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Research Article

Original Research Article

COMPARISON OF SERUM URIC ACID LEVELS AMONG PATIENTS ON SGLT2 INHIBITORS AND THOSE NOT ON SGLT2 INHIBITORS.

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Abstract:

Background: SGLT2 are exclusively expressed in kidneys, especially in early proximal tubule and promotes reabsorption of 80-90% of glucose filtered by glomerulus. Uric acid is a weak acid generated from the metabolism of purine and that high circulating uric acid levels may increase risk of type 2 diabetes, metabolic syndromes. SGLT2 inhibitors have demonstrated an effect in reducing serum urate levels among patients with type 2 diabetes mellitus.

Objective: To compare the serum uric acid levels in patients on SGLT2 inhibitors with those not on SGLT2 inhibitors.

Methods: We adopted hospital based prospective comparative study design under the department of general medicine at Vydehi Institute of Medical Sciences and research Centre, Bangalore and we used simple random sampling technique to recruit 80 patients diagnosed with type 2 diabetes mellitus. Enrolled patients were divided into two groups based on randomization table. In group A, the enrolled type 2 diabetic patients received SGLT2 inhibitors and in Group B, the enrolled type 2 diabetic patients were on other oral hypoglycemic drugs but not on SGLT2 inhibitors. Blood samples for assessment of uric acid and creatinine was collected and after 2 weeks of treatment serum uric acid was repeated and the values were compared between the two groups.

Results: The mean age of our study participants was 59.28±11.97 years with 67.50% males with an average duration of diabetes recorded 8.55 ± 5.04 years and 37.50% were on insulin treatment. Serum uric acid levels among those with and without SGLT2 inhibitors were 6.98 ± 1.25 mg/dL and 7.81 ± 1.28 mg/dL, respectively, after 2 weeks of treatment.

Conclusion: The observed reduction in serum uric acid levels highlights the potential of SGLT2 inhibitors to provide an additional therapeutic benefit beyond their primary use in diabetes management. These findings underscore the value of considering SGLT2 inhibitors not only for their primary effects but also for their impact on associated conditions like

elevated uric acid.

Key words: Type 2 Diabetes Mellitus, SGLT2 inhibitors, Serum Uric acid levels.

INTRODUCTION

SGLT2 inhibitors act by blocking SGLT2 receptors located in early proximal renal tubule and renal absorption of glucose is approximately about 80 grams per day and thus lowering glucose burden. Raised serum urate levels have been associated with other common co-morbidities such as hypertension, metabolic syndrome, non-alcoholic fatty liver disease and chronic kidney disease. SGLT2 inhibitors have demonstrated an effect in reducing serum urate levels among patients with type 2 diabetes mellitus.[1]

An ideal hypoglycemic drug is considered not onlyto improve glycemic control but also to benefit combined metabolic disorders. The beneficial effects of SGLT2 inhibitors include decreasing the risk of cardiovascular diseases, heart failure, kidney diseases and also reduces serum uric acid levels and its related gout flares among type 2 diabetes patients. Few studies have also shown an improvement in insulin resistance and function of islet beta cell function.[2]

Our study was conducted to compare the serum uric acid levels in patients on SGLT2 inhibitors with those not on SGLT2 inhibitors.

MATERIAL AND METHODS

This hospital based prospective comparative study was conducted among Patients diagnosed with type 2 diabetes mellitus at Medicine OPD or admitted in the wards under the department of general medicine and endocrine OPD, at Vydehi Institute of Medical Sciences and research Centre, Bangalore. Duration of study was 18 months beginning from July 2022 till end of January 2024.

Inclusion criteria

- Patients aged more than 18 years.
- Patients diagnosed with type 2 diabetes mellitus (known and newly detected).
- Patients willing to participate in the study.

Exclusion criteria:

- Patients with diagnosis of gout.
- Patients with type 1 diabetes and other type of diabetes (Maturity onset diabetes of the young, Gestational diabetes).
- Patients with chronic kidney disease with eGFR<60 mg/mol.
- Patients with genitourinary infection.
- Patients who are on thiazides and uricosuric drugs.

Sampling technique: The sampling technique adopted for our study was simple random sampling technique.

