadas da própria patologia-mãe mas também pelo avançar da esperança de vida. Esta tendência crescente não conseguiu, infelizmente, ser mitigada pelos melhores esforços para impedir que pacientes diabéticos desenvolvessem nefropatia diabética.

Estima-se que em Portugal, em 2017, mais um milhão de pacientes se encontravam num qualquer estadio de doença renal crónica, com pesados custos pessoais, sociais e económicos, sendo que, para o mesmo ano, três mil pacientes terão falecido devido a doença renal crónica.

Existe, portanto, um esforço crescente transversal e internacional não só de protelar ao máximo o desenvolver de doença renal crónica, mas também de tentar manter os pacientes nos estadios mais baixos, impedindo que avancem para estadios com maiores custos, menor qualidade de vida e pior prognóstico.

O tratamento da doença renal crónica tem evoluído ao longo dos anos, sendo, por exemplo, hoje impensável não prescrever um inibidor da enzima de conversão da angiotensina na doença renal crónica hipertensiva como fator modificador de prognóstico. Na mesma linha, os inibidores do cotransportador sódio-glucose 2, uma proteína presente nos túbulos contornados proximais responsável pela reabsorção de sódio e glucose, surgiram como uma alterativa terapêutica a considerar.

Os inibidores da SGLT2 tratam-se de uma classe de antidiabéticos orais com efeito hipotensor ligeiro que demonstraram em ensaios clínicos um efeito cardioprotetor considerável, tendo por isso sido adicionados à terapia de doentes com patologia cardiovascular, particularmente insuficiência cardíaca, independentemente da concomitância de diabetes. São também atualmente considerados nos pacientes com

doença renal crónica que tenham comorbilidade cardiovascular associada, igualmente independente da presença ou não de diabetes.

Simultaneamente, esta classe demonstrou também um efeito renoprotetor independente da preservação da função cardíaca, nomeadamente demonstrando indícios de estabilização da função renal e manutenção da taxa de filtração glomerular, podendo assim potencialmente diminuir o ritmo de progressão da doença.

Atualmente algumas guidelines internacionais já aconselham, ainda que com cautela, o seu uso na doença renal crónica, no entanto ainda há muito a definir.

Apoiado nos resultados entusiasmantes dos primeiros ensaios clínicos, foram desenhados novos estudos, alguns ainda a decorrer, por forma a melhor balizar o efeito renoprotetor dos inibidores da SGLT2, a entender se esse efeito se mantém mesmo em estadios de doença avançada e a definir exatamente qual a melhor forma de incorporar a classe nas terapias atuais de forma a obter o melhor retorno.

Esta revisão visa, assim, clarificar o estado da arte relativamente ao uso desta classe em doentes renais crónicos, mesmo em estadios de doença mais avançados, indo para o efeito debruçar-se sobre a fisiopatologia da nefropatia diabética, os fatores fisiopatológicos que atualmente são alvo das terapias atuais e na discussão do papel que esta classe de antidiabéticos poderá ter no tratamento da doença renal crónica, independentemente da presença de diabetes.

Abstract

Type 2 diabetes mellitus is an endocrine disease that promotes both micro and macrovascular complications. Of those, diabetic nephropathy poses a large burden worldwide, one which we have, so far, failed to properly contain, with diabetic nephropathy accounting for the majority of end stage renal disease cases.

Sodium-glucose cotransporter inhibitors are a class of antidiabetic drugs that has come to the forefront of treatment for its favourable results in heart failure. Newer research has suggested their positive role in other conditions, apart from glycaemic control, namely in delaying the progression of diabetic nephropathy.

This review aims to clarify the state of the art regarding SGLT2 inhibitors effect on renal function and the rationale of including this drug class in the treatment of chronic kidney disease, even at late stages of disease. To achieve it, this review will focus on the process of disease in diabetic nephropathy, the current rationale for treatments, and on discussing the role that the addition of SGLT2 inhibitors could have on the disease process.

Keywords

“Diabetic nephropathy”; “Diabetic kidney disease”; “Renal function”; “SGLT2 inhibitors”; “Type 2 diabetes mellitus”

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List of Acronyms

ACR – Albumin Clearance Rate
AER – Albumin/Creatinine Ratio
CKD – Chronic Kidney Disease
DKD – Diabetic Kidney Disease
ESRD – End-Stage Renal Disease
GFR – Glomerular Filtration Rate
KDIGO – Kidney Disease Improving Global Outcomes
SGLT2 – Sodium-Glucose Cotransporter 2
T2DM – Type 2 Diabetes Mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is an endocrinal disease which, when untreated, has systemic effects on the human body that go further than just hyperglycaemia (1). It is well established that T2DM promotes, in time, both micro and macrovascular disease if the hyperglycaemic state is not adequately managed (1,2). One of such effects is diabetic nephropathy or diabetic kidney disease, a specific type of chronic kidney disease (CKD) that results directly from untreated or poorly treated T2DM (3).

