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THE ROLE OF INHIBITORS SGLT2 IN DIABETIC NEPHROPATHY; LITERATURE REVIEW

Sultan Mohammad Allihybi[1*], Rakan Ayyadah Alshammari[2], Basil Ayyadah Alshammari[2], Khalid Turki Althobaiti[3], Futun Hamed Almufarriji[3], Ahmed Yousef Almuqaytib[4], Doaa Mohammed Alrebeh[5], Zahra Mahdi Almadeh[6], Fatimah Ali Alhulw[7], Fatimah Ahmed Al Abdrabalnabi[8], Noura Shawki Saati [9], Barrak Abdullah Alshalawi[10]

1. ***Bahrah Primary Health Care Centre, Makkah, KSA.***
2. ***Faculty of Medicine, Hail University, Hail, KSA.***
3. ***Faculty of Medicine, Taif University, Taif, KSA.***
4. ***Faculty of Medicine, Qassim University, Qassim, KSA.***
5. ***Al Kharj Maternity and Children Hospital, KSA.***
6. ***Dar Al-Uloom University, Riyadh, KSA.***
7. ***Medical University of Warsaw, Warsaw, Poland.***
8. ***Saud Albabtain Cardiac Center, Dammam, KSA.***
9. ***Faculty of Medicine, King Abdulaziz University, Jeddah, KSA.***
10. ***Faculty of Medicine, Shaqra University, Shaqra, KSA.***

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ABSTRACT

Diabetes mellitus is the foremost fons et origo of immedicable kidney disorder all over the world. It is essential to provide glycemic control as well as reduce micro and macrovascular complications, particularly diabetic nephropathy. Inhibitors of co-transporter Sodium-glucose 2 were suggested to provide cardiorenal protection, regardless of glycemic control. This literature review aims to assess the renal protection of patients with inhibitors of SGLT2 in diabetes mellitus type-2 and the commonly reported adverse effects. We used the PubMed database and search for relevant articles. We used the following Mesh words: SGLT2 inhibitors, diabetes mellitus Type-2, CKD, Diabetic nephropathy, cardiovascular risk. The use of SGLT2 inhibitors appears to provide cardiorenal protection by certain mechanisms, particularly through albuminuria reduction. Nonetheless, specific adverse effects have been reported, such as increasing the risk of diabetic ketoacidosis, amputation, and genital infection. Caution must be taken to account once an individual started on one of the SGLT-2 inhibitors.

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Introduction

Diabetes mellitus (DM) is a set of metabolic disarrays outlined by increased blood glucose levels [1]. People affected by DM are at greater menace for morbidity and mortality compared to the broad spectrum of people and carry a high-cost burden worldwide [1, 2]. In 2017, the estimated prevalence of DM was approximately 425 million cases and will increase to 629 mill by the year 2040 [2]. Diabetes mellitus T-2 is one of the common T-2 diabetes, count for almost 90-95% of all patients [2, 3]. Notably, the global increase of unhealthy lifestyles, the aging population, and the rising incidence of obesity can potentially explain the diabetes pandemic, especially in the United States [2, 3]. It is essential to manage adequately diabetes to control the cardiovascular risk, the most common cause of diabetic populations, since early phases of vascular involvement may already exist before diagnosing diabetes or even in the pre-diabetic status [2, 3].

Corresponding Author: Sultan Mohammad Allihybi; Bahrah Primary Health Care Centre, Makkah, KSA. E-mail: Allehybi.sultan@gmail.com.

Microvascular complications induced by diabetes include renal failure, diabetic eye disease (DED), and neuropathy; additionally, vascular tube problems emerge as supplementary pervasive, incorporating Heart attack, peripheral vascular occlusive disorder (PVOD), and carotid artery stenosis [3]. T2DM is an important threat component for (CKD), atherosclerotic heart disease, and heart failure, of all, are related to an elevated rate of disease, death rate, poor high-quality life, and surge healthcare cost [4]. Diabetes frequently causes (ESRD) kidney failure, necessitating renal substitute remedy in developed countries for the last ten years [5], and the unexpectedly growing occurrence of diabetes globally might also predict that the percentage of renal failure induced through diabetes will further increase [6]. However, the persistent Renal Insufficiency Cohort (CRIC) observation has concluded that in multi-center observational research that the occurrence of T2DM is soaring amongst patients with CKD as compared to the overall population [7]. Moreover, a report issued from the (NHANES) determined that the pervasiveness of diabetic kidney disease had accelerated continuously from 1988 thru 2008, and the latest United States (USRDS) record suggests that almost 30% growth within the prevalence of ESRD in diabetic populations in the United States among 1992 and 2008 [6]. Diabetic nephropathy (DNP) is manifested by albuminuria that developed in nearly 40% of type 1 and 2 diabetes mellitus [5, 8]. The classic pathophysiological changes in DNP are progressive hyper-filtration of glomerular, moderately increased albumin, urinary protein creatinine ratio, and a drop within the renal ultrafiltration (GFR), fundamentally ending with dialysis [9]. Microscopically, disperse and enlargement of mesangial nodular with the basement of glomerular membrane solidifying is the hallmark of DNP [10]. Diffuse mesangial growth progresses rapidly as the fifth year from the onset of diabetes, which is the most primitive substantial exchange through light microscopy [10]. The stages of DNP are listed in **Table 1** [10].

