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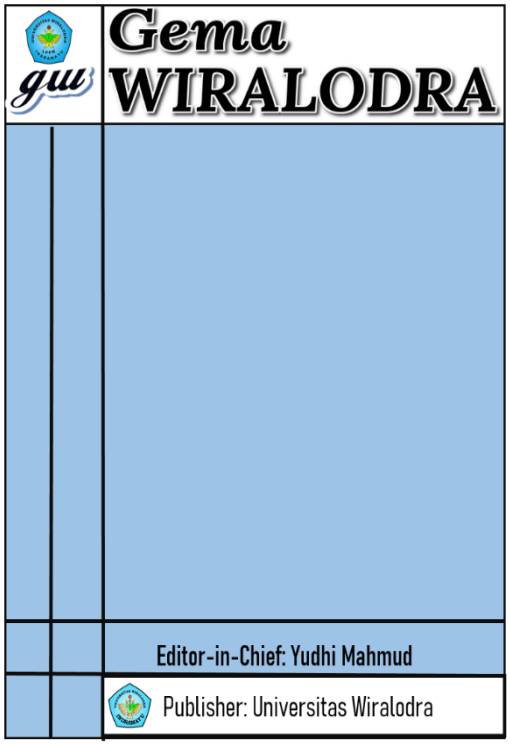

The role of sodium-glucose transport Protein-2 (Sglt-2) inhibitor on albuminuria and the progressive of diabetic kidney disease

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Orginal Article

The role of sodium-glucose transport protein-2 (Sglt-2) inhibitor on albuminuria and the progressive of diabetic kidney disease

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Abstract
Diabetes mellitus (DM) is a non-communicable disease with an increasing incidence every year. Sodium-Glucose Transport Protein-2 (SGLT-2) inhibitors are a class of insulin-independent antidiabetic drugs that can reduce the incidence of kidney function damage. This study aimed to determine the role of SGLT-2 inhibitor therapy in preventing the incidence of albuminuria so that it can be used as a consideration for treatment applications in type 2 DM patients. This study used the literature review method. Stages in data collection using the PRISMA method from several Journal Databases based on inclusion and exclusion criteria. SGLT-2 inhibitors are antidiabetic drugs that can help glycemic control with a good safety profile. The effectiveness of SGLT2 inhibitor class drugs has been proven to reduce the occurrence of albuminuria and impact the progression of diabetic kidney disease. Further research can be carried out to prove the benefits of this modality comprehensively.
Keywords: Type 2 diabetes mellitus, Albuminuria, SGLT-2 inhibitors

1. Introduction

Diabetes mellitus (DM) is a metabolic disease characterized by chronic hyperglycemia resulting from impaired insulin action, secretion, or both (PERKENI, 2015). The global population of DM sufferers in 2015 reached 7.3 billion people; in 2040, it is estimated to increase and reach 9 billion people. The World Health Organization (WHO) states that the number of DM sufferers in Indonesia has increased from 8.4 million sufferers in 2000 to around 21.3 million sufferers in 2030, of which 90% are type 2 DM sufferers (PERKENI, 2015; Amandari et al., 2018).

Diabetes is the most common cause of end-stage renal failure, with its incidence and prevalence set to double by 2030 (Kemenkes RI, 2018). The 2018 Riskesdas results show that the prevalence of diabetes mellitus in Indonesia is 2%. This figure shows an increase compared to the prevalence of diabetes mellitus in the 2013 Riskesdas results of 1.5%. The Bali Provincial Health Office in 2020 showed that 37,736 people with diabetes mellitus had received health services from the 52,282 people with diabetes mellitus who were there (Kemenkes RI, 2018; Dinkes Prov. Bali, 2021).

The most significant cause of end-stage renal disease (ESRD) is diabetic nephropathy, also known as diabetic kidney disease, which is as much as 52%, and only 0.6% are diagnosed (PERKENI, 2015). Diabetic kidney disease is one of the highest causes of death of all DM complications, causing mortality 70-100 times higher than the population without DM (Dronavalli et al., 2018). The clinical and socio-economic impact of diabetic kidney disease is aggravating because of the risk of progression to ESRD and the associated increased cardiovascular risk and costly renal replacement therapy.

