Time to completely eradicate diabetic nephropathy

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Abstract

Diabetes mellitus (DM) is the most important cause of end-stage renal disease, blindness, autonomic neuropathy, and heart failure. These complications endanger life expectancy, quality of life, and health costs in patients suffering from DM. These complications start to develop, especially in type 2 DM (T2DM), before the onset of this disease. Accumulating evidence proves that complications of diabetes are due to hyperglycemia that develops many years before the patients fulfill the diagnostic criteria of T2DM. Pathologic changes of diabetic kidney disease (DKD) in these patients have already developed by the time of onset of frank DM but are still clinically silent. These facts can explain the failure of the different sodium–glucose cotransporter 2 inhibitors (SGLT2is) to completely prevent renal events even in diabetic patients with apparently normal kidneys. Many studies have used different SGLT2is in patients devoid of diabetes without the fear of hypoglycemia. Available evidence pushes toward the use of SGLT2is as early as the onset of prediabetes. This approach would eradicate not only DKD but also other known complications. The use of these agents by the onset of T1DM might be also justifiable. The early use of SGLT2is as early as the onset of prediabetes might abort the development of DKD completely. This review provides insights for prospective studies that would make this hope a reality.

Keywords

type 1 diabetes mellitus • type 2 diabetes mellitus, diabetic kidney disease • diabetic nephropathy • sodium–glucose cotransporter 2 inhibitors • empagliflozin • canagliflozin • dapagliflozin

1. Introduction

Among the different causes of end-stage renal disease (ESRD), diabetic kidney disease (DKD) is the most frequent worldwide. Approximately 30% of type 1 diabetes mellitus (T1DM) and 40% of type 2 diabetes mellitus (T2DM) patients develop DKD [1]. In 2019, 463 million people worldwide (9.3%) had diabetes mellitus (DM). By 2030, this number is expected to be 578 million (10.2%) and 700 million (10.9%) by 2045. Similar figures for prediabetes are 374 million (7.5%) in 2019, 454 million (8.0%) by 2030, and 548 million (8.6%) by 2045 [2]. Table 1 shows the diagnostic criteria of prediabetes.

The consistent rise in the incidence of DKD parallels the inflating prevalence of DM [3]. The mortality rate attributed to DKD is the highest among the different chronic diseases [1]. One person loses his life annually among every 20 British patients with T2DM and DKD [4]. Among the Japanese DKD patients, the incidence rate of all-cause mortality is 12.3/1000 person-years. When estimated glomerular filtration rate (eGFR) is < 30 mL/min/1.73m², the incidence reaches 57.4/1000 person-years [5].

The earliest stage of DKD is the stage of glomerular hyperfiltration [6]. Glomerular hyperfiltration starts before the onset of DM. Many reports from different continents report glomerular hyperfiltration in personnel suffering from prediabetes [7–9]. The second stage of DKD is the stage of clinical quiescence that is characterized by the development of pathologic glomerular changes while eGFR becomes normal and urinary albumin excretion (UAE) is below 30 mg/gm creatinine. These changes precede the appearance of clinical manifestations, the development of microalbuminuria, or the decline of GFR. During this stage, progressive glomerular basement membrane thickening occurs together with mesangial expansion and glomerulosclerosis. Once microalbuminuria is clinically apparent, the patient already passed into the third stage called the stage of incipient nephropathy characterized by structural lesions that are often considerably advanced. Stage four starts when UAE exceeds 300 mg/day or 300 mg/gm creatinine (overt nephropathy). The GFR decline may then proceed rapidly toward the last stage of ESRD when eGFR becomes < 15 mL/min/1.73m² (Figure 1) [10]. The pathology of diabetic nephropathy (DN) progresses in six stages as follows: Stage 0 = no diabetic lesions; stage I = mild or nonspecific light microscopy changes and glomerular basement membrane thickening proven by electron microscopy; stage IIa = mild mesangial expansion; stage IIb = severe mesangial expansion; stage IIc = nodular glomerulosclerosis; stage III = advanced glomerulosclerosis; stage IV = end-stage renal disease.
**DIABETIC NEPHROPATHY**

