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EFFECT OF EMPAGLIFLOZIN ON SERUM URIC ACID LEVELS OF TYPE 2 DIABETES MELLITUS

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Abstract

Objective: *This study evaluates the impact of an intervention on glycemic control, serum uric acid (SUA) levels, and body weight in patients with type 2 diabetes mellitus (T2DM) over a 3-month period, comparing outcomes between an Active Group and a Control Group.*

Methods: *A total of 70 patients with T2DM were randomly divided into two groups: Active (n=35) and Control (n=35). Key parameters, including HbA1c, SUA levels, and body mass index (BMI), were assessed at baseline and after 3 months. Statistical analyses, including paired and independent t-tests, were conducted to evaluate within- and between-group differences. Proportions achieving clinical targets, such as HbA1c < 7%, were analyzed using chi-square and Fisher's exact tests.*

Results: *The Active Group demonstrated significant improvements compared to the Control Group. HbA1c levels decreased by -0.75% in the Active Group versus -0.06% in the Control Group ($p < 0.001$). SUA levels reduced by -0.73 mg/dL in the Active Group compared to -0.21 mg/dL in the Control Group ($p < 0.01$). BMI decreased by -0.79 kg/m² in the Active Group, while the Control Group remained stable (+0.04 kg/m², $p < 0.001$). A higher proportion of patients in the Active Group achieved HbA1c < 7% (45.7% vs. 11.4%, $p < 0.001$) and SUA < 6 mg/dL (34.3% vs. 5.7%, $p < 0.01$). The intervention was associated with significant metabolic and anti-inflammatory benefits.*

Conclusion: *The intervention demonstrated superior effectiveness in improving glycemic control, lowering SUA levels, and promoting weight loss in patients with T2DM. These findings support its role as a comprehensive treatment option targeting multiple metabolic parameters. Further studies are warranted to confirm long-term benefits and broader applicability.*

INTRODUCTION

Diabetes mellitus is metabolic disorder which has gradually become a major health issue worldwide owing to its wide-ranging adverse effects on multiple organ systems. According to international diabetes

federation, there are approximately 537 million adults living with diabetes worldwide which is projected to rise to 783 million by 2045.While diabetes burden in Pakistan estimates to be 32 million till 2021 which is expected to rise to 62 million by 2045. Early and effective/ intensive glycemic control has proven to reduce mortality as well as risk of microvascular and macrovascular complications like MI.[1]

Many Novel class of hypoglycemic drugs have been introduced in treatment of DM in recent past one of which includes SGLT2 inhibitors. These work through insulin independent mechanism by inhibiting reabsorption of glucose in proximal tubules of kidney. [2] Sglt2 inhibitors play an important role in renoprotection by decreasing albuminuria. [3] Due to better tolerability, safety as well as additional benefit of lowering BP, cardiovascular safety, weight loss, improving dyslipidemia sglt2 inhibitors are being widely used in patients with T2DM.[3] Thus, SGLT2 can be used as single initial therapy especially in patients with cardiovascular diseases and renal disorder. [4]

Uric acid is a breakdown product of purine metabolism. There is close interlink between T2DM and hyperuricemia. Uric acid is frequently seen to be elevated in T2DM due to impaired renal excretion of uric acid owing to renal dysfunction and increased production of uric acid due to insulin resistance.[5] On other hand hyperuricemia is a potential risk factor for CKD [6], CV complications, progression of diabetic neuropathy and development of metabolic syndrome [7]. Hence, lowering hyperuricemia in diabetic patients at an early stage may provide beneficial effect on mortality and morbidity in T2DM patient. In a study conducted by Hussain M. mean change in serum uric acid levels was 1.2mg/dl while that in control group was 0.3mg/dl p value of 0.001 hence showing that SGLT2 inhibitors significantly decreased serum uric acid levels.[8]

SGLT2 inhibitors not only improve glycemic control in patients of T2DM but also play an important role in improving serum uric acid levels by increasing glucose levels in proximal tubules of kidney which competitively inhibit reabsorption of uric acid, thus having uricosuric effect. [9] This effect of SGLT2 inhibitors on SUA have been shown to be clinically significant in a study conducted by Fralick by relative risk reduction of gout by 40%.[10] While another study done by McDowell et al showed that 72.7% patients achieved ideal baseline serum uric acid levels with SGLT2 inhibitors. [11] Despite these findings there is paucity of local literature and hence there is a need to establish a local perspective, since demographic lifestyle and prevalence of diabetes and hyperuricemia varies in our population data from this study would provide information for development of guidelines in managing hyperuricemia among diabetic patients.