Diabetic nephropathy poses a large burden worldwide, in both developed and less developed nations, with intensive and expensive treatments being necessary for the management of disease and maintenance of life (4). Furthermore, no therapies on the market are capable of adequately reverting kidney damage when the spiral of disease has initiated (5,6), hence the effort skews towards delaying the disease process to impede the loss of functional nephrons for as long as possible in order to delay more invasive therapeutic options, namely renal replacement therapy such as haemodialysis or kidney transplant (3).

SGLT2 inhibitors are a class of antidiabetic drugs that has come to interest in the last few years, particularly due to the better outcomes on heart failure patients that undergo therapy with them (7). The evidence seems to also indicate that, not only is this class of drug capable of lowering glycaemia, but indeed it might also have a further effect at preventing renal deterioration (8,9).

This review aims to clarify the need for further study into the therapy of diabetic nephropathy, namely regarding the use of SGLT2 inhibitors, in an effort to delay end-stage renal disease (ESRD), given not only the burden of disease for the patient but for the healthcare system as well. To that effect this review will focus on the process of disease in diabetic nephropathy, the rationale for treatment for the disease, and on discussing the role that the addition of SGLT2 inhibitors could have on the disease process.

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Methods

From September 2021 to August 2022, a literary search was conducted on *PubMed*, *Web of Science*, *Google Scholar* and *MEDLINE Complete*.

The search parameters focused on articles in English only, with no temporal limitation and using the keywords "SGLT2", "SGLT2 inhibitors", "sodium-glucose co-transporter", "renoprotection", "antidiabetics", "diabetic kidney disease", "proteinuria", "glomerular filtration rate", "renal clearance", "hyperfiltration" and "renal function", without filtering for any specific field.

Articles were included or excluded based on title and abstract, with all articles integrated on this review having been analysed in full to prevent author bias.

Where applicable, reference manuals, clinical guidelines and the latest scientific consensus and discussions were included in the drafting of this review.

As such, a total of 74 references were consulted for this review, the oldest from 1978 and the most recent from 2022. The breakdown of the references by type can be found on the following table:

Table 1 – Analysis of type of reference cited during this review

Type of reference	**Number of references per type**
Case Report	1
Expert opinion	3
Clinical Trial Registry	2
Reference Manual	4
Guideline (entity that published; year)	1 (American Diabetes Association; 2022) 1 (Direção-Geral da Saúde; 2011) 2 (KDIGO; 2013, 2021) 1 (UK Kidney Association; 2021)
Original Article Of which Clinical Trials	27 5
Review Of Clinical Trials	22 5
Meta-Analysis Of Clinical Trials	4 1
Systematic Review and Meta-Analysis Of Clinical Trials	6 1
TOTAL	**74**

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Burden of disease

Chronic kidney disease (CKD) is broadly defined by KDIGO (Kidney Disease Improving Global Outcomes) as an abnormality in kidney structure or function that has been present for more than three months and that has implications in the health of the affected person (10).

More objectively, CKD can be diagnosed following the criteria as stated in table 2 and further staged according to either glomerular filtration rate (from G1 to G5 – as shown on table 3) or albuminuria (from A1 to A3 – as shown on table 4) (10). Of importance, outcomes of CKD, while resultant from a number of factors, can be calculated and correlated with the aforementioned staging, and the inverse proportional effect from higher staging with poorer prognosis has been established (10–12).

With the epidemiological transition of the last century, noncommunicable diseases have come to the forefront of medical concern compared to past focus on communicable diseases as the main driver of mortality and morbidity in the world (13). Diabetes, namely T2DM, and hypertension, have become common realities that plague modern living, with both being known factors in causing CKD and, when not controlled, further deteriorating renal function until eventually reaching ESRD (3,4,10,13).

Worldwide, and according to the Global Burden of Disease, Injuries and Risk Factors study pooled data, chronic kidney disease was known to affect close to 700 million people in 2017, a global prevalence of 9.1%, with an account of 1.2 million deaths directly caused by CKD for the same year, becoming the 12th leading cause of death in 2017 (4,13).

While the data is particularly concerning regarding less developed countries or regions of lower socio-economic status, CKD affects higher income countries as well, with Western Europe having in 2017 close to 42 million people with CKD and 90 thousand deaths attributed to it. Portugal, for the same year, had more than a million patients fitting the criteria for any-stage CKD, and a further three thousand having perished as a result of the disease (4,13–15).

More concerning yet, only an estimated 10% of patients with CKD are aware they are suffering from it, a trend that is similar in both high and low social development index countries (4).

