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# CLINICAL TRIAL TO EXAMINE EFFECTS OF DAPAGLIFLOZIN ON HIGH DOSE INSULIN RECEIVING PATIENTS OF TYPE 2 DIABETES

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**Abstract:**

***Aim of study:*** *We held this study to examine the safety and efficiency of dapagliflozin in those patients of diabetes who are already using high dose of insulin.*

***Study design:*** *Clinical trials.*

***Study place and duration:*** *This study was conducted in Holy Family Hospital, Rawalpindi for the duration of on year starting from March, 2018 to February, 2019.*

***Methodology:*** *We included a total number of 30 patients of diabetes who were using oral antidiabetic other than SGLT 2 inhibitors and getting insulin more than 0.5 U/Kg. Observing the doses of insulin, variations of serum electrolyte and HbA1C levels with additional treatment of dapagliflozin (10mg) for the duration of 03 months was the primary end point of our study.*

***Results:*** *After the 03 months treatment with dapagliflozin (10mg) we observed reduction in BMI from 33.31 ± 4.51 to 32.14 ± 4.66 with the P-value of 0.001. We also noted the reduction in the requirement of insulin from 76 ± 23.15 U/kg to 57.60 ± 17.61 U/kg per day with the P-value more than 0.001. On the other hand, we also observed the decrease in HbA1C level as Δ1.6% and reduction in level of fasting plasma glucose as Δ68.6mg/dl with P-value less than 0.001. A little bit significant increase was observed in sodium levels and blood urea nitrogen (BUN) during the assessment of serum electrolyte levels with P-values as 0.044 and 0.026 respectively. No significant changes were observed in electrolytes like vitamin D, phosphorus magnesium, calcium and potassium while examining the serum cholesterol levels and P-value was found more than 0.05.*

***Conclusion:*** *At the end of the study we concluded that to get optimal levels of BMI, HbA1C and fasting plasma glucose with minimum side effects, dapagliflozin might be another choice of combination to reduce the need of insulin in the patients of diabetes who are already using high dose of insulin to control their inadequate sugar levels.*

**Key Words:** *High dose insulin, Dapagliflozin, Efficacy, HbA1C, fasting plasma glucose.*

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## INTRODUCTION:

In 2017 there were 451 million patients of diabetes globally and this figure was predicted to rise to 693 million by 2045 as estimated in a report by International Diabetes Federation (IDF) [1]. Diabetes mellitus (DM) is also known as a chronic metabolic disease which necessitates lifelong treatment and follow-up, categorized by partial or absolute loss of insulin excretion or reduction of the secondary effect of insulin. It is linked with the increase of both microvascular and macrovascular complications with the upsurge of mortality and morbidity [2]. With the oral antihyperglycemic medicines only >50% patients attained glycemic targets and maximum patients entailed insulin treatment [3]. Even though treatment with insulin is beneficial and its dosage can be up titrated to deal continuing decline in glycemic control with the passage of time, insulin therapy with high dose may have the risk of fluid retention, hypoglycemia and unwanted increase in weight [3].

Consequently, it is obvious that an oral antidiabetic is required in addition to treatment with insulin to reduce the necessity of insulin dosages. Dapagliflozin is an effective, extremely discriminating inhibitor of renal sodium glucose cotransporter-2(SGLT2) [4]. Dapagliflozin upsurges urinary emission of glucose by preventing renal glucose re-assimilation consequently reducing blood sugar level. It postulates extra glycemic control when used in addition with insulin and operates individualistically from the insulin action or emission [5]. Inhibition of renal sodium glucose cotransporter-2(SGLT2) may also influence sodium defecation and reabsorption that may have influences on renin angiotensin system [6].

The aim of our study was to examine the safety and efficiency of dapagliflozin in those patients of diabetes who are already using high dose of insulin. Even though some studies were conducted on the same topic but none of them assessed the effects of dapagliflozin on the insulin dose reduction in patients using high-dose insulin and serum electrolytes.

## METHODOLOGY:

We conducted this study at Holy Family Hospital, Rawalpindi for the duration of on year starting from March, 2018 to February, 2019. We included a total number of 30 patients of diabetes who were using oral antidiabetic other than SGLT 2 inhibitors and getting insulin more than 0.5 U/Kg. Age of all selected patients was in between of 18 years to 75 years. HbA1C level was from 7.5% to 12% and using insulin more than 0.5 U/kg from at least last 01 month of selection. ethical committee of services hospital Lahore duly approved contents and pattern of the study. Informed all the participants of the study about sequence of the study and took written consent from all of them.

