

## Comparison of Effect of Sodium-Glucose Co-Transporter-2 (SGLT-2) Inhibitors with Dipeptidyl Peptidase-4 (DPP-4) Inhibitors on HbA1c Level in Type 2 Diabetes in Pakistani Population

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### ABSTRACT

**Objective:** To compare the effect of SGLT-2 inhibitors with DPP-4 inhibitors as the add on therapy to Metformin on HbA1c level in type 2 diabetes patients in Pakistani population.

**Study Design:** Quasi-experimental study.

**Place and Duration of Study:** Combined Military Hospital Sialkot, Pakistan from Nov to Apr 2020.

**Methodology:** The study population comprised of 300 type-II diabetes patients with poorly controlled diabetes on Metformin managed at Combined Military Hospital Sialkot, Pakistan. Patients were divided into two groups via lottery method. Group-A received the SGLT-2 inhibitors at standard dose while group-B received the DPP-4 inhibitors at the usual standard does as recommended by the consultant medical specialist. Values of glycosylated hemoglobin were compared three months after the start of study.

**Results:** Mean age of the patients was  $44.31 \pm 5.841$  years. Mean duration of type 2 diabetes mellitus in the study participants was  $4.18 \pm 6.369$  years. HbA1c after three months of treatment in the SGLT-2 inhibitors-group was  $7.01 \pm 0.14$  mmol/L while in the DPP-4 inhibitors-group was  $7.89 \pm 0.99$  mmol/L. Difference between the two groups was statistically significant ( $p$ -value  $< 0.01$ ). The result showed SGLT-2 inhibitors as the better option for add on therapy to Metformin as compared to DPP-4 inhibitors.

**Conclusion:** SGLT-2 inhibitors emerged as better option to lower the HbA1c level as compared to DPP-4 inhibitors as the add on therapy to Metformin as there was statistically significant difference in HbA1c levels after three months of therapy in both the groups.

**Keywords:** Dipeptidyl peptidase-4 (DPP-4) inhibitors, Sodium-glucose co-transporter-2 (SGLT-2) inhibitors, Typ-2 diabetes mellitus.

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### INTRODUCTION

Epidemiological data suggest that incidence of type 2 diabetes has been on a rise in all parts of the world including Pakistan.<sup>1,2</sup> Glycemic control has been the first and foremost goal to achieve a good control over various clinical parameters of this syndrome.<sup>3</sup> Multiple direct and indirect methods have been used to assess the glycemic control among the individuals suffering from diabetes. Glycosylated hemoglobin (HbA1c) has been one of the most widely parameters used for this purpose.<sup>4</sup>

A lot of research and clinical trials have been conducted to find the best management option for this long-standing multisystem disease. Parenteral insulin

therapy and oral hypoglycemics have been the main stay of treatment so far in this illness.<sup>5</sup> Non-pharmacological treatment is also widely advised and practiced as it usually has no adverse effects and it remains cost effective when compared to pharmacological treatment. It usually have options related to life style modifications, physical activity and dietary changes.<sup>6</sup>

New agents have been introduced in clinical practice. SGLT-2 inhibitors and DPP-4 inhibitors have been widely prescribed medications as add on therapy in last few years. Scheen in 2020 published a trial in this regard and concluded that HbA1c was slightly greater with SGLT-2 (slope:  $-0.39$ ,  $r^2 = -0.43$ ;  $p < 0.001$ ) than with DPP-4 (slope:  $-0.26$ ,  $r^2 = -0.25$ ;  $p < 0.001$ ).<sup>7</sup> Goldenberg in 2017 did a similar study and came up with the findings that both DPP-4 and SGLT-2 are effective add-on oral hyperglycemic therapies to Metformin.

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Baseline characteristics, such as HbA1C, renal functions and age, should be considered when choosing between these two classes to allow for optimal and timely diabetes management.<sup>8</sup>

Cha *et al*, observed the lipid profile with the use of both the agents. They revealed that SGLT-2 inhibitor was associated with a significant increase in HDL-C and LDL-C after 24-weeks of SGLT-2 inhibitor treatment, in the patients of type 2 diabetes when compared with with DPP-4 inhibitor.<sup>9</sup>

Cost effectiveness has been main concern of countries like ours in addition to efficacy and side effect of the medication. Shera *et al*, outlined the local practices of our country from primary to tertiary care set ups.<sup>10</sup> In Pakistan, these new agents have been used based on the evidence mostly generated by the studies done in West or other parts of the world. We therefore planned this study with the rationale to compare the effect of SGLT-2 inhibitors with DPP-4 inhibitors as the add on therapy to Metformin on HBA1c level, in the type 2 diabetes patients in our tertiary care hospital.