### Criterion

<table>
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<tr>
<th>ADA</th>
<th>WHO</th>
<th>Nomenclature</th>
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<tr>
<td>100–125 mg/dL</td>
<td>110–125 mg/dL</td>
<td>High fasting glucose</td>
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<tr>
<td>140–199 mg/dL</td>
<td>140–199 mg/dL</td>
<td>Impaired glucose tolerance</td>
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<td>5.7%–6.4%</td>
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ADA, American Diabetes Association; WHO, World Health Organization; FPG, fasting plasma glucose; OGTT, oral glucose tolerance test; HbA1c, hemoglobin A1c.

**Table 1. Prediabetes as defined by ADA and WHO.**

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**Figure 1. Stages of diabetic nephropathy. Stage 2 is characterized by the progressive increase in mesangial deposits on light microscopy without corresponding clinical or laboratory findings.** ESRD when eGFRs ≤ 15 mL/min/1.73m². ESRD, end-stage renal disease; eGFRs, epidermal growth factor receptors.

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Stage III = nodular sclerosis (Kimmelstiel-Wilson lesion); and stage IV = advanced diabetic glomerulosclerosis [11]. According to Comai et al., biopsies obtained from deceased donors with GFR > 60 mL/min/1.73m² and normal urine protein excretion showed pathologic changes from stage I to stage III. The most frequent pathology in these kidneys was stage IIa [12].

Early diagnosis and intervention are the core strategies to prevent the development of DN [13]. Patients with prediabetes not only experience glomerular hypertension, but some of them may progress further. Impairment of kidney functions occurs in patients suffering from prediabetes [14,15]. Out of the newly diagnosed T2DM patients, 3.0% show overt nephropathy [3]. Histopathologic examination proved a variable degree of diabetic kidney disease in 32 out of 35 (91.4%) deceased donors that had diabetes, eGFR > 60 mL/min/1.73m², and normal UAE [16].

Persons having prediabetes might develop other diabetic complications. Diabetes prevention program (DPP) disclosed that 7.9% of the persons recruited who did not have a history of frank diabetes but had stigmata of prediabetes showed diabetic retinopathy on examination by stereoscopic fundus photography [17]. About 9.0% of personnel having prediabetes had signs of cardiac autonomic neuropathy [18]. A growing link between prediabetes and the risk of peripheral neuropathy is well recognized in the literature [19]. In a recent study of 40,117 participants from the United States up to 10.8% of prediabetes cases developed heart failure [20]. Another meta-analysis that appeared within the same year and included 15 observational studies of nearly 10 million candidates with a median follow-up of 8.0 years disclosed similar results [21].

**2. Methods**

A systematic search for diabetic kidney disease, sodium-glucose cotransporter (SGLT) inhibitors, and prediabetes was performed using the PubMed, Embase, and Cochrane Library electronic databases. The individual and joint search terms included: diabetic nephropathy; diabetic kidney disease; SGLT inhibitors; SGLT2 (SGLT2) inhibitors; dapagliflozin; empagliflozin; canagliflozin; prediabetes. No publication type, publication date, or publication language was used.

**2.1. Pathogenesis of DKD**

The hyperglycemia-mediated renal injury occurs through hemodynamic, multiple metabolic, and inflammatory pathways. The metabolic pathways include increased reactive oxygen species (ROS), excess advanced glycation end products (AGEs) deposition, the activation of the renin-angiotensin system (RAS), the activation of polyol, and hexosamine pathways. Inflammatory pathways include Janus Kinase 2 (JAK2), protein kinase C (PKC), nuclear factor-kappa B (NF-κB), tumor necrosis factor-α (TNF-α), transforming growth factor-β (TGF-β), interleukin-1 (IL-1), IL-6, and IL-18.

