EFFECTIVENESS OF SGLT2 INHIBITOR (EMPAGLIFLOZIN) IN REDUCTION OF ALBUMINURIA IN TYPE 2 DIABETICS

Muhammad Sajjad Sadiq[1], Muhammad Atiq Ur Rehman Khan[2], Muhammad Adnan Khan[3], Adil Shabbir[3], Feroza Zarin[4]

1. Consultant medicine Mayo General Hospital Castlebar, Ireland
2. Registrar cardiology Sligo University Hospital, Ireland
3. Registrar Endocrinology Mayo General Hospital Castlebar, Ireland
4. SHO Medicine Mayo General Hospital Castlebar, Ireland

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Corresponding author:
Muhammad Sajjad Sadiq
Email: muhammad.sadiq1@hse.ie

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ABSTRACT

Introduction: Diabetic kidney dysfunction is a leading cause of end-stage renal disease (ESRD) globally. Empagliflozin is a highly selective inhibitor of sodium-glucose cotransporter 2 (SGLT2). It is significantly related to the reduction of albuminuria, blood glucose, systolic blood pressure (SBP), and body weight in t2DM. In individuals with diabetic renal dysfunction, empagliflozin has been proven to reduce glomerular hyperfiltration and albuminuria.

Objective: To evaluate the effectiveness of empagliflozin in reduction of albuminuria in patients with type 2 diabetes mellitus.

Methods: A retrospective observational study was carried out. Data were collected retrospectively by reviewing charts using a structured data collection questionnaire. Urinary albumin creatinine ratio (UACR), eGFR, BMI, HbA1c, blood pressure, and body weight were noted before the start of empagliflozin and after 12 months of treatment as well for comparison. This study was conducted at Mayo General Hospital, Castlebar.

Results: A total of 80 diabetic individuals were recruited for the study based on inclusion criteria attending the endocrinology outpatient department. ACR levels were improved after empagliflozin therapy, with 90% of patients demonstrating reduced ACR levels to the normal limit (<3.4 mg/mmol) and only 10% of the patients having abnormal ACR levels between 3.4 and 33.9 mg/mmol.

Conclusion: Empagliflozin therapy significantly reduced the urinary albumin-creatinine ratio in patients with albuminuria over a period of 12 months. It also improved HbA1c levels, systolic blood pressure, BMI reduction, and eGFR.

INTRODUCTION

Type 2 diabetes mellitus is a syndrome of longstanding hyper-glycaemia because of progressive loss of beta cell functions along with insulin resistance.[1] It represents a paragon of chronic illnesses in which family and environmental factors are in close association. This medical problem has significant global impact with the estimation of continuous growth.[2] The type 2 diabetes mellitus (DM) prevalence has reached epidemic proportions and is believed to affect over 400 million people worldwide.[3] Moreover, it is expected that incidence of diabetes will continue to rise and in the United States alone, it is projected to affect nearly every third person by the year 2050.[4] These projections are alarming and suggesting an urgent dire for development and implementing novel preventive and treatment measures to combat this rise in type 2 diabetes mellitus prevalence worldwide. As per healthy Ireland survey, 854165 adults above 40 years of

age in the Irish Republic are either having growing risk of Type 2 diabetes mellitus or already diagnosed with it. According to statistics, there are 15600 people above the age of 75 living with Type 2 diabetes mellitus in Ireland.5 In Ireland, overall prevalence of Type 2 diabetes mellitus among adults aged 50 and above is 8.5% and it is increasing along with global trends, largely because of the growing prevalence of obesity and aging population[6]

Type 2 diabetes mellitus is one of the major risk factors for macro-vascular and microvascular complications[7] Macro-vascular complications comprise of myocardial infarction, transient ischemic attack, stroke, and limb ischemia. Microvascular complications include nephropathy, retinopathy, autonomic neuropathy and peripheral neuropathy. Diabetic kidney disease is a micro vascular complication of diabetes mellitus which is one of the most significant causes of chronic kidney disease worldwide[8]

