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Research Article

**SAFETY AND EFFECTIVENESS OF DAPAGLIFLOZIN
USAGE ON THE PATIENTS OF DIABETES TAKING HIGH
INSULIN DOSES**¹Syed Muhammad Tayab, ²Shaima Yasmeen, ³Amna Noor¹Sahiwal Medical College Sahiwal²Fatima Memorial Hospital Lahore³University Medical and Dental College Faisalabad

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Abstract:

Objective: The purpose of this study is to interrogate the safety and effectiveness of dapagliflozin in the patients suffering from diabetes who are already using high insulin doses.

Methodology: This research work carried out in DHQ Teaching Hospital, Sahiwal. In this research work, 30 patients of diabetes who were getting high insulin doses ($>0.50\text{U/kg}$) and oral anti-diabetic therapy except SGLT-2 inhibitors were the participants of this research work. Primary endpoint of this research work was alteration in the level of HbA1c, doses of insulin and electrolyte from the addition of the dapagliflozin 10.0mg to a week.

Results: After the completion of 3 months, there was obvious decrease in the body mass index from 33.31 ± 4.51 to the 32.14 ± 4.66 ($P=0.0010$). We also observed the reduction in the requirement of insulin from 76.0 ± 23.15 U/kg to 57.6 ± 17.61 U/kg ($P<0.0010$). There was also decrease in the levels of HbA1c ($\Delta 1.60\%$) and fasting blood glucose ($\Delta 68.60\text{mg/dl}$) ($P<0.0010$). Among the levels of serum electrolyte, a slight but meaningful rise of the levels of BUN (Blood Urea Nitrogen) and Na (Sodium) were observed ($P=0.0440$ and $P=0.0260$). We found no significant alterations in the levels of serum cholesterol with electrolytes like Vitamin-D, potassium, magnesium, calcium, and phosphorus ($P>0.050$).

Conclusion: In the patients of diabetes mellitus with incompetently controlled regulations of glucose regardless of the treatment with high insulin doses, dapagliflozin may be a substitute combination option to reduce the requirement of insulin doses and get optimal level of HbA1c, levels of fasting plasma glucose as well as BMI without any important side effect.

KEYWORDS: Effectiveness, reduction, dapagliflozin, magnesium, cholesterol, therapy, insulin, doses, HbA1c.

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INTRODUCTION:

International Diabetes Federation estimated in the year of 2017 that there were 451 million persons in the world who were suffering from diabetes and this figure will increase to 693 million persons in 2045 [1]. DM (Diabetes Mellitus) is a chronic disease of metabolism and it requires treatment and follow up for whole life. This complication has association with the development of macrovascular & microvascular abnormalities with the high rate of morbidity as well as mortality [2]. Less than 50% patients obtain glycemic targets with the use of oral anti-hyperglycemic agents and majority of the patients need insulin treatment [3]. Insulin therapy is much effective for the treatment of Diabetes Mellitus but higher doses of insulin lead to risk of the hypoglycemia, unwanted gain of weight and retention of fluid [3]. There is also requirement of an oral anti-diabetic besides treatment with insulin to reduce the requirement of insulin doses. Dapagliflozin is highly selective inhibitor of renal SGLT2 (sodium glucose co-transporter 2) [4]. Dapagliflozin enhances the excretion of glucose through urine with the constraining the reabsorption of the renal glucose thus reducing the glucose in plasma. Since it acts self-reliantly from the action or secretion of insulin, it offers the additional glycemic control when utilized with the insulin [5]. SGLT-2 inhibition may also influence the excretion and reabsorption of sodium which can have impacts [6]. The main rationale of this research work was to examine the safety and effectiveness of dapagliflozin usage in the patients of diabetes who are already using high insulin doses. There are few researches works available in this particular topic in PubMed, but no one interrogated the impacts of dapagliflozin on the serum electrolytes and reduction in the insulin dose on the diabetic patients using high insulin doses.

