Sodium Glucose Transporter 2 Inhibitor (SGLT2) Dapagliflozin in Diabetes: An Update of AACE 2016

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Abstract: This review provides an overview of the novel mechanism of action of SGLT2 inhibitors, discusses how these drugs may contribute to hyperglycemia management in patients with Diabetes Mellitus (DM). This review summarizes the most current clinical data available on the SGLT2 inhibitors. Dapagliflozin is the first SGLT2 inhibitor introduced in India in April 2015. In the first study authors investigate whether the addition of Dapagliflozin, a SGLT2 inhibitor to insulin and liraglutide would further improve glycemic control. In another study authors assessed the effectiveness of dapagliflozin in Asian Indian patients with type 2 diabetes. The primary objective was to study the change in HbA1c and secondary objectives were the change in body weight, blood pressure and decrease in the ongoing therapy requirements.

Keywords: SGLT2, T2DM, T1D, AACE , ADA , EASD

Introduction: Type 2 diabetes mellitus (T2DM) rates have increased dramatically over the past 30 years (1) and have generally paralleled the worldwide epidemic of obesity (2). Worldwide projections suggest that 592 million people will have T2DM by 2035, and another 471 million people will have impaired glucose tolerance and will thus be at high risk of developing T2DM in subsequent years (3).The sodium glucose cotransporter 2 (SGLT2) inhibitors are a novel class of oral antihyperglycemic medications that lower ambient blood glucose levels through an insulin-independent mechanism by inhibiting proximal tubular reabsorption of glucose in the kidney, resulting in glucosuria. Thus, these agents hold some promise as adjunct therapy to insulin in type 1 diabetes owing to an insulin-sparing effect with overall reduction in glucose levels and glycated hemoglobin A1c (HbA1c), reduced total daily insulin usage and modest weight reduction (4,5), and possibly even decreasing the rate of progression of diabetic nephropathy (6). SGLT2 inhibitors were incorporated into the 2015 American Diabetes Association (ADA)/European Association for the Study of Diabetes (EASD) position statement on the management of hyperglycemia and received an even more prominent position in the American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) comprehensive diabetes management guidelines and algorithm. (Endocr Pract. 2015;21:1054-1065)

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Effect of Dapagliflozin in addition to Liraglutide and Insulin in Patients with Type 1 Diabetes

In this study 30 patients with T1D on insulin and liraglutide therapy for at least last 6 months were randomized (in 2:1 ratio, drug: placebo) to receive either dapagliflozin 10mg or placebo daily for 12 weeks. Dapagliflozin was initiated at 5 mg daily for one week and increased to 10 mg daily thereafter. This study completed by 26 Patients (Placebo=9; Dapagliflozin = 17).

Results of this study shows that All patients had T1D for at least one year, on insulin therapy and had no detectable c-peptide in plasma and were on 1.8 mg of liraglutide for 7±1 months(mean body weight:82.69±3.43 kg; mean HbA1c:7.68±0.15%, mean weekly glucose levels: 163±6 mg/dl ,total insulin dose: 52.3±4.8 units, mean age:54±2 years, mean age at T1D diagnosis: 29±2years, mean BP:122±2/76±1 mmHg, 8 males,17 females,23 Caucasian,1 African American and 1 Asian) with no difference in these parameters between the two groups. HbA1c fell by 0.6±0.08% in the dapagliflozin group($p<0.01$ vs placebo) with no changes in placebo group. The average weekly glucose concentration fell in the dapagliflozin group by 15±6 mg/dl($p<0.05$ vs baseline, $p=0.07$ vs placebo) with no changes in placebo group. There was no additional hypoglycemia(<70 mg/ dl; $p=0.52$ vs placebo). The basal insulin dose fell by 0.72±0.96 from 33.70±4.53 units while it increased by 1.9±0.5 units($P<0.01$ vs baseline) in placebo($p<0.05$ vs placebo). However, total insulin dose remained unchanged in both groups. The body weight fell by 1.9±0.54kg($p<0.05$ vs placebo) in the dapagliflozin group while it remained unchanged in placebo group. The total cholesterol and LDL cholesterol increased by 6 and 8% from 167±8 and 90±7 mg/dl($p<0.01$ vs placebo for both) in dapagliflozin group while it decreased by 11 and 17% in the placebo group($p<0.05$ for both vs baseline) from 176±11 and 89±8 mg/dl respectively.Two of the drop-out patients in Dapagliflozin group developed DKA (one patient with euglycemic DKA with total insulin dose reduced from 33 to 26 units and the other with hyperglycemic DKA with total insulin dose unchanged at 26 units) within 24 hours of increasing the dose to 10 mg daily.

Discussion: Care has to be exercised in terms of the reduction in the insulin dose and increasing dapagliflozin dose to prevent the occurrence of DKA (7).

Efficacy and Safety of Dapagliflozin- In Type 2 diabetes Indian Patients

In this study authors evaluated the real world efficacy and safety of dapagliflozin amongst the continuous dapagliflozin users (defined as continuous treatment at 12 weeks). It was used as an add on drug to the ongoing therapy. The data was collected retrospectively from patient records. Data is presented as mean± SD and comparison between the groups has been done using Mann-Whitney and Fisher's exact test.

Results of this study shows that the study participants (n=59) had a mean age of 54.2 ± 10.56 years, diabetes duration 13.2 ± 7.9 years(CI 11.2-15.3), body weight 77.3 ± 12.8 kg (CI 74.4-81.1), BMI 30.2 ± 4.6 kg/m2 (CI 29-31) and HbA1c of 8.6 ± 1.5% (CI 8.3-9.1). HbA1c reduced significantly as compared to the baseline (7.6 vs 8.7%, difference -1.1) ($p<0.0001$). The proportion of patients attaining the goal of HbA1c level < 7.0% trebled (5 patients to 15 patients) after 12 weeks. The mean reduction in the body weight (1.64 kg; $p=0.48$) and the mean reduction in blood pressure (systolic -2.05 mmHg; diastolic -1.3 mmHg; $p=0.49$) were not statistically significant. The sulphonylurea usage dropped in 55% of patients with continued use of metformin (94%) and DPP IV inhibitors (98%) in most of the patients. Insulin use could not be commented upon as most patients were not on a stable insulin dose when started on dapagliflozin (8).

Conclusion: Addition of dapagliflozin to insulin and liraglutide in patients with T1D results in significant improvement in glycemia. At the end of 3 months of evaluation, dapagliflozin resulted in significant HbA1c reduction (consistent with previous studies) irrespective of gender, age, duration of diabetes, or BMI. Dapagliflozin was well tolerated, with adverse events consistent with previous studies. Only 1 patient reported mild urinary tract infection; none developed diabetic ketoacidosis or severe urosepsis after 3 months of use. Dapagliflozin is useful in the Indian setting for improved glycemic control; with additional reduction in systolic and diastolic BP and weight. Dapagliflozin can be effectively and safely combined with other agents, including insulin, sulphonylureas, metformin, DPP4 inhibitors; and can be used either as monotherapy, or in dual or triple agent combinations. This study is limited for a short follow up. However, this is perhaps the first largest real time, interim evaluation of the effectiveness of dapagliflozin in Indian setting.

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