Mortality aside, the morbidity of the disease is of particular interest given how troubling it is: worldwide it is estimated that in 2017 CKD had resulted in 7.3 million of years of healthy life lost to disability and 28.5 million of years of life lost, resulting in a total of 35.8 million of disability-adjusted life-years (4). From these numbers it follows that despite the overall high prevalence of CKD, the years lost to disability account for only a fifth of disability-adjusted life-years, with stage 5 and ESRD accounting for more than 60% of those years lost

to disability. This demonstrates both the higher prevalence of lower stages of CKD compared to stage 5 and ESRD, the fact that in lower stages there is relatively low health affliction and that higher stages account for the majority of the burden of disease, further expanding on the importance of actively trying to prevent disease progression: keeping patients in as low as possible stage, for as long as can be achieved, in order to reach the lowest values (4).

Since 1990, both mortality and prevalence of CKD have not significantly decreased, unlike disability-adjusted life-years, demonstrating that treatment of the condition has pushed mortality towards older individuals with higher stages of CKD, this being of particular concern in aging societies that will have to deal with the economic burden of caring for more and more CKD patients that continue to die of the disease, despite best treatment (4). This is also concordant with the fact that roughly only 1 to 2% of patients with CKD ever reach ESRD levels, necessitating renal replacement therapy, which nevertheless places a significant economic burden on the healthcare systems (10,16).

The data likewise clearly indicates the disparity between low and high social-development index countries, particularly regarding mortality, further reflecting the costs associated with therapy, particularly for ESRD (4,10,13).

Chronic kidney disease can have several aetiologies, ranging from diabetes, hypertension, previous acute kidney injury (particularly glomerulonephritis) among other causes, but of them, a history of diabetes is the primary factor in developing CKD, with a diagnosis of diabetes accounting for upwards of 60% of cases of CKD in some developed countries (3). Using the data collected by the Global Burden of Disease, Injuries and Risk Factors study, diabetes was responsible for 11 million of the total disability-adjusted life-years attributed to CKD, making it the highest contributor of any cause to CKD disability-adjusted life-years, at roughly 30.7% (4). Furthermore, and contrary to hypertension which showed a decrease since 1990, the age-standardized incidence rate for CKD due to diabetes has increased, this being further problematic given the higher mortality and risk of developing ESRD in patients with diabetes (13,17).

While both type 1 and type 2 diabetes carry the risk of developing diabetic nephropathy, it is important to note that studies show that around a third of type 1 patients will develop the condition, while it rises to closer to 50% in T2DM. It is also important to remember that T2MD is subject to prevention through lifestyle modifications but has steadily risen across all regions of the globe, with an estimated prevalence of 7079 per 100.000 people in 2030 (1,3,5,18). In 2014, 422 million people were already living with diabetes, partially explaining the high CKD prevalence (13).

Despite the gravity of the problem presented here, there are relatively less pressing medical issues and risk factors being given more attention both by the general people and by the

governments, such as second-hand smoking or drug use, with only 17% of countries having a national strategy on handling any-stage CKD (4). Awareness aside, the international societies have written guidelines towards not only preventing deterioration into higher stages of CKD, but also in disease prevention and early identification and intervention (10,15). More specifically, there are also guidelines in place that deal directly with screening, preventing and managing diabetic nephropathy, both internationally and specific for Portugal, in an effort of mitigating the burden of CKD (1,19).

Table 2 – Criteria for Chronic Kidney Disease, from KDIGO (10)

KDIGO criteria for CKD (either of the following present for > 3 months)	
Markers of kidney damage (one or more)	Albuminuria (AER ≥ 30 mg/d; ACR ≥ 30 mg/g Urine sediment abnormalities Electrolyte and other abnormalities due to tubular disorders Abnormalities detected by histology Structural abnormalities detected by imaging History of kidney transplantation
Decreased glomerular filtration rate (GFR)	GFR < 60 mg/min/1.73m² (category G3a-G5)
AER: Albumin excretion rate; ACR: albumin/creatinine ratio	

Table 3 – Staging of Chronic Kidney Disease according to Glomerular Filtration Rate, from KDIGO (10)

GFR category	**GFR (ml/min/1.73 m²)**	**Definition**
G1	≥ 90	Normal or high
G2	60-89	Mildly decreased
G3a	45-59	Mildly to moderately decreased
G3b	30-44	Moderately to severely decreased
G4	15-30	Severely decreased
G5	< 15	Kidney failure
In the absence of evidence of kidney damage, neither G1 or G2 fulfill the criteria for CKD		

Table 4 – Staging of Chronic Kidney Disease according to Albuminuria, from KDIGO (10)

Albuminuria category	**AER (mg/d)**	**ACR (mg/g)**	**Definition**
A1	< 30	< 30	Normal to mildly increased
A2	30-300	30 – 300	Moderately increased
A3	> 300	> 300	Severely increased

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Diabetic nephropathy overview

Diabetes is a complex, chronic endocrine disease with multisystemic effects that go beyond just hyperglycaemia by itself (1). While focus has traditionally been skewed towards glycemic control, newer guidelines are increasingly addressing the micro and macrovascular effects of the disease in the various organs and tissues (1,2).