Tight control of blood glucose is critical in diabetic kidney disease. Although many antidiabetic agents are available today, the treatment of diabetes in diabetic kidney disease is a challenge (Gembillo et al., 2021). Many antidiabetic drugs are contraindicated in advanced chronic kidney disease (CKD) and require dose adjustment due to the increased risk of drug toxicity due to decreased renal excretion (PERKENI, 2015).

There are two glucose-lowering therapeutic agents, namely Sodium-Glucose Transport Protein 2 (SGLT-2) inhibitors and Glucagon Like Peptide-1 (GLP-1) agonists, which work

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similarly to glucagon which are currently believed to be agents that can reduce the risk of cardiovascular disease and at the same time can inhibit the course of kidney disease associated with diabetes. Trials with GLP-1 agonists and SGLT-2 inhibitors showed a significant reduction of albuminuria. Experimental results from post hoc analysis of SGLT-2 inhibitors show a slowing of the development of diabetes-related kidney disease (Gembillo et al., 2021).

The results of a previous study by Wulandari et al. (2021) SGLT-2 inhibitor through the blockade effect of sodium and glucose reabsorption inhibition in PCT. As a result, glucose and sodium have increased in the distal tubule and juxtaglomerular apparatus, resulting in increased glomerular perfusion. This causes a feedback signal that causes afferent arteriolar vasoconstriction, an acute decrease in glomerular perfusion and pressure, and a decrease in extracellular plasma volume and blood pressure. This effect clinically manifests as decreased eGFR and albuminuria (Wulandari et al., 2021). From the illustration above, the authors are interested in writing about the role of SGLT-2 inhibitor therapy in preventing the incidence of albuminuria so that it can be used as a consideration in the treatment application for patients with type 2 DM.

2. Method

The method of this article is a literature review that describes descriptively the selected topic of discussion. Stages in data collection using the PRISMA method (preferred reporting items for systematic reviews and meta-analyses). Data search using Pubmed Database, ScienceDirect, SpringerLink, Proquest, and Ebsco. This review was carried out based on studies of the last ten years. Furthermore, the data obtained were selected according to the inclusion and exclusion criteria. The topic that is being discussed holistically is the role of SGLT-2 inhibitor therapy in preventing the occurrence of albuminuria so that it can be considered as a treatment application for type 2 DM patients.

3. Results and Discussion

Pathophysiology of Diabetic Kidney Disease

The pathophysiology of diabetic kidney disease is multifactorial and is characterized by severe metabolic disturbances. Hyperglycemia in DM patients causes dysregulation of intracellular metabolism, inflammatory lesions, increased apoptotic processes, and tissue fibrosis. Renal parenchyma damage in diabetic kidney disease goes through three stages, including (1) glomerular hypertrophy leading to hyperfiltration. Glomerular hyperfiltration occurs in up to 75% of patients with type 1 DM and up to 40% of patients with type 2 DM and is a hallmark of the early manifestations of diabetic kidney disease; (2) glomerular and tubulointerstitial inflammation, associated with activation of chemokines, cytokines, and profibrotic factors; (3) irregular cellular apoptosis and changes in the extracellular matrix. This mechanism causes the thickening of the glomerular basement membrane, thinning of the podocytes, expansion of the mesangial matrix, and tubular damage. These factors may contribute to the development of diabetic kidney disease, resulting in vascular remodeling, endothelial dysfunction, glomerulosclerosis, and tubulointerstitial fibrosis (Prasad & Jha, 2015).