Diabetes Mellitus is a common cause of kidney disease, accounting for more than 30% of people needing dialysis. The frequency and severity of albuminuria, as well as chronic renal function deterioration, are currently used as clinical markers of underlying renal dysfunction and development of nephropathy[9] Micro-albuminuria has been associated with a higher risk of cardio-vascular disorders and renal dysfunction in individuals with Diabetes Mellites type 2, despite not being an ideal indicator of renal impairment[10] Macro-albuminuria has been linked to an increased risk of both kidney and cardio-vascular disorders. As a result, routine albuminuria monitoring remains an essential clinical parameter for determining the development and progression of renal dysfunction in diabetics.[11,12]

Diabetes-related renal dysfunction is related to structural and functional modifications, which appear as albuminuria and a lower estimated glomerular filtration rate (eGFR). The pathological processes leading to renal dysfunction consist of metabolic alternations and late cellular remodeling. In a hyperglycemic state, tubular reabsorption of glucose and hence sodium reabsorption increases.[13] As a result, a reduced amount of sodium enters the macula densa, activating the renin-angiotensin-aldosterone system (RAAS) leading to vasoconstriction of the efferent arteriolar system and vasodilation of afferent arteriolar system, resulting in higher glomerular pressure. This physio-pathological process, over time, leads to glomerular injury.

These modifications in glomerular hemodynamics as a result of type 2 diabetes cause hyper-filtration and renal hypertensive changes, hypertrophy of renal structures, and alternations in the structure and morphology of glomeruli, leading to sign and symptoms of characteristic of diabetes-related renal injury such as albuminuria, reduced eGFR, and hypertension.[14]

The existing standard reno-protective interventions in type 2 diabetes consists of strict glycemic and blood pressure monitoring and control, as well as inhibition of the renin–angiotensin–aldosterone system (RAAS).15 Lifestyle modifications, such as salt restriction and weight reduction, are the only management alternatives for individuals with chronic albuminuria who have good glycemic and blood pressure regulation. These lifestyle modifications are backed by little evidence and are generally challenging to attain.

Empagliflozin is a highly selective inhibitor of sodium glucose cotransporter 2 (SGLT2). It is significantly related to lower blood glucose, systolic blood pressure (SBP), and bodyweight in t2DM. In individuals with diabetes type 1, empagliflozin has been proven to reduce glomerular hyper-filtration.16 In both types of

diabetes, this physiological feature of the kidney leads to the progression of renal dysfunction. Additionally, by inhibiting sodium–glucose reabsorption at the proximal convoluted tubule, SGLT2 suppression may ameliorate these early glomerular pathophysiological abnormalities. Effects of the drug ultimately cause lower sodium reabsorption and enhanced delivery to macula densa, activating the feedback mechanism that results in vasoconstriction of afferent arteriolar system and drop in glomerular pressure.[17] This hemodynamic mechanism reduces glomerular hyper-filtration and, as a result, glomerular hypertension, reducing albuminuria, one of the major pathophysiological aspects in the development of nephropathy, that also explains the drug therapy's benefits further than glycemic control.

SGLT2 inhibitors have been shown to have positive effects on renal function in several trials. When compared to placebo, empagliflozin lowered the incidence and progression of albuminuria, slowed the decline in kidney function, ultimately reducing the risk of renal morbidity and mortality.[18] In another study, SGLT2 inhibitors lowered the progression of renal dysfunction reducing the chances of eGFR decline, chronic kidney failure, and renal mortality.[19] These trials, however, were conducted on individuals who had a history of coronary heart disease or were at increased risk of getting it.

In the Empagliflozin Event Trial in Type 2 DM patients' trial, Empagliflozin considerably reduced the need for renal replacement therapy, but had limited impact on recent onset micro-albuminuria.[20] However, Canagliflozin dramatically reduced the incidence of micro-albuminuria, with no changes in the requirement for renal replacement therapy. Kidney findings were not primary endpoints in both trials, and the data indicating renal dysfunction was insufficient to give solid evidence. As a result, more compelling literature is needed to support the reno-protective effects of Empagliflozin.

Therefore, the effect of empagliflozin therapy on the urine albumin-to-creatinine ratio (UACR) in type 2 diabetic patients was investigated for a duration of 12 months. We hypothesised that adding empagliflozin to glucose and blood-pressure-lowering regimen would lower albumin-to-creatinine ratio.

MATERIALS AND METHODS

Study design: This is a single-center retrospective observational study

Duration: The study was done between 2018 – 2020.