## METHODOLOGY

This quasi-experimental study was conducted at the Combined Military Hospital Sialkot Pakistan, from November 2019 to April 2020.

**Inclusion Criteria:** The patients of type 2 diabetes mellitus who were taking Metformin at the maximum dose but their HBA1c level was still more than 6.5%.

**Exclusion Criteria:** The patients of type 1 diabetes mellitus or those using insulin or who had suffered from diabetic coma in past three months were excluded from the study. Patients with comorbidities like HTN, IHD, RA, autoimmune illnesses, bleeding disorders and hematological or solid cancers, patients on corticosteroids, those with severe infection or signs of any end organ damage, those who had history of severe adverse effects or allergic reactions to these agents were also excluded from the study. Patients who did not adhere to medications or were lost to follow up in three months' time were also not included in the study.

Sample size was calculated by using the WHO sample size calculator taking population prevalence of 16.3.<sup>11</sup> Patients were already diagnosed cases of type 2 diabetes made by a consultant medical specialist or diabetes expert.<sup>12</sup>

Five milliliter of venous blood was drawn and secured in two separate K2-EDTA filled plastic vacutainer tubes by venipuncture under aseptic precautions for the measurement of HBA1c in patients of both

groups after three months of the designated treatment. Technique of high-performance liquid chromatography was used to measure the levels of glycosylated hemoglobin the sample.<sup>13</sup>

Patients were provided with a detailed description of the study and were inducted into the study after the written informed consent. Patients of type 2 DM, not achieving glycemic control with maximum dose of metformin were randomly divided into equal groups via lottery method. Group-A patients received the SGLT-2 (Dapagliflozin) inhibitors while group-B patients received DPP-4 (sitagliptin) inhibitors in a standard dose in addition to metformin they were already taking.<sup>14,15</sup> Difference in the glycemic control of both the groups was assessed with the help of glycosylated hemoglobin level after three months of the designated treatment.

All the statistical analysis was performed by using Statistical Package for Social Sciences (SPSS) version 24. Frequency and percentages were calculated for the gender of the patients and type of medications they received in the study. Mean and standard deviation were calculated for age of the patients, duration of diabetes mellitus and HBA1c levels done after three months of the allocated treatment. Difference in mean HBA1c levels of both the groups was compared by using the student t-test. The *p*-value of  $\leq 0.05$  was considered statistically significant.

## RESULTS

A total of 330 patients with poorly controlled type 2 DM on metformin were approached to participate in the study. Thirteen refused to the add on oral medications and preferred insulin and 17 were ineligible due to exclusion criteria. Therefore, 300 patients participated in this study and were randomly divided into two groups via lottery method. 161 (53.7%) received the SGLT-2 inhibitors while 139 (46.3%) received DPP-4 inhibitors as the add on therapy to Metformin to control the type 2 DM. Mean age of the patients was  $44.31 \pm 5.841$  years (Table-I).

Mean duration of DM in the study participants was  $4.18 \pm 6.369$  years. Out of 225 (75%) patients were males while 75 (25%) were females. HBA1c level after three months of treatment in the SGLT-2 inhibitors-group was  $7.01 \pm 0.14$  while in the DPP-4 inhibitors-group was  $7.89 \pm 0.99$  (Table-II). Difference between the two groups was statistically significant (*p*-value  $< 0.01$ ), showing SGLT-2 inhibitors as the better option as add on therapy to Metformin when compared to DPP-4 inhibitors.

