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Sodium-Glucose Transporter Inhibitors and Diabetic Nephropathy in Humans and Animal Model

Nakhoul Rola¹, Koch Elias², Nakhoul Farid^{3,4,5*}, Dahan Inbal⁴, Evgeny Farber³, Hanut Anam³, and Nakhoul Nakhoul³

¹Department of Medicine, University of Szeged, Szeged, Hungary

²Department of Medicine, Friedrich-Alexander-Universität, Erlangen-Nürnberg Schlossplatz, Erlangen, Germany

³Department of Nephrology and Hypertension, Baruch Padeh, Poriya Medical Centre, Israel

⁴Diabetes and Metabolism Lab, Baruch Padeh Poriya Medical Centre, Israel

⁵Department of Medicine, Bar Ilan University, Ramat Gan, Israel

*Corresponding author: Nakhoul Farid, Department of Nephrology and Hypertension, Baruch Padeh, Poriya Medical Centre, Israel, Tel: +9724-665-2587; E-mail: fnakhoul@poria.health.gov.il

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Abstract

Diabetic nephropathy as the leading cause for end stage renal disease and replacement therapy is increasing every year. Treatment of T2DM with the present oral blood glucose lowering drugs and insulin is challenging, with an enormous number of patients are able to achieve the target glycaemic control (HbA1C<6.5%). Despite the use of new Insulin compounds and different recommended combination of oral anti-diabetic drugs, the benefits of these recommendations are offset by side effects such as weight gain and recurrent hypoglycaemia. Therefore, the need for new agents that control blood glucose strictly and have other proactive cellular pathways is challenging. The sodium glucose transporter protein 2 (SGLT2) inhibitors, are recently being widely used.

The main therapeutic effect of these new drugs, SGLT2 inhibitors (SGLT2-I), is lowering the blood glucose levels *via* inhibitory effect on the transport of glucose and sodium in the proximal tubular cells by sodium glucose transport 1. SGLT2-I reduce plasma sodium level by natriuretic and diuresis, with decreasing blood pressure and body weight. These new medications can be used as first and second lines of treatment especially in patients with normal glomerular filtration rate, with or without cardiovascular complications. The most effective combination of SGLT2I is Metformin especially in albuminuria and slowing the progression of diabetic nephropathy especially if initiated in early stages of DM. The new class of medication (SGLT2I) are less effective in patients with moderate CKD (eGFR<45 ml/min). This review will focus on the new pathways such as autophagy as a new pathway where SGLT2 are involved with protective effects.

Keywords: Diabetes mellitus; Glomerular filtration rate; Diabetic kidney disease; Chronic kidney disease; End stage renal disease; Sodium glucose transporter protein 2 inhibitors; Autophagy

Abbreviations

DKD: Diabetic Kidney Disease, DN: Diabetic Nephropathy, ESRD: End Stage Renal Disease, mTORC1: Mammalian Target of Rapamycin Complex 1, RAAS: Renin-Angiotensin-Aldosterone-System, SGL2I: Sodium Glucose Transporter Inhibitors, T2 DM: Type 2 Diabetes Mellitus, MR: Magnetic Resonance

Introduction

Diabetic nephropathy is the leading cause of end stage renal failure worldwide. And at present it accounts for approximately 50% of all ESRD patients on replacement therapy [1,2]. The most known risk factors can be classified as susceptibility factors such as sex and genetics (es. Haptoglobin genotype) and initiation factors for DN such as hyperglycaemia, and progressive factors such as uncontrolled glucose level and arterial hypertension [3]. The main risk factor for DKD is the glucose cell toxicity [4,5]. Strict blood glucose control early in the course of the disease exerts a long-lasting favourable effect on the risk of DN development. This “legacy effect”, also named “metabolic memory”, suggests that early intensive glycaemic control can prevent irreversible renal parenchymal damage and replacement therapy [6].

The natural history of diabetic nephropathy includes different stages: Glomerular hyper filtration, micro albuminuria with incipient diabetic nephropathy, and diabetic nephropathy until irreversible renal failure. The early stages almost reversible with blood glucose control. High glucose is associated with podocytes

and PCT cells damage (Glomerular and tubular damage) with consequent glomerular hypertrophy, mesangial expansion and sclerosis. The uses of converting enzyme inhibitor, angiotensin receptor blocker alone or in combination with aldosterone blockers are insufficient in the early stages of diabetic nephropathy. Despite the RAAS and combined anti hyperglycaemic drugs, still there is a risk for the progression of diabetic nephropathy [7-10]. The clinical diagnosis of diabetic nephropathy is based on glomerular filtration rate (eGFR) and albuminuria along with clinical features, such as the hyperglycaemic state duration, proliferative retinopathy or other cardiovascular complications. However, intensive glucose and blood pressure control after onset of proteinuria and plasma creatinine elevation has not been shown to reduce risk of diabetic nephropathy progression [5,6].