Setting: The research was carried out at Mayo General Hospital in Castlebar,

Sample size: This was a duration-based study, so 80 patients were taken in this study. The study was conducted in individuals with Type 2 DM who were admitted to the endocrinology outpatient clinic between 2018 and 2020 and was commenced were retrospectively identified from our facility's computerized data.

Sample selection criteria

Inclusion criteria

- Participants had HbA1c levels between 7 to 11 percent.
- Patients on Empagliflozin, an SGLT-2 inhibitor

Exclusion criteria:

- Individuals with chronic kidney disease due to factors other than hyperglycemia and those on renal replacement therapy for kidney failure were excluded from this study.
- Individuals with gestational diabetes and those who are nearing the end of their lives were excluded as well.

Data collection procedure: Participants were chosen retrospectively from type 2 DM

adult patients attending this diabetic outpatient facility. Before the further assessment, data from medical records were anonymized and de-identified. Formal approval was acquired from the ethical committee of Mayo University Hospital, Castlebar.

Eighty diabetic patients were recruited in this study who attended the Mayo General Hospital's endocrinology outpatient clinic and were treated with Empagliflozin. We included individuals with type 2 DM who consulted the clinic between 2018 and 2020 and had a urine albumin-to-creatinine ratio compatible with micro-albuminuria ›30miligram/gram before initiating empagliflozin medication with or without other oral hypoglycemic drugs and/or insulin therapy. The data was collected using a thorough well-structured questionnaire (attached to the annexure). Prior to the initiation of empagliflzin therapy, baseline urine albumin-creatinine ratio (UACR) and estimated glomerular filtration rate (eGFR), as well as glycosylated hemoglobin (HbA1c), blood pressure, and body weight, were collected retrospectively. After 12 months of empagliflozin therapy, all of these outcomes were noted from the charts.

The consequences of SGLT2 inhibitors on albuminuria, estimated glomerular filtration rate, as well as systolic and diastolic blood pressure, were studied over one year. A number of parameters including duration of diabetes, ACR, HbA1c, and anthropometric measures such as systolic blood pressure (SBP) and diastolic blood pressure (DBP) body weight, were measured throughout a 1-year period. Patients' documents were prepared after a thorough inspection.

Biochemical and Anthropometric measures were obtained at the time of the evaluation, as well as data on fasting blood sugar and HbA1c levels evaluated at our facility were noted and used as diabetes control measures. The levels albumin-to-creatinine ratio, eGFR, BMI, HbA1c and blood pressure were all measured. Patients' estimated glomerular filtration rates (eGFR) were estimated using the Modification of Diet and Renal Disease (MDRD) method, which was customised for the individuals. Estimated Glomerular Filtration Rate (eGFR) = 194 × age - 0.287×serum creatinine–1.094 (× 0.739, if female)

Statistical analysis

All analyses were conducted using the statistical software SPSS (Statistical Package for the Social Sciences) version 22.0 that is available on our unit. The independent sample T-tests were utilized to demonstrate the results as per prediction of normal distribution. A dependent sample T-test was utilized to compare the numerical variables. For continuous variables (such as blood sugar level, BMI, and weight), the mean values along with standard deviation was calculated, and the number (N) and percentage values for ordinal variables were calculated. A p-value of less than 0.05 was regarded as significant statistically.

RESULTS

A total of 80 diabetic individuals were recruited for the study based on inclusion criteria attending the endocrinology outpatient department. The baseline characteristics of the patients treated with empagliflozin revealed a mean age of 62.46 ± 11.83 (Table 4). Individuals with albuminuria had a longer diabetes duration, higher blood pressure, and lower eGFR.

ACR effects of SGLT2 inhibition with Empagliflozin

After 12 months of empagliflozin therapy, urinary ACR values were significantly lower than before the initiation of empagliflozin

therapy. A significant number of diabetic patients (51. 3%) had abnormal ACR between 3.4 and 33.9 mg/mmol with only 48.8 percent individuals having normal ACR i.e., <3.4 mg/mmol (Figure 1, Table 1). With the 12 months of empagliflozin therapy, empagliflozin had a significant effect on urinary ACR levels, and these levels were sustained throughout the treatment period. ACR levels were improved after empagliflozin therapy with 90% of patients demonstrating reduced ACR levels to normal limit (<3.4 mg/mmol) and only 10% of patients having abnormal ACR levels ACR between 3.4 and 33.9 mg/mmol (Figure 2, Table 2). After a year of empagliflozin therapy, equivalent effects of empagliflozin 10 mg (n =48) and empagliflozin 25 mg (n = 32) were reported in individuals with albuminuria (adjusted mean difference: 0.05). There was no significant change in eGFR following empagliflozin therapy with a mild reduction with a mean difference of 0.100 ± 0.439 (Table3).

