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Invited Commentary

# Sodium-Glucose Cotransporter (SGLT2) inhibitors: A new Era in renovascular protection

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ABSTRACT

Diabetic kidney disease (diabetic nephropathy), one of the most serious renovascular diabetic complication represents the leading cause of chronic kidney disease worldwide and is characterized clinically by impaired renal functional indices, hypertension, systemic and renal hemodynamic changes and pathologically by a spectrum of glomerulotubulointerstitial and vascular lesions. Diabetic nephropathy is initiated by persistent hyperglycemia and glomerular hyperfiltration and, if untreated, progresses to increasing albuminuria, declining glomerular filtration rate (GFR), development of end-stage renal failure (ESRF) and or enhanced risk of poor cardiovascular outcomes. The emergence of sodium glucose co-transporter 2 (SGLT2) inhibitors, a novel class of antidiabetic drugs endowed with a wide range of pleiotropic actions revolutionized care of diabetes and its complications. These drugs reduce major cardiovascular events, heart failure hospitalization, rate of progression of albuminuria, and decline in GFR in both diabetic and non-diabetic patients with preserved or impaired renal function and development of ESRF.

Diabetes Mellitus (DM), a complex metabolic disorder remains a significant public health burden of cardiorenal morbidity and mortality. Due to the increasing obesity epidemic, the prevalence of diabetes mellitus has recently increased significantly worldwide reaching pandemic proportions.

Diabetes mellitus is clinically characterized by hyperglycemia due to insulin insufficiency caused by lack of insulin production (type 1 DM) or insulin insensitivity (type 2 DM). Hyperglycemia mediates mainly microvascular complications including diabetic kidney disease, retinopathy and neuropathy. In contrast, elevated blood glucose is only one of the multiple factors mediating the development of macrovascular complications.

Diabetic kidney disease (DKD), one of the most serious diabetic complications represents the leading cause of chronic kidney disease (CKD) and end-stage renal failure (ESRF) worldwide, accounting for 40–50% of new patients requiring renal replacement therapy and is associated with significantly enhanced risk of poor cardiovascular outcomes.

DKD can be defined as a renovascular disorder characterized clinically by parameters of renal functional impairment (albuminuria and decline in glomerular filtration rate), hypertension, systemic and renal hemodynamic changes, neurohormonal activation, a constellation of cardiovascular risk factors and pathologically by a spectrum of glomerulotubulointerstitial and vascular lesions, and if untreated by relentless progression to ESRF. In diabetics, the risk of death is increased fivefold with development of DKD and 100 fold with development of ESRF.

The early stages of DKD are characterized by glomerular hyperfiltration and albuminuria (proteinuria).

Glomerular hyperfiltration and intraglomerular capillary hypertension initiate the development of DKD.

In DM, renal autoregulation is impaired. Chronic hyperglycemia stimulates sodium-glucose co-transporter 2 (SGLT2) expression and activity leading to enhanced proximal tubular glucose and sodium (Na) reabsorption reduced sodium chloride (NaCl) delivery to the juxtaglomerular macula densa blunting the tubuloglomerular feedback (TGF), and inhibiting adenosine secretion, a strong pressor, and activating the renin-angiotensin system (RAS). Dysregulation of these vasoactive substances induce pre-glomerular dilatation, post-glomerular constriction, increased intra-glomerular capillary pressure and progressive nephron destruction [1].

Although albuminuria (proteinuria) has been considered to be the major clinical manifestation of DKD, several recent cross-sectional studies indicate that some patients with DM may develop progressive decline in renal function without proteinuria. In the light of these observations, DKD has been classified into proteinuric and non-proteinuric phenotypes [2].

Proteinuric DKD phenotype is characterized by a decline in renal function (estimated glomerular filtration rate (eGFR) $<$ 60ml/min/1.73m$^2$) associated with macroalbuminuria or proteinuria (urine albumin to creatinine ratio – UACr $>$ 300mg/g), hypertension, systemic and hemodynamic changes and a spectrum of proliferative and exudative glomerular lesions (diabetic glomerulopathy) leading to glomerulosclerosis, tubulointerstitial fibrosis and nephrosclerosis.