Diagnosis of Diabetic Kidney Disease

The 2021 Indonesian Endocrinology Association (PERKENI) consensus has determined to establish a clinical diagnosis of diabetic kidney disease by finding albuminuria and decreased eGFR. Typical presentations of diabetic kidney disease include long-duration of diabetes, retinopathy, gross hematuria without albuminuria, and a progressive decrease in eGFR. UACR examination with a random sport unit sample was performed to confirm the diagnosis. Albumin levels are persistent in the 30-299 mg/24 hours range and change to persistent albuminuria at levels ≥ 300 mg/24 hours. Albuminuria is considered a sensitive marker of chronic kidney disease and cardiovascular risk and is currently used as the first clinical indicator of diabetic

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kidney disease (Nazar, 2014; Chawla et al., 2010). Based on the approximate equivalent (ACR), patients were classified into three categories of albuminuria from kidney disease improving global outcomes (KDIGO), namely A1, A2, and A3. Normal or mildly elevated albuminuria (A1) was defined as creatinine <30 mg/g and moderately elevated albuminuria (A2) was defined as creatinine 30-300 mg/g, and patients with ACR greater than 300 mg/g were categorized as severely increased albuminuria (A3) (Koroshi, 2007; Suarez et al., 2013; Kim et al., 2016).

Renal Glucose Handling

The primary role of the kidney in human physiology is to maintain intravascular volume, acid-base balance, and electrolytes through filtration, secretion, and reabsorption of vital minerals sodium, potassium, and metals; hydrogen and bicarbonate ions. The amount of glucose reabsorbed by the kidneys is equivalent to the amount entering the filtration system. The kidney has a role in regulating glucose homeostasis through 3 mechanisms, namely (1). Release of glucose into circulation through gluconeogenesis (renal gluconeogenesis). (2). Uptake of glucose from the circulation to meet energy needs (renal glucose uptake). (3). Reabsorption of glucose into circulation from the glomerular filtrate to maintain blood glucose levels (tubular glucose reabsorption) (Poudel, 2013).

Glucose reabsorption from the glomerular filtrate occurs via the SGLT co-transporter in the proximal convoluted tubule. In animal models, approximately 90% of glucose is reabsorbed by SGLT-2, and the remaining 10% of glucose reabsorption is mediated by SGLT-1 located on the luminal surface of epithelial cells lining the S3 segment of the proximal tubule. SGLT-1 is also expressed extensively in the small intestine and other tissues (Poudel, 2013).

Glucose reabsorbed from the proximal tubule by SGLT is then released into the circulation via facilitated glucose transporter (GLUT) action on the basolateral membrane of the epithelial cells lining the proximal tubule (GLUT2 in segments S1 or two and GLUT1 in segments S3). SGLT-mediated glucose transport is an active process, moving glucose against a concentration gradient, utilizing energy derived from the electrochemical potential gradient of sodium across the brush boundary membrane and maintained by intracellular sodium transport into the blood via sodium: potassium adenosine triphosphatase (ATPase) pumps on the basolateral membrane. In contrast, GLUT facilitates glucose's passive transport (equilibrium) across membranes and does not require an energy source (Poudel, 2013; Vasilakou et al., 2013; Bailey et al., 2022).

This reabsorption capacity has a maximum limit (TmaxG), or what is also called the glucose filtration rate, of 350 mg/min/1.73 m2 or the equivalent of 180-200 mg/dL under normal conditions. The system becomes saturated at this threshold, the reabsorption rate is maximum, and maximum glucose transport is reached. There is no more glucose to absorb, and the kidneys begin to excrete it in the urine, the beginning of glycosuria. In patients with DM who have chronic hyperglycemia, the reabsorption capacity is when the serum glucose level is >240 mg/dL. The amount of glucose reabsorbed by the kidneys is equivalent to the amount entering the filtration system. Glucose transport varies among individuals but averages about 375 mg/min for healthy subjects. Although 180–200 mg/dL represents a theoretical threshold glucose concentration, the concentration varies due to nephron heterogeneity, resulting in slight differences in glucose reabsorption rates and TmaxG values between individual tubules (Vasilakou et al., 2013).

