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Is it Feasible to Completely Prevent Diabetic Kidney Disease?

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ABSTRACT

When SGLT2Is were first introduced as hypoglycemic agents during the year 2008, no body was aware about their protective action on the heart, kidney, and retina of patients suffering type 2 diabetes mellitus (T2DM). SGLT2Is have revolutionized the treatment of T2DM patients with established or at risk for diabetic kidney disease (DKD). When Dapagliflosin was studied in T2DM patients with estimated glomerular filtration rate [eGFR] >90 mL/min/1.73m2, and normal urine albumin excretion, these cases were still susceptible to develop the renal end points. These results have raised the question about the ideal time to use SGLT2Is to completely abort the incidence of DKD. This review will try to answer this question.

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Introduction

Diabetic kidney disease (DKD) is the leading cause of end stage renal disease (ESRD) worldwide. It develops in approximately 30% of type1 DM and approximately 40% of type 2 DM patients [1,2]. The global prevalence of diabetes in 2019 was estimated to be 9.3% (463 million people worldwide). This figure is expected to rise to 10.2% (578 million worldwide) by 2030 and to 10.9% (700 million worldwide) by 2045. Meanwhile, the estimated global prevalence of prediabetes was 7.5% (374 million) in 2019 and is expected to reach 8.0% (454 million) by 2030 and 8.6% (548 million) by 2045 [3]. Table 1 shows diagnostic criteria of prediabetes.

Table 1: Diagnostic Criteria of Prediabetes

Criterion	ADA	WHO	Nomenclature
Fasting plasma glucose (FPG)	100 to 125 mg/dL	110 to 125 mg/dL	High fasting glucose
2-hr plasma glucose during 75 gm OGTT	140 - 199 mg/dL	140 - 199 mg/dL	Impaired glucose tolerance
Glycosylated hemoglobin (HbA1c)	5.7-6.4%	6-6.4%	

OGTT= oral glucose tolerance test, ADA=American Diabetes Association, WHO= World Health Organisation

The incidence of DKD parallels the increasing prevalence of DM [4]. The distinct rise in the mortality rate attributed to DKD is considered the highest among the different chronic diseases [5]. The incidence rate of all-cause mortality among Japanese DKD patients is 12.3/1000 person-years. In cases with eGFR <30 mL/min/1.73 m2, this incidence becomes 57.4/1000 person-years [6]. One death will occur annually among every 20 British patients with type 2 DM and DKD [7].

DKD passes into 5 stages, the earliest is the stage of glomerular hyperfiltration [8]. In the last 10 years, there is increasing awareness that glomerular hyperfiltration starts before the onset of DM. many studies from different continents report glomerular hyperfiltration in the prediabetes phase [9-13]. The second stage is characterized by the development of pathologic glomerular changes. These changes develop years before the appearance of the clinical manifestations, the development of microalbuminuria or the decline of GFR. During this clinically silent period, progressive glomerular basement membrane thickening occurs together with mesangial expansion, and glomerulo-sclerosis. Once microalbuminuria is clinically apparent, structural lesions are often considerably advanced, and GFR decline may then proceed rapidly toward end-stage kidney disease [14-16], (Figure 1)

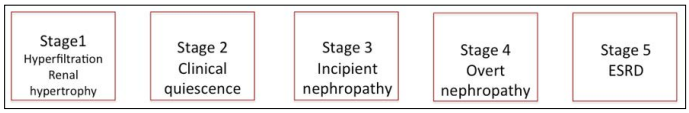

Figure 1: Stages of Diabetic Nephropathy. Stage 2 is characterized by the progressive increase in mesangial deposits on light microscopy without corresponding clinical or laboratory findings. ESRD: End Stage Renal Disease when eGFR≤15 mL/min/1.73m^2

Prediabetes and Diabetic Complications

Impairment of kidney function may occur in patients suffering impaired glucose tolerance before the onset of diabetes [17]. 3% of newly diagnosed type 2 DM patients were reported to have overt nephropathy [4].

