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EFFECTS OF DAPAGLIFLOZIN ON RENAL FUNCTION TESTS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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ABSTRACT

Previously, diabetes mellitus was thought to be kidney disease. However, the role of the renal system in the development and maintenance of elevated glucose levels has piqued interest in the last decade. This has sparked the introduction of brand-name medications that block sodium-glucose transporter-2 (SGLT2) to improve glucose regulation while also encouraging calorie loss, and lower insulin, blood pressure, and uric acid levels. This study aimed to investigate the effects of dapagliflozin-5mg and dapagliflozin-10mg on serum creatinine, urinary protein/creatinine ratio, serum sodium (serum Na+), and serum potassium (serum K+). The study included 59 male and female patients with T2DM. After 6-months of treatment with dapagliflozin 5mg, dapagliflozin 10mg, there was significant modulation of the level of serum creatinine, serum K+ level, Urinary creatinine/protein ratio. The study concluded that dapagliflozin in a dose of 5mg, 10mg is associated with statistically significant elevation in serum creatinine and urinary protein/creatinine ratio after 6-months of treatment. No alteration in serum Na+ and serum K+ level with dapagliflozin 5mg but in a dose of 10mg, dapagliflozin causes significant hyperkalemia after 24-week treatment.

Keywords: *dapagliflozin; diabetes; nephropathy; hyperfiltration, SGLT.*

INTRODUCTION

T2DM is usually considered the key driver of end-stage renal illness. Insulin resistance was initially conceived as a kidney ailment. If glucose levels are consistently raised, the risk of long-term kidney disease is raised [1]. Insulin's invention shifted the conversation of diabetes care. However, there was growing interest in the kidney's function in the establishment and improvement of increased blood glucose levels in the previous decade [2, 3]. Each day, the kidneys process approximately 180 liters of plasma containing 5.5 mM glucose in healthy individuals.

This indicates that 180 g of sugar is processed via the tubules each day and eliminated in the main. Salt cross-over all the nephron's outer membrane efficiently resorbs nearly most of this processing load (99.9%), which is then transported back to the bloodstream by glucokinase [2, 3]. A low binding, a large capacity process mediated by sodium-glucose transporter-2 (SGLT2) reabsorbs more than 90% of the glucose that is originally handled in the proximal tubule's early convoluted segment (s1)[2]. Dapagliflozin is an SGLT2 inhibitor that is orally accessible, selective, and reversible [4,5]. In people with Type 2 diabetes and adequate renal function, that has been shown to enhance glycemic control parameters and help with weight loss [6,7]. The use of dapagliflozin to inhibit SGLT2 induces urine glucose drainage [8], leading to the elimination of excess glucose and a reduction in blood glucose levels. The present study aimed to determine the effect of dapagliflozin on kidney parameters [9, 10, 11].

PATIENTS AND METHODS

This is a randomized comparative and prospective study. Fifty-nine T2DM patients enrolled in the study; (age range 38 and 72 years). The study excluded patients who were known to have any chronic kidney diseases, pregnancy, nursing mothers, cigarette smoking, the use of any glucose-altering medications.

A total of 30 presumably healthy individuals, whose ages mirrored those of the study participants, were included in the study to provide a concept of the typical values and to estimate how much the medicine employed in the study caused changes in the parameters tested. Their information

was collected, altered, and evaluated similarly to the study participants' information. All the recruited individuals (n=59) were informed about our research aim and consent was obtained from each of them. Thereafter, the patients were divided into two groups as follow:

Group 1: This includes 33 patients, treated with dapagliflozin (AstraZeneca), 5 mg orally in the morning throughout 6-months.

Group 2: include 26 patients treated with dapagliflozin (AstraZeneca), 10mg orally in the morning also throughout 6-months.

For each patient laboratory analysis has been done, including serum creatinine (mg/dl), Urinary protein/creatinine ratio (mg/mg) (should be less than 0.2), serum sodium (Na+) and serum potassium (K+) (mmol/L) were measured. Standard biochemical tests using spectrophotometer were utilized to perform biochemical analysis suggested in this study. Renal function tests were performed and the results were assessed according to the normal range for each parameter.