Many markers have been used to predict early-stage renal dysfunction in diabetic patients. Neutrophil gelatinase-associated lipocalin (NGAL) and serum cystatin C (CysC) as markers of renal dysfunction in T2D. The presence of micro-albuminuria is a sign of the presence of diabetic kidney disease and marks the need for more intense glucose and blood pressure control. Diffusion-weighted MR imaging is an imaging modality that utilizes diffusion of water to characterize the structural changes of the tissue (Diffusion tensor imaging). This method is in use in assessment of normal renal parenchyma, renal fibrosis, and diabetic nephropathy in human in some centres in the world [11,12].

Once the irreversible state characterized with increased excretion of protein and plasma creatinine elevation is established, it is only possible to slow the progression of DN toward ESRD. Until recently, treatments with drugs that block the renin-angiotensin-aldosterone system (RAAS) have a proven beneficial effect in slowing kidney disease progression among those with diabetes; but their benefit is limited and they do not stop disease progression. Despite aggressive use of dual blockade of the renin-angiotensin-aldosterone system, and combination anti-diabetic therapy, the number of patients with diabetes mellitus who progress to end stage renal disease and replacement therapy is increasing [2,13,14].

Recently, new sodium-glucose transporters-2 inhibitors have become available: (Canagliflozin, Dapagliflozin, and Empagliflozin). This new drugs belong to the latest class of anti-diabetic agents to be introduced as first or second line treatment of diabetes mellitus type II. This decrease reabsorption of glucose to the PCT cells, which is enhanced in individuals with type 2 diabetes mellitus (T2DM), contributes to maintain near normal blood glucose levels, decrease glomerular hyperfiltration via tubuloglomerular feedback (TGF). Impressive the data in the literature showing the dual protective effect of SGLT2-I in improving glycaemic control in T2DM, and also through activation of the autophagic process [14-17].

Pathogenesis

Regarding the complicated pathogenesis of DN, there are several separate stages, including: reversible glomerular hyperfiltration, normal glomerular filtration, normoalbuminuria, normal or decreasing glomerular filtration and micro-

albuminuria, declining glomerular filtration and macro-albuminuria, until proteinuria with ESRD [17,18]. The pathophysiology of DN is composed from metabolic and hemodynamic factors such as oxidative stress, inflammation, and activation of the RAAS (**Figure 1A**). These activate inflammatory mediators and ischemic and fibrotic pathways leading to mesangial matrix accumulation, podocytes loss, glomerular basement membrane (GBM) thickening, tubular atrophy, tubulointerstitial inflammation, and fibrosis. Hyperglycaemia mediated alteration in extra- and intra-cellular metabolism including advanced glycation end products (AGEs), the enhancement of diacylglycerol/protein kinase C (DAG/PKC) activity, and increased flux through the polyol and hexosamine pathways constitute the main classical pathways involved in the pathogenesis of diabetic nephropathy [18-20]. Recently, the well-known autophagic process had been supposed as the main driven pathway involved in the evolution and generation of DN. Down regulation of the basal autophagic process activity in the podocytes and PCT cells, *via* the mTORC1 pathway. Autophagy, a lysosomal degradation pathway, plays a crucial role in cleaning protein aggregates and damaged organelles, including mitochondria, to maintain intracellular homeostasis. Therefore, autophagy may promote cellular health against various stress conditions, including endoplasmic reticulum (ER) stress. Increased cellular stresses induced by metabolic dysfunction, which is often observed in hyperglycaemia, impairs autophagy through activation of mammalian target of rapamycin complex 1 (mTORC1) and the reduction of AMP-activated kinase (AMPK) and Sirt1 activity [21-23].