Albuminuria (proteinuria), the earliest clinical manifestation of DKD results from renal hemodynamically-induced injury to the glomerular filtration barrier at the level of the highly differentiated glomerular epithelial cells, the glomerular podocytes. Injury to the podocytes, a process referred to as podocytopathy represents the key event that triggers glomerular damage and loss of nephrons. Activation of the intrarenal RAS and hyperglycemia participate in the mechanisms that mediate the development of DKD and progression to chronic kidney disease (CKD).

Non-proteinuric DKD represents a diabetic nephropathy phenotype characterized by decreased renal function (eGFR $<$ 60 ml/min/1.73m$^2$ associated with normoalbuminuria or microalbuminuria (UACr $<$ 30–300 mg/g) with a prevalence of 20% in type 1 and 40% in type 2 DM. Most patients are elderly females, have a decreased waist

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circumference, a better controlled BP with less prescribed renin-angiotensin-aldosterone system (RAAS) inhibitors, and a lower incidence of microangiopathic complications (represented as diabetic retinopathy). Risk of progression to CKD is lower in non-proteinuric diabetic nephropathy phenotype as < 10% become proteinuric. Renal histopathologic changes are non-specific and include a wide spectrum of vascular and tubulointerstitial lesions. Diabetic glomerular lesions (diabetic glomerulopathy) are infrequently observed.

The pathophysiologic mechanisms underlying development of non-proteinuric DKD have not been completely elucidated but appear to be multifactorial. It has been postulated that glomerular hyperfiltration, long standing hypertension, poorly controlled diabetes mellitus initiate tubulointerstitial fibrosis and loss of tubular function leading to renal functional impairment. However, the minimal injury to the glomerular filtration barrier and epithelial podocytes might explain the absence of macroalbuminuria and decreased risk of CKD progression.

Hypertension is a frequent comorbidity in diabetes mellitus and their coexistence is associated with significantly enhanced cardiorenal morbidity and mortality.

About 40% of patients are already hypertensive when diagnosed with type 2 DM. Similarly, hypertension is exceedingly common in type 1 DM with about 30% of patients being hypertensive about 20 years after the onset of the metabolic disorder.

Hypertension develops in 85–90% of patients during the course of DKD and accelerates progression to ESRF.

Special features characterize hypertension in DKD patients [3]. In about 30% of these individuals, the circadian blood pressure (BP) rhythm is impaired. Both nocturnal fall in BP and nocturnal dipping pattern are blunted leading to nocturnal (night-time) hypertension (defined as SBP/DBP > 120/70 mmHg) and or non-dipping pattern (as reflected by a reduction of nocturnal BP of less than 10%). The uncontrolled nocturnal hypertension and altered dipping pattern enhance the risk of adverse cardiorenal events, even in diabetics with tight BP and glycemic control.

Similar mechanisms appear to mediate development of BP elevation in DKD and the impaired circadian BP rhythm: reduced renal function, volume expansion, decreased urinary Na excretion, impaired glucose/insulin metabolism, decreased arterial distensibility, and activation of neurohormonal systems and inflammatory pathways.

The interaction of hemodynamic and metabolic pathways alter mechanical properties of vascular system. In type 2 DM hypertensive renal patients, progressive loss of elastic fibers and accumulation of collagen fibers in central (elastic) arteries lead to progressive stiffening of the walls of the central arterial circulation, increased pulse wave velocity, increasing systolic BP, widening of pulse pressure, further deterioration of renal function and enhanced risk of poor cardiovascular outcome [1].

In contrast, in type 1 DM, persistent uncontrolled hyperglycemia and a poor metabolic profile mediate endothelial dysfunction of the systemic muscular arteries and arterioles leading to impaired vasomotor tone and sustained precapillary vasoconstriction, early reflection of incident pulse wave and enhanced central augmentation pressure and index, with the latter 2 parameters representing measures of arterial stiffness [4].

Endothelial dysfunction and enhanced arterial stiffness promote increased risk of BP elevation, CKD and cardiovascular events.

Non-alcoholic fatty liver disease (NAFLD) is a recently recognized serious risk in obese individuals for cardiorenal events. It represents the most frequent cause of liver disease, encompassing a wide spectrum of liver disorders spanning from hepatic steatosis to hepatocellular carcinoma with a prevalence of 25–50% worldwide. NAFLD confers a substantial risk for incident CKD and type 2 DM.

Despite the availability of a large number of therapeutic modalities including blockade of the RAAS, the management of DKD remains suboptimal. Further, there is a trend in the continued increase in the incidence of DKD, ESRF and enhanced risk of nephropathy associated adverse cardiovascular events.