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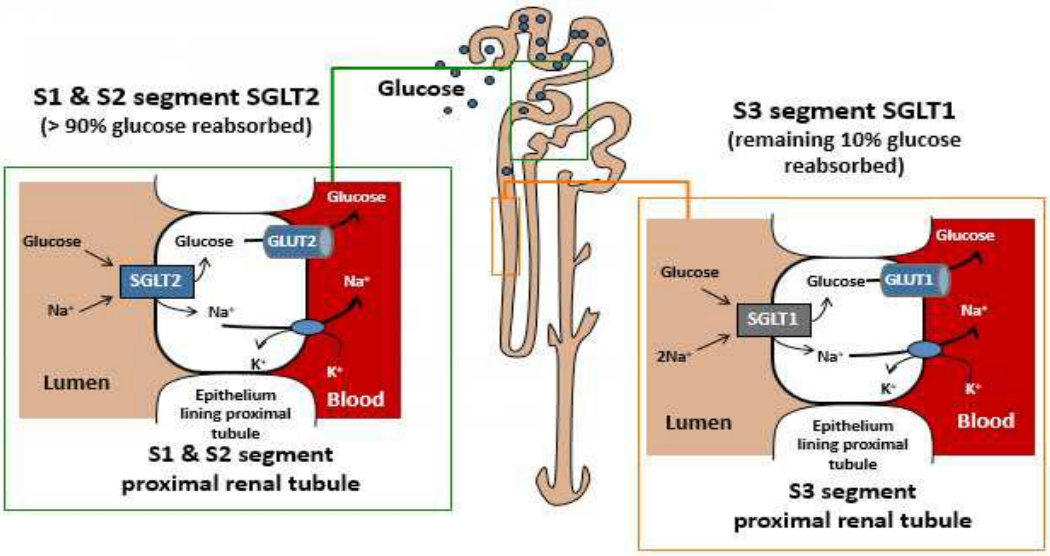
Figure 1
Glucose Reabsorption and Excretion Curves From the Proximal Tubules of the Kidney (Bailey & Day, 2010; Vasilakou et al., 2013)



Thus, the true threshold is not a point but a curve, at which excretion begins at the plasma glucose level (180 mg/dL), and increases gradually. As reabsorption approaches TmG, it stops and becomes parallel to the threshold concentration of glucose (Vasilakou et al., 2013).

Kidney Morphological Damage in Diabetic Kidney Disease

Extensive hyperglycemia causes 1) Expansion of the mesangial membrane due to prolonged hyperglycemia which causes increased matrix formation and/or protein glycosylation in the matrix. 2) Freezing of glomerular cell tissue due to various inflammatory processes. 3) Factors such as an expansion of the afferent renal artery or ischemic injury caused by contraction of the vessels innervating the glomerular apparatus due to hyaline deposition (Nazar, 2014; Fonseca-Correa & Correa-Rotter, 2021).

The Role of SGLT2 Inhibitors against Albuminuria in Diabetic Kidney Disease

Sodium-glucose transport protein 2 inhibitors are a new class of oral anti-diabetic drugs and are known to affect improving kidney and cardiovascular conditions in patients with kidney and heart disorders, both with and without DM. SGLT-2 functions for the process of glucose reabsorption in the proximal tubules of the kidney (Cowie & Fisher, 2020). If this cotransporter is inhibited, the reabsorption process will decrease, causing a decrease in TmaxG to 40-80 mg/dL. This condition can cause a process of significant energy loss so there is a compensatory mechanism in the form of increasing glucose reabsorption by SGLT-1 up to around 40%. Inhibition of the SGLT-2 cotransporter does not significantly cause hypoglycemia but can provide a good glycemic control effect. Several studies and clinical trials related to the use of SGLT-2 inhibitors show evidence of good glycemic control due to the use of these drugs and state that there is a decrease in HbA1c of up to 0.5-1% (Cowie & Fisher, 2020; Satyarsa, 2019; Adachi et al., 2000).