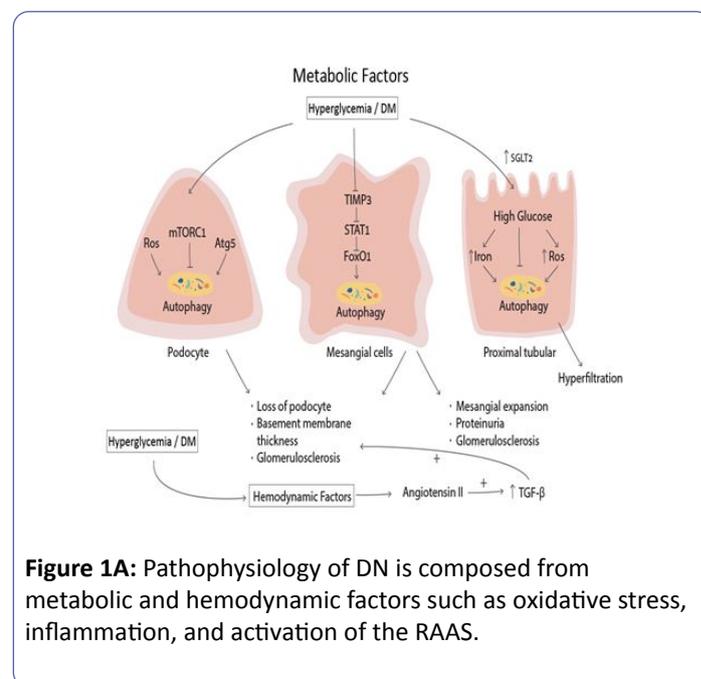


Figure 1A: Pathophysiology of DN is composed from metabolic and hemodynamic factors such as oxidative stress, inflammation, and activation of the RAAS.

Different studies hypothesize that up-regulation of sodium glucose co-transporter 2 (SGLT2) expressions due to hyperglycaemia, result in functional and structural changes including down regulation of the autophagy pathway in podocytes and PCT cells. So the new class of drugs including the SGLT2I can be of maggior benefit in slowing the progression of DN especially in early stages.

Mechanism of action of SGLT2 inhibitors

SGLT2-I are glucose-lowering agents that reduce the reabsorption of glucose and promote glucose excretion in the urine, thereby reducing hyperglycaemia in patients with T2DM [24]. Three SGLT2-I—Canagliflozin, Dapagliflozin, and Empagliflozin—have been approved for the treatment of T2DM in the United States and Europe. Effectively, all of the glucose filtered by the kidney in a healthy individual is reabsorbed and returned to the blood circulation. Renal glucose reabsorption is predominantly mediated by SGLT2. Evidence suggests that in patients with T2DM, the expression and activity of SGLT2 is increased in the presence of hyperglycaemia, resulting in additional glucose reabsorption and preservation of elevated blood glucose levels. Pharmacologic inhibition of SGLT2 in the kidney reduces the capacity for renal glucose reabsorption by up to 50% [25-28].

As SGLT2 reabsorbs sodium and glucose in a co-transport manner, SGLT2-I also cause natriuresis and diuresis with concomitant blood pressure and body weight lowering effects [29]. The use of these specific SGLT2-I can decrease the glomerular filtration rate via restoration of the TGF. These treatments are associated with an initial decrease in glomerular filtration rate (GFR), followed by normalization and stabilization of the GFR [29,30]. Dapagliflozin was the first SGLT2-I approved in Europe in 2012 and therefore the one with the longest usage in clinical practice. Dapagliflozin, a potent and selective SGLT2-I, has been shown to have synergistic glycemic control in patients with type 2 diabetes when used in combination with metformin, or insulin [31-33].

SGLT2 inhibitors and glomerular hyperfiltration

Treatment of T2DM continues to present challenges, with a significant number of patients using different oral anti-diabetic drugs in combination with insulin, but without achieving the target HbA1c. Despite the availability of new generation insulin and oral anti-diabetic agents, therapeutic efficacy is also offset by side effects such as weight gain and recurrent hypoglycaemia episodes, and the number of patients reaching ESRD and replacement therapy are increasing every year.

The two most important pathophysiological mechanisms leading to renal hyperfiltration in diabetes are glomerular hemodynamic abnormalities due to neurohormonal activation and tubular factors. The hemodynamic hypothesis is based on changes in afferent and efferent arteriolar tone, resulting in glomerular hyperfiltration, mostly due to RAAS activation [34]. The tubular hypothesis is based on the fact that hyperglycaemia causes an increase in proximal tubule glucose filtered load in hyperglycaemic state. This results in over-activity of SGLT2 and consequent increased proximal tubular reabsorption of glucose and sodium and activation of the tubuloglomerular feedback system. This increased proximal sodium reabsorption leads to decreased sodium delivery to the macula densa, with consequent reduction in ATP breakdown and adenosine production. Adenosine is a strong vasoconstrictor, and its reduction as in hyperglycaemia causes vasodilation of the afferent arteriole and thus glomerular hyperfiltration.

However, the renal protection could have been due to the known effects of Empagliflozin to reduce hyperfiltration and presumably intra-glomerular pressure with consequent renal tissue protection and slow kidney disease progression. The SGLT2 inhibitors, in addition to renal hemodynamic effects, including reducing glomerular hyperfiltration, also have inhibitory effects on the inflammatory and fibrotic responses of podocytes and proximal tubular cells to hyperglycaemia (**Figure 1B**) [35].

