EFFECT OF DAPAGLIFLOZIN THERAPY ON SERUM URIC ACID IN TYPE 2 DIABETIC PATIENTS.

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ABSTRACT

INTRODUCTION: Diabetes mellitus (DM) is a complicated chronic glucose metabolic disorder. Primary defect is the insulin insufficiency. **OBJECTIVE:** Analyze and determine the effects of dapagliflozin on serum uric acid in type 2 diabetic patients. **STUDY DESIGN:** Comparative cross sectional study**. PLACE AND DURATION:** Suleman Roshan Medical College from January 2019 to December 2020. **METHODS:** A sample of 200 diabetics; divided into controls 100 taking oral hypoglycemic drugs (OHD) and 100 cases taking OHD+ Dapagliflozin was selected by non-probability convenient sampling. Blood glucose (FBG & RBG), A1C, BUN, creatinine and serum uric acid were performed at baseline and 12 weeks of therapy. Data was collected and saved in a pre – structured proforma. Data was analyzed on *Statistic* software (ver 18.0) using Student`s t-test for continuous variables. Data was analyzed at 95% CI (P≤ 0.05). **RESULTS:** FBG, RBG, A1C and Uric acid were decreased in both control and cases however decrease was highly significant in dapagliflozin group. Serum uric acid in control group A at baseline was 7.6±1.3 mg/dl that decreased to 7.3±3.1mg/dl. However, uric acid shows significant decrease in cases group B, from baseline 7.7±1.7 mg/dl to 4.3±1.1 mg/dl after 12 weeks dapagliflozin therapy. **CONCLUSION:** Dapagliflozin therapy significantly reduces the serum uric acid along with improvement of glycemic status.

KEY WORDS: Dapagliflozin, Uric acid, Glycemic status, Diabetes mellitus

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INTRODUCTION

Diabetes mellitus (DM) is a complicated chronic glucose metabolic disorder. Primary defect is the insulin insufficiency. Type 2 diabetes mellitus (T2DM) is often caused by relative insulin deficiency characterized by hyperinsulinemia and concomitant insulin resistance.[1] Target organs are resistant to the insulin actions and include the adipose tissue, liver and skeletal muscles. DM is often associated with dyslipidemia and hyperlipidemia, obesity, hyperuricemia and NAFLD (non-alcoholic fatty liver disease). An ideal hypoglycemic agent is considered one that provides optimal glycemic control and benefits the metabolic disorders as well.[1] various hypoglycemic agents have emerged recently including the sodium-glucose cotransporter-2 (SGLT2) inhibitors (SGLT2i). SGLT2 is a transport protein of early proximal renal tubule (EPRT) that absorbs 90% of filtered glucose load. Expression of SGLT2 in EPRT is increased in diabetic animal models and in diabetic subjects. SGLT2i impair the glucose absorption in EPRT let the glucose lost in

urine. Thus SGLT2 inhibitors provide an insulin independent way.[2,3] A variety of SGLT2i are marketed throughout the World with increasing utilization. Studies have highlighted the advantages of SGLT2i for the glycemic control that has attracted much attention of clinicians. SGLT2i have additional benefits of reducing risk of cardiovascular diseases, cardiac failure and renal disease, also uricosuric action reducing the serum uric acid levels.[4-6] A few found SGLT2i reduced the insulin resistance with improvement of islet β-cell secretory function.[7,8] Weight reduction has been reported with SGLT2i through increased lipolysis and inhibiton of lipogenesis. Instead of this information, many discrepancies are reported by most previous making it difficult to understand whether the improved islet β-cell function are produced by decreased glucotoxicity, changes in body weight and dyslipidemias.[2,3] Currently, Dapagliflozin is widely used SGLT2i in the country, and studies are lacking on the therapy effects on serum uric acid levels in addition to glycemic control. The present study was conducted to analyze and determine the effects of dapagliflozin on serum uric acid in type 2 diabetic patients.