Selection criteria was as patients using insulin with additional treatment of dipeptidyl peptidase-4 (DPP-4) inhibitor, appraised glomerular filtration rate (eGFR) of 60 ml/min/1.73m$^2$ or greater and metformin were entered in the study. Exclusion criteria was as all those patients who were having cardiovascular events like unstable angina or myocardial infarction with hospitalization, acute coronary syndrome and acute stroke, previous history of type 1 diabetes mellitus, having pregnancy and mothers performing breast feeding were not included in the study. At the beginning of our study we added dapagliflozin (10mg) in addition to the present treatments of the patients and after a period of 03 months we assessed the serum electrolyte changes, HbA1C levels and doses of insulin. We observed clear clinical for reduced titration as hypoglycemic symptoms with self-observation of blood glucose (SMBG) as more than 70mg/dL without any major changes in daily life or activities which means that patients were at a high risk of hypoglycemia.

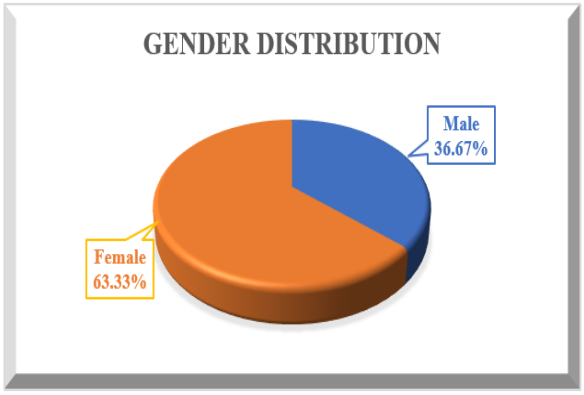
Used SPSS V.20 for analysis of all statistical data of the patients. The outcomes of all parameters related to patients were shown as Mean±SD. Values of parametric data before and after dapagliflozin therapy were analyzed through dependent T-test method. The data that was nor compatible with parametric distribution was analyzed through Wilcoxon test method. P-value of less than 0.05 was considered statistically significant. Determined the non-parametric and parametric data distributions through Kolmogorov Smirnov test method. Non-parametric values were considered having P-value of less than 0.05 and parametric data was considered having P-value of more than 0.05.

## RESULTS:

In the present study we included a total number of 30 patients of diabetes who were using oral antidiabetic other than SGLT 2 inhibitors and getting insulin more than 0.5 U/Kg with a total insulin dose as 76±23.15 and the average duration of diabetes as 11.46±6.7 months. Age of all selected patients was in between of 18 years to 75 years with the average age as 57.73±6.13 years. Gender distribution of the selected patients was as 11 males and 19 females.

**Table No 01: Gender distribution of the patients**

| Gender | Quantity | Percentage |
|---|---|---|
| **Male** | 11 | 36.67% |
| **Female** | 19 | 63.33% |




Amongst the admission time and at 03 months after the appliance of dapagliflozin therapy we examined the changes in biochemical parameters, body mass index (BMI), blood pressure levels and insulin requirements. Patients BMI was considerably reduced from 33.31±4.51 to 32.14±4.66 with a P-value of 0.001, after the 03 months of treatment with dapagliflozin therapy. As for the daily insulin consumption we observed clear reduction in the requirement of insulin as from 76±23.15U/kg/day to 57.60±17.61U/kg/day. A significant reduction was also observed in levels of fasting plasma glucose as Δ 68.6 mg/dl and HbA1C as Δ 1.6 % with the P-value less than 0.001. Results are shown below in tabular form.

**Table No 01: Effect of dapagliflozin in glucose regulations**

| Parameters | Baseline | After 3 months | P-value |
|---|---|---|---|
| Total insulin dose U/day | 76±23.15 | 57.60±17.61 | <0.001 |
| HbA1c (%) | 9.67±1.44 | 8.07±1.15 | <0.001 |
| FPG (mg/dl) | 234.7±67.89 | 166.07±43.93 | <0.001 |
| BMI (kg/m$^2$) | 33.31±4.51 | 32.14±4.66 | <0.001 |

Even though the serum hematocrit level was augmented but it was not statistically important. Conversely, the serum blood urea nitrogen (BUN) levels were expressively augmented from 14.90±3.17 to 16.66±0.54 with P-value of 0.044. Amongst serum electrolytes, serum potassium levels were augmented to some extent with P-value more than 0.05. Serum sodium (Na) was the other electrolyte that increased the levels considerably with P-value of 0.026. Serum magnesium, calcium and phosphor levels were also augmented, but not enough high to be statistically important with P-value more than 0.05. There was insignificant reduction of serum uric acid levels with P-value more than 0.05. Tabular form is shown below.