SAMPLE SIZEE STIMATION

Sample size: Sample size was calculated usingthe formula for prospective comparative study,

$$n = \sigma^2 \frac{pq}{d2}$$

where, n =sample size

σ=1.96 (95%confidenceinterval)

p = 6.67 (Serum uric acid concentration among diabetic individuals not on SGLT2 inhibitors[7])

q=(100 – p)=100 – 6.67 = 93.33

d=5.5(absolute error)

By substituting the above values in the formula, the sample size was calculated to be 79. Finally, the sample size was taken as 80 for our study.

Method of data collection:

The patients attending the General Medicine OPD or admitted in the wards of department of General medicine and Endocrine OPD at Vydehi Institute of Medical sciences and research Centre with clinical diagnosis of diabetes mellitus fulfilling the inclusion and exclusion criteria were selected for our study. The patients and their attenders were informed about our study and informed written consent was obtained from them. Based on sample size estimation 80 patients were recruited for our study.

The participants were clinically examined and demographic information and detailed clinical history was sought related to presenting symptoms, habits, history of co-morbidities using a pre-structured questionnaire. The enrolled patients were divided in to two groups based on randomization table. In group A, the enrolled type 2 diabetic patients received SGLT2 inhibitors and in Group B, the enrolled type 2 diabetic patients were on other oral hypoglycemic drugs but not on SGLT2 inhibitors. The blood samples for assessment of uric acid and creatinine were collected and sent to the laboratory at Vydehi Institute of Medical Sciences and research Centre at the beginning of the therapy and after two week of treatment and all the enrolled patients in both the groups were advised to follow strict diabetic diet.

The following investigations were carried out,

1. Complete blood count.

2. Fasting blood sugar.
3. Postprandial blood sugar.
4. HbA1c.
5. Random blood sugar.
6. Serum uric acid level (at enrolment and after 1 week of treatment).
7. Serum creatinine.
8. Blood urea.
9. Urine routine and microscopy.

Ethical clearance: The ethical clearance was obtained on from the Institutional Ethics Committee.

Data Analysis plan: The data collected from the patients was coded and entered into MS Excel sheet and master chart was prepared. The data was presented in the form of tables, rates, ratios and percentages. Univariate analysis was reported as mean and standard deviation and associations were established using t test, chi square test and ANOVA test was conducted for multivariate analysis. Pie chart, bar diagram and line diagram were used for graphical representation of data. The association was considered statistically significant if the p value was less than 0.05. EPI software was used for statistical analysis.

Definition of study variables:

A. Blood sugar levels:[3]

I. Fasting blood sugar

- Normal: <100mg/dL
- Impaired: 100to 125mg/dL
- Diabetes: >126mg/dL

II. Post-prandial blood sugar

- Normal: <140mg/dL
- Impaired: 140 to 199 mg/dL
- Diabetes: >200mg/dL

III. HbA1c

- Normal: <5.6%
- Borderline: 5.7-6.4%
- Diabetes: >6.5%

B. Serum uric acid levels:[4]

I. Normal range among men is between 3.5 to 7.2 mg/dL

II. Normal range among women is between 2.6to 6mg/dL.

RESULTS

Mean age of our study subjects in OHD +SGLT2 group was 59.35±11.48 years with 12.50% aged less than 40 years, 12.50% aged in between 41 to 50 years, 15% aged in between 51 to 60 years, 42.50% aged in between 61 to 70 years and rest 17.50% aged more than 71 years and in OHD group mean age was 59.20 ± 12.58 years with 10% aged less than 40 years, 17.50% aged in between 41 to 50 years, 15% aged in between 51 to 60 years, 42.50% aged in between 61to70 years and rest 15% aged more than 71 years.
In OHD + SGLT2 group 57.50% were males and 42.50% were females and in OHD group 77.50% were males and 22.50% were females.

In OHD + SGLT2 group mean duration of diabetes was 8.20 ± 5.22 years with 40% having diabetes for duration less than 5 years, 37.50% in between 6 to 10 years and rest 22.50% had duration of diabetes for more than 11 years and in OHD group mean duration of diabetes was 8.90 ± 4.89 years with 32.50% having diabetes for duration less than 5 years, 32.50% in between 6 to 10 years and rest 35% had duration of diabetes for more than 11 years.

Table1: Distribution ofstudy subjects based on diabetes treatment.