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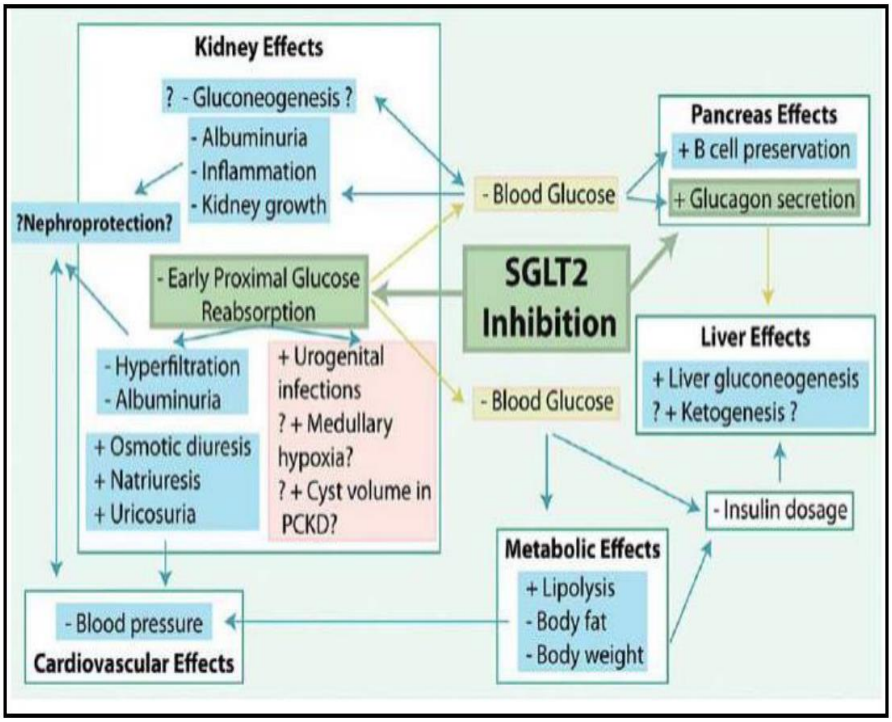
Figure 2
Direct and indirect effects of SGLT-2 inhibition on the kidneys and other organs (Amandari, 2018).



Along with glycosuria, inhibition of SGLT2 inhibitors also causes natriuresis and loss of sodium in the urine is followed by water loss. This condition causes a decrease in plasma volume and shows a decrease in systolic blood pressure of about 3-6 mm Hg and diastolic blood pressure of 1-1.5 mm Hg. Pathophysiologically, hyperglycemia in diabetes causes increased glucose and sodium reabsorption, activating tubuloglomerular feedback, which causes afferent arteriolar dilatation, increased glomerular pressure, and hyperfiltration. Increased natriuresis causes sodium to reach the distal nephron, which then inhibits tubuloglomerular feedback, causing a decrease in intraglomerular pressure and reducing hyperfiltration, which has a protective effect on the kidney. This condition is reflected in a decrease in GFR. This decrease in GFR is reversible if the administration of SGLT2 inhibitors is stopped (Koroshi, 2007; Poudel, 2013).

Other effects caused by SGLT2 inhibitors include a decrease in microalbuminuria, a secondary effect due to natriuresis (Nazar, 2014). SGLT2 transporter blockade inhibits the reabsorption of sodium and glucose in the proximal convoluted tubules, resulting in increased glucose and sodium in the distal tubules and the juxtaglomerular apparatus, resulting in an increase in glomerular perfusion. This causes a feedback signal that causes afferent arteriolar vasoconstriction, an acute decrease in glomerular perfusion and pressure, and a decrease in extracellular plasma volume and blood pressure (Nazar, 2014). In addition, this effect reduces atrial natriuretic peptide secretion, which may also be important in reducing intraglomerular pressure. This effect is clinically manifested as decreased albuminuria and eGFR. This condition also causes an improvement in the performance of the kidney proximal tubules, reducing the need for energy and oxygen. The effectiveness of this SGLT2 inhibitor class of drugs in type 2 DM patients has summarized several studies that benefit kidney function with SGLT2 inhibitor therapy in diabetic kidney disease (Isidto et al., 2023).

