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Original Article

The Effect of SGLT-2 Inhibitors on Serum Potassium and Serum Sodium Levels in Diabetic Patients taking SGLT-2 Inhibitors, Reporting in A Tertiary Care Hospital, Rawalpindi

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ABSTRACT

Objective: To evaluate how SGLT2 inhibitors, in comparison to a placebo and the maximum dose of Metformin, affect the levels of serum potassium and sodium in individuals with Type II Diabetes.

Study Design: Quasi- Experimental study

Place and Duration of Study: Department of Medicine (Endocrinology) in a tertiary care hospital, in Rawalpindi Pakistan from Oct 2022 to Mar 2023.

Methodology: A total of 200 patients with type II diabetes were recruited and divided into two groups. 100 diabetic patients were placed in Group-A and were given SGLT-2 inhibitors (Dapagliflozin and Empagliflozin) while 100 diabetic patients were placed in Group-B, given a placebo in addition to a maximum dose of 2000mg/day of Metformin they were already taking. Patients were observed over 24 weeks and the levels of serum potassium and sodium were assessed at the end of this period.

Results: Mean sodium levels of patients receiving SGLT-2 inhibitors were 139.3±3.18 mmol/L while of those who received placebo were 138.94±3.5 mmol/L with a p-value of 0.44. The mean potassium levels of patients who received SGLT-2 inhibitors were 3.96±0.33 mmol/L while of those who received placebo were 3.97±0.38 mmol/L with a p-value of 0.8. There was statistically no difference in serum sodium and potassium levels of the two groups.

Conclusion: SGLT-2 inhibitors (Dapagliflozin and Empagliflozin) do not affect serum sodium and potassium levels when compared to patients who were given placebo as there was statistically no significant difference among the two groups.

Keywords: Dapagliflozin, Empagliflozin, Endocrinology, SGLT2 inhibitors, serum potassium and sodium levels, Type 2 diabetes.

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INTRODUCTION

An imbalance in the ability of the body to synthesize or react to insulin and control the blood sugar levels is known as diabetes mellitus[1]. The hallmark of type 2 diabetes mellitus is hyperglycemia due to decreased response to insulin, and in uncontrolled cases, it is associated with high morbidity and mortality owing to its micro-vascular and macro-vascular complications[2]. Treatment is primarily based on dietary restriction, aerobic exercise, administering oral hypoglycemics, and mostly insulin in advanced uncontrolled diabetes with oral medications, in addition to the use of insulin in advanced chronic kidney disease. Various oral hypoglycemic agents are being used nowadays including Metformin, Sulfonylureas, DPP-4 Inhibitors, Thiazolidinediones, Alpha Glucosidase Inhibitors, Meglitinides, GLP1 Agonists, among which Sodium Glucose Cotransporters-2 Inhibitors are a rapidly emerging group of drugs[3]. They have garnered attention for their multifaceted impact on various physiological effects. The approved SGLT-2 inhibitors being used nowadays world over are Dapagliflozin, Empagliflozin and Canagliflozin.

The transport of glucose in many tissues is carried out by a family of proteins called Sodium Glucose Co-Transporters. The human cardiac myocytes express SGLT1, while kidneys are the primary organs where SGLT2 is expressed, but pancreatic alpha cells also express this protein[4]. 80–90 percent of the filtered glucose is reabsorbed by SGLT2 on the apical membrane of the epithelium of the first segment of the proximal tubule in the kidney, whereas SGLT1 absorbs the remaining 10–20 percent of the glucose in the distal regions of the proximal tubule.

The mechanism of action is the suppression of the sodium glucose co-transporter in the kidney's proximal convoluted tubule, which increases the glucose excretion and, as a result, lowers the blood glucose levels and blood pressure because of sodium excretion[5]. Conversely, increased sodium supply to

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the macula densa as a result of decreased sodium re-absorption triggers the tubuloglomerular feedback and results in the vasoconstriction of the afferent arteriole. As a result of this, the glomerular hyperfiltration is lowered, and thus the kidneys are protected from damaging. As to the findings of the CANVAS Trial, canagliflozin reduces the likelihood of both cardiac and renal failure. Dapagliflozin has also been shown to have similar effects[6]. In the Empagliflozin, Cardiovascular Outcome, and Mortality in Type II DM Trial, it was found that the addition of Empagliflozin to the standard therapy reduced hospital admissions for heart failure by 35 percent relative risk and deaths due to cardiovascular events by 38 percent. The data on the handling of electrolytes by the kidney in Type II DM patients who are using SGLT2 is limited. Numerous prior investigations have examined the impacts of various SGLT2 in traditional pairwise meta-analyses. However, there was insufficient statistical power in a few of the results of these studies to examine the impact of a particular medicine or class on the serum levels of electrolytes [7].