Glycemic control and HbA1c

Considering all individuals involved in this analysis, after 12 months of empagliflozin therapy, a considerable HbA1c decrease was found with a mean HbA1c level of 9.670±1.94 before therapy decreasing to 7.539± 0.96 after a year of drug therapy (Table 4) (mean difference= 2.13, p 0.001). This shows a significant glycemic control with drug therapy.

Bodyweight & BMI

The average body weight and body mass index (BMI) both reduced substantially after 12 months of empagliflozin therapy. The mean BMI before drug therapy was 34.1 ± 4.31 and was 33.1 ± 4.39 after treatment, with a mean difference of 1.013 (Table 3). Ninety percent (90%, n= 72) of diabetic individuals were obese with a BMI of above 30.0, before the empagliflozin therapy. Patients taking empagliflozin for a year were able to reduce their weight and BMI with only 62.4% (n=50) individuals being obese after a year of empagliflozin therapy (Table 4).

Blood pressure Empagliflozin therapy was only moderately related to changes in systolic and diastolic blood pressure after 12 months of follow up. The mean SBP before drug therapy was 127.5 ± 30 and was 129.8 ± 11 after treatment, with a mean difference of -2.262. Moreover, the mean DBP before drug therapy was 77.6 ± 8 and was 75.9 ± 8 after treatment, with a mean difference of 1.688 (Table 3).

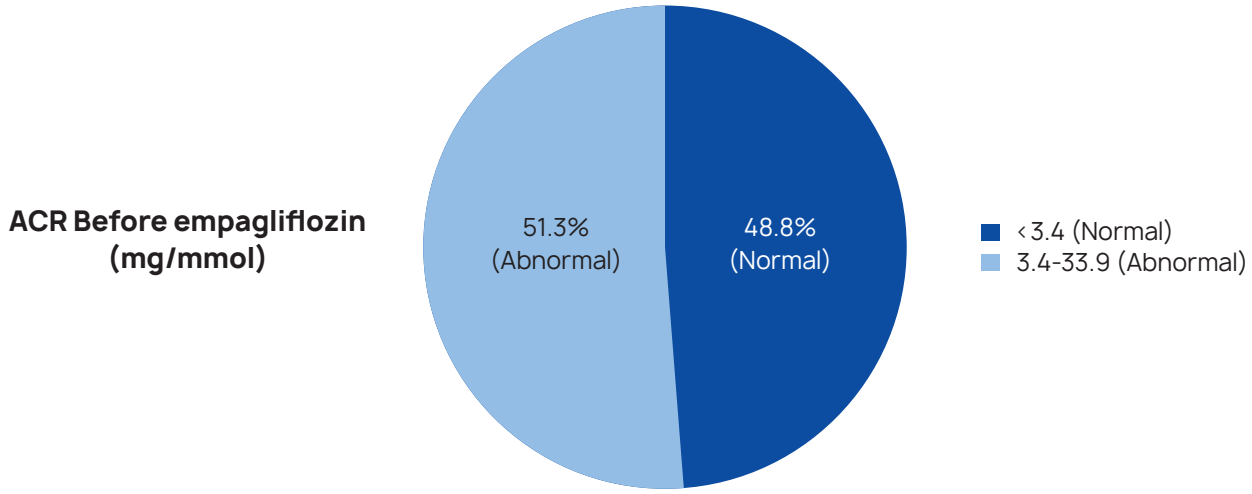

Fig-1: Descriptive statistics of ACR Before empagliflozin (mg/mmol)

Table-1: Frequency distribution of ACR before and after empagliflozin (mg/mmol)

		Frequency	Percent
ACR Before empagliflozin (mg/mmol)	<3.4 (Normal)	39	48.8
	3.4-33.9 (Abnormal)	41	51.3
ACR After Emagliflozin Use (mg/mmol)	<3.4 (Normal)	72	90.0
	3.4-33.9 (Abnormal)	8	10.0