One of the targets for microvascular affection of diabetes is the kidney and, arguably, it is the most important target for microvascular damage given that roughly 30 to 40% of patients with diabetes will develop diabetic nephropathy (3). Diabetes is also commonly pointed as the leading cause of ESRD in the world, with CKD being the main predictor of excess mortality in diabetes and, as previously stated, the incidence for CKD due to diabetes has only increased, not decreased, despite best efforts that reduced the percentage of people with diabetes that develop CKD (3,5,6,13,20).

Diabetic nephropathy, like T2DM itself, is more efficaciously addressed through primary prevention measures, namely optimal glycaemic control; as with most chronic diseases, early intervention also leads to better outcomes, but at this stage the goal shifts to slowing disease progression as current therapies do not seem to be able to adequately halt or revert the disease (6,20).

Apart from hyperglycaemia, hypertension, dyslipidaemia, smoking, obesity, ethnic, familial and genetic predisposition have all been shown to be risk factors that influence the evolution to diabetic nephropathy (3,6). While the list is varied, it is nevertheless important to point out that hyperglycaemia is the main driver of disease progression, followed by hypertension, and with both factors acting synergically (3). Predictably optimal control of both has been shown to be the most effective strategy in slowing disease evolution and reducing mortality (20–24).

Hyperglycaemia and hypertension, acting in concert, lead to the formation of glycation end-products and intraglomerular hypertension which result in an inflammatory environment that ultimately foments the expansion of extracellular matrix and ultimately apoptosis of cells in nephrons (21).

The basis for the expansion of extracellular matrix actually develops as a physiological response in the kidney. Due to the increased filtered load of glucose in diabetes, SGLT2 receptors in the proximal tubule end up reabsorbing a higher concentration of sodium (20). In keeping with the normal function of the nephron, a lower sodium concentration reaching the *macula densa* activates the renin-angiotensin-aldosterone system, primarily promoting vasoconstriction of the efferent arteriole of the nephron, resulting in glomerular hyperfiltration, in an effort to increase the sodium filtration load through an elevated GFR

(3,20,21). Of note, this physiological mechanism is further expanded by the increased blood pressure that by itself also promotes a state of hyperfiltration (20).

The chronic increase in glomerular filtration has been shown, in animal models, to promote tubular hypertrophy and eventually glomerular hypertrophy and, ultimately, glomerulosclerosis as a secondary response to the tubular hypertrophy (25). It is important to note this sequence, because tubular hypertrophy occurs as a response to glomerular hyperfiltration, in fact, SGLT2 proteins have been shown to be higher expressed in these augmented tubules, showcasing the increased filtered load in glucose and the subsequent need for more SGLT2 proteins (20,26,27).

This increased filtration, while by itself able to eventually lead to glomerulosclerosis, actually acts in other ways to promote that end result, namely by increasing oxygen demand by the now hypertrophic cells. CKD patients, with or without diabetes, have been shown to have renal hypoxia, a result that inversely correlates with GFR (20,28). This hypoxic state of the environment triggers further inflammation, leading to extracellular matrix expansion and fibrosis, in doing so devolving into apoptosis of the nephron and a higher demand for the remaining, still healthy, nephrons (20,21,27). Hence, both mechanisms, the enhanced GFR through hyperfiltration, and the higher oxygen demand, will eventually result in the ever-declining GFR that the condition is known for (3,20).

Further compounded, there is a high comorbidity between T2DM and obesity or metabolic syndrome. Obesity is found to be an independent risk factor in the development of CKD, apparently due to the development of renal lipotoxicity. In both diabetic nephropathy and obesity-associated nephropathy, podocytes become injured and are found to present with lipid vacuolization, decreased density and foot-process effacement (3,20). The alterations in podocytes result in a loss of barrier that allows albumin to pass onto the tubules, resulting in albuminuria, a feature in diabetic nephropathy, but also, the presence of albumin itself in the tubules has been further showed to also promote tubular injury, mesangial proliferation and glomerulosclerosis (20,29,30).

With every factor pushing towards fibrosis and ultimately apoptosis of the nephrons, diabetic nephropathy, like other forms of CKD, evolves towards an ever-declining GFR with increasing albuminuria, leading to higher stages of CKD and eventually necessitating kidney replacement therapy (3,5). While originally diabetic nephropathy was described as starting with the loss of low amounts (upwards of 300 mg/day) of albumin in the urine, and despite it still being used as a marker today, we now know that neither the presence of microalbuminuria is sufficient for the development of nephropathy, nor is the absence of it the guarantee that the patient will have a maintained GFR (3,5). Hence, some of the efforts have focused on better understanding the correlation between GFR, albuminuria and CKD, to develop new and more accurate equations capable of predicting CKD (11,12,29).