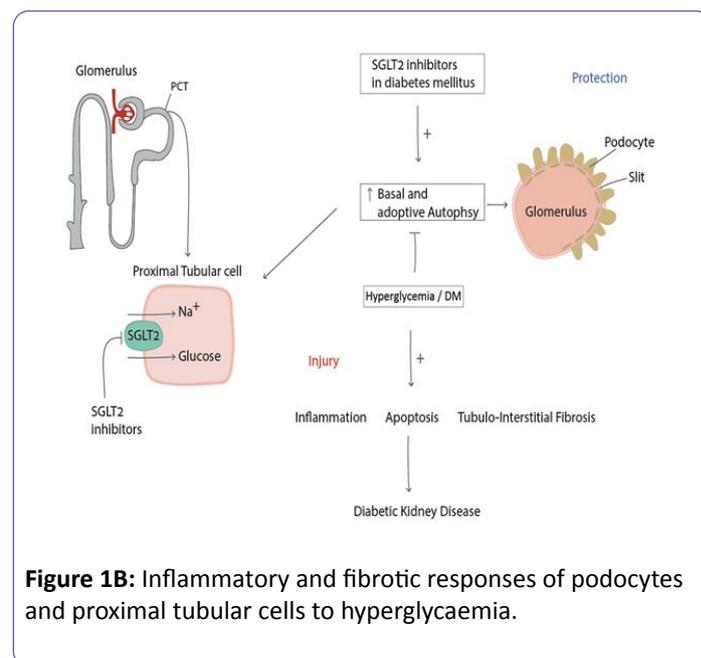


Figure 1B: Inflammatory and fibrotic responses of podocytes and proximal tubular cells to hyperglycaemia.

SGLT2 inhibitors and the diabetic kidney disease

The renal outcomes trial by Wanner et al. [36] recently reported that Empagliflozin (EMPA) administration was also associated with significant reductions in the progression of diabetic kidney disease including the rate of decline in eGFR, progression of albuminuria, and initiation of renal replacement therapy. There was a 38% risk reduction for progression to macroalbuminuria and a 44% relative risk reduction in doubling of serum creatinine in the EMPA group compared to placebo. Other studies demonstrate that in patients with eGFR of 30–60 mL/min/1.73 m² the efficacy of SGLT2 inhibitors in reducing HbA1c is less than in patients with preserved GFR. Moreover, in patients with eGFR of 45 mL/min/1.73 m², SGLT2 inhibitors are not recommended, and for this reason discontinuation is recommended when the eGFR is less than 45 mL/min.

The changes in GFR during SGLT2 inhibition are similar in patients with normal renal function and in those with mild to moderate CKD. In early stages of treatment, there is rapid decrease in GFR during the first weeks of treatment, followed by a progressive recovery that is faster and more evident in patients with normal renal function than with low GFR at baseline. Studies performed in patients with moderate renal impairment demonstrated significant renal protective effects on albuminuria and eGFR [37,38]. Overall, different studies consistently demonstrate a significant reduction in UACR during SGLT2 inhibition and stabilization of GFR. These renal effects

occur early after treatment initiation and last, in the longest trial, for up to 2 years [39].

Studies in animal models with diabetic nephropathy

Hyperglycaemia-mediated alterations of intracellular metabolism, including the accumulation of advanced glycation end products (AGEs), activation of protein kinase C (PKC), and oxidative stress (free radical species) are the major contributing factors to the pathogenesis of DN. Chronic hyperglycaemia also activates the diacylglycerol-PKC pathway, which contributes to the regulation of vascular permeability, vasoconstriction, extracellular matrix (ECM) synthesis and turnover, cell growth, angiogenesis, and cytokine activation.

Other cellular insults from hyperglycaemia, apoptosis, autophagy, and cell cycle arrest, are supposed to play fundamental roles in initiation and progression of diabetic nephropathy. Apoptosis (programmed cell death) and autophagy (cellular process that transfers intracellular components to lysosomes for degradation to keep homeostasis and cell integrity) are the main pathways involved in DN. Autophagy, a well-coordinated multi-step process regulated by autophagy-related gene (Atg) products (Atg5/Atg13), serves as an essential mechanism to maintain homeostasis of glomeruli and tubules, and plays important roles in human health and diseases such as high glucose and diabetes mellitus. Impairment of autophagy by up regulation of mTORC1 is implicated in the initiation and progression of DN.