**Table No 03: Effect of dapagliflozin on serum hemogram and electrolytes**

| Parameters | Baseline | After 3 months | P-value |
|---|---|---|---|
| Creatin (mEq/L) | 0.81±0.11 | 0.84±0.12 | 0.15 |
| BUN (mEq/L) | 14.90±3.17 | 16.66±0.54 | 0.04 |
| Klorür (mEq/L) | 102.70±2.72 | 102.13±2.27 | 0.28 |
| Potassium (mEq/L) | 4.70±0.53 | 4.71±0.37 | 0.88 |
| Sodium (mEq/L) | 138.23±2.64 | 139.40±1.95 | 0.03 |
| Hematocrit (%) | 41.23±4.28 | 41.59±4.53 | 0.47 |
| Hemoglobin (g/dL) | 13.64±1.39 | 13.58±1.26 | 0.70 |
| Uric acid (mg/dL) | 5.15 ±1.41 | 4.86±1.46 | 0.23 |
| Magnesium (mg/dL) | 1.74±0.27 | 1.81±0.25 | 0.20 |
| Vitamin D (ng/ml) | 18.61±8.31 | 19.01±10.05 | 0.36 |
| Phosphate (mg/dL) | 3.89±0.76 | 4.02±0.63 | 0.48 |
| Calcium (mg/dL) | 9.53±0.57 | 9.62±0.40 | 0.44 |
| GFR (mL/min/1.73 m2) | 84.00±12.68 | 81.87±11.27 | 0.17 |

Inconsequential changes were observed amongst lipid parameters of LDL and HDL. Even though there was an apparent reduction in triglyceride level but it was still statistically not important with P-value of 0.136. Data in tabular form is presented below.

**Table No 04: Effect of dapagliflozin on lipid parameters**

| Parameters | Baseline | After 3 months | P-value |
|---|---|---|---|
| Triglyceride (mg/dL) | 199.23±100.01 | 175.89±66.83 | 0.14 |
| 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 |

## DISCUSSION:

Diabetes Mellitus (DM) is an increasing disease which frequently needs insulin treatment throughout the treatment of the disease. The important factors that bound effectiveness and optimal titration of insulin are fluid retention, hypoglycemia and weight gain [7]. As a result, there is yet a necessity of medication for Type 2 diabetes mellitus (T2DM) even with insulin dosage. Sodium glucose cotransporter 2 (SGLT2) inhibitors also known as gliflozins, that slow down re-absorption of glucose in the kidney and hence reduces blood sugar individualistically of insulin [8,9]. It has been observed in various studies that eradication of glucose via urine due to SGLT2 inhibitors results in loss of energy approximately 200 kcal to 300 kcal per day which further result as a negative balance of energy

[10]. Various other studies also presented the loss of weight normally from 2kg to 4kg, reduction of HbA1C, fasting blood glucose, improved glycemic control and slight increase in hematocrit level when added with insulin therapy [11,12].

In a study by James et al it was observed that dapagliflozin resulted a glucose induced osmotic diuresis with a little rise in BUN and low dose dependent raised hematocrit levels. Changes in estimated glomerular filtration rate and serum creatinine was clinically insignificant [13]. Treatment through SGLT2 inhibitor (canagliflozin) is related with minor surges in serum potassium concentration, particularly in patients with decreased renal function [14]. In the EMPA-REG trial, observed no change in serum potassium levels with treatment through empagliflozin and in patients with mild renal impairment dapagliflozin was not associated with serum potassium changes [15,16]. Augmented osmotic diuresis SGLT2 inhibitors and glucagon levels may result in a minor reduction of potassium levels, which in sequence, rises serum potassium levels with restructuring because of reduced insulin levels [17]. In another study analysis it was observed that dapagliflozin in addition with SGLT2 inhibitors dose addiction can upsurge magnesium levels by nearly 0.08 mEq/L to 0.2 mEq/L in patients deprived of kidney disease [18].

End-result of purine metabolism is uric acid. With association of augmented cardiovascular risks, hyperuricemia also causes gout [19]. SGLT2 inhibitors upsurge urinary excretion due to which decrease in serum uric acid levels was observed [20]. In a study on chronic kidney disease (CKD), dapagliflozin (10mg) was given to 9.40% patients and observed bone fractures whereas no fractures were spotted in patients treated with placebo [21]. Moreover, in an 8 pooled clinical trial study with longer mean duration of 68 weeks, noticed 30% increase in bone fractures where patients were treated with canagliflozin [22]. Probable cause of this complication was defined as the rise of serum phosphate which was followed by upsurge in parathormone (PTH) levels and moreover added hyperphosphatemia related to the upsurge of fibroblast growth factor-23 (FGF-23) due to which vitamin D concentrations may reduce and cause the reduction of bone mineral density [23]. On the other hand, various studies didn't authenticate the side effects on hormones regulating calcium levels or on calcium homeostasis and according to the findings of these studies reduction in BDM is surely related with loss of weight [24,25]. As per findings of our study, we didn't saw any significant change in Vitamin D levels, serum phosphate and calcium levels after the treatment of patients through dapagliflozin which was operated for 03 months.

## CONCLUSION:

we concluded in our study that to get optimal levels of BMI, HbA1C and fasting plasma glucose with minimum side effects, dapagliflozin might be another choice of combination to reduce the need of insulin in the patients of diabetes who are already using high dose of insulin to control their inadequate sugar levels.

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