At the same time, the effect that acute kidney injuries have on kidney function has been well established, with acute kidney injury being both a risk factor and capable of progressing CKD (31), as with before, care has been taken to reduce the probability of developing acute kidney injuries as much as possible, with international recommendations made for assessment after such an event, to better map out the future prognosis regarding kidney function (31).

Finally, as expounded before, since reversion of disease is still not achievable, first prevention and eventually the delay of the disease progression is the goal to strive for, as advanced CKD is associated with several other complications, as shown in figure 1 below, and as ESRD itself presents an immense burden for both the patient and for society itself (5). As such, in earlier stages of CKD, both the patient and the care team should work towards optimal control of the known risk factors, reason why all guidelines advise on intensive glycaemic control as well as the use of antihypertensive drugs, namely angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to likewise manage hypertension, allied with lifestyle measures such as losing weight, stop using tobacco, reducing salt intake and exercising regularly (3,5,23,24,32). Meanwhile, more robust research has been conducted in hopes of both finding new avenues of treatment and optimizing the current care in the earlier stages as much as possible, to retain patients in lower stages of CKD, with higher quality of life, for as long as possible (5).

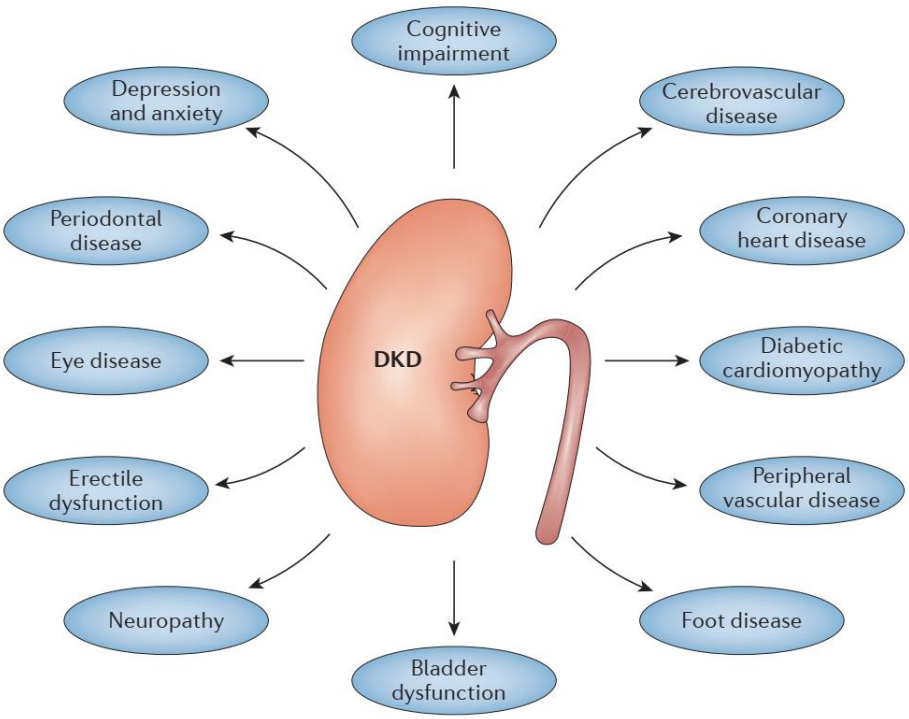

Figure 1 – Systemic complications of diabetic kidney disease, reproduced from Thomas, *et al.* (5)

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Mechanism of action of SGLT2 inhibitors

Sodium-glucose cotransporter 2 (SGLT2) is a protein responsible for moving glucose across the cell membrane, while using sodium as a cotransporter (33). It belongs to a family of proteins with the same name, of which there are six – SGLT1 through 6 (34); of them, SGLT1 and 2 are the main proteins handling glucose by the kidney, with SGLT2 only existing in the proximal tubule, while SGLT1 is found in the distal tubule and in other structures of the human body such as in enterocytes (34,35).

Codified by the solute carrier family 5 (SLC5A2), SGLT2, being a low-affinity but high-capacity glucose transporter, plays a significant role in the proximal tubule reabsorption of glucose (35). It is in the proximal tubule of the nephron that the majority (roughly 90%) of glucose is reabsorbed, following it's filtration by the glomerulus (3,33,35,36), the remainder being reabsorbed in the distal convoluted tubule, through SGLT1 effect (low capacity but high affinity) (33,35,36).