Sl. No	Diabetes treatment	Frequency	Percentage
01	**Oral hypoglycemic drugs with SGLT2 inhibitors**	40	50%
02	**Oral hypoglycemic drugs Without SGLT2 inhibitors**	40	50%
Total		**80**	**100%**

Table 4 show that 50% of our subjects with diabetes were on treatment with oral hypoglycemic drugs along with SGLT2 inhibitors and rest 50% were on oral hypoglycemic

drugs, but without SGLT2 inhibitors.

Table 2: Distribution of study subjects based on insulin treatment.

Sl. No	Insulin treatment	OHD + SGLT2	OHD
		Frequency (%)	Frequency (%)
01	Yes	15 (37.50%)	15 (37.50%)
02	No	25 (62.50%)	25 (62.50%)
Total		40 (100%)	40 (100%)

Findings from table 5 show that, in both OHD + SGLT2 and OHD group 37.50% of the diabetic subjects were on insulin treatment and rest 62.50% were not on insulin treatment.
In OHD + SGLT2 group 77.50% did not have any associated co-morbidities, 22.50% had hypertension, 2.50% had CVDs and 7.50% with thyroid disorders. In OHD group 70% did not have any associated co-morbidities, 22.50% had hypertension, 5% had CVDs and 7.50% with thyroiddisorders.

Table 3: Distribution of study subjects based on historyof habits.

Sl. No	H/o habits	OHD + SGLT2	OHD
		Frequency (%)	Frequency (%)
01	Nil	30 (75%)	30 (75%)
02	Smoking	03 (7.50%)	04 (10%)
03	Alcoholconsumption	02 (5%)	02 (5%)
04	Smoking+Alcoholism	05 (12.50%)	04 (10%)
Total		40 (100%)	40 (100%)

In OHD + SGLT2 group 75% were not on any habitual behavior, whereas 7.50% were smokers, 5% of them had habit of alcohol consumption and rest 12.50% of them had habit of both smoking and alcohol consumption. In OHD group 75% were not on any habitual behavior, whereas 10%were smokers, 5% of them had habit of alcohol consumption and rest

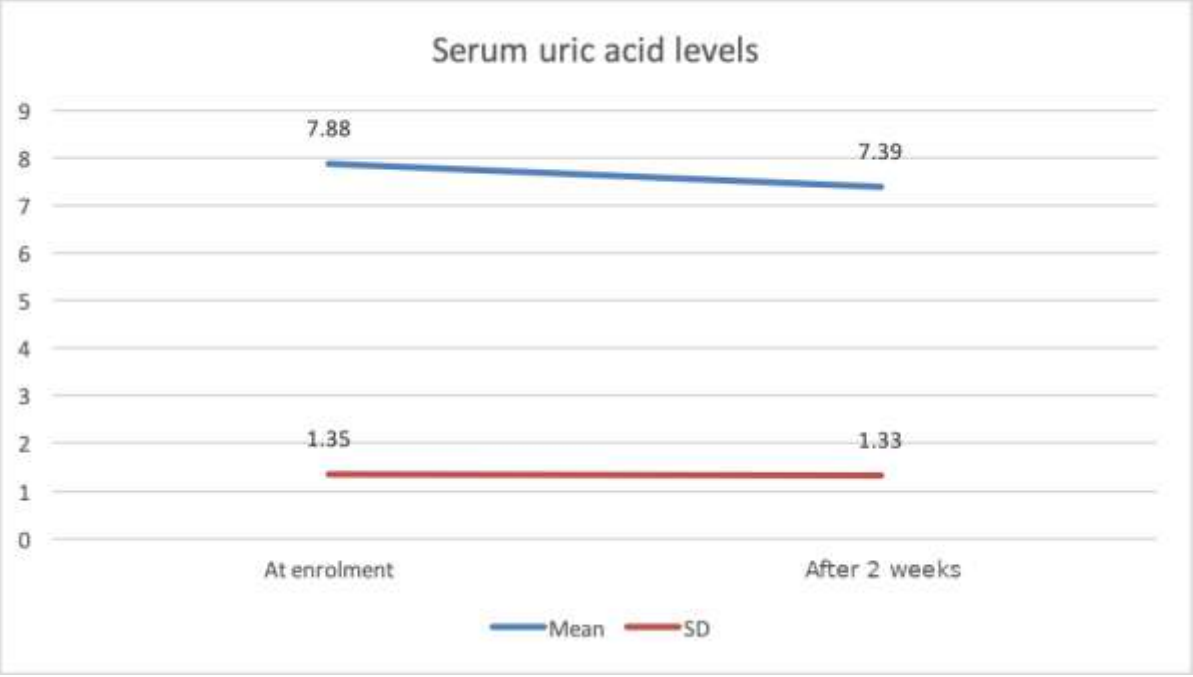
10% of them had habit of both smoking and alcohol consumption.