**2.2. Glomerular hyperfiltration**

The glomerular hemodynamic changes are due to decreased afferent and to less extent efferent arteriolar resistance mediated by different biochemical factors, including nitrous oxide, atrial natriuretic factor, adenosine, glucagon, and insulin [22]. Increased glucose in glomerular ultrafiltrate stimulates SGLT2 with consequent increased proximal tubular absorption of filtered sodium and glucose. SGLT2 is...
present in the apical membrane of the proximal convoluted tubule (PCT) cells and is responsible for the absorption of 90% of the glucose in the ultrafiltrate [23]. Increased sodium and glucose absorption by the PCT results in decreased distal tubular sodium delivery with consequent decreased distal tubular sodium absorption. The consequent decrease in energy expenditure in the macula densa leads to less adenosine activity. Adenosine is a potent vasoconstrictor. Decreased activity of adenosine leads to vasodilatation of afferent arterioles (Figure 2) [24].

2.3. Uric acid (UA)

In humans, the kidney excretes 70% of the daily produced UA [25]. By increasing serum UA in experimental animals, these animals develop systemic hypertension, glomerular hypertension, glomerulosclerosis, and interstitial fibrosis [26]. However, the role of hyperuricemia in DKD is debatable [27–30]. The clinical and experimental evidence propose that intracellular UA behaves differently in comparison to extracellular UA. While extracellular UA has anti-oxidant nature, intracellular UA poses harmful pro-oxidant properties [31].

In the case of diabetes, intracellular UA production within the PCT cells increases thanks to increased fructose production through the activated polyol pathway and increased breakdown of adenosine triphosphate (ATP). Fructose metabolism increases intracellular adenosine and UA synthesis [32]. Intracellular UA activates nicotinamide adenine dinucleotide phosphate (NADPH) oxidase enzyme leading to increased intracellular oxidative stress [33,34]. Increased NADPH oxidase activity stimulates the production of monocyte chemoattractant protein 1 (MCP1) with consequent increased macrophage infiltration of the kidney [35]. By inhibiting glucose absorption, SGLT2Is decrease intracellular UA synthesis (Figure 3) [23]. Moreover, the increased availability of glucose within the tubular lumen after SGLT2Is administration triggers the apical PCT epithelium glucose transporter 9 (GLUT9) isoforms to absorb glucose in exchange with UA. GLUT9 activation thus depletes intracellular UA within the PCT [39].

2.4. Sodium hydrogen exchanger

There are nine isoforms of the sodium hydrogen exchangers (NHE) [40,41]. NHE3 is the isoform encountered in the kidney and gut epithelium. By increasing NHE3 in the PCT and the ascending loop of Henle of patients having diabetes, sodium retention occurs and systemic hypertension ensues [42,43]. While hyperglycemia stimulates, SGLT2Is inhibit renal NHE3 [43]. SGLT2Is exert their natriuretic effect mainly through NHE3. In normoglycemic NHE3 knock-out mice, Empa fails to induce natriuresis while they do induce diuresis in wild mice [44].

2.5. Impaired autophagy

Autophagy is an intracellular lysosome-dependent self-cleaning process to sweep dysfunctional organelles out of the cytoplasm. The accumulation of these dysfunctional organelles is a feature of diabetic kidneys secondary to increased oxidative stress and endoplasmic reticulum stress. These accumulating organelles pose changes in ion channels and trigger cellular inflammation and endanger cell survival. Deficiency of sirtuin-1 (SIRT1), and adenosine monophosphate (AMP)-activated protein kinase (AMPK) are the direct causes of impaired autophagy of the podocytes and the renal tubular cells in patients having diabetes [45]. By mimicking a fasting state, SGLT2Is stimulate AMPK/SIRT1 signaling and stimulate autophagy, thereby decreasing the accelerated damage of podocytes and renal tubular cells within the kidney [46].