In a normal, healthy kidney, glucose is usually fully reabsorbed or otherwise only trace amounts make it into the urine (35,37). This will be dependent on both filtration and reabsorption, noting, however, that there is no secretion taking place for this molecule (37). Particularly in diabetes, glucose might be excreted in the urine, owning to its elevated concentration in blood, leading to increased filtration that saturates the reabsorption capacity somewhere between a plasmatic concentration of 200 to 250 mg/dL, a value in itself already higher than the general threshold for glucose in non-diabetic patients, which is between 170 and 200 mg/dL, owning to the increase in SGLT2 receptors in diabetic patients (26).

To achieve the transport of a substantial molecule such as glucose, SGLT2 makes use of the electric potential formed by the disparity between the intratubular and extratubular concentration of sodium and the subsequent difference in electric charge on both sides of the membrane (37); by moving sodium according to its electrochemical gradient through facilitated diffusion, SGLT2 proteins are able to lower the differential across membranes, and in doing so generate enough energy for the co-transport of glucose, without the need for further direct or indirect energetic inputs (37). As with everything else, glucose transport follows the most important role of the kidney, maintenance of homeostasis (37).

SGLT2 inhibitors act by blocking the co-transporter, actively preventing glucose reabsorption, and resulting in glycosuria (37). They have a significant effect on lowering glycaemia, while simultaneously having a discreet effect on blood pressure, a decrease between 4 and 5mmHg for systolic and 1 and 2mmHg for diastolic blood pressure, through augmenting sodium excretion, albeit with no markedly increase on the fractional sodium excretion, given the tight sodium control that occurs in the nephron (20,38,39).

SGLT2 inhibitors, a family of drugs called gliflozins, have made it to the market in Portugal and became successful additions to the pharmaceutical strategy of diabetes management, with three drugs in the portuguese market belonging to this family – canagliflozin, empagliflozin and dapagliflozin – that have both standalone pill presentations or associations with other antidiabetic drugs, such as metformin, in the same pill. Gliflozins have also demonstrated the added benefit of providing cardiovascular protection to patients with T2DM (40,41).

SGLT2 inhibitors outcomes on hyperglycaemia

Phlorizin, the first gliflozin to be characterized, was first isolated in 1835 from the bark of an apple tree, it has since been shown to both increase glycosuria and decrease glucose transport into the erythrocyte (34,42). By 1994, a high-affinity sodium-glucose cotransporter, SGLT1, had been described, including its functional characteristics as well as its tissue distribution (43).

Both of these events permitted the advance of a class of drugs that selectively inhibited SGLT2 function in the proximal tubule, with comparably fewer side effects, particularly intestinal side effects, than non-selective inhibition such as the one promoted by phlorizin would have (44); the first such compound to be approved by the European Medicines Agency was dapagliflozin in 2012, followed by canagliflozin approval in 2013 and empagliflozin in 2014 (45).

SGLT2 inhibitors, by acting through renal reabsorption inhibition, are an antidiabetic drug class that is insulin independent, hence being possible to use SGLT2 inhibitors both in monotherapy or associated with exogenous insulin or insulin dependent drugs such as metformin (1,34,35). In fact, the paradigm of only treating type 1 diabetes mellitus with insulin has been slowly changing with new evidence on the potential benefits of using insulin independent drugs even on this population, with SGLT2 inhibitors showing lower HbA1C levels, decreasing weight and improving blood pressure (1).

As previously alluded, in diabetes, the glucose reabsorption threshold is augmented as a result of a maladaptive response to extended hyperglycaemia. That, in turn, increases the tubular concentration of glucose and upregulates SGLT2 proteins in the proximal tubule, resulting in an increased glucose reabsorption of upwards to 20% compared to the euglycemic state (35,46).

The SGLT2 inhibitors in the market being all selective for the SGLT2 protein alone, and by acting as reversible competitors of the receptor, are able to contradict this effect resulting in up to 80 g/day of glucose being excreted (34,45,47). This amount is lower than the total daily filtered due to the action of SGLT1 reabsorption alone, a protein that, despite its low capacity for glucose, is modestly upregulated when SGLT2 inhibitors are used, hence the interest in developing SGLT1/2 inhibitors that are safe to use, without the deleterious effects described for phlorizin (36,46). Of note, apart from SGLT1 upregulation, the use of SGLT2 inhibitors has also been associated with an increase in the endogenous production of glucose probably mediated by an increased secretion of glucagon (36,38).