Other diabetic complications might also show up before the onset of diabetes. 7.9% of the persons recruited to the Diabetes Prevention Program (DPP) that had elevated fasting glucose and impaired glucose tolerance, but without history of frank diabetes showed evidence of diabetic retinopathy on examination by stereoscopic fundus photography [18]. In a cohort of 3736 Chinese subjects, 2.5% of the subjects showing laboratory evidence of impaired glucose tolerance had diabetic retinopathy when examined using non-mydriatic retinal photographs [19]. Diabetic retinopathy was also reported in 3% of persons with impaired glucose tolerance in a nord study [20]. Deterioration of flicker light-induced retinal arteriolar dilation was encountered in prediabetic subjects [21]. Autonomic neuropathy was detected in 9% of prediabetic personnel [22]. A growing link of prediabetes to the risk of peripheral neuropathy is recognized in the literature [23]. In a recent study of 40,117 participants from 6 population-based cohorts in the United States, up to 10.8% prediabetes developed heart failure [24]. Similar findings were disclosed by a meta-analysis that appeared within the same year of this last mentioned study and included 15 observational studies of nearly 10 million candidates with a median follow-up of 8.0 years [25].

SGLT2Is and DKD

After establishing the role of renin angiotensin system (RAS) blockers in DKD, little was added to the management of this disease. These agents failed to show a significant impact on patient survival. In addition, the failure of RAS blockers in primary prevention of DN in T1DM was very disappointing [26]. After this long inertia, the results of the large cardiovascular outcome trials (CVOT) for the different SGLT2Is have added a large dose of optimism to the medical community. These studies highlighted the distinguished role of SGLT2Is as renoprotective and cardioprotective agents beyond their hypoglycemic effects [27-29]. The EMPA-REG OUTCOME trial was the first trial that showed the significant decrease in the need for dialysis in DKD patients. The renal-specific composite outcome was reduced by 39% in EMPA-REG, 40% in CANVAS, and 47% in DECLARE-TIMI 58 study. The greater surprise is the significant favorable effect of SGLT2Is on overall mortality in DKD patients. The favorable impact on mortality was never reported in any previous interventional studies in DKD patients [30]. The renal outcome parameters in these trials were secondary end points. For this reason, further studies were designed to look more thoroughly on the renal end points. In the CREDENCE trial, T2DM patients with eGFR of 30 to <90 ml/min/m^2 and albuminuria >300 to 5000 mg/gm creatinine were assigned to receive canagliflozin (Cana) at a dose of 100 mg daily or placebo. All the patients were treated with the maximum tolerable dose of RAS blockers. The primary outcome was a composite of end-stage renal disease (ESRD), doubling of serum creatinine, or death from renal or cardiovascular causes. This trial was prematurely terminated after a median follow-up of 2.62 years instead of the planned duration of 5.5 years. This premature termination was due to the overwhelming efficacy of Cana that lead to a highly significant reduction of the primary composite endpoint by 34%, a lower risk of ESRD, hospitalization for heart failure, and the composite of CV death, myocardial infarction, or stroke [31]. DAPA-CKD enrolled both DKD and nondiabetic kidney diseases patients with eGFR 25 to 75 ml/min/ 1.73 m^2, and albuminuria 200 to 5000 mg/g that were kept on the maximal tolerated dose of RAS blockers. The total number recruited was 4304 adults that were followed for a median of 2.4 years. Dapagliflozin (DAPA) reduced the primary composite outcome of sustained decline in the eGFR by >50%, ESRD, and renal or cardiovascular death by 39%. The effects of DAPA were similar in patients with T2DM or without T2DM [32]. In a real world clinical study that involved 2396 diabetic patients 1198 of them were kept on Dipeptidyl peptidase-4 (DPP4) inhibitor while the other half were on SGLT2I, the rate of renal events significantly decreased by 54% in the SGLT2I group compared to those on DPP-4 inhibitor ($p = 0.0007$). The in between-group difference in eGFR was 0.86 _ 0.18 mL/min/1.73 m^2/year ($p < 0.0001$) [33].

We would like to emphasize that most of the patients in these trials were already receiving RAS blockers. In DECLARE-TIMI 58 study, 81.2% of the studied candidates were on RAS blockers. The beneficial effect of DAPA was only observed in the patients consuming the RAS blockers [29]. SGLT2Is stimulate the RAS system [34]. This stimulation in patients already kept on RAS blockers will result in a significant increase in angiotensin-(1-7) level [35]. By acting on MAS receptors, angiotensin–(1-7) reduces the renal albumin excretion, decreases glomerular mesangial matrix expansion, normalizes protein kinase C activity in the renal tissue, muffles the increased α-smooth muscle actin and collagen III expression within the kidneys and thus decreases renal fibrosis [36].