It is not certain whether SGLT2 cause hyperkalemia or protect from high potassium levels and what is the resultant effect on serum sodium levels as they cause its excretion[8]. Initial studies showed that SGLT-2 inhibitors have the effect of raising serum potassium levels because of the inhibitory effect on sodium potassium ATPase. However, a pooled analysis has shown that the serum potassium levels remain unaltered[9]. The significantly elevated serum levels of magnesium and phosphate were seen in a different investigation that examined the impact of SGLT-2 inhibitors on different electrolyte levels in serum, and this supports an SGLT2 inhibition class impact.

However, no statistical proof was found that using these medications affected the levels of other electrolytes in the blood, such as potassium and sodium[10].

In this comparative analysis, we aim to elucidate the ramification of Sodium-Glucose Cotransporter-2 Inhibitors on levels of serum sodium and serum potassium in patients with Type II DM in our setup with the results being expected to provide us with a comprehensive overview of any electrolyte imbalance which is associated with these compounds, in addition to their pharmacodynamic nuances and clinical relevance.

METHODOLOGY

This Quasi-experimental study was carried out from October 2022 till March 2023 in the Department of Medicine of a tertiary care hospital Rawalpindi, Pakistan, with prior permission from hospital ethical review committee (vide IRB/CMH RWP/Ser 328). Sample size was calculated using WHO sample size calculator taking mean sodium level of 136+2.34 and mean potassium of 4+0.30 [11]. The estimated sample size came out to be 200 patients (100 patients in each group). Non-probability, consecutive sampling was done to recruit the patients.

Inclusion criteria: Patients of either gender with age ranging from 40 to 80 years, with uncontrolled Type II Diabetes. Patients taking Metformin at a maximum dose of 2000 mg /day with the latest HbA1c of 6.5 to 7% were included in the study.

Exclusion criteria: Patients with Type 1 diabetes mellitus, those taking insulin, patients with chronic kidney disease and people with heart failure were excluded. Patients taking oral hypoglycemics other than Metformin, SIADH, diabetes insipidus, existing malignancy including CNS tumors, active infection, surgery, trauma, pregnancy, already existing hypo or hypernatremia and hypo or hyperkalemia and lastly the people who failed to follow up were also excluded from the study.

Informed consent after being fully told about the goal and methodology of this research. Patients were randomly split into two equal groups A and B, each with 100 individuals (Figure). Group-A was given Dapagliflozin 5mg once or twice a day or Empagliflozin 10mg once or twice a day in addition to an already maximum dose of Metformin. Group-B who was already receiving Metformin up to 2000 mg was given a placebo. Baseline serum sodium and potassium levels were measured at the beginning of the study which were normal. Patients were followed over a period of 24 weeks. Patients were followed with blood sugar random charting done at home, and 3 monthly HbA1c to evaluate for worsening of diabetes and development of any complications. The serum sodium and potassium of these patients were measured again at the end of the 24-week observation period.

The Statistical Package of Social Sciences (SPSS-2020 was used to examine the data. For categorical variables, percentages and frequencies were determined. The mean and standard deviation for continuous variables were computed.To determine the

statistically significant differences between serum sodium and potassium levels of these patients taking SGLT-2 inhibitors, independent sample t-test was done. The *p*-value of less than 0.05 was considered significant.

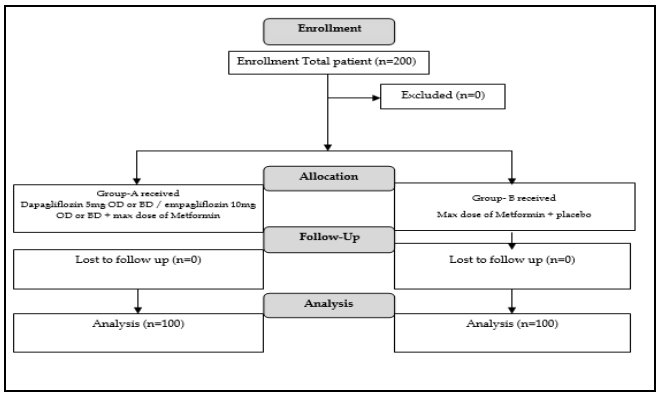

Figure:Patient flow diagram

RESULTS

The mean age of study population was 58.33±7.33 years, the distribution of which is shown in Table-I, after checking the normality of data, the mean years of having diabetes in our selected sample was 4.84±2.68 years. Out of 200 selected sample, 112(56%) were male and 88(44%) were female. The only co-morbid included was hypertension not treated with diuretics or ACE/ ARB inhibitors. Out of 200 people, 119(59.5%) were non hypertensive whereas 81(40.5%) of the included patients who had hypertension, as shown in Table-II. Out of 200 patients was divided into two equal groups of 100 each.

Group-A received SGLT-2 Inhibitors either Dapagliflozin or Empagliflozin. The patients in Group-B received a placebo, in addition to Metformin.