Clinical trials of SGLT2 inhibitors demonstrated remarkable similar results between the drugs in the class, with dapagliflozin, canagliflozin and empagliflozin, either in monotherapy or in association, significantly, if modestly, reducing HbA1C and achieving

lower fasting plasma glucose levels, regardless of baseline glucose-lowering therapy (27,38,45,47,48). Additionally, while initially being restricted to a higher than 60 ml/min/1.73m^2 GFR and thought to have diminished results regarding glycaemic control with lower levels, SGLT2 were shown not to promote hypoglycaemic events while maintaining effect, with dose adjustment, in upwards to stage 3 CKD or even as low as 20 to 25 ml/min/1.73m^2 (1,6,38,49). Finally, all drugs in this class lead to a statistically significant weight loss, probably from the loss of energy in the form of glycosuria and accompanied shift to lipid use, and lower blood pressure from the accompanying natriuresis, both effects generally welcomed additions to the treatment of diabetes (38,45,47,50,51).

The most important side effect of note is a statistically significant increase in lower urinary track infections, due to the glycosuric effect of the drugs, but events were generally mild and well controlled with standard treatment (38). Other possible side effects, such as increased fracture risk, orthostatic hypotension or acute renal injuries have been further evaluated with seemingly no association to be found (38,45,47,52,53).

As with other antidiabetic drugs, concerns arose for its potential to cause hypoglycaemia or ketoacidosis. While hypoglycaemic events were comparable to other classes of antidiabetic drugs (excluding sulfonylureas) (38), the data is not completely clear on the propensity of ketoacidosis compared to placebo, with studies showing both similar (54) or increased events (55,56). Following an abundance of caution, current guidelines inform of the risk and generally advise the use of SGLT2 inhibitors for patients on which ketoacidosis is not expected, leaving its use on other patients to the discretion of the care team (49).

Despite the vast armamentarium used to treat diabetes, particularly T2DM, SGLT2 inhibitors are a much-appreciated class that certainly has accrued merit in the treatment of diabetes. They do so by being a class that is insulin independent, able to be associated with other antidiabetic drugs, capable of lowering weight and blood pressure, being generally safe and well tolerated, and most of all effective in lowering glucose plasma levels without inducing hypoglycaemia (1,27,38,57).

SGLT2 inhibitors outcomes on renal function

Apart from lowering plasma glucose SGLT2 inhibitors have displayed a remarkable pleiotropic effect on the organism that sheds some light on its capacity of delaying renal function deterioration in CKD (58).

SGLT2 inhibition promotes such varied events as weight loss, lower blood pressure, reduced serum urate concentration, protection against endothelial dysfunction, decreased norepinephrine concentration in kidney tissue or even a possible positive impact on non-alcoholic steatohepatitis (51,59–61).

More importantly, because diabetes also has cardiovascular effects, newer antidiabetics need to prove to be safe with regards to the cardiovascular system. This led to clinical trials demonstrating a positive effect of SGLT2 inhibition, regardless of the presence of diabetes, in cardiovascular function (40,41,49,55,62).

The cardioprotective effect is particularly appreciated in CKD and diabetic nephropathy, where almost half of disability-associated life-years are due to cardiovascular disease, with 7.6% of worldwide deaths in 2017 attributed to cardiovascular disease having CKD as the root cause (4). In fact, currently SGLT2 inhibitor use is recommended in patients with CKD, regardless of glycaemic control, in which ketoacidosis is not expected, particularly CKD patients presenting with heart failure with reduced ejection fraction (27,49).

While the cardioprotective effect has been well established and the interplay between heart failure and renal disease, the cardiorenal syndrome, is of immense relevance, the direct gain in renal function, apart from the indirect benefit ascribed to a better heart function, is less clear than the cardiac protection itself.

As previously stated, the diabetic kidney undergoes a process of hypertrophy, that, in part, leads to an upregulation of SGLT2 proteins on the proximal tubule membrane and promotes a downwards spiral, starting with more glucose, sodium and chlorine reabsorption in the proximal tubule, that subsequently result in lower concentration of salt reaching the *macula densa*, triggering a process of hyperfiltration of the glomerulus, further enhanced by increased intraglomerular pressure due to the heightened reabsorption (27). The use of SGLT2 inhibitors was therefore theorized to lower GFR and albuminuria, hence mitigating hyperfiltration, and that was in fact observed in the very first trial that directly studied the effect of empagliflozin on the kidney. Of note, this reduction is independent of blood glucose levels, is reversible after discontinuation of treatment, is achievable even with low levels of kidney function, leads to long-term GFR preservation compared to placebo, and is also observed with the other drugs in the class (27,63–66).

The reduction of GFR and hyperfiltration leading to long-term preservation of kidney function, namely slowing the decline of GFR shown by the placebo arms in the trials, may

at first seem counter-intuitive, but one must take into consideration the stress that hyperfiltration puts on the nephron, allowing higher filtration of potential toxic compounds, and leading to hypoxia, oxidative stress, inflammation and fibrosis by itself (20,27). In effect, through hyperfiltration, there is an increase in oxygen consumption for the kidney, particularly in the proximal tubule owning to this being the prime location for reabsorption in the nephron, this will eventually lead to hypoxia and fibrosis when the nephron cannot comport with the energy expenditure created by the hyperfiltration (20,27). Hence the use of SGLT2 inhibitors, acting by the same rationale that governs angiotensin blocker use in CKD, leading to long-term benefits by lowering GFR, an effect that is in fact independent but cumulative when using both drugs, and still present in patients with as low as 30 ml/min/1.73m^2 of GFR (20,23,27,67).