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Table 1
Benefits of SGLT2 inhibitor therapy in diabetic kidney disease (Suarez et al., 2013; Yohanes, 2020)

Study	Study Design	Population	SGLT2i Agent	Outcome
CANVAS program randomized clinical trials	Randomized, double-blind, parallel, placebo-controlled study	10,142 patients UACR 30 to 300 mg/dl	Canagliflozin 100 mg daily or placebo	Giving canagliflozin reduces the risk of decreased kidney function, reduces the incidence of albuminuria and decreases eGFR
Canagliflozin Slows Progression of Renal Function Decline Independently of Glycaemic Effect	Randomized, double-blind, active-controlled trial	1.450 UACR ≥ 30 mg/g	Canagliflozin 100 mg or 300 mg daily	Canagliflozin doses of 100 and 300 mg have the effect of reducing the progression of kidney complications, characterized by decreased albuminuria and slowing the rate of decline in eGFR for 2 years
Effects of ertugliflozin on renal function over 104 weeks of treatment: a post hoc analysis of two randomized controlled trials	Randomized controlled	1936 patients Patients with initial albuminuria UACR ≥3.39 g/mmol and no albuminuria (UACR <3.39 mg/mmol)	Administration of ertugliflozin	Administration of ertugliflozin reduces albuminuria (UACR) at duration of administration above 6 weeks and in patients with baseline microalbuminuria.
EMPA – REG OUTCOME trial	Randomized, double-blind placebo-controlled trial	6,185 patients GFR > 30 ml/min/1,73 m^2	Empaglifozine 10/25 mg daily	Albuminuria decreased by 7% in those with normoalbuminuria, 25% with microalbuminuria, and 32% with macroalbuminuria.
Impact of sodium–glucose cotransporter 2 inhibitors on renal function in participants with type 2 diabetes and chronic kidney disease with normoalbuminuria	Retrospective observational study	86 patients UACR 30mg/g	SGLT2 inhibitor	GLT-2 inhibitors have a more beneficial effect on participants with type 2 DM and CKD with normal albuminuria, SGLT-2 inhibitors have a renoprotective effect depending on the degree of albuminuria

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Safety concerns remain the most important parameters determining the future of any drug under development. By their nature, SGLT-2 inhibitors cause glycosuria, leading to urinary and genital tract infections, electrolyte imbalances, and increased frequency of urination. The most frequently reported side effects in phase II and III trials included constipation, diarrhea, nausea, urinary frequency, and genitourinary infections involving urinary tract and vulvovaginal infections (Vasilakou et al., 2013).

Indications for the use of SGLT2 inhibitor therapy

There are four SGLT2 inhibitors approved by the Food and Drug Administration (FDA) since 2013, namely canagliflozin (Invokana), dapagliflozin (Forxiga), empagliflozin (Jardiance), and ertugliflozin (Steglatro). SGLT2 inhibitors are recommended for people with stage 3 or higher CKD and type 2 diabetes because they can slow the progression of CKD and reduce the independent risk of heart failure. SGLT2 inhibitors differ primarily in their binding, affinity, and selectivity to SGLT transporters. For people with type 2 DM and CKD, the choice of a specific agent depends on comorbidities and the stage of CKD. For patients with type 2 DM and diabetic kidney disease, the use of SGLT-2 inhibitors can be used in individuals with eGFR ≥ 20 mL/minute/1.73 m2 and UACR ≥ 200 mg/g creatinine, which can be recommended to reduce the development of CKD and cardiovascular events (Pathni, 2019; ElSayed et al., 2023). SGLT-2 inhibitors are recommended by several guidelines such as the PERKENI Consensus, the American Diabetes Association (ADA), the European Association for the Study of Diabetes (EASD), or The American Association of Clinical Endocrinologists/ American College of Endocrinology (AACE/ACE) as add-on therapy to metformin if therapeutic goals are not being achieved with monotherapy, especially in patients wishing to avoid weight gain or hypoglycemia. Several SGLT-2 inhibitors are available globally, some of which are available in Indonesia.

4. Conclusion

SGLT-2 inhibitors are antidiabetic drugs that can help glycemic control with a good safety profile. It is hoped that further research can be carried out to comprehensively prove the benefits of this modality.

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