Regarding the mortality rate of DNP, it was suggested that the mortality rate has increased by 94% between 1990 and 2012 [8]. The world health organization predicts that mortality associated with diabetes will be two-fold by 2030 [8]. Ordinarily, the greatest diabetic complications will be controlled by strict control of hyperglycemia, arterial hypertension (BP), CH3(CH2) nCOOH, and way of life [8]. Although initial proof recommended renin-angiotensin-aldosterone blockade agents to prevent CKD progression, current statistics from cardiac results trials and renal particular trials have provided a unique extra perception into the (SGLT2i) benefits in lowering the evolution of CKD and cardiovascular threat [8]. There is ongoing evidence recommended that SGLT2i provides renal protection regardless of glycemic control [9].

Table 1. Diabetic nephropathy stages based on glomerular lesions

CLASS	DESCRIPTION AND CRITERIA
I	Non-specific or mild changes on light microscopy and conformed GBM thickening confirmed by electron microscopy: GBM> 395 nm (female), GBM> 430 nm (male).
IIA	Mild mesangial expansion in >25% of the observed mesangium; area of mesangial proliferation < area of the capillary cavity.
IIB	Severe mesangial expansion in >25% of the observed mesangium. Area of mesangial proliferation < area of the capillary cavity.
III	At least one apparent nodular sclerosis (Kimmelstiel-Wilson lesion)
IV	Advanced diabetic glomerulosclerosis in >50% of glomeruli.

Results and Discussion

SGLT2 Inhibitors and The Renoprotection Mechanism

In an individual with normal glycemia and kidney function, both kidneys can filter up to 180g of $C_6H_{12}O_6$ per day, and the clarified $C_6H_{12}O_6$ is almost totally re-engrossed inside the proximal convoluted tubules (PCT) through several actions of both apical /basolateral epithelial transporters [11]. SGLT-2 and SGLT-1 are tributary dynamic symporters articulated within the proximal tubules' brush of the apical edge [11]. SGLT engross $C_6H_{12}O_6$ alongside Sodium succeeding a gradient of electrochemical potential for Sodium that is mounted through the basolateral Sodium/Potassium-ATPase, vigorously energies Na from the tubular cells into the circulation [11, 12]. Furthermore, SGLT-2 performs a small but crucial position in the manner of $C_6H_{12}O_6$ /Sodium egression. To clarify, reabsorbing one Sodium-ion for each $C_6H_{12}O_6$ from the lumen of the initial proximal convoluted tubule (PCT) [13].

Within the overdue proximal convoluted tubule, the high-affinity/low-ability SGLT-1 engross two Sodium ions for each $C_6H_{12}O_6$ molecule [13]. However, the mechanism is under-exploited in the ordinary kidneys as >90% of the clarified $C_6H_{12}O_6$ is reabsorbed through SGLT-2 [13]. SGLT-2 is the dominant kidney transporter, accountable for nearly 97% of transporter throughout the cell membrane, and SGLT-1 is liable for about 3% of the transport [12]. Several SGLT2i are present within the market, for instance, dapagliflozin, empagliflozin, ertugliflozin, canagliflozin, and sotagliflozin (dual SGLT inhibitor). Moreover, the beneficial effect of SGLT2i on the kidneys appears independently to glycemic control [14].