2.6. Chronic renal hypoxia

Chronic renal hypoxia is a cause of renal damage encountered in DKD patients. Renal hypoxia is due to a mismatch between oxygen delivery and oxygen demand. Microangiopathy of the small intra-renal arteries together with the glomerular mesangial expansion that compromises the downstream tubular blood flow result in decreased oxygen delivery. Increased activity of the sodium pumps in parallel with SGLT upregulation is behind the increase in oxygen demand. Once the imbalance between demand and delivery exists, subsequent tissue hypoxia causes the observed renal damage encountered in DKD. Tissue hypoxia stimulates hypoxia-inducible factor (HIF) expression in renal tissue. HIF-1α is upgraded in response to hypoxia of the PCT (Figure 4), while the distal convoluted tubule (DCT) hypoxia up-regulates HIF-2α. Both HIF-1α and HIF-2α try to control hypoxia by decreasing oxygen demand and increasing oxygen delivery. Decreased oxygen demand is done through the inhibition of the metabolic pathways and intracellular organelles that consume oxygen. HIF-1α promotes the autophagy of the damaged mitochondria (mitophagy) [47] whereas HIF-2α stimulates the autophagy of injured peroxisomes.
angiogenesis is the function of HIF-1α while erythropoiesis is the function of HIF-2α. Hypoxia of the PCT stimulates HIF-1α while hypoxia of the DCT stimulates HIF-2α. HIF-1α triggers inflammation and has profibrotic properties while

![Figure 2. Hypeglycemia induced glomerular hypertension and role of SGLT2Is. SGLT2Is, sodium–glucose cotransporter 2 inhibitors; UF, ultrafiltrate; Na+, sodium; PCT, proximal convoluted tubule; DCT, distal convoluted tubule; ATP, adenosine triphosphate; MD, macula densa; AMP, adenosine monophosphate; VD, vasodilatation; AA, afferent arteriole; VC, vasoconstriction.](image)

![Figure 3. Hyperlycemia mediated increase intracellular UA with consequent increased production of ROS, and induction of vascular and interstitial inflammation and fibrosis together with degeneration of proximal tubular epithelium. VSMC, vascular smooth muscle cells; MCP1, macrophage chemotactant protein 1; SGLT2, sodium–glucose cotransporter 2; UA, uric acid; NADPH, nicotinamide adenine dinucleotide phosphate; NF-κB, nuclear factor-kappa B; ROS, reactive oxygen species; ATP, adenosine triphosphate; RAS, renin-angiotensin system; EMT, epithelium mesenchyme transition.](image)
HIF-2α inhibits inflammation and fibrosis and stimulates erythropoiesis [49,50]. Induction of SGLT2 in hyperglycemia increases the activity of the sodium pump in the PCT, this increased workload in these cells leads to increased oxygen consumption that stimulates HIF-1α. In contrast, sodium delivery to the distal segment of the nephron significantly decreases with subsequently decreased sodium absorption by the DCT. Decreased oxygen consumption by the DCT leads to decreased activation of HIF-2α. Increased HIF-1α induces inflammation and renal fibrosis while decreased HIF-2α results in decreased erythropoietin and eventually leads to anemia. When SGLT2Is are used, decreased activity of the PCT sodium pump leads to increased sodium delivery to the DCT with consequently increased activity of the DCT sodium pump. Consequently, HIF-1α activity decreases while the activity of HIF-2α increases. This explains the anti-inflammatory, and anti-fibrosis actions and the increased erythropoiesis encountered with the use of these agents (Figure 5) [51]. Nephron loss increases the workload of surviving units. This exaggerates the delivery/demand of the surviving nephrons and establishes a vicious cycle that exaggerates subsequent damage [52].
2.7. SGLT2Is and prevention of DKD

SGLT2 co-transporters are located within the epithelial brush border of the S1 and S2 segments of the PCT and reabsorb 90% of the glucose delivered in the glomerular ultra-filtrate. Under normal conditions, SGLT2 and SGLT1 located in the S3 segment of the PCT reabsorb all delivered glucose if its concentration in blood and glomerular ultrafiltrate is below 180 mg/dL (the renal threshold). It seems that the increased renal threshold of glucose in T2DM is due to the increased activity of the existent transporters. Solini et al. have discovered that the expression of SGLT2 and SGLT1 in T2DM patients’ kidneys is slightly less than the well-matched normal personnel [53].