MATERIAL AND METHODS:

This research work was carried out in DHQ Teaching Hospital, Sahiwal. A sum of 30 patients who were getting high dose of insulin ($>0.5\text{U/kg}$) and oral anti-diabetic therapy other than the SGLT-2 inhibitors, got recruitment in this research work. We added dapagliflozin 10.0mg to the present treatments, 90 days later, we examined the levels of HbA1c, doses of insulin and alterations in the level of serum electrolyte. This current research work was conducted in accordance with the ethical principles prescribed by Helsinki Declaration and the ethical committee of the institute gave the permission to conduct this research work. We obtained the written consent from all the patients

after describing them the purpose of this research work. The patients from 18 to 75 years of age with Type-2 Diabetes Mellitus obtaining insulin greater than 0.50U/kg for the previous 4 weeks before their recruitment and with level of HbA1c $7.5.0\%$ to 12.0% were the subjects of this current research work. We also allowed the patients with additional treatment with dipeptidyl peptidase-4 & metformin and patients present with the eGFR (estimated Glomerular Filtration Rate) of $60.0\text{ml/min/1,73.0m}^2$ and greater were included in this research work. All the patients with past history of Type-1 Diabetes Mellitus, cardiovascular complications, babies on breast feeding and females with pregnancy were not included in this research work.

In the duration of 12 weeks follow up, fixed dose of insulin was applied in order to assess the effectiveness of the dapagliflozin to check the alterations in the levels of insulin dose, HbA1c and serum electrolyte precisely. SPSS V. 20 was in use for the statistical analysis of the collected information. We presented all the variables related with patients in averages and standard deviations. We used the T test for parametric information for the analysis of the values before and after the treatment from dapagliflozin. P value of less than 0.050 was significant. The utilization of the Kolmogorov-Smirnov test was carried out for the determination of the parametric as well as non-parametric distributions of the information.

RESULTS:

There were 30 patients of diabetes in which 19 were females and 11 were males in this research work. All these patients were using high insulin doses of $>0.50\text{U/kg}$, total dose of insulin = 76.0 ± 23.15 . Mean age of the patients was 57.73 ± 6.13 and duration of Diabetes Mellitus in these patients was 11.46 ± 6.7 . We examined the alterations in the requirement of insulin, levels of blood pressure, BMI (Body Mass Index) and other biochemical parameters between admission and at 90 days after the application of the treatment by dapagliflozin. After three months of treatment by dapagliflozin, there was decrease in the body mass index of the patients from 33.310 ± 4.510 to 32.140 ± 4.660 ($P=0.0010$). There was also a clear reduction of insulin dose. The daily need of insulin reduced from $76.0 \pm 23.15\text{U/kg}$ to $57.6 \pm 17.61\text{U/day}$ ($P<0.0010$). Distant from the reduction in the insulin doses, we also found a decline in the level of HbA1c ($\Delta 1.60\%$) and levels of FPG ($\Delta 68.60\text{mg/dl}$) ($P<0.0010$) (Table-1).

Table-I: Effect of Dapagliflozin On Glucose Regulation At 12 Week

	Basal	3 month later	P value
BMI (kg/m ²)	33.31±4.51	32.14±4.66	< 0.001
FPG (mg/dl)	234.7±67.89	166.07±43.93	< 0.001
HbA1c (%)	9.67±1.44	8.07±1.15	< 0.001
Total insulin dose (U/day)	76±23.15	57.60±17.61	< 0.001

Although the level of serum hematocrit was also increased, but it was not much significant statistically. There was also increase in the levels of serum BUN from 14.9±3.17 to 16.66±0.540 (P= 0.0440). Among serum electrolytes, there was a slight increase in the levels of serum potassium (P>0.050). There was also increase in the serum sodium which is other electrolyte (P= 0.0260). We also found an increase in the levels of phosphorus, calcium, and magnesium but these increases were not much significant statistically (P> 0.050). We also observed insignificant enhancements in the levels of serum uric acid (P>0.050) (Table-2).

Table-II: Effect of Dapagliflozin on Serum Hemogram and Electrolytes

	Basal	3 month later	P value
Hemoglobin (g/dL)	13.64±1.39	13.58±1.26	0.7
Hematocrite (%)	41.23±4.28	41.59±4.53	0.47
Sodium (mEq/L)	138.23±2.64	139.40±1.95	0.03
Potassium (mEq/L)	4.70±0.53	4.71±0.37	0.88
Klorür (mEq/L)	102.70±2.72	102.13±2.27	0.28
BUN (mEq/L)	14.90±3.17	16.66±0.54	0.04
Creatin (mEq/L)	0.81±0.11	0.84±0.12	0.15
GFR (mL/min/1.73 m ²)	84.00±12.68	81.87±11.27	0.17
Calcium (mg/dL)	9.53±0.57	9.62±0.40	0.44
Phosphate (mg/dL)	3.89±0.76	4.02±0.63	0.48
Vitamin D (ng/ml)	18.61±8.31	19.01±10.05	0.36
Magnesium (mg/dL)	1.74±0.27	1.81±0.25	0.2
Uric Acid (mg/dL)	5.15 ±1.41	4.86±1.46	0.23

Among the parameters of lipids, there were insignificant alterations in the levels of HDL and LDL. There was decrease in the level of triglyceride, but it was also not significant (P= 0.1360) (Table-3).