**Table-I: Characteristics of study participants n=300.**

Parameters	n (%)
<b>Age (Years)</b>	
Mean ± SD	44.31 ± 5.841
Range (min-max)	29-58 years
<b>Gender</b>	
Male	225 (75%)
Female	75 (25%)
Duration of Diabetes mellitus	4.18 ± 6.369 years 12 months - 15 years
<b>Add on Therapy</b>	
SGLT-2 inhibitors	161 (53.7%)
DPP-4 inhibitors	139 (46.3%)

**Table II: Comparison of HBA1c levels of both groups.**

	Group A n=161	Group B n=139	p-value
HBA1c	7.01 ± 0.14	7.89 ± 0.99	<0.001

## DISCUSSION

Metformin has been the first line of treatment when any patient is diagnosed with type 2 DM in our setup. It is efficacious and cost-effective option for a country like ours with limited health care budget.<sup>16</sup> Considerable number of patients may not respond to even maximum dose of Metformin and might need add on therapy for adequate glycemic control. A lot of oral hypoglycemic medications have been used in the past by the diabetic physicians. They all have their own merits and demerits. Past few years may be considered as an era for the use of new oral hypoglycemics like SGLT-2 inhibitors and DPP-4 inhibitors. These drugs have been first choice of a lot of physicians as the add on therapy to Metformin. This practice has usually been based upon the data generated by studies done in other parts of the world. We therefore decided to conduct this study in our own population with the rationale to compare the effect of SGLT-2 inhibitors with DPP-4 inhibitors as the add on therapy to Metformin on HBA1c level in type 2 diabetes of Pakistani population.

Wang *et al*, analyzed 25 randomized trials, which involved 14,619 patients.<sup>17</sup> They found out that SGLT-2 inhibitors were associated with a significantly stronger reduction in hemoglobin A1c (HbA1c) (WMD 0.13%, 95% CI, 0.04-0.22%,  $p=0.005$ ) and fasting plasma glucose (FPG) (WMD 0.80 mmol/L, 95% CI, 0.58-1.01 mmol/L,  $p<0.001$ ) than were DPP-4 inhibitors. However, no significant difference between the 2 drug categories was found in the risk of hypoglycemic events (RR, 0.99; 95% CI, 0.78-1.26,  $p=0.92$ ). SGLT-2is with Metformin was associated with a more significant decrease in FPG (WMD 0.71 mmol/L, 95% CI, 0.43-1.00

mmol/L,  $p<0.001$ ) than was DPP-4is with Metformin. However, no differences were found in the reduction of HbA1c (WMD 0.11%, 95% CI, -0.03%-0.25%,  $p=0.12$ ) or the risk of hypoglycemic events (RR, 1.02; 95% CI, 0.80-1.31,  $p=0.86$ ). Our results were also in accordance with their analysis as SGLT-2 inhibitors were more effective in achieving a better glycemic control as compared to DPP-4 inhibitors.

A systematic review conducted by Scheen,<sup>7</sup> compared the reduction of glycated hemoglobin (HbA1c) with sodium-glucose cotransporter type-2 inhibitors (SGLT2is) with dipeptidyl peptidase-4 inhibitors (DPP-4is) as add on to Metformin in patients with type 2 diabetes mellitus (T2DM), with a specific focus on HbA1c changes according to baseline HbA1c. It concluded that the small difference in the baseline HbA1c level with SGLT2is with DPP-4is as add-ons to metformin.<sup>7</sup>

Goring *et al*,<sup>18</sup> to estimate the effect of dapagliflozin, a new agent with a novel mechanism of action (SGLT-2 inhibition), relative to other anti-diabetes therapies after one year of treatment. They concluded that compared with DPP-4 inhibitors, thiazolidinediones and sulphony-lureas, dapagliflozin offers similar HbA1c control after one year, with similar or reduced risk of hypoglycemia and the additional benefit of weight loss, when added to metformin.<sup>18</sup> Our aim was to compare SGLT-2 inhibitors with DPP-4 inhibitors and that too after three months and in that SGLT-2 were clearly superior.

## LIMITATIONS OF STUDY

This study had certain limitations. Follow up period was short, therefore we could not observe the long term effects on glycemic control by both the agents. Moreover, adverse effects and dropouts were not compared in both the groups which are most important considerations in order to generalize the data about the use of any medication. Studies in future may address these complications and generate better results to make clinical guidelines for our own population suffering from this chronic illness.

## CONCLUSION

SGLT-2 inhibitors emerged the better option to lower the HBA1c level as compared to DPP-4 inhibitors as the add on therapy to Metformin as there was statistically significant difference in HBA1c levels after three months of therapy in both the groups.

**Conflict of Interest:** None.

## Authors' Contribution

MAMUQ:, TS:, AK:, KRB:, EA:, AR: Direct contribution.

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