Primary physical tests were performed and all the above biochemical parameters were measured initially, before intervention (baseline values), then on the second week and 24th week of the study time.

The statistical analysis was carried out using SPSS. V21. Data expressed as mean±standard deviation (±SD). The differences between the groups were significant at p <0.05. Within one treatment group, a one-way analysis of variance (ANOVA) followed by a T-test comparison t-test for one sample was used to compare between parameters.

RESULTS

A total of fifty-nine patients (38 males and 21 females), age ranged (38-72 years) with a mean age ±SD (49.5±7.93) for females and (46.5±11.57) for males.

After 2 weeks of treatment with dapagliflozin 5 mg, there was a transient significant elevation in serum creatinine level with mean ±SD at baseline level was (0.72±0.087) and a second week (1.57±0.7), but at week 24, the serum creatinine level dropped significantly (p value= 0.011) with mean±SD (0.81±0.69). No significant alteration in serum Na+ and K+ level throughout the treatment period with mean±SD at baseline and after 24 weeks was (135±1.55→144±0.00) for serum Na+ and (3.7±0.87→4.9±0.71) for serum K+. After 24 weeks of treatment, the urinary protein/creatinine ratio (mg/mg) increased substantially with mean±SD at baseline level (0.15± 0.1), at week 2 and 24th week from treatment was (0.20±0.00) (0.29±0.1) respectively (Table .1)

When the outcome of dapagliflozin-5mg (after 6 months of continuous therapy) versus control group; no significant difference between them presents.

except for urinary protein/creatinine ratio showed significant difference (p value=0.042) (Table. 2)

After 15 days of continuous therapy with dapagliflozin 10mg there was a significant elevation in serum creatinine level with mean ±SD at baseline level (0.67±0.13) and at week 2 was (1.78±0.00) but at week 24 the level of serum creatinine showed an apparent insignificant reduction (p value=0.105) with mean±SD was (1.00 ±0.15). No significant alteration in serum Na+ level throughout the study period with mean±SD before and after 6 months treatment was (138±1.6→147±1.2)

After 6 months of continuous therapy by Dapagliflozin 10mg, there was a significant elevation in serum K+ level (hyperkalemia) with mean±SD at baseline (4.5±0.82), at week-2 and week-24 week was (5.1±0.11) (5.9±0.91) respectively. Urinary protein/creatinine ratio (mg/mg) showed significant elevation after 2 weeks from treatment with mean±SD at baseline and week-2 was (0.11±0.5), (1.6±0.1) respectively, an apparent elevation also noticed after 24-week treatment with mean±SD (0.21±0.00) but it was statistically insignificant (p value= 0.087) (Table .3)

Compared to the control group and After 24 weeks of treatment with dapagliflozin 10mg; it was shown that all the parameters were not comparable to the control group values except for serum Na+ (p value=0.820) (Table .4)

Comparison between the effects dapagliflozin 5mg, dapagliflozin 10mg on serum creatinine during the study period

The effects of dapagliflozin 5mg, dapagliflozin 10mg on serum creatinine level showed statistically significant alteration (Table.5)

Comparison between the effects of dapagliflozin 5mg, dapagliflozin 10mg on Urinary protein/ creatinine ratio levels during the study period.

The effects of dapagliflozin 5mg, dapagliflozin 10mg on Urinary protein/creatinine ratio showed statistically significant elevation throughout the study period (Table 6)

Comparison between the effects of dapagliflozin 5mg, dapagliflozin 10mg on serum Na+ levels during the study period.