Phlorizin is a natural compound extracted from apple parks that was discovered to competitively inhibit both SGLT1 and SGLT2. When used in rats having diabetes, urine glucose excretion increases together with a decrease in blood sugar. Inhibition of SGLT1 within the gut decreases intestinal glucose absorption and causes gastrointestinal upset associated with diarrhea. Moreover, phlorizin bioavailability after oral intake is poor [54]. Fourteen years ago, Dapa was the first to introduce highly selective SGLT2Is [55] followed by canagliflozin (Cana) and empagliflozin (Empa) [54]. SGLT2Is reach the brush border of the PCT cells to a similar extent via the glomerular ultrafiltrate and through tubular secretion [56].

In 2022, SGLT2Is have completed 10 years in European and USA markets. The different Cardiovascular Outcomes Trial (CVOT) studies together with the canagliflozin and renal events in diabetes with established nephropathy clinical evaluation (CREDENCE) and the Dapagliflozin and Prevention of Adverse outcomes in Chronic Kidney Disease (DAPA-CKD) represent a strong win for the physicians handling DKD. These studies proved the renoprotective and cardioprotective effects of these agents beyond their hypoglycemic action [57–59]. The impressive benefit of SGLT2Is on the hard renal endpoints in patients with DKD should encourage researchers to find out the most ideal approach to prevent DKD. The EMPA-REG OUTCOME trial was the first study to show a significant decrease in the need for dialysis in DKD patients. It showed a significant reduction in the renal-specific composite outcome by 39%. In comparison, this outcome was reduced by 40% in the CANVAS trial, and by 47% in Dapagliflozin Effect on Cardiovascular Events (DECLARE-TIMI) 58 study. The more astonishing news was the significant favorable effect of these three compounds on overall mortality. The significant reduction of mortality was never reported before in the different previous interventional studies on DKD patients [27]. Because the renal outcome parameters in these trials were secondary endpoints, further studies were planned to look at the renal outcome as primary endpoints. The CREDENCE trial recruited T2DM patients (30 mL/min/m² ≤ eGFR < 90 mL/min/m², 300mg/gm < UAE ≤ 5000 mg/gm creatinine). These patients were prescribed 100 mg of Cana daily or a placebo together with the maximum tolerable dose of RAS blockers. The primary outcome was a composite of ESRD, serum creatinine doubling, or death due to renal or cardiovascular causes. Instead of the planned duration of 5.5 years of follow-up, the CREDENCE trial was prematurely terminated after a median follow-up of 2.62 years. The premature termination was a consequence of the overwhelming results. Cana led to a highly significant reduction of the primary composite endpoint by 34.0%, together with a lower risk of ESRD, hospitalization for heart failure, and the composite of cardiovascular (CV) death, myocardial infarction, or stroke [60]. DAPA-CKD trial enrolled DKD and non-diabetic kidney disease patients with eGFR 25 to 75 mL/min/1.73m², and UAE 200 to 500 mg/g already prescribed the maximally tolerated dose of RAS blockers. This trial recruited 4304 adults and followed them for a median of 2.4 years. DAPA reduced the primary composite outcome (sustained decline in the eGFR by > 50.0%, ESRD, and renal or cardiovascular death) by 39.0% [61].

A real-world clinical study looked for 2396 patients having diabetes, 1198 of them were kept on dipeptidyl peptidase-4 (DPP-4) inhibitor while the other 1198 were on SGLT2I. Treatment by SGLT2Is significantly decreased the rate of renal events by 54.0% in comparison to DPP-4 inhibitors (P = 0.0007) [62].

