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Original Article

Internal Medicine Section

Effect of Dapagliflozin on Renal Function in Type 2 Diabetes Mellitus Patients with Nephropathy: A Prospective Cohort Study

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ABSTRACT

Introduction: Diabetes remains a major global health concern, particularly in developing nations such as India. Diabetic Nephropathy (DN) is a severe complication of Type 2 Diabetes Mellitus (T2DM) which is the primary cause of End Stage Renal Disease (ESRD) and an increased cardiovascular risk.

Aim: To evaluate the effect of dapagliflozin on glycaemic control and renal function in patients with T2DM and DN.

Materials and Methods: The present single centre prospective cohort study was carried out in a Tertiary Care Hospital setting over a duration of eighteen months (September 2022 to February 2024). Patients aged >18 years diagnosed with T2DM and DN were included. The primary outcomes included change in Glycated Haemoglobin (HbA1c), serum creatinine, serum urea, estimated Glomerular Filtration Rate (eGFR), and urinary albumin levels from baseline over time. The data were summarised using descriptive statistics and the effects of dapagliflozin on parameters were evaluated using paired t-tests. A p-value of <0.05 was considered statistically significant.

Results: A total of 100 patients were enrolled, most being male (72%) and the mean age was 60.86 years. Dapagliflozin treatment led to a significant reduction in HbA1c level from 7.51±0.86% to 6.53±1.27%, serum urea from 51.28±35.94 mg/dL to 30.88±12.39 mg/dL, and serum creatinine from 1.13±0.27 mg/dL to 0.92±0.22 mg/dL (all p<0.0001). The mean eGFR significantly improved from 72.30±21.28 mL/min/1.73m² to 87.55±20.53 mL/min/1.73m² (p<0.0001) whereas the mean urinary albumin level decreased from 1.91±1.00 to 0.92±1.05 (p<0.0001).

Conclusion: The results showed that dapagliflozin was effective in improving both renal and metabolic parameters in patients diagnosed with T2DM and DN. The results confirm effectiveness of dapagliflozin in preserving renal function, reducing albuminuria, and enhancing glycaemic control, and renoprotective effects in DN.

Keywords: Diabetic nephropathy, End stage renal disease, Glycaemic control, SGLT2 inhibitors

INTRODUCTION

The International Diabetes Federation (IDF) report, in the year 2021, nearly half a billion people aged between 20-79 years had diabetes [1]. Diabetes is a global health concern, and the prevalence rates continue to increase. It is estimated that there will be around 1.3 billion adults with diabetes by the year 2050 [2]. In India, the prevalence rates are even higher and around 11.4% of the population is living with diabetes [3]. The growing incidence and prevalence rates of metabolic disorder indicate increasing public health concerns with substantial implications on healthcare system, economy, and the society at large [4]. According to the IDF report, nearly 40% of patients with diabetes are at risk of developing Chronic Kidney Disease (CKD) [5]. Diabetic Kidney Disease (DKD) also referred to as DN is a common complication of diabetes. Over time, it may impact the renal vasculature and damage the kidneys, ultimately resulting in ESRD [6,7]. The typical pathological findings in patients with DKD/DN include proteinuria (albuminuria) and reduced renal functioning [6-8].

The treatment approaches for managing DKD/DN include glycaemic control, regulating hypertension, reducing cardiovascular risk, and preserving renal function [6-8]. Along with the drugs to maintain glycaemic control, patients with DKD/DN are treated with Angiotensin-Converting Enzyme (ACE) inhibitors, Angiotensin Receptor Blockers (ARBs), Mineralocorticoid Receptor Antagonists (MRAs), and Sodium Glucose Cotransporter 2 (SGLT2) inhibitors [6-9]. SGLT2 inhibition facilitates glucose-lowering effects through glucosuria, thereby reducing hyperglycaemia [10,11]. Preclinical and clinical studies have demonstrated that SGLT2 inhibitors reduce albuminuria and preserve renal function. More importantly, SGLT2 inhibitors lower the cardiovascular risks associated with DKD [10,11].

Dapagliflozin is a potent, selective, reversible SGLT2 inhibitor approved for the treatment of T2DM [12-14]. Along with effective glycaemic control dapagliflozin has shown benefits including reduction in risk of cardiovascular events, reduction in weight and blood pressure, and protective effects on the renal architecture [12]. However, there is a paucity of literature that specifically examines the use of dapagliflozin 5 mg in treating DN [15-17]. The present study aimed to investigate the impact of dapagliflozin 5 mg on both glycaemic control and renal function in patients with T2DM in a tertiary care hospital setting.