The mean sodium levels of patients receiving a placebo were 138.9±3.5 mmol/L while those of receiving SGLT-2 inhibitors were 139.3±3.10 mmol/L after 24 weeks of treatment. There was statistically no difference in the serum sodium levels in patients of the two categories (*p*-value>0.05) as shown in Table-II.

Table-I : Demographic Variables of Both Groups (n=200)

Variable		Frequency = n (%)
Age (years)	41-60	107(53.5)
	61-80	93(46.5)
Gender	Male	112(56)
	Female	88(44)
Hypertension	Yes	119(59.5)
	No	81(40.5)

Table-II: Comparison of Serum Sodium and Potassium levels between Group-A and Group-B

Variables	Groups		*P*-value
	Group-A (n=100)	Group-B (n=100)	
Serum Sodium	138.94 + 3.51	139.30 + 3.18	0.44
Serum Potassium	3.965 + .33	3.973 + .38	0.87

DISCUSSION

The study found out that the SGLT-2 inhibitors (Dapagliflozin and Empagliflozin) do not affect serum sodium and potassium levels when compared to patients who were given placebo as there was statistically no significant difference among the two groups. The CANVAS study, which specifically investigated the impact of Canagliflozin, has likewise shown that Canagliflozin did not have any significant effects on serum potassium levels in either the general population or important subgroups. Hyperkalemia as a consequence was not frequently seen as an adverse effect, and the rates of incidence were comparable between canagliflozin and placebo [11].

In the same way, clinical trials have not shown any changes in serum sodium levels despite the possibility of a negative sodium balance following SGLT2 injection, even in the absence of hemoconcentration symptoms [12]. A cross sectional retrospective study found that SGLT2 inhibitors are ineffective in preventing hyponatremia and that patients who are at risk cannot benefit from using them as a prophylactic measure. Although, natriuretic effect of SGLT2i has been quoted at many sites but its long term effect on serum levels of sodium has been insignificant. Very little research has been done on how different electrolytes are affected by SGLT2 medications, despite clinical data suggesting that Ertugliflozin, Canagliflozin, Ipragliflozin, Dapagliflozin, and Empagliflozin are safe, cardioprotective, and reno protective. Some effects on water and electrolyte balance have been reported, similar to other antidiabetic drugs. In addition to causing weight loss by reducing glucose levels, the effects of SGLT2i in natriuresis and water depletion also reduces blood pressure and blood volume[13].

Diabetes Mellitus is a very common disease associated with high morbidity and mortality due to its complications. Many oral hypoglycemic agents have been introduced with the purpose of glycemic control within normal limits and to improve the quality of life of patients. SGLT-2 inhibitors are a relatively newer class of drugs that are being used for

the control of diabetes mellitus, with the benefit of having a role in renal as well as cardio-protection. They also have the benefit of weight control, a promising effect on Hypertension, and a very low risk of decreased blood glucose[14]. Because they have the renal site of action, involving sodium-glucose cotransporters and Na-K ATPase, there have been concerns regarding their effect on levels of various electrolytes, particularly sodium and potassium. Despite that, not a lot of effort has been dedicated to determining these effects.

One of the major limitations in our study was the availability of only two types of drugs but not Canagliflozin, which in some studies including the CANVAS program, has been shown not to affect serum sodium levels however some of the data is available in favor of its association with risk of hyperkalemia[15].

The results of our study were consistent with previous meta-analyses including pooled analysis. A previous RCT has shown that empagliflozin is associated with a considerable increase in blood sodium when compared with a placebo in the treatment of hyponatremia in patients with SIADH[16-17]. Nevertheless, the effect of empagliflozin on serum sodium levels was essentially reliant on the degree of baseline hyponatremia, and the main distinction between empagliflozin and placebo was severe hyponatremia, with a serum sodium level of 125 mmol/L. Similarly, there were no clinically evocative effects of SGLT2i on serum potassium levels observed in previous trials using dapagliflozin, canagliflozin, or empagliflozin. In fact, Dapagliflozin has been approved to be used to slow down the progression of kidney damage leading to failure in patients with chronic kidney disease but without diabetes by reducing the glomerular hyperfiltration and pressure thus reducing microalbuminuria. Furthermore, there is no evidence available in favor of its role in causing hyperkalemia[18]. Another limitation of our study was a short follow up period of 24 weeks due to which we could not analyze the effects of these drugs on serum sodium and potassium levels in the long run. Furthermore, the study was conducted at a single centre which did not represent a large population size or patients reporting at other hospitals of the same city.

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CONCLUSION

SGLT-2 Inhibitors Dapagliflozin and Empagliflozin do not affect serum sodium and potassium levels in patients with T2DM without CKD when compared with patients receiving placebo.

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Authors' Contribution

The Following authors have made substantial contributions to the manuscript as under:

ALK & AR: Conception, study design, drafting the manuscript, approval of the final version to be published.

FJ & SA: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

FAS & SA: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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