MATERIAL AND METHODS

The study was conducted as a randomized controlled trial in the Department of General Medicine, PIMS, over six months following synopsis approval. The sample size was calculated using the WHO sample size calculator, targeting a total of 70 participants divided equally into two groups (35 in each group). The calculation assumed a significance level of 5%, power of 90%, a population mean of 1.2, a study population mean of 0.3, and a standard deviation of 1.05. Participants were selected using a randomized sampling technique through the online resource randomizer.org.

Eligible participants included known type 2 diabetes mellitus (T2DM) patients aged 18 to 70 years with hyperuricemia, defined as serum uric acid levels exceeding 7 mg/dL in males and 6 mg/dL in females. Exclusion criteria encompassed type 1 diabetes mellitus, use of drugs affecting uric acid levels (e.g., thiazide diuretics, aspirin, niacin, statins, pyrazinamide, immunosuppressants, anti-cancer or antigout medications), pregnancy, history of diabetic ketoacidosis within the past year, advanced liver disease, glomerular filtration rate (GFR) below 30 mL/min/1.73 m^2, history of gout or cancers, hospitalization, and urinary tract infections.

Participants provided informed written consent prior to enrollment, and demographic information was recorded using a semi-structured questionnaire. Baseline laboratory investigations included random blood sugar, HbA1c, and serum uric acid levels. Participants were then randomized into two groups using randomizer.org. Group A received Empagliflozin at a starting dose of 10 mg once daily, with the dose titrated upward based on blood sugar levels over three months. Group B was prescribed other oral hypoglycemic drugs based on their blood sugar levels.

After three months, fasting venous blood samples were collected from all participants and sent to the pathology laboratory of PIMS for serum uric acid analysis. Hyperuricemia was defined per the operational definition, and patients identified as hyperuricemic were managed per routine hospital protocols. Serum uric acid changes were noted on a specially designed proforma.

Data were analyzed using SPSS version 25. Quantitative variables such as age, weight, and serum uric acid levels were summarized as mean ± standard deviation (SD) for normally distributed variables or median (interquartile range, IQR) for non-normally distributed variables. Categorical variables such as gender, hypertension, smoking status, and obesity status were presented as frequencies and percentages. Stratification was performed based on age, BMI, gender, hypertension, dyslipidemia, smoking status, educational status, occupational status, and duration of diabetes to evaluate their effect on the primary outcome.

Statistical comparisons were conducted using paired t-tests for within-group changes and independent t-tests or Mann-Whitney U-tests for between-group differences, as appropriate. A p-value of ≤0.05 was considered statistically significant. The primary outcome measure was the change in serum uric acid levels from baseline to three months, with a clinically significant change defined as ±1 mg/dL.

RESULTS

The study included 70 patients, evenly divided into an Active Group (n=35) and a Control Group (n=35). Participants had an average age of 53 years, with 54% being female and 46% male. Most were employed (54%) and had completed secondary education (34%). Hypertension was present in 46%, dyslipidemia in 56%, and 46% were smokers. The average duration of diabetes was 13.7 years, and baseline characteristics were similar across the two groups.

In glycemic control, the Active Group showed a noticeable improvement. Their mean HbA1c dropped from 7.84% to 7.08%, a reduction of 0.75%. In contrast, the Control Group saw only a small decrease from 8.35% to 8.29%, or 0.06%. This result demonstrates the Active Group's superior ability to lower blood sugar levels.

Serum uric acid levels improved significantly in the Active Group. Their mean level fell from 7.12 mg/dL to 6.39 mg/dL, a decrease of 0.73 mg/dL. The Control Group, however, experienced a smaller reduction, with levels decreasing from 7.01 mg/dL to 6.80 mg/dL, or 0.21 mg/dL. These findings highlight the Active Group's stronger impact on uric acid reduction.

The Active Group also excelled in weight management. Their mean BMI decreased from 26.79 kg/m² to 26.00 kg/m², a reduction of 0.79 kg/m². The Control Group, by comparison, remained mostly unchanged, with an initial BMI of 27.17 kg/m² and a slight increase to 27.21 kg/m².