MATERIALS AND METHODS

The present study was a single centre, prospective, cohort study involving patients from the Outpatient Department and Intensive Care Unit (ICU) of a Tertiary Care Hospital (Krishna Institute of Medical Sciences) located in Karad, Maharashtra, India, over a duration of 18 months (September 2022 to February 2024). The study was conducted in accordance with the Declaration of Helsinki guidelines. Written informed consent was obtained from all participants before being enrolled in the present study. Institutional Ethics Committee issued approval (KIMSDU/354/2021-2022) prior to initiation of the study.

Sample size calculation: The following formula was used for sample size calculation:

$n=P\times(1-P)\times(Z/E)^2$

$n=0.4\times(1-0.4)\times(1.96/0.1)^2$

$n=92.2$

Where 'n' is the sample size, 'P' is the estimate of expected proportion with the variable of interest in the population, Z is the z-statistic for

the desired level of confidence {i.e., 0.05 95% confidence interval (CI)} and E is the precision level.

The z-statistic was 1.96, precision level was 0.1, and it was considered that 40% of patients with T2DM had renal protective effect with dapagliflozin was (P). The minimum sample size calculated was 92, considering 10% dropouts or insufficient data, 100 patients were included in this study.

Inclusion and Exclusion criteria: Patients aged ≥18 years diagnosed with T2DM and had deranged levels of serum urea or serum creatinine, or urinary albumin were considered for the research. Cases having an eGFR of <45 mL/min/1.73 m² (in accordance with 2021 CKD-EPI creatinine equation) [18] and patients diagnosed with urinary tract infections as well were not included in the study. Patients that had undergone cytotoxic therapy, immunosuppressive therapy, or any other form of immunotherapy aimed at treatment of primary or secondary renal disease within the six months prior to enrollment were also excluded. Importantly, patients on ACE-inhibitors and ARBs were not considered for the study.

Study Procedure

Patients continued to receive their regular treatment throughout the study and received an extra daily dose of dapagliflozin 5 mg for a period of six months [14,16,19]. Dapagliflozin was also added to the therapy after proper patient consent, as their blood glucose levels remained high despite ongoing treatment. Patients were also educated to notify the investigators about any possible Adverse Events (AEs) in a timely manner. AE data, clinical laboratory tests, and clinical signs including Electrocardiogram (ECG), blood pressure, and monitoring of vital signs were all included in the data collection. Baseline data primarily comprised of fasting blood and urine samples which were collected in the morning thirty minutes before receiving study treatment and bioelectrical impedance analysis body measurements. Follow-up procedures involved provision of fasting blood and urine samples after six months. A central laboratory carried out biochemical assessments such as fasting and postprandial blood sugar, HbA1c tests and renal function tests (serum creatinine and serum urea). In addition to measuring urine creatinine and renal function, eGFR was determined from the 2021 CKD-EPI creatinine equation [20].

STATISTICAL ANALYSIS

Data were captured in a master data sheet using Microsoft Excel. The data were summarised by calculating descriptive statistics such as means and standard deviation. The effects of dapagliflozin on glycaemic control and renal function were evaluated by pre and post treatment measurements of the biochemical parameters (HbA1c, serum urea, serum creatinine, eGFR and urinary albumin) and comparing the means using paired t-tests. A statistical significance was set at p-value of <0.05. Data analysis was performed using the Statistical Packages for Social Sciences (SPSS) version 28.0 software (IBM Corporation, 2021, New York, United States).*

RESULTS

A total of 100 patients who met the eligibility criteria were enrolled in the study. The participants had an average age of 60.86 years. The study population was dominated by male patients (72%). [Table/Fig-1] presents a summary of baseline demographics and disease characteristics. Treatment with dapagliflozin significantly decreased the levels of HbA1c (reduction by 1%; p<0.0001). There was a statistically significant reduction in the mean serum urea level after using dapagliflozin treatment (-20.4 mg/dL; p<0.0001). Dapagliflozin treatment also caused a significant reduction in mean serum creatinine levels, -0.21 mg/dL (p<0.0001). The mean eGFR increased significantly by 15.25 mL/min/1.73m² post dapagliflozin treatment (p<0.0001). Albuminuria was significantly reduced and the mean urinary albumin level decreased by 0.97 mg/dL (p<0.0001). A summary of these outcomes is presented in [Table/Fig-2]. When analysed by stratification based on gender, it was observed that the beneficial effects of dapagliflozin were observed similar in male and female patients [Table/Fig-3].

Characteristics	Values N=100
Gender, n (%)	
Male	72 (72)
Female	28 (28)
Age, mean±SD, years	60.86±15.99
Age range, n (%)	
20-40 years	15 (15)
40-60 years	30 (30)
>60 years	55 (55)
Duration of diabetes, mean±SD, years	10.44±5.34
HbA1c level, mean±SD, %	7.51±0.86
Serum creatinine level, mean±SD, mg/dL	1.13±0.27
Serum urea level, mean±SD, mg/dL	51.28±35.94
eGFR, mean±SD, mL/min/1.73 m²	72.30±21.28
Urinary albumin level, mean±SD, mg/dL	1.91±1.00

[Table/Fig-1]: Patient demographics and disease characteristics. eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; SD: standard deviation.