Dapagliflozin 5mg, dapagliflozin 10mg caused insignificant alteration in serum Na+ level after 24 weeks of treatment (Table .7)

Comparison between the effects of dapagliflozin 5mg, dapagliflozin 10mg on serum K+ levels during the study period

Serum K+ level showed no significant change with dapagliflozin 5mg and significant elevation by dapagliflozin 10mg during the study period (Table .8)

Table 1. Dapagliflozin-5mg modulated measured parameters

Drug	Duration	serum creatinine	Protein /creatinine ratio	serum. Na+	serum K+
Dapagliflozin 5mg	Base line	0.72±0.87	0.15±0.1	135±1.55	3.7±0.87
	Week 2	1.57±0.7	0.20±0.00	138.7±2.56	4.1±0.85
	Week 24	0.81±0.96	0.29±0.1	144±1.89	4.9±0.71
p value (t-test)		0.015	0.010	0.936	0.887

Table 2. Comparison between dapagliflozin-5mg versus control on measured parameters

Drug	Serum creatinine	Urinary protein/ creatinine ratio	serum. Na+	serum K+
Dapagliflozin 5mg	0.81±0.69	0.29±0.1	144±1.89	4.9±0.71
Control	0.66±0.12	0.13±0.00	139±1.77	4.2±0.2
p value (independent Samples t-test)	0.885	0.042	0.932	1.000

Table 3. Dapagliflozin-10mg modulated measured parameters

Drug	Duration	Serum creatinine	Urinary protein /creatinine ratio	Serum. Na+	Serum K+
Dapagliflozin 10mg	Base line	0.67±0.13	0.11±0.5	138±1.6	4.5±0.82
	Week 2	1.78±0.00	1.6±0.1	144±3.2	5.1±0.11
	Week 24	1.00±0.15	0.21±0.00	147±1.2	5.9±0.91
p value (t-test)		0.014	0.023	0.956	0.026

Table 4. Comparison between dapagliflozin-10mg versus control on measured parameters

Drug	Serum creatinine	Urinary protein /creatinine ratio	Serum Na+	Serum K+
Dapagliflozin 10mg	1.00±0.15	0.21±0.00	147±1.2	5.9±0.9
Control	0.66±0.12	0.13±0.00	139±1.77	4.2±0.2
p value (independent Samples t-test)	0.047	0.050	0.820	0.037

Table 5. Comparison between dapagliflozin-5mg versus 10mg on serum creatinine

parameter	Duration	Dapagliflozin 5mg	Dapagliflozin 10mg	*p* value (t-test)
Serum creatinine	Base line	0.72±0.87	0.67±0.13	0.001
	Week 2	1.57±0.7	1.78±0.00	0.001
	Week 24	0.81±0.96	0.94±0.15	0.001
p value (t-test)		0.015	0.014	(F test) 0.000

Table 6. Comparison between dapagliflozin-5mg versus 10mg on Urinary protein/creatinine ratio**.**

Parameter	**Duration**	**Dapagliflozin 5mg**	**Dapagliflozin 10mg**	***p* value (t-test)**
Urinary protein: creatinine ratio	**Base line**	0.15±0.1	0.11±0.5	0.002
	Week 2	0.29±0.00	1.6±0.1	0.000
	Week 24	0.2±0.1	0.21±0.00	0.001
***p* value (t-test)**		0.010	0.023	(F test) 0.000

Table 7. Comparison between dapagliflozin-5mg versus 10mg on serum Na+ level.

parameter	Duration	Dapagliflozin 5mg	Dapagliflozin 10mg	*p* value (t-test)
Serum Na+	Base line	135±1.55	138±1.6	0.009
	Week 2	138.7±2.56	144±3.2	0.011
	Week 24	144±1.89	147±1.2	0.010
p value (t-test)		0.936	0.956	(F test) 0.000

Table 8. Comparison between dapagliflozin-5mg versus 10mg on serum K+ level.

parameter	Duration	Dapagliflozin 5mg	Dapagliflozin 10mg	*p* value (t-test)
Serum K+	Base line	3.7±0.87	4.5±0.82	0.002
	Week 2	4.1±0.85	5.1±0.11	0.003
	Week 24	4.9±0.71	5.9±0.91	0.007
p value (t-test)		0.887	0.026	(F test) 0.000

DISCUSSION

This study investigates the effects of dapagliflozin (5mg and 10mg) on plasma creatinine concentration, urinary protein/creatinine ratio, plasma Na^+, and plasma K^+ concentration. Data available about the effects of dapagliflozin on renal function tests is limited. This study showed that after 2 weeks of treatment with dapagliflozin 5mg or 10mg there was a transient significant elevation in plasma concentration of creatinine while at week 24, the plasma concentration of creatinine dramatically decreased. This finding might be related to dapagliflozin cause a decrease in glomerular filtration rate (GFR) so plasma concentration of creatinine elevated or it might be the outcome of inhibition of aldosterone action on their receptors site on the kidney.