METHODOLOGY

A comparative cross sectional study was conducted at the Department of Pharmacology and Outpatients department (OPDs) of Suleman Roshan Medical College from January 2019 to December 2020. A sample of 200 diabetics; divided into Group A – controls 100 taking oral hypoglycemic drugs (OHD) and Group B – 100 cases taking OHD+ Dapagliflozin was selected by non-probability convenient sampling. Diagnosed cases of Type 2 DM according to the ADA criteria were selected for study protocol. Inclusion criteria were; diagnosed cases of T2DM, male gender, age ≥ 50 years, taking oral hypoglycemic drugs (OHDs) and poor glycemic control. Exclusion criteria were; no alcoholism, no drugs such as the aspirin, diruetics, vitamin supplements, corticosteroids, amlodipine, angiotensin receptor blockers, agiotensin II antagonists, febuxostat and allopurinol. Diabetic nephropathy, diabetic foot, diabetic diarrhoea, malabsorption syndrome, diabetic complications, connective tissue disorders, myeloproliferative disorders, thyroid disease, chronic liver disease, mental illness, anemia, heart failure, gouty arthritis and pregnancy were excluded. Oral hypoglycemic drugs (OHDs) used was an oral sulfonylurea. Sulfonylurea dose was given according to the glycemic need of individual diabetic patient. Dapagliflozin was given in dose of 10 mg once daily – early morning to the case group only. Diabetics were examined by a medical officer followed by a consultant physician. Age and body weights were noted. Systolic and diastolic BP was recorded using a mercury sphygmomanometer. Blood samples were taken from ante cubital fossa vein under aseptic measures. Blood glucose (FBG and RBG) was estimated by hexokinase method. Glycated hemoglobin A1 (A1C), blood urea nitrogen and serum creatinine were estimated by standard validated laboratory methods. Serum uric acid was estimated by colorimetric method. Biochemical analysis was performed on Cobas Chemistry Analyzer. Laboratory investigations were performed at baseline and 12 weeks of therapy. Data was collected and saved in a pre – structured proforma. Data was analyzed on Statistics software (ver 18.0) using Student`s t-test for continuous variables after normal distribution and homogeneity of variance were satisfied by the statistician. Data was analyzed at 95% CI ($P \leq 0.05$).

RESULTS

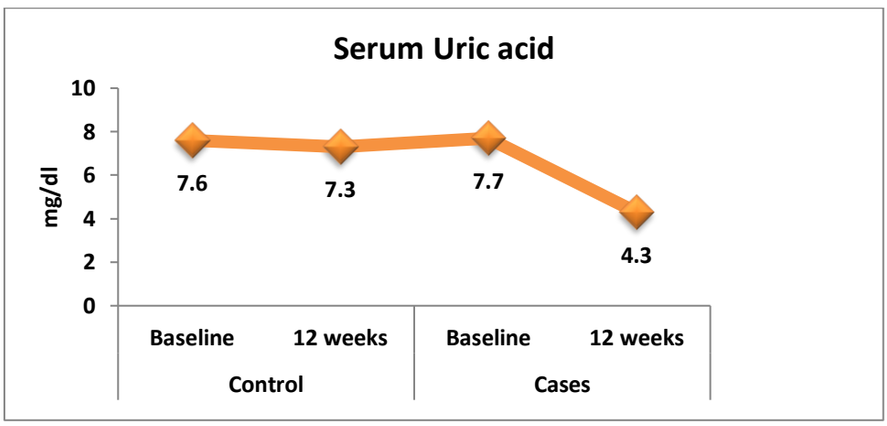
Age of control group A was 54.7±3.6 and case group B was 55.7±5.6 years (P=0.98). Table 1 shows the demographic findings of study groups. Group A and B participants were matched for age, body weight, body mass index (BMI), systolic and diastolic blood pressure (P>0.05). Blood urea nitrogen (BUN) and serum creatinine (S Cr) were found within normal range in both groups. FBG, RBG, A1C and Uric acid estimated at baseline were found raised in both groups. Significant reduction was noted in FBG, RBG, A1C and Uric acid in both groups however decrease was more significant in dapagliflozin group (Table 2). Serum uric acid in control group A at baseline was 7.6±1.3 mg/dl that decreased to 7.3±3.1mg/dl. However, uric acid shows significant decrease in cases group B, from baseline 7.7±1.7 mg/dl to 4.3±1.1 mg/dl after 12 weeks dapagliflozin therapy (Graph – 1).