In OHD + SGLT2 group mean fasting blood sugar level recorded was 171.88±44.44 mg/dL and in OHD group it was 166.35 ± 41.26 mg/dL and in both the groups 10% recorded FBS less than 110 mg/dL, 7.50% had FBS in the range between 111 to 125 mg/dL and rest 82.50% had FBS more than 126 mg/dL.

InOHD+SGLT2 group mean PPBS was 230.45 ± 67.12 mg/dL with 10%having PPBS values less than140 mg/dL, 22.50%in between 141 to 199 mg/dL, 67.50% had more than 200 mg/dL and in OHD group it was 227.33 ± 64.82 mg/dL with 7.50% recorded PPBS less than 140 mg/dL, 35% had PPBS in the range between 141 to 199 mg/dL and rest 57.50% had PPBS more than 200 mg/dL.

In OHD + SGLT2 group mean HbA1c level recorded was 8.91 ± 1.81% with 17.50% recorded HbA1c less than 7%, 30% in the range between 7 to 8% and rest 52.50% had HbA1c more than 8% and in OHD group mean HbA1c level recorded was 8.92±1.89 mg/dL with 22.50% recorded HbA1c less than 7%, 15% in the range between 7 to 8% and rest 62.50% had HbA1c more than 8%. Above values suggest similar HbA1c values between both controls and subjects were similar.

Graph 1: Distribution of study subjects based on serum uric acid levels.



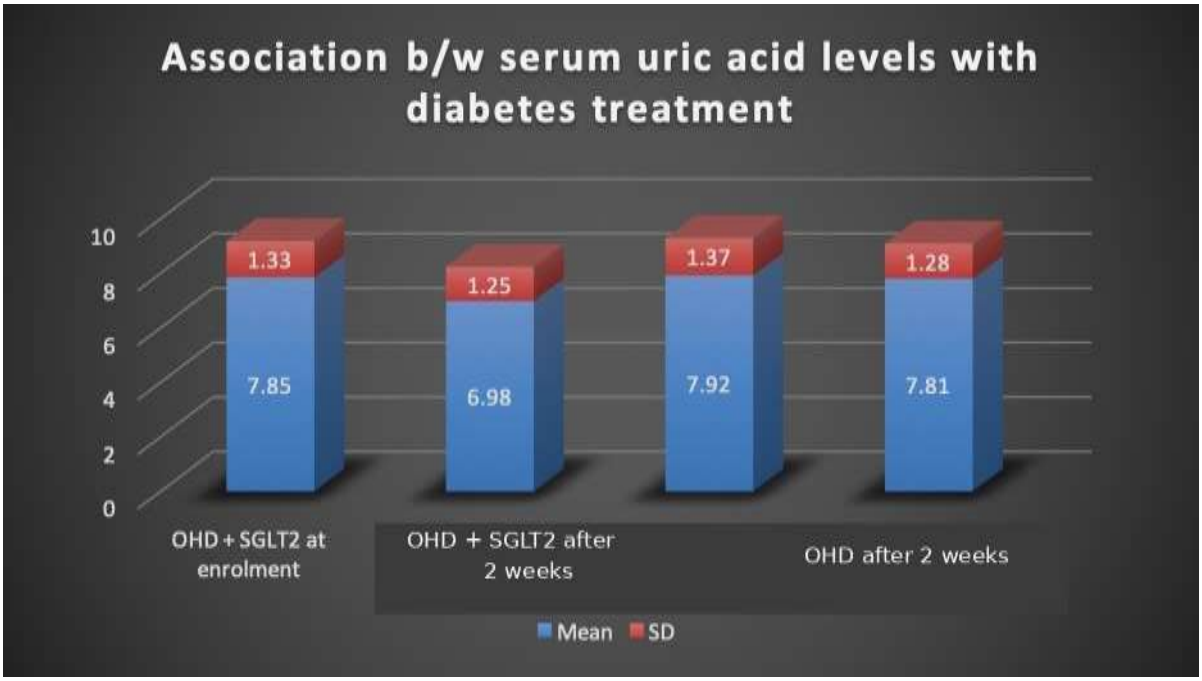
Graph1show that at enrolment mean serum uric acid levels was 7.88±1.35 mg/dL and after 2 week the mean serum uric acid levels was 7.39±1.33 mg/dL. In OHD + SGLT2 group mean serum creatinine levels were 0.91±0.21 mg/dL and mean blood urea levels was 26.77±10.55 mg/dL among our subjects and in OHD group mean serum creatinine levels was 1.66± 1.47mg/dL and blood urea levels was 27.49± 11.10 mg/dL.