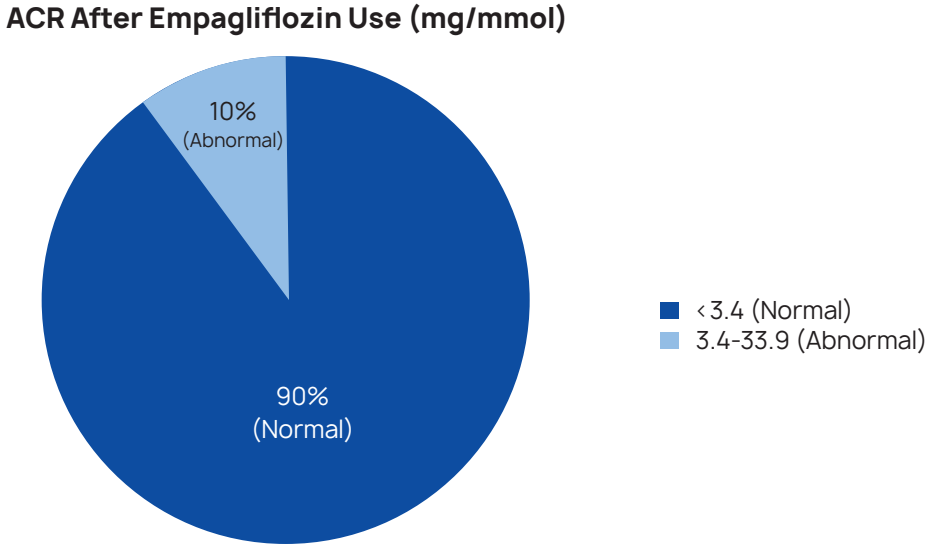

Fig-2: Descriptive statistics of ACR after empagliflozin use (mg/mmol)

Table-2: Mean comparison of ACR, eGFR, HbA1c, weight, SBP and DBP bempagliflozin (before and after 1year)

		Mean	S.D	95%CI
Pair 1	ACR Before empagliflozin (mg/mmol) - ACR After Emagliflozin Use (mg/mmol)	**0.412**	**0.495**	**(0.30-0.52)**
Pair 2	eGFR before Empagliflozin (ml/min) - eGFR after Empagliflozin (ml/min)	**0.100**	**0.439**	**(0.002-0.198)**
Pair 3	HbA1c before Empagliflozin (%) - HbA1c after Empagliflozin (%)	**2.1312**	**1.5796**	**(1.78-2.48)**
Pair 4	BMI before Empagliflozin (Kg/M2) - BMI after 1 year of Empagliflozin (Kg/M2)	**1.0125**	**2.6861**	**(0.41-1.61)**

Pair 5	Weight before Empagliflozin (kg) - Weight after 1 year of Empagliflozin (kg)	**3.956**	**3.859**	**(3.098-4.82)**
Pair 6	SBP before Empagliflozin (mmHg) - SBP after 1 year of Empagliflozin(mmHg)	**-2.262**	**30.181+**	**(-8.98-4.45)**
Pair 7	DBP before Empagliflozin (mmHg) - DBP after 1 year of Empagliflozin (mmHg)	**1.688**	**9.124**	**(-.34-3.72)**

Table-3: Comparison of age, Dose of Empagliflozin, ACR, eGFR, HbA1, BMI, weight (kg), SBP and DBP bempagliflozin (before and after)

	Mean	S.D
Age	**62.46**	**11.84**
Dose of Empagliflozin (mg)	**16**	**7.40**
ACR Before empagliflozin (mg/mmol)	**1.51**	**0.50**
ACR After Emagliflozin Use (mg/mmol)	**1.1**	**0.30**
eGFR before Empagliflozin (ml/min)	**1.86**	**0.69**
eGFR after Empagliflozin (ml/min)	**1.76**	**0.60**
HbA1c before Empagliflozin (%)	**9.67**	**1.94**
HbA1c after Empagliflozin (%)	**7.54**	**0.96**
BMI before Empagliflozin (Kg/M2)	**34.08**	**4.31**
Weight before Empagliflozin (kg)	**95.67**	**14.54**
Weight after 1 year of Empagliflozin (kg)	**91.71**	**15.01**
BMI after 1 year of Empagliflozin (Kg/M2)	**33.06**	**4.39**
SBP before Empagliflozin (mmHg)	**127.59**	**30.47**
DBP before Empagliflozin (mmHg)	**77.6**	**8.55**
SBP after 1 year of Empagliflozin(mmHg)	**129.85**	**11.90**
DBP after 1 year of Empagliflozin (mmHg)	**75.91**	**8.07**