Importantly, SGLT2i also provides kidney benefit in an individual with the presence of normal $C_6H_{12}O_6$ in the blood (HbA1C<7%), in whom additional $C_6H_{12}O_6$ decreasing changed into the slightest [14]. The DAPA-HF trial had shown that individuals without or with diabetes have some beneficial up-shot of SGLT2i on coronary heart failure and kidney disease, regardless of the diabetes status [14]. Additionally, SGLT2i was found to restore tubuloglomerular feedback, which explains the salutary kidney effects of SGLT2i [14]. Restoration of tubuloglomerular feedback resulted from increased NaCl to (the microscopic preparations seem dimmer and nuclei eminence causes the distal tubule wall section to close juxtaposition); as a

result, endogenous materials, including adenosine, are established and emancipated, constricting the afferent arteriole via the adenosine-1 receptors [14, 15]. Thus dropping glomerular blood flow and hyperfiltration of glomerular, the primary mechanism for gradual glomerular injury [14]. Furthermore, by increasing sodium excretion, the proximal up-shot of natriuretic may be excited through the observed practical blockade of NHE3 [15]. In addition, the soaring volume of intraluminal leads to a surge of regressive hydraulic pressure in Bowman's space, constraining filtration pressure [15]. Besides, SGLT2i consistently reduces body weight and blood pressure and may enhance numerous mediators of vascular renal blood flow in each abstaining and state of postprandial, for instance, lower in natriuretic atrial hormone and $C_{257}H_{383}N_{65}O_{77}S_6$, glucagon increase, and peptide glucagon-like 1 (GLP-1) [15].

Evidence-Based Supporting SGLT2 Inhibitors Benefit for the Kidneys

In a scientific overview and meta-analysis of randomized placebo-managed trials, Husam *et al*. determined that SGLT2i reduces the chance of dreadful kidney outcomes by 38% in 59,747 patients [16]. In one trial among patients with diabetic nephropathy, it was found that canagliflozin reduces the threat of last-phase of kidney disorder, doubling up serum creatinine and kidney or cardiac mortality by 30% compared with standard care [16]. Furthermore, the $C_{23}H_{27}ClO_7$ (Jardiance) final results Trial in patients with chronic coronary heart Failure with dwindled E-tRial was confirmed the beneficial up-shot of SGLT2i on cardiac and kidney consequences in patients with HFrEF, without or with T2DM [16].

Moreover, Nespoux *et al*. concluded in a literature review that SGLT2i provides an advantage up-shot at the renal and cardiac structures by targeting the renal $C_6H_{12}O_6$ reabsorption within the proximal convoluted tubules [17]. The Invokana (3--4-methylphenyl) and renal activities in Diabetes with mounted Nephropathy Scientific Assessment (CREDENCE) trial confirms the cardiorenal advantage of SGLT2i in T2DM patients with CKD despite minor glucose reduction [17]. Moreover, empagliflozin effectively provides cardiorenal protection; dwindling albuminuria and $C_5H_4N_4O_3$, mounted consequences on hyperglycemia, weight, visceral adiposity, and blood pressure [18].

Besides, the Invokana (3--4-methylphenyl) Cardiovascular Evaluation Observation (CANVAS) application assessed the cardiac protection of Invokana compared to placebo [19]. As a result, patients who had been managed with Invokana had a dwindling chance of hospitalization secondary to coronary heart failure, albuminuria development, and sizeable loss of kidney feature compared with patients who obtained a placebo; however, it was not statistically significant [19]. Similarly, the renoprotection mechanism of SGLT2i inhibitors is possibly secondary to improved glycemic and blood pressure control, discount in albuminuria, and amelioration of dimensions overload [19]. Interestingly, the cardiorenal beneficial effect of SGLT2i in T2DM patients has been suggested to provide a similar impact on patients with type-1 diabetes [20].

Safety Consideration

Overall, SGLT2i is proven to be an effective treatment for diabetes with a favorable renal side effect profile and patient satisfaction [21, 22]. Adverse effects, such as genital infections, can be avoided by adequate self-hygiene and patient education [22]. Nevertheless, SGLT2i initiation resulted in an improved chance of amputation and approximately doubled the risk of diabetic ketoacidosis, although hospitalization accordingly was infrequent [23, 24]. As a result, this was directed to a cautionary from the (FDA) in May 2015 [23].

Conclusion

In the magnitude of macro and microvascular complications of diabetes mellitus, it is essential to provide an antidiabetic agent that is not only effective in improving glycemic control but also offers cardiorenal protection and reduced all-cause mortality. SGLT-2 inhibitors are novel oral antidiabetic agents that effectively provide renal protection in the diabetic population, especially through the reduction of albuminuria. Hence, the progression of diabetic nephropathy will be subsequently reduced. However, certain adverse outcomes have been reported, and the use of these agents must be done with caution. We recommended further meta-analysis for separated SGLT-2 inhibitors agents to assess the beneficial renal effect, especially in patients with established diabetic nephropathy.

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