During hyperglycaemia, increased glucose entry into renal proximal tubular cells stimulates oxidative stress generation with increased production of ROS and subsequently causes pro-apoptotic and pro-inflammatory processes. There is a decreased number of podocytes and effusion due to decreased autophagy (podocytopathy). Therefore, insufficient autophagy against cellular stresses such as hyperglycaemia may lead to renal cells injuries. In addition, recent reports have shown that alterations in the pathways such as mTORC1, AMPK, and Sirt1 in renal cells are related to the pathogenesis of diabetic renal injuries. The activation of mTORC1 and the decreased activation of AMPK and Sirt1, in conditions such as hyperglycaemia, may result in an impairment of autophagy. Thus, adaptive autophagy may protect renal cells, including podocytes, mesangial cells, glomerular endothelial cells, and tubular epithelial cells, against cellular stresses under diabetic conditions; therefore, regulating autophagy may be a therapeutic option in diabetic nephropathy in the future.

In hyperglycaemias there is increased mTORC1 expression in podocytes and PCT cells with consequent decreased autophagic activity with renal injury and fibrosis. Thus, autophagy activation in tubular epithelial cells contributes to maintenance of cellular and organelle homeostasis/stress resistance, preventing tubulo-interstitial fibrosis, apoptosis, and inflammation in the podocytes as described with rapamune treatment in animals. SGLT2 inhibition may be expected to induce autophagy in proximal tubular epithelial cells and podocytes in diabetic kidney disease by down regulation of the mTORC1 pathway.

In the diabetic mouse model, the increased creatinine clearance in diabetic ob/ob mice was associated with significant glomerular hypertrophy (using PAS-stained kidney sections) compared with WT mice. Empagliflozin treatment of ob/ob mice led to a significant reduction of the glomerular and tubular basement membrane hypertrophy. Hyper-albuminuria in the hyperfiltration state was markedly decreased in Empagliflozin-treated BTBR ob/ob mice. Glomerular matrix expansion in the diabetic BTBR ob/ob mice treated with Empagliflozin (SGL2 Inhibitor) showed a significant decrease in mesangial expansion compared with WT mice. Similar to the effects on albuminuria and glomerular hypertrophy, Empagliflozin treatment was able to ameliorate the increased glomerular matrix expansion. These findings suggest that SGLT2 inhibitors may protect against tubulointerstitial injury and fibrosis in diabetes if started in early stages of DM. Interestingly, there was a dose-dependent decrease in mesangial expansion and interstitial fibrosis, accompanied by reductions in macrophage infiltration, the gene expression of mediators of inflammation and oxidative stress, and transforming growth factor- β 1 (TGF β 1). Taken together, results in animal models suggest that SGLT2 inhibition has hemodynamic effects, attenuating glomerular hyperfiltration and reducing albuminuria, and progression of DN. At the cellular level, activation of autophagy by the suppression of mTORC1 may be a novel therapeutic target for treatment of diabetic nephropathy, such as treatment with the mTORC1 inhibitor Rapamycin or SGLT2 inhibitors and Metformin. Rapamycin and metformin improved proteinuria and slow the progression of DN [40,41].

Therefore, improvement of autophagy may be a novel therapeutic option for the suppression of diabetic nephropathy through activation of mTORC1 and reduction of AMPK and Sirt1, which use impairment of autophagy in concomitant use of RAAS blockers. Therefore, an mTORC1 inhibitor, or AMPK and Sirt1 activators, may be important for slowing of diabetic nephropathy [42].

Conclusions

The prevalence of type 2 diabetes is expected to continue to increase significantly over the next few years. Microalbuminuria and serum NGAL with Cystatin C are in clinical use to predict early renal parenchymal damage, and to encourage early treatment. Abdel Razek and his group describe a novel method of diffusion tensor imaging to detect early renal parenchymal damage. There was a significant difference in the diffusion MR imaging of the renal cortex in diabetic patients compared to volunteers, and patients with macroalbuminuria compared to micro-normoalbuminuria. Also, they describe a good correlation of these imaging parameters in the diabetic kidney with urinary and serum biomarkers of diabetic patients.

The use of new anti-diabetic SGLT2 inhibitors creates a new era of diabetes mellitus treatment and reduction in micro- and macro-vascular complications. They are efficacious in monotherapy and function as well as add-ons to oral anti-hyperglycaemic agents. SGLT2 inhibitors can be effectively combined with insulin and Metformin for individuals of all ages and at all stages of type 2 diabetes. It is anticipated that SGLT2

inhibitors will be increasingly prescribed, given the associated promising reductions in cardiovascular and renal events due to strict control of glucose and the extra glucose effect on cellular defence mechanisms such as apoptosis and autophagy [43-46].

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