In OHD + SGLT2 75% of them had normal urine routine findings and 25% had abnormal urine routine findings and in OHD group 70% had normal and 30% had abnormal urine

routine findings.

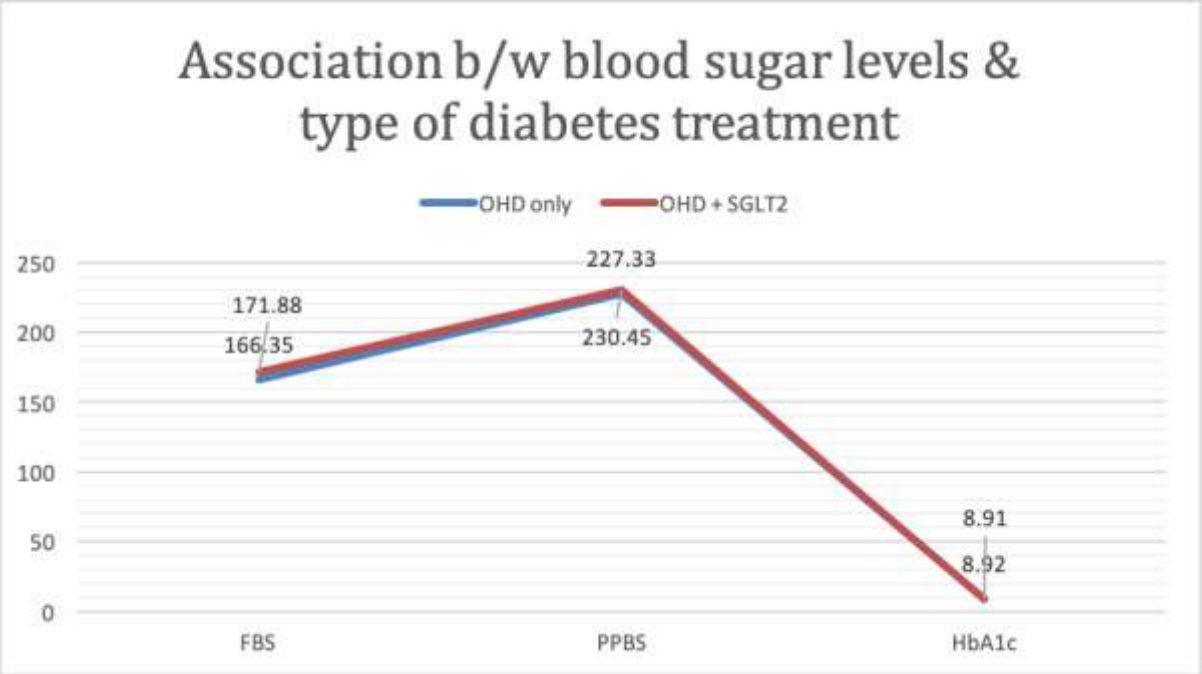
Mean serum uric acid levels after 2 weekss among oral hypoglycemic drugs with SGLT2 inhibitors were 6.98 ± 1.25 mg/dL and among those on oral hypoglycemic drugs without SGLT2 inhibitors were 7.81 ± 1.28 mg/dL and this difference was statistically significant indicating SGLT2 inhibitors had a significant role in lowering serum uric acid.

Graph 2: Comparison of serum uric acid levels two weeks apart with diabetes treatment.



Graph 2 revealed significant difference in serum uric acid levels in subject with OHA+SGLT2 inhibitor when compares to subject only on OHA.

Graph 3: Association between blood sugar levels and diabetes treatment type.



Graph 3 reveal that there was no significant difference in the fasting blood sugar levels, post prandial sugar levels and HbA1c among subjects who were on oral hypoglycemic drugs with or without SGLT2 inhibitors.