DISCUSSION

SGLT2 inhibitors have a large body of research demonstrating that they not only improve an individual's glycemic control but also have favorable effects on various vital organ systems, involving the cardiovascular, hepatic, and renal systems. The key outcome of our study backs up our hypothesis that SGLT2 inhibition such as empagliflozin decreases the albumin-to-creatinine ratio in individuals with type 2 DM. The degree of decreasing albuminuria levels in diabetic patients was clinically significant, and was not fully explained by levels of improvements of biochemical and anthropometric measures such as eGFR, HbA1c, weight, and blood pressure. Apart from enhanced rates of urinary tract infections and a proportional rise in instances of volume depletion, SGLT2 inhibitor was usually well-tolerated in our study group.

SGLT2 inhibition has been shown to reduce renal dysfunction in previous studies utilising several animal models of renal disease. In animal models of type 2 DM, SGLT2 inhibitors have been shown to produce similar albuminuria lowering effects in animal models of type 2 DM, particularly a new study that empagliflozin decreased ACR in mice models of type 2 DM, irrespective of effects on blood pressure or hyperglycemia.[18, 21] According to recent clinical trials in diabetic individuals with and without renal dysfunction, SGLT2 inhibitors are linked with a sudden but moderate drop in estimated GFR within 1-2 months of the start of therapy.[20, 22] It is followed by a phase of consistent kidney physiology function for 13–26 months. These alternations are reversible after the complete withdrawal of drugs for two weeks. Safety analyses of SGLT2 inhibitors have also indicated a decline in albumin creatinine ratio or urine albumin release in individuals with type 2 DM and renal dysfunction throughout the same management period.[21] Furthermore, while the SGLT2 inhibitor dapagliflozin was unable to have a meaningful effect on HbA1c after 6 months in a focused investigation of individuals with renal dysfunction, it did lower ACR, blood pressure, and BMI. Moreover, dapagliflozin lowered eGFR initially before stabilising kidney function over a 26-month therapy period. In another analysis encompassing individuals who underwent baseline renin-angiotensin-aldosterone system inhibition, dapagliflozin treatment for 3 months was observed to decrease albuminuria. As a result, available experimental and observational evidence point to SGLT2 inhibitors as a medication group that could reduce urine ACR regardless of affecting blood pressure, HbA1c, or BMI.[23]

The effect of SGLT2 inhibitors on albuminuria could be attributable to a variety of processes. Firstly, SGLT2 inhibition done through drugs or genetic processes lowers hyper-filtration through the glomeruli, which is used as a potential indicator for renal glomerular pressure. 12 Such a process of lowering glomerular pressure would be assumed to lower UACR independent of alterations in blood pressure, through a process of afferent arteriolar vasoconstriction. Moreover, the effect of SGLT2 inhibitor, empagliflozin, on albuminuria remained substantial and of important clinical magnitude as shown in the current pooled studies. In addition, simultaneous alterations in glycemic index, BMI, or blood pressure could only account for about half of the overall UACR-lowering effect of empagliflozin vs placebo, with blood pressure alterations comprising the most. This promotes the concept that albuminuria reductions were primarily mediated through mechanisms other than those potentially resulting in albuminuria improvements, such as

blood sugar, blood pressure, or BMI.[11]

Secondly, the peripheral arterial effects of these SGLT2 inhibitors make a second significant process that may play a significant role to lower albuminuria. SGLT2 inhibition lowers blood pressure and arterial stiffness, both of which have been linked to the preservation of renal function. Our observations imply that alteration in systolic pressure only accounts for a minor portion of albuminuria-lowering effect, as the effects on albuminuria remained substantial even after controlling for alteration in this parameter. Our findings in individuals with diabetes type 1 support the idea that renal hemodynamic effects are significantly greater than blood pressure decline. Additionally, recent clinical findings propose that direct renal hemodynamic processes of SGLT2 inhibitors impact renal glomerular pressure significantly, resulting in lower albuminuria.[21]