Another potential effect on tissue oxygenation results from the possible enhanced erythropoiesis driven by the lesser oxygen pressure in the oxygen sensor regions in the kidney while using SGLT2 inhibitors. Patients on SGLT2 inhibitors have slightly higher levels of haemoglobin and haematocrit, a small increase that nevertheless accounts for roughly half of the reduction of risk in cardiovascular death seen with the drug empagliflozin against placebo, but possibly further oxygenating the kidneys themselves and leading to better renal function as a result (27,68).

While not yet established in humans, the improved oxygenation is postulated to improve mitochondrial function and autophagy, as well as ameliorating tubular function, although the effect on tubular hypertrophy is still contentious (20,27). Likewise, the podocyte dysfunction previously mentioned has been shown, in animal models, to be ameliorated, with an increase of podocyte autophagy that resulted in less podocyte effacement, detachment and apoptosis, leading to reduced mesangial expansion, improved glomerular histology and a decrease in albuminuria in these models (20).

Finally, in both *in vitro* human cultured cells and in animal models, an antifibrotic effect has been observed with the use of SGLT2 inhibitors, resulting in reduced mesangial expansion, interstitial fibrosis and lowering of inflammatory factors. In fact, it has been postulated that the histologic effects on lesser macrophage infiltration and fibroblast action stems from a direct result of lowering inflammatory markers (20).

Mechanisms aside, the real-world results from large scale trials are encouraging, with a multinational study following 65231 patients showing a significant prevention of decline in GFR in patients using SGLT2 inhibitors, and further protection from major kidney events, even compared to other antidiabetic drugs (8), a result that was reproduced in real-world clinical practice showing again an improvement compared to other antidiabetic drugs (69)) or even in non-diabetic patients with CKD (70). Further, an analysis of another four large

scale trials showed a significant reduction of the risk of incidence of acute kidney injury, dialysis, transplantation and death due to CKD (67).

A summary of the effects mediated by SGLT2 inhibition of interest to renal function expounded in this and previous sections can be seen below, in table 5.

Table 5 – SGLT2 inhibition effects on renal dysfunction, adapted from DeFronzo, *et al.* (20)

SGLT2 inhibition shown to improve	**Results not yet established**
Hyperglycaemia Hypertension Obesity or lipotoxicity Altered tubuloglomerular feedback Podocyte loss Albuminuria Inflammation Hypoxia Fibrosis	Endothelial dysfunction Mitochondrial injury Tubular hypertrophy or growth factors Autophagy

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Conclusion and Future Perspectives

Chronic kidney disease and particularly diabetic nephropathy is prevalent condition with a significant mortality and morbidity that strains both public health as well as posing a severe economic burden worldwide, regardless of how well developed a country is (4,13).

While controlling hypertension has shown decreases in CKD incidence and progression, we have so far failed to achieve the same result regarding diabetes, indicating further need for research in optimizing therapeutic goals, such as glycaemic indexes, or on furthering and strengthening primary prevention measures in an effort of lowering T2DM prevalence itself (13,17).

Regardless of strategy, the approach should be multifactorial and focus on both preventing CKD altogether and keeping the patients with the maximum health possible for as long as possible, which can be operationalized as managing patients to prevent further climbing on the KDIGO stages for CKD (5,10).

The treatment of CKD has been evolving in recent years, particularly regarding the treatment of cardiovascular comorbidities associated with CKD, which are a main factor in mortality and morbidity in this disease (27,40,41,49,55).

Of the recent treatment implementations, SGLT2 inhibitors have also seemingly displayed an independent effect on renal function, that is not associated with betterment of cardiovascular function. Several recent clinical trials have in fact pushed SGLT2 inhibitors as a mainstay therapy in the most recent guidelines, with increased indications of use (8,67,69–72).

Given early encouraging results on the improvement of renal function, the focus of clinical trials has steadily begun to shift to the effect of using this pharmaceutical class in CKD regardless of cardiovascular disease.

The first clinical trials, such as CREDENCE (23) or DAPA-CKD (70) have reproduced the initial results, sustaining the addition of SGLT2 inhibitors to the armamentarium of treatment, with ongoing trials focusing on better defining the effect on mortality and disease progression (73) and on the possible inclusion of patients with ESRD on haemodialysis in the treatment group (74).

Hopefully, the addition of SGLT2 inhibitors to CKD therapy, and optimization of its use therein, brings about a much-needed respite for such a debilitating disease in its end stages.

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