DISCUSSION

In our study it was noted that there was a significant reduction in serum uric acid levels in subject with OHA+SGLT2 inhibitor when compared to subject only on OHA with p-value being significant. Chino Y, et al, conducted a systematic review and meta-regression of 43 randomized controlled trials at Japan to see the effect of sodium glucose co-transporter-2 (SGLT2) inhibitors on serum urate levels among patients with and without diabetes. The study involved 399 subjects with type 2 diabetes mellitus. It demonstrated that SGLT2 inhibitors significantly reduced serum urate levels among patients with and without diabetes and it was also noted that SGLT2 inhibitors were proven to be beneficial in the treatment of patients with diabetes with concomitant hyperuricemia.[5]

Sujik DLS, et al, in their prospective trial on effects of dapagliflozin on serum and urinary uric acid levels among patients with type 2 diabetes conducted at Amsterdam in 2022.This study was done in 44 people with type 2 diabetes were randomized to dapagliflozin or gliclazide for 12 weeks. It concluded that after initiation of treatment with dapagliflozin 10 mg which is a SGLT2 inhibitor once daily for one week reduced plasma uric acid levels from 0.20.3 and 0.40.3 mg/dL and also by increasing fractional excretion of uric acid level (by 3.2%3.1% and 8.9%4.5% respectively ;both $p < 0.0001$) . The study concluded by increasing uric acid excretion by the kidneys and further a certain degree of improvement was seen in islet beta-cell function and positive correlation changes in glucose levels and islet beta cell function were observed without interference of change in weight and lipid metabolism.[6]

Ouchi M, et al, conducted a study on factors influencing change in serum uric acid after the administration of sodium-glucose co transporter 2 inhibitor Luseogliflozin among patients

with type 2 diabetes mellitus at Japan in 2016, showed that reduction in serum uric acid was greater among patients with higher serum uric acid before SGLT2 inhibitor administration and that SGLT2 inhibitors reduced serum uric acid by promoting urinary excretion of uric acid and hence SGLT2 inhibitors were expected to reduce serum uric acid desirably and consistently among patients with type 2 diabetes mellitus with high uric acid levels requiring reduction.[7]

Fralick M, et al, conducted a population-based cohort study on 300000 adults assessed risk for gout with sodium-glucose cotransporter-2 inhibitors among patients with type 2 diabetes in 2020. It was population–based new–user cohort study. The study identified 295907 adults with type 2 diabetes mellitus who were newly prescribed an SGLT2 inhibitor with those on GLP1 agonist. The study observed that lower rate of gout was seen among those on SGLT2 inhibitors compared to those on GLP1 agonist or DPP4 inhibitors and they also added that SGLT2 inhibitors might be an effective class of medication for the prevention of gout for patients with diabetes or metabolic disorders.[8]

Chino Y, et al, in them to understand the mechanism of SGLT2 inhibitors in lowering serum uric acid conducted in 2014. 57 and 24 healthy Japanese men participated in single dose study between the age of 20–39 years. Itdemonstrated that serum uric acid lowering effect of SGLT2 inhibitors could be accounted for by the increase in urinary excretion of uric acid. The study concluded that changes in serum uric acid levels from baseline values decreased significantly in single dose study and multiple dose study.

This increase in urinary excretion of uric acid is not due to a direct effect of drug on renal handling of uric acid, but could be attributed to glycosuria caused by SGLT2 inhibitors on GLUT9 isoform 2 or any other transporters at proximalTubule.

It may inhibit uric acid reabsorption mediated by GLUT9 isoform 2 at the collecting duct of renal tubule. This mechanism also explains relation between glycosuria and reduction in serum uric acid observed among diabetic individuals.[9]

Ouchi M, et al, conducted integrated analysis from phase 2 and 3 studies of tofogliflozin in type 2 diabetes mellitus up to 24 weeks. In this study. Multivariate analysis was followed with stepwise model selection and result were obtained with p value <0.05. On uric acid lowering in relation to reduction in HbA1c with SGLT2 inhibitor in 2018 demonstrated that serum uric acidlevels decreased among patients with diabetes who received SGLT2 inhibitor especially among those whose HbA1c levels were not greatly elevated before the treatment.[10]

CONCLUSION

In our study, we observed a significant reduction in mean serum uric acid levels in diabetic individuals who were treated with SGLT2 inhibitors compared to those who were not receiving these medications. This reduction in uric acid was noteworthy and points to the effectiveness of SGLT2 inhibitors in addressing elevated uric acid levels in this patient population.

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