A study conducted by Lambers Heerspink *et al* [12] reported that after 3 months, treatment with dapagliflozin 10mg there was a dramatic increase in serum creatinine level with reductions in GFR and possibly circulatory volume. These findings suggest that the blood pressure–lowering effect of dapagliflozin could be directed by a reduction in circulating volume to the kidney owing to reduction in GFR of the drug with elevated serum creatinine and they recommended for further mechanistic studies regarding this action.

In this study, urinary protein/creatinine ratio increased significantly with dapagliflozin 5mg or 10mg after 24 weeks' treatment. In contrast, *Lambers Heerspink et al* [13] showed that dapagliflozin 10 mg once daily for 12 weeks causes a significant reduction in urinary protein/creatinine ratio.

Furthermore, dapagliflozin 5mg did not affect serum Na+ and K+ levels throughout the trial, whereas dapagliflozin 10mg had a non-significant effect on serum Na+ levels throughout the study, but a substantial increase in serum K+ level after 2 years of therapy.

Hyperkalemia crisis was triggered in diabetes, according to Palmer BF and Clegg DJ [14]. Hyperkalemia, that may have been observed variation to osmotic pressure; triggered by increased plasma concentration of glucose, resulting in a modulation of potassium outside of cells, can be increased by depleted potassium termination, especially in patients with renal insufficiency or those taking angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), or spironolactone. Yshai Yavin *et al* [15] study showed that no overt relevant mean alteration from baseline in serum potassium ≤24 weeks were reported for dapagliflozin 10 mg in case of patients receiving ARBs/ACE inhibitors, or potassium-sparing diuretics, or in those with moderate renal impairment. They concluded that Dapagliflozin in a dose of 10mg for 24 weeks is not associated with the risk of hyperkalemia in patients with T2DM which was contrary to this study.

Deborah Hinnen [16] and Kohan *et al* [17] reported that dapagliflozin 5 and 10 mg/day caused a reduction in estimated GFR (eGFR) with dramatical elevation in plasma creatinine concentration over the first 1–2 weeks, followed by steady-state through 2 years of therapy which was in agreement with this study. They reported no changes from baseline were observed for mean serum Na+, K+. Urinary albumin/creatinine ratio increased from baseline with dapagliflozin 5 mg/day and decreased with dapagliflozin 10 mg/day.

Food and Drug Administration, 2013 [18] reported a decrease in creatinine clearance, increased blood creatinine, decreased urine flow were more common in patients treated with dapagliflozin 10 mg/day especially in patients ⩾65 years. they recommended that renal function tests should be assessed before initiating dapagliflozin.

A recent study performed by Filippatos TD, 2017 [19] showed that SGLT2 inhibitors induce small increases in serum concentrations of Na+ and potassium mainly seen with canagliflozin and dapagliflozin throughout more than 6 months of treatment.

CONCLUSION

Dapagliflozin is an inhibitor of SGLT2 that optimizes glycemic management in patients who have been unable to regulate their blood sugar levels with exercise and diet alone or with diabetic medicines. After 24 weeks of treatment, dapagliflozin (5mg and 10mg) was linked to statistically large increases in blood creatinine and urinary protein/creatinine ratio.. There was no change in serum Na+ and K+ levels with dapagliflozin 5mg, whereas dapagliflozin 10mg caused severe hyperkalemia after a 24-week treatment. The use of dapagliflozin in the treatment of T2DM patients is promising, but more research is needed to determine its safety, particularly concerning the renal system.

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