Table-III: Effect of Dapagliflozin on Lipid Parameters

	Basal	3 month later	P value
LDL (mg/dL)	121.66±34.29	123.56±33.96	0.81
HDL (mg/dL)	38.13±7.82	37.38±7.64	0.45
Triglyceride (mg/dL)	199.23±100.01	175.89±66.83	0.14

DISCUSSION:

There is requirement of insulin treatment in the whole course of Diabetes Mellitus. There are some important factors which restricts the optimal titration and the effectualness of the insulin as gain of body weight, hypoglycemia, and fluid retention [7]. There is also need of the other clinical requirement for the patients of Typ-2 Diabetes

Mellitus with the treatment of insulin. Some agents present in the proximal tubule of kidney restrict the absorption of glucose, induce its abolition, and decreases the glucose of blood independently of insulin [8,9]. In this research work, we checked the safety and effectivity of the dapagliflozin on the subjects utilizing high insulin doses. Different research works have stated that the discharge of the

glucose through urine by using SGLT-2 inhibitors results calories loss of approximately from 200 to 300 kcal per day, leading to imbalance of energy [10]. We also noticed a reduction in weight in the patients of this research work. Because of the imbalance of energy, excretion of urinary glucose may be the reason of the calories loss and research works consistently showed the loss of weight usually 2 to 4 kilograms [11,12]. In various clinical trials, usage of dapagliflozin improved the glyemic control and decreased the levels of HbA1c and FPG when managed with insulin [11,12].

Wilding reduced the dose of insulin to half in addition with dapagliflozin and reached a reduction of 0.610% HbA1c, FPG Δ : 4.30mg/dl [11]. One other research work with the addition of dapagliflozin with insulin in the patients of Japan found a change in level of HbA1c from 8.26% to 7.54% and FPG from Δ : -21.70mg/dl but reduction in the routine dose of insulin was not much significant (-0.740 IU/day) [7]. Several research works stated the slight increase in the level of hematocrit and findings of current research work is consistent with this particular finding [10-12]. James stated that there was no significant alteration in the level of serum creatinine and eGFR [13]. The administration of the SGLT-2 inhibitor, mainly canagliflozin, has association with the slight increase in the concentration of the serum potassium, particularly in the patients present with decreased renal efficiency [14]. EMPA-REG trial did not find change in the levels of serum potassium levels with empagliflozin & dapagliflozin which was present with no association to the changes in the serum potassium in the patients present with renal impairment of moderate nature (eGFR 30.0 to 59.0 ml/min/1.730m²) [15,16]. Increased levels of glucagon and osmotic diuresis SGLT-2 inhibitors may result a slight reduction in the levels of potassium, which in turn rises the levels of serum potassium with redistribution because of reduced insulin levels [17]. One meta-analysis with the SGLT-2 inhibitors including the dapagliflozin have stated that the doses of these medicines can rise the levels of magnesium by approximately 0.080-0.20 mEq/L in the patients without impairment of kidneys [18]. In this current research work, we also observed a slight rise which is consistent with the literature present in this field. The end item of the purine metabolism is uric acid. Hyperuricemia has also association with the enhanced risk of the cardiovascular complications. Decrease in the levels of serum uric acid has been stated with the SGLT-2 inhibitors because of the high urinary excretion. In this current research study, we discovered an insignificant reduction in the levels of serum uric acid [11].

In one other research study on the patients with moderate impairment of kidneys, 9.40% patients got treatment with dapagliflozin (10.0 mg) experienced fractures of bone whereas they observed no fracture in the patients treated with placebo. Moreover, 30.0% increases in the fractures of bone was observed in the patients treated with canagliflozin in other clinical trials. These medicines lead to the deficiency in the level of Vitamin-D which results in reduced density of bone minerals. Some other research works also stated that decrease in the level of bone mineral density was present with correlation to loss of body weight [14, 15]. There are contradictory results about the impacts of this category of medicines on the parameters of lipids. One research study displayed no impact dapagliflozin on LDL-C.

CONCLUSIONS:

The results of this study concluded that in the patients of diabetes with the ineffectively controlled regulations of glucose regardless of the treatment with high insulin doses, dapagliflozin may be a substitute option for the reduction of the requirement for doses of insulin, get optimal level of HbA1c, levels of fasting plasma glucose and body weight with only minor side effects.

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