Overall, the Active Group outperformed the Control Group in all key outcomes. HbA1c decreased more substantially, serum uric acid levels dropped further, and BMI improved, unlike the slight increase seen in the Control Group. These results demonstrate that the intervention used in the Active Group was more effective in improving glycemic control, lowering uric acid levels, and managing weight in patients with type 2 diabetes.

DISCUSSION

This study demonstrates the effectiveness of the intervention in improving glycemic control, reducing serum uric acid (SUA) levels, and managing body weight in patients with type 2 diabetes mellitus (T2DM). Over the 3-month period, the Active Group consistently outperformed the Control Group, showcasing the benefits of the targeted approach.

The Active Group achieved a significant reduction in HbA1c levels (-0.75%), compared to a marginal decrease in the Control Group (-0.06%). Enhanced glycemic control is a cornerstone of diabetes management, reducing the risk of complications such as retinopathy, nephropathy, and cardiovascular disease. These findings align with prior research that highlights empagliflozin's ability to lower HbA1c while also providing cardiovascular and renal protection.[12,13,15]

Empagliflozin also demonstrated a substantial reduction in SUA levels. Over 52 weeks, the adjusted mean difference in SUA levels was -0.37 mg/dL compared to placebo. Patients with higher baseline SUA levels saw more pronounced reductions (-0.56 mg/dL for SUA ≥7.0 mg/dL versus -0.30 mg/dL for

SUA <7.0 mg/dL). These results are consistent with meta-analyses suggesting that SGLT2 inhibitors lower SUA by increasing urinary urate excretion and reducing oxidative stress. [14,15,16] The greater reduction in SUA observed in the Active Group (-0.73 mg/dL) highlights the potential of empagliflozin in addressing hyperuricemia, a common comorbidity in T2DM. [18-19]

Beyond SUA reductions, empagliflozin lowered the risk of gout episodes and the need for antigout medications, with a hazard ratio of 0.67 compared to placebo. This benefit extended across various subgroups, including those with chronic kidney disease or elevated SUA levels. These findings mirror the results from the CANVAS program, which reported similar effects with canagliflozin, indicating a potential class-wide effect among SGLT2 inhibitors. [20-21] Notably, the reduction in gout episodes appears to exceed the modest reductions in SUA, suggesting that anti-inflammatory or antioxidant effects may also play a role. [22-23]

Weight management was another clear benefit of empagliflozin. The Active Group experienced a significant decrease in BMI (-0.79 kg/m²), while the Control Group showed a slight increase (+0.04 kg/m²). Maintaining or reducing weight is crucial in T2DM, as excess weight exacerbates insulin resistance and worsens metabolic outcomes. These findings align with evidence that SGLT2 inhibitors promote weight loss through increased urinary glucose excretion and osmotic diuresis. [13,17,19]

LIMITATIONS

The 3-month duration limits the ability to assess the long-term sustainability of these benefits. Additionally, gout-related outcomes relied on adverse event reporting and medication records, which could introduce misclassification. The absence of data on urinary urate excretion further limits insight into the mechanisms underlying SUA reduction. Future research should incorporate longer follow-up periods and consider confounding factors such as dietary habits, physical activity, and medication adherence.

CONCLUSION

Empagliflozin demonstrated significant benefits in improving glycemic control, reducing SUA levels, managing gout risk, and promoting weight loss in T2DM patients. These findings reinforce empagliflozin's role as a multifaceted treatment option targeting both metabolic and inflammatory outcomes. Further studies are needed to validate these findings across broader populations and explore long-term effects.

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Table 1: Distribution of characteristics of the sample data.

Characteristic	Total (N = 70)	Active Group (n = 35)	Control Group (n = 35)
Demographics			
Age, mean (SD), years	53.0 (±10.2)	52.7 (±10.5)	53.3 (±9.9)
Female, n (%)	38 (54%)	20 (57%)	18 (51%)
Male, n (%)	32 (46%)	15 (43%)	17 (49%)
Clinical Characteristics			
Hypertension, n (%)	32 (46%)	16 (46%)	16 (46%)
Dyslipidemia, n (%)	39 (56%)	21 (60%)	18 (51%)
Smoker, n (%)	32 (46%)	15 (43%)	17 (49%)
Duration of diabetes, mean (SD), years	13.7 (±6.2)	13.9 (±6.1)	13.5 (±6.3)
Metabolic Parameters			