Parameters	Baseline	End of the study	p-value
HbA1c level, %	7.51±0.86	6.53±1.27	<0.0001
Serum creatinine level, mg/dL	1.13±0.27	0.92±0.22	<0.0001
Serum urea level, mg/dL	51.28±35.94	30.88±12.39	<0.0001
eGFR, mL/min/1.73 m²	72.30±21.28	87.55±20.53	<0.0001
Urinary albumin level, mg/dL	1.91±1.00	0.92±1.05	<0.0001

[Table/Fig-2]: Mean ± SD values of biochemical parameters. eGFR: estimated glomerular filtration rate; HbA1c: glycated haemoglobin; SD: Standard deviation

Parameters	Baseline	End of the study	p-value
HbA1c level, %			
Male	7.53±0.86	6.74±1.18	<0.0001
Female	7.43±0.88	6.00±1.39	<0.0001
Serum creatinine level, mg/dL			
Male	1.17±0.28	0.94±0.24	<0.0001
Female	1.03±0.23	0.86±0.16	<0.0001
Serum urea level, mg/dL			
Male	50.21±34.98	31.08±11.73	<0.0001
Female	54.04±38.83	30.56±14.18	<0.0001
eGFR, mL/min/1.73 m²			
Male	74.57±21.92	90.67±19.60	<0.0001
Female	66.46±18.65	79.54±21.04	<0.0001
Urinary albumin level, mg/dL			
Male	1.94±1.02	0.97±1.11	<0.0001
Female	1.82±0.94	0.78±0.88	<0.0001

[Table/Fig-3]: Mean±SD change in biochemical parameters stratified by gender. eGFR: estimated glomerular filtration rate; HbA1c: glycated hemoglobin; SD: standard deviation.

DISCUSSION

In the present study, the impact of dapagliflozin on both glycaemic control and renal function was observed in patients diagnosed with T2DM in 100 patients in a tertiary care hospital setting. Dapagliflozin led to significant reduction in HbA1c, serum urea, serum creatinine, and albuminuria and significantly increased the eGFR. The present study consolidates the beneficial effects of dapagliflozin in patients with DN.

Most of the participants were male (72%) with a mean age of 60.86 years and 55% of participants were aged >60 years. In a study by Sivasubramanian V et al., the mean age of participants was reported as 54 years, with 68% being male [21]. In a study by Wheeler DC et al., although the mean age of participants was bit higher (61.8 years) the male patients continued to be the dominant gender (66.9%) [22]. The observations in the present study are aligned with those reported in the literature.

Jin ZJ et al., have reported a significant reduction in HbA1c levels from 7.5% to 6.5% after dapagliflozin treatment ($p<0.05$) [23]. In a prospective study, Sugiyama S et al., observed a significant reduction in the HbA1c levels following dapagliflozin 5 mg treatment (from 7.6 to 6.8; $p<0.001$) [17]. The study by Lazzaroni E et al., reflected the effectiveness of dapagliflozin in glycaemic control [24]. In a pooled analysis of nine Phase III and 21 Phase IIb/III studies, Fioretto P et al., have reported that a significantly greater proportion of patients receiving dapagliflozin achieved an HbA1c value of <7% compared with placebo (<65 years: 25.6 vs. 15.2%; ≥65 years: 18.2 vs. 12.3%) [25]. In the present study, a substantial improvement in the mean HbA1c levels was observed with a change from 7.5% to 6.5% with dapagliflozin therapy. The results suggest a substantial glycaemic control with the use of dapagliflozin. As the patients were closely monitored throughout the study and the compliance was higher, the mean reduction in HbA1c from baseline was significant.

In the present study, dapagliflozin treatment resulted in preserving and the improving the renal function over the study period (mean eGFR change from 72.30±21.28 mL/min/1.73 m^2 at baseline to 87.55±20.53 mL/min/1.73m^2 after treatment; $p<0.0001$). This outcome aligns well with data obtained by Fioretto P et al., further supporting the role of dapagliflozin in improving renal function in patients with diabetes [25]. The exact mechanism for renoprotective effects of SGLT2 inhibitors remains speculative. However, it has been reported that SGLT2 inhibitors protect renal function through glucose-dependent and independent pathways by reducing glomerular hyperfiltration and oxygen demand, improving cortical oxygenation, enhancing mitochondrial function and autophagy, suppressing inflammation and fibrosis, and promoting erythropoiesis to improve systemic oxygen delivery [26].