Table 1. Demographic findings of study subjects

	Group A (Control)	Group B (Cases)	P
Age (years)	54.7±3.6	55.7±5.6	0.98
Body weight (kg)	83.5±11.5	85.0±11.7	0.61
BMI (Kg/m^2)	29.3±2.1	30.0±3.1	0.72
Systolic BP (mmHg)	139.1±7.5	140.1±11.0	0.72
Diastolic BP (mmHg)	87.5±9.5	86.1±11.0	0.71
BUN (mg/dl)	11.2±0.3	11.1±0.5	0.93
S Cr (mg/dl)	0.9±0.03	0.87±0.01	0.97

Table 2. Laboratory findings of study subjects

	Group A (Control)		Group B (Cases)		P
	Baseline	12 weeks	Baseline	12 weeks	-
FBG	219.1±21.4	129.1±15.6	225.9±11.5	107.0±11.3	0.0001
RBG	419.0±11.7	219.0±11.3	417.5±17.5	201.3±12.3	0.0001
A1c	13.2±5.3	11.1±3.2	13.5±4.7	10.9±3.9	0.0001
Uric acid	7.6±1.3	7.3±3.1	7.7±1.7	4.3±1.1	0.0001



Graph 1. Serum Uric acid in control and cases

DISCUSSION

A comparative cross sectional study was conducted at our tertiary care hospital. To the best of knowledge and search of published it is the first study reporting on the effect of dapagliflozin therapy on serum uric acid along with glycemic control. Age of control group A was 54.7±3.6 and case group B was 55.7±5.6 years (P=0.98). The findings are supported by previous studies.[9-15] A previous study[9] reported mean age in control as 58.97±10.50 years and 57.77±12.29 years in Dapagliflozin cases. Old age diabetics were selected because the dapagliflozin is indicated for older subjects.[9, 14, 15]

Dapagliflozin is one of the sodium-glucose cotransporter-2 (SGLT2) inhibitors (SGLT2i). Dapagliflozin monotherapy or in combination with sitagliptin, metformin or insulin is reported significantly improve glycemic control.[10-13] SGLT2i (including dapagliflozin) reduces glucose reabsorption in the early proximal renal tubule (EPRT) and increase glucose excretion in the urine.[10] In addition to glycemic control, other benefits of SGLT2i include body weight and systemic blood pressure reduction, reduced risk of cardiovascular events, and lowering of serum uric acid.[9,14-16] We found uric acid was decreased significantly after 12 weeks

dapagliflozin therapy with positive effects on FBG, RBG and A1C of diabetic participants. Serum uric acid in control group A at baseline was 7.6±1.3 mg/dl that decreased to 7.3±3.1mg/dl. However, uric acid shows significant decrease in cases group B, from baseline 7.7±1.7 mg/dl to 4.3±1.1 mg/dl after 12 weeks dapagliflozin therapy (Graph – 1). Finding of uric acid lowering effect of dapagliflozin is in agreement with previous studies.[9,14-16] Elevated uric acid has proved a risk factor for different metabolic disorders including type 2 DM (T2DM).[15] Prevalence of elevated uric acid (hyperuricemia) is high in diaebtics and proved positive correlation with micro – and macro – vascular complications of diabetes mellitus.[17] Uric acid is a waste catabolic end product of purine compounds. High frequency of hyperuricemia in diabetics has been attributed to its decreased uric acid renal excretion and increased renal reabsorption caused by hyperinsulinemia.[18,19] Another reason of hyperuricemia is diabetics is impaired glomerular filtration rate caused by diabetic nephropathy. Uric acid lowering potential of SGLT2i is proved by other previous studies.[11,20] A previous study[20] used canagliflozin in type 2 diabetics and reported reduced serum rate concentration. In present study, we used dapagliflozin for 12 weeks that is in agreement with previous studies.[9,14,15] Serum urate was reduced after 12–26 weeks in a previous study.[9,11] While other study reported serum urate reduction within first couple of weeks.[13] A meta-analysis of 62 RCTs, with sample size of 34 941 type 2 diabetic patients, reported the SGLT2i were found effective in reducing serum uric acid.[11] The present study noted uric acid lowering effect of dapagliflozin that was much pronounced after 12 weeks therapy. The findings are supported by above studies. One proposed mechanism of uric acid excretion is glucose induced polyuria that increases its excretion.[9,10] the uric acid lowering potential effect of dapagliflozin is worth finding as this is the first study reporting from our indigenous population. Dapagliflozin is a unique drug that decreases serum uric acid in addition to glycemic control in type 2 diabetics. One major limitation of present study is a small sample size hence findings are not generalizable to other settings, racial and ethnic groups. However, the strength of study is its prospective study designs and control diabetics that adds to its clinical significance.

CONCLUSION

Dapagliflozin therapy significantly reduces the serum uric acid in addition to improvement of glycemic status in type 2 diabetes mellitus patients.

ETHICS APPROVAL: The ERC gave ethical review approval

CONSENT TO PARTICIPATE: written and verbal consent was taken from subjects and next of kin

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CONFLICT OF INTEREST: No competing interest declared.

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