Most of the patients in the different SGLT2Is trials were already receiving RAS blockers. 81.2% of the studied candidates in the DECLARE-TIMI 58 study were kept on RAS blockers. The significant impact of DAPA was only observed in patients kept on RAS blockers [59]. SGLT2Is stimulate the RAS system [63]. This stimulation in patients already kept on RAS blockers will result in a significant increase in angiotensin 1–7 level [64]. Angiotensin 1–7 acts on the Mas receptors to reduce UAE, decrease glomerular mesangial matrix expansion, normalize renal PKC activity, muffle the increased α-smooth muscle actin and collagen III renal expressions, and decrease renal fibrosis (Figure 6) [65].

In the DECLARE-TIMI 58 study, 47.6% of the recruited patients had eGFR > 90 mL/min/1.73m² and 68% of cases had normal UAE. These cases were still amenable to developing the renal endpoints. The Hazard ratio of development of the renal endpoints is 0.50 and 0.52 respectively.

3. DISCUSSION

By the time of development of T2DM, the patients have passed through a variable but lengthy period of hyperglycemia. These long years of hyperglycemia invite the development of irreversible renal pathologic changes even in the absence of evident clinical or laboratory changes [66,67]. The development of pathologic changes would render primary prevention of DKD a very tedious mission. This would suggest an earlier intervention in the pre-diabetes stage in patients prone to T2DM and by
the very early days of diagnosis of T1DM. SGLT2is have created the hope to prevent DKD. Their favorable effect on body weight and the decreased likelihood of hypoglycemia promote their use even in T1DM. The use of these agents can prevent not only DKD, but also the development of T2DM [68,69], and the other disastrous complications of diabetes. DKD is the major cause of the increased risk of mortality for patients having diabetes [70] and deserves intensive attention to completely eradicate it. Prompt and accurate risk stratification should warrant clinical examination and frequent screening in high-risk personnel having prediabetes for early identification of cases susceptible to developing DKD. This approach would lead to therapeutic interventions and lifestyle changes that prevent the development of not only DKD but also other serious diabetic complications as well as costly healthcare spending. Screening personnel having prediabetes using a machine learning algorithm based on electronic medical records (EMR) might help the selection of people that could benefit from the DKD eradication program [71,72]. These susceptible cases should be kept on lifelong SGLT2I plus the maximal tolerable dose of angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) [73]. Long-term primary preventive studies recruiting patients that are still devoid of pathologic changes should be encouraged, as the duration to get enough endpoints for adequate statistical analysis will be very long. Such studies will be very costly. Given the documented safety and non-inferiority of SGLT2is, we are optimistic about such studies. The different serious complications of this diabetes namely DKD, heart failure, diabetic retinopathy, and diabetic neuropathy should constitute the primary endpoints. This primary preventive approach will supposedly abort the development of DKD instead of the current target to postpone ESRD for a few months or years. The primary prevention studies should involve patients with new onset T1DM but with great attention to diabetic ketoacidosis. Although this preventive approach carries some risks, especially in T1DM, the benefits obtained on health status and economic savings will outweigh the drawbacks. The development of ESRD in patients having diabetes is a real nightmare for nephrologists. Morbidity and mortality are significantly higher among patients having diabetes who start dialysis compared to other patients [74,75]. In one
series none of the patients having diabetes survived for five years on dialysis in comparison to over 50% of other patients [75].

So far, no randomized controlled trials are looking for the impact of the use of SGLT2Is in patients having prediabetes on the incidence of T2DM or diabetic complications [76].

Author Contribution

Sharaf El Din UAA: Conceptualization, Writing—Original draft, Writing—Review and Editing. Salem MM and Abdulazim DO: Writing—Original draft. All authors have read and approve the final manuscript.

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Conflict of Interest

The authors have nothing to declare.

Data Sharing

No additional data.

REFERENCES