The emergence of Sodium-Glucose-Cotransporter 2 (SGLT2) inhibitors represents a novel class of glucose lowering agents endowed with very effective cardiorenovascular protection. These drugs which reduce major cardiovascular events, heart failure hospitalization, rate of progression of macroalbuminuria, and decline in GFR in both diabetic and non-diabetic patients with preserved mild or even severe renal functional impairment, represent a breakthrough in the medical care of diabetes mellitus and its associated complications [5].

A wide spectrum of mechanisms appear to be involved in the cardiorenovascular protective properties of SGLT2 inhibitors in diabetic patients.

SGLT2 inhibitors lower blood glucose, independently of insulin action and beyond glucose lowering, and improve glucose-insulin metabolism, lipid profile, and decrease serum uric-acid. Further, by inhibiting proximal tubular glucose/Na reabsorption, they induce an osmotic diuresis and natriuresis, volume contraction, hemoconcentration and body weight reduction. Further, the glycosuria induces a significant calorie loss, contributing to body weight reduction. They also are involved in BP control, reversal of altered renal functional parameters and attenuation of pro-inflammatory markers.

SGLT2 inhibitors reduce systemic and nocturnal hypertension, reverse non-dipping pattern and normalize circadian BP rhythm. Further, they restore normal elastic properties of the central (elastic) arteries, and precapillary resistance vessels and reverse endothelial dysfunction. They may also provide liver and renal protection in obese diabetic patients with NAFLD.

The antihypertensive property of this class of antidiabetics is independent of glycemic control, appears to be related to body weight loss, extracellular volume contraction and improvement in vascular wall properties of the systemic circulation. Further, SGLT2 inhibitors enhance the antihypertensive action but do not overcome resistance to RAAS.

Several factors appear to contribute to the renal beneficial actions of SGLT2 inhibitors: i) reversal of glomerular hyperfiltration and intraglomerular capillary hypertension related to blockade of tubular glucose/Na reabsorption. The increased Na delivery to the macula densa as a consequence of inhibition of Na/glucose proximal tubular reabsorption activate the TGF mechanism, resulting in secretion of adenosine which induces preglomerular constriction, post-glomerular dilatation, decreased glomerular blood flow, glomerular filtration and filtration fraction. This effect manifests initially as a decline and then long-term stabilization of GFR, thereby lessening progression of DKD; ii) inhibition of pro-inflammatory and pro-fibrotic pathways, attenuating glomerulotubulointerstitial inflammation; iii) inhibition of neurohormonal cascade and generation of protective ACE 2 enzyme in podocytes; iv) reduction in systemic and nocturnal hypertension; v) improved distensibility of central (elastic) and musculoelastic circulation; vi) preservation of the integrity of glomerular filtration barrier, preventing/reducing albuminuria. SGLT2 inhibition reduces significantly urinary albumin excretion, whether in the micro/macroalbuminuric range, in type 1/2 diabetic patients with preserved or impaired renal function. However, the antialbuminuric response appears to vary between individuals. The antialbuminuric response appears to be due to a direct renal action, independent of metabolic and systemic factors.

Two mechanisms may be involved in the antialbuminuric actions of SGLT2 inhibitors: i) attenuation or reversal of glomerular hyperfiltration and intraglomerular capillary hypertension via TGF restoration; ii) prevention/reversal of damage to the glomerular filtration barrier and podocytes. Recent clinical and experimental studies provide support to this theory. In a cohort of non-diabetic proteinuric patients, SGLT2 inhibition attenuates proteinuria and appears to preserve integrity or reverse podocyte pathology [5].

Except for frequently encountered and easily treatable urogenital infections, SGLT2 inhibitors have proved to be safe and very effective. The risk of euglycemic ketoacidosis, hypoglycemia, hypotension and cancer are minimal. Although rare, SGLT2 inhibitors administration may precipitate acute kidney injury in the setting of extracellular volume depletion which however is generally reversible.

In conclusion, the introduction of SGLT2 inhibitors has

revolutionized the care of diabetes and its complications and improved our understanding about the pathophysiology of DKD. However, some concerns remain regarding their long-term efficacy and safety in type 2 DKD and their role in type 1 diabetic nephropathy [6].

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## Declaration of competing interest

None.

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