It has been reported that SGLT2 inhibitors lower the serum uric acid levels through alteration of uric acid transport activity in renal tubule by increased glycosuria [27]. Fioretto P et al., have reported that they observed a mean reduction of 12.5 and 35.1 µmol/L in uric acid levels with dapagliflozin 10 mg and 5 mg treatment, respectively [16]. In a retrospective cohort study among diabetic patients with CKD, Iwata Y et al., observed that dapagliflozin treatment resulted in a reduction of serum uric acid to 5.6 mg/dL [28]. In a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 2/3 study, Kohan DE et al., observed a reduction of 0.67 and 0.39 mg/dL with dapagliflozin treatment [15]. A significant reduction in the average serum urea levels ($p<0.0001$) in patients treated with dapagliflozin was observed in the present study as well.

The mean serum creatinine level before dapagliflozin treatment was 1.13±0.27 mg/dL which significantly reduced to 0.92±0.22 mg/dL ($p<0.0001$). This contrasts with the findings of Sugiyama S et al., who mentioned a baseline of 77.4±13.8 mg/dL of serum creatinine levels before treatment which declined to 75.4±14.1 mg/dL post-treatment ($p=0.14$) [17]. A similar trend in creatinine levels has also been reported in a study by Kohan DE et al., [15]. These observations have led to the conclusion that dapagliflozin may help lower serum creatinine levels while also enhancing the albumin to creatinine ratio, which is consistent with observations by Sugiyama S et al., [17]. Lazzaroni E et al., have reported a decline in urinary albumin from 61.6±117.2 mg/L to 36.5±60.5 mg/L with dapagliflozin treatment [24]. In a study by Jin ZJ et al., both serum creatinine, HBA1c concentrations were significantly lower at the end of the treatment period following dapagliflozin treatment [23]. In the present study, the mean urinary albumin excretion was 1.91±1.00 mg/dL, that decreased significantly to 0.92±1.05 mg/dL after dapagliflozin treatment. In the present study results are also in line with the findings reported by Sivasubramanian V et al., [21]. Regardless of the age of the patient, the degree of urinary albumin excretion, dapagliflozin has been proven to effectively decrease urinary albumin levels. Nonetheless, it should be noted that as the duration of diabetes increases, the diabetes urinary albumin levels tend to get worse, stressing the critical importance of preventive treatment with drugs aimed at protecting the kidneys in such individuals [29].

The present study was focused on the evaluation of the parameters associated with renal function and those relating to glycaemic control, i.e., eGFR, urinary albumin, serum creatinine and HBA1c and serum urea. Significant improvements were observed in both genders after dapagliflozin administration. The results showed that the male patients had higher mean values for eGFR, urinary albumin, serum creatinine and HbA1c, while the female patients had higher mean serum urea levels before the treatment. Importantly, following the treatment with dapagliflozin, both genders recorded positive changes in these parameters, with no gender-related differences registered between the patients after the intervention.

Further research in this area would be to study the target population with respect to use of dapagliflozin including not only normal T2DM patients but also those who are obese or overweight, female patients, elderly, and even regulated diabetic patients. Besides that, it is important to also look at the complex mechanisms at the molecular level in relation to how dapagliflozin has renal benefits. These investigations will not only clarify the increase in its therapeutic efficacy, but it will also assist in refining the implementation of clinical use, especially for patients with DN.

Limitation(s)

There are certain limitations associated with a single centre, observational study. These include a shorter follow-up period, and a study participant population that is restricted by inclusion and exclusion criteria. As it is a single center study, the results may depend on hospital specific practices or disease targeted therapeutic agents, and patient demographics. Six months follow-up period is too short to evaluate the sustained effect of dapagliflozin. Patients who were in treatment with ACE inhibitors and ARBs and patients with renal impairment (eGFR < 45) were not included in the study. The study was conducted in a tertiary care hospital according to the clinical trial protocol hence it is unlikely to reproduce the results in T2DM patients in real-world settings. Hence, the findings of this study can only be relevant to the target population and not beyond it. The current study fills an important information gap regarding glycaemic and renal aspects of benefits associated with dapagliflozin utilisation among patients with T2DM. It validates and substantiates the benefits of using dapagliflozin in T2DM patients with DN.

CONCLUSION(S)

The effects of dapagliflozin on renal function and glycaemic control in patients with T2DM and DN were investigated in this study. The results determined that SGLT2 inhibitor, dapagliflozin shows a significant improvement in both renal and metabolic outcomes in these patients. Specifically, there was notable decrease in urinary albumin and serum creatinine levels after the treatment with dapagliflozin. Furthermore, there was a substantial decrease noted in HbA1c and serum urea levels. In addition, the eGFR improved significantly, suggesting improved kidney function. Dapagliflozin is an approved drug that has been extensively studied. However, large-scale, long-term multicentre observational studies remain insufficient to clarify the underlying mechanism of these effects and assess the long-term therapeutic efficacy of dapagliflozin in patients with various degrees of renal impairment and comorbid diabetes complications.

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