Another important mechanism of SGLT2 inhibitors that leads to a reduction in UACR is the effect on pro-inflammatory processes, which is a well-known feature of diabetic nephropathy and can play a vital role to cause albuminuria. The effects of SGLT2 inhibition have been shown to decrease the release of inflammatory markers. Although inflammatory mediators were not measured in the current study, future research should look into the impact of SGLT2 inhibitors on inflammatory and fibrotic processes in patients with type 2 DM and related renal dysfunction. In addition, empagliflozin reduces uric acid levels of plasma by about 20%. [24, 25] Uric acid has a potential role in the progression of kidney and cardiovascular disorders via stimulation of pro-inflammatory processes, therefore, lowering plasma urate levels with empagliflozin may have a beneficial effect on albuminuria.[26]

Finally, another major mechanism that contributes to albuminuria -lowering effects of empagliflozin include alternations in effective volume of circulating body fluids caused by natriuresis, as evidenced by the reduction in albuminuria achieved by restriction of salt intake. [27] This natriuretic effect of SGLT2 inhibition on decreasing the UACR may be therapeutically important because SGLT2 inhibition causes a persistent and substantial drop in effective circulating fluid volume. Moreover, SGLT2 inhibitors may result in a decrease in natriuretic hormones like atrial natriuretic peptide (ANP) that is raised in the blood of diabetic mice and may play a significant role in diabetes-related hyper-filtration[28,29]

While SGLT2 inhibition has been shown to have reno-protective effects in animal models, such as preserved kidney function, reduced interstitial fibrosis, and reduced UACR, these effects may be amplified when paired with classical ACE inhibitors. However, because of the potential utility of this therapy for the prevention of kidney dysfunction, investigations exploring the combined effects of SGLT2 and ACE inhibitors in diabetes are necessary.

Our study has a few limitations that must be taken into account. First of all, the focus of this analysis was to assess how the SGLT2 inhibitors affected UACR and how that related to changes in the estimated glomerular filtration rate. The nature of this study design i.e., retrospective study precludes accurate assessment of albuminuria due to several incomplete data. Secondly, this study was conducted to look into the albuminuria-lowering effects of empagliflozin in individuals with type 2 DM, so this study should be considered to form a hypothesis. In this rather healthy group, most of the individuals had micro-albuminuria instead of macro-albuminuria. Secondly, albumin and creatinine levels of urine were acquired through

predetermined spot urine tests, obtained as part of the ongoing and complete safety checks during study. The urinary albumin creatinine ratio may undergo potential variation, which we tried to minimize by using a large sample size. The study was able to recognize a substantial effect of SGLT2 inhibition such as empagliflozin on albuminuria, implying that the outcome is authentic and persistent. Furthermore, randomization and blinding made it less likely that variability caused any significant influence in diabetic individuals. Despite the fact that our sample size was sufficient to evaluate significant impacts on UACR, the overall number of people with macro-albuminuria was limited. Lastly, while empagliflozin had a significant effect on UACR decline over 12 months, the effect on longer-term albuminuria-lowering and eGFR has to be investigated further. More thorough research on the effects of SGLT2 inhibitors on UACR and long-term kidney outcomes would be beneficial.

In conclusion, sodium-glucose cotransporter 2 (SGLT2) inhibitors such as empagliflozin are a novel class of glucose-lowering drugs that have significant effects on diabetes risk factors such as glycemic control, albuminuria reduction, and systolic and diastolic blood pressure control. Empagliflozin is also linked to reduced BMI and urate levels. Empagliflozin had a significant effect on renal function by reducing UACR leading to the reduced development and progression of diabetes related albuminuria resulting in a lower risk of end stage kidney disease. Furthermore, SGLT2 inhibitors had a better renal protective impact in individuals with higher albuminuria and eGFR, as well as a longer management duration. Recent clinical trials have demonstrated that SGLT2 inhibitors can improve kidney hemodynamics by lowering hyper-filtration and glomerular pressure.

Further researches using wide-scale ongoing studies with hard renal outcomes will presumably reveal if SGLT2 inhibitors, in addition to their well-recognized effects on blood glucose levels and BP, have beneficial effects on the development and progression of diabetes related renal dysfunction.

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Conflict of Interests:

There was no conflict of interest throughout the conductance of this study.

AUTHORS CONTRIBUTION

MSS: Research idea conception, data management,
MAURK: Discussion writing,
MAK: Data collection,
AS: Data collection,
FZ: Data analysis

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