In DECLARE-TIMI 58 study, 47.6% of the recruited patients had eGFR >90 mL/min/1.73m2, and 68% of cases had normal urine albumin excretion. These cases were still susceptible to develop the renal end points, namely sustained decline of at least 40% in eGFR to less than 60 mL/min per 1•73m², ESRD, or death from renal cause with Hazard ratio 0.5 and 0.52 respectively. The main acceptable mechanism behind the renoprotective effect of SGLT2Is is related to the complete reversal of glomerular hyperfiltration encountered in diabetic cases [37-41]. Glomerular hyperfiltration starts in the prediabetic stage. Microalbuminuria may also occur in prediabetic personnel [42]. By the time of diagnosis of type2 DM, many patients have already developed pathologic glomerular changes that render the reversal of diabetic kidney disease difficult or even impossible. Overt nephropathy was encountered in 3% of newly diagnosed type 2 DM patients [4]. More than 90% of kidneys obtained from deceased T2DM donors had variable degrees of histopathologic changes of diabetic nephropathy yet had normal urine and had eGFR>60 ml/min [43]. These facts might give a good answer for the failure of DAPA to completely abort the composite renal end-points in patients with eGFR>90 ml/min and those with normoalbuminuria.

Discussion

SGLT2Is represent a new hope to prevent DKD. Their favorable effect on body weight and the decreased likelihood of hypoglycemia promote their use even in T1DM. The strong evidence of the significant renal and cardiac protective effects of SGLT2Is has enforced the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), the American college of Endocrinology (ACE), and the American Association of Clinical Endocrinology (AACE) to recommend the use of SGLT2Is as a second-line treatment in T2DM patients with cardiovascular disease or CKD [44-46]. The United Kingdom Prospective Study (UKPDS) is the most famous primary prevention trial in T2DM patients. Ten years after the end of this study to show the significant impact of tight sugar control

on the cardiovascular endpoints [47]. The shortened duration of the CREDENCE trial rendered the patients with eGFR ≥ 60 mL/min/1.73 m^2 and patients with UAE ≤1000 mg/gm creatinine unable to get the expected benefit. [31]. The DECLARE – TIMI 58 study has supported this view. This last study continued for 4.2 years and showed a significant impact of dapagliflozin in patients having baseline eGFR >90, and even in normoalbuminuric patients [29]. The reported favorable effects are likely due to the relatively lengthy duration of follow-up.

Based on these findings, it seems that longer primary preventive studies recruiting patients still devoid of pathologic changes are needed. These primary preventive studies should select the relatives of type 2 DM patients suffering prediabetes.

Perspectives

The very high cost is the main obstacle for these studies as the duration needed to get enough endpoints for adequate statistical analysis is very long. Given the documented safety and non-inferiority of SGLT2Is, we are optimistic for such studies. These patients should be prescribed SGLT2Is aiming at prevention of type 2 DM, and the most serious complications of this disease, namely, DKD, heart failure, diabetic retinopathy, and probably diabetic neuropathy. This primary prevention approach will supposedly abort the development of DKD instead of the current approach that only postpones ESRD for few months or years. The primary prevention studies should involve patients with new onset T1DM patients but with great caution to avoid diabetic ketoacidosis. Although this preventive approach caries some risk especially in T1DM, the benefits obtained on health status and economic saving will definitely outweigh the drawbacks. The development of ESRD in diabetic patients is a real nightmare for nephrologists. Morbidity and mortality are significantly higher among diabetic patients starting dialysis compared to non-diabetic patients [48,49]. In one series none of the diabetic patients survived for five years on dialysis in comparison to over 50% in non-diabetic patients [49]. These agents proved to be safe, data from large randomized clinical trials and real-world population-based studies did not show a significant increase in the risk of urinary tract infections in patients on SGLT2Is [50].

So far, there are no randomized controlled trials looking for the impact of use of SGLT2Is in patients having prediabetes on the incidence of T2DM or diabetic complications [51].

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