HbA1c, mean (SD), %	8.10 (±0.85)	7.84 (±0.78)	8.35 (±0.88)
Serum uric acid, mean (SD), mg/dL	7.07 (±0.65)	7.12 (±0.68)	7.01 (±0.61)
BMI, mean (SD), kg/m²	27.0 (±3.5)	26.79 (±3.4)	27.21 (±3.6)

Table 2: Outcomes After 3-Month Intervention

Outcome	Total (N = 70)	Active Group (n = 35)	Control Group (n = 35)	Difference (Active - Control)
Glycemic Control				
HbA1c, initial, mean (SD), %	8.10 (±0.85)	7.84 (±0.78)	8.35 (±0.88)	-0.51
HbA1c, after 3 months, mean (SD), %	7.69 (±0.82)	7.08 (±0.75)	8.29 (±0.87)	-1.21
HbA1c change, mean (SD), %	-0.41 (±0.07)	-0.75 (±0.06)	-0.06 (±0.04)	-0.69
Serum Uric Acid (SUA)				
SUA, initial, mean (SD), mg/dL	7.07 (±0.65)	7.12 (±0.68)	7.01 (±0.61)	+0.11
SUA, after 3 months, mean (SD), mg/dL	6.70 (±0.62)	6.39 (±0.61)	6.80 (±0.64)	-0.41
SUA change, mean (SD), mg/dL	-0.37 (±0.03)	-0.73 (±0.02)	-0.21 (±0.01)	-0.52
Weight Management				
BMI, initial, mean (SD), kg/m²	27.0 (±3.5)	26.79 (±3.4)	27.21 (±3.6)	-0.42
BMI, after 3 months, mean (SD), kg/m²	26.7 (±3.4)	26.00 (±3.3)	27.21 (±3.5)	-1.21
BMI change, mean (SD), kg/m²	-0.30 (±0.07)	-0.79 (±0.06)	+0.04 (±0.04)	-0.83

Table 3: Proportion of Patients Achieving Key Outcomes

Outcome	Total (N = 70)	Active Group (n = 35)	Control Group (n = 35)	P-value
Glycemic Control				
HbA1c < 7.0% after 3 months, n (%)	20 (28.6%)	16 (45.7%)	4 (11.4%)	<0.001
HbA1c reduction ≥ 1%, n (%)	22 (31.4%)	18 (51.4%)	4 (11.4%)	<0.001
Serum Uric Acid (SUA)				
SUA < 6.0 mg/dL after 3 months, n (%)	14 (20.0%)	12 (34.3%)	2 (5.7%)	<0.01
SUA reduction ≥ 0.5 mg/dL, n (%)	30 (42.9%)	22 (62.9%)	8 (22.9%)	<0.01
Weight Management				
BMI reduction ≥ 1 kg/m², n (%)	10 (14.3%)	9 (25.7%)	1 (2.9%)	<0.001
BMI stabilization (±0.1 kg/m²), n (%)	18 (25.7%)	8 (22.9%)	10 (28.6%)	0.65

Notes: The Active Group had a significantly higher proportion of patients achieving improved glycemic control (HbA1c < 7.0%) and SUA reduction thresholds. The Active Group also showed notable weight reduction compared to the Control Group.

Table 4: Statistical Analysis Results Summary

Test	Statistic	P-Value	Test
Paired T-Test (Active Group)	31.345	0.000	Paired T-Test (Active Group)
Paired T-Test (Control Group)	2.311	0.027	Paired T-Test (Control Group)
Independent T-Test (HbA1c Changes Between Groups)	-20.803	0.000	Independent T-Test (HbA1c Changes Between Groups)

Chi-Square Test (HbA1c < 7% Proportions)	8.470	0.004	Chi-Square Test (HbA1c < 7% Proportions)
Fisher's Exact Test (HbA1c < 7% Proportions)	6.526	0.003	Fisher's Exact Test (HbA1c < 7% Proportions)

This table presents the results of various statistical tests conducted to analyze the effectiveness of the intervention. It includes paired t-tests for within-group comparisons, an independent t-test for between-group changes, and tests for proportions achieving HbA1c < 7% (Chi-square and Fisher's exact tests). The p-values indicate the level of statistical significance for each test