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Comparison of the effects of sitagliptin and dapagliflozin on Adiponectin and Lipid Profile

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Abstract

Introduction: Type 2 diabetes mellitus (T2DM) is an acquired form of diabetes often associated with being overweight and having an unhealthy lifestyle with respect to diet and exercise. It also shows a stronger association of onset with increasing age and is more common in certain ethnic groups such as South Asian and Afro-caribbeans. Although SGLT2 inhibitors have become an early recommended drug for patients with type 2 diabetes at a high risk of cardiovascular events, its effectiveness as a first-line medication for patients with newly diagnosed type 2 diabetes with no history of cardiovascular events is unclear. Dapagliflozin is a selective inhibitor of SGLT2 and acts to reduce hyperglycemia independently of insulin secretion or action. Dapagliflozin reduces systemic glycemic load by inhibiting this transporter, allowing some filtered glucose to pass into the urine for elimination. **Material and Methods:** This is a Prospective, randomized, Open-label was conducted in Type 2 DM patients attending the outpatient department of Medicine in Index Medical College and Hospital over a period of 2 years. All the Type 2 DM patients attending outpatient department (OPD) of Medicine were randomly divided into Dapagliflozin Group and Sitagliptin Group. The treatment drug (dapagliflozin 5.0 mg/day and sitagliptin 50 mg/day) was administered for 12 weeks. Follow-up visits were scheduled at the end of every month for 12 weeks for assessment, including measurement of weight and general and systemic examination. The following laboratory investigation was performed on sample of Type 2 DM patients before and after Dapagliflozin and Sitagliptin therapy. Adiponectin was estimated by DRG Diagnostic adiponectin Enzyme linked immune sorbent assay (ELISA) Kit. (B-Bridge International Inc., San Jose, CA, USA) with range of assay between 83-104 pg/Ml. **Results:** In our study body weight was 81.7 ± 8.3 kg in Dapagliflozin group and Sitagliptin group was 79.5 ± 7.10 kg. However, there were no significant differences in the changes in these metabolic parameters among the two study groups. Body mass index (kg/m^2) was 24.9 ± 6.7 in Dapagliflozin group and Sitagliptin group was 24.3 ± 8.8. Hypertension was seen in 25 (17.9%) in Dapagliflozin group and Sitagliptin group was 60 (42.9). However, there were no significant differences between among two study groups. The change in serum adiponectin level from baseline to week 12 increased significantly only in the dapagliflozin group (P = 0.004) (Table 4). The mean ± SD change in Serum adiponectin at 12 weeks from baseline to 12 weeks were 0.75 ± 1.03 and 0.11 ± 0.05 in the dapagliflozin and sitagliptin groups, respectively. The subgroup analysis results for patients categorized according to their

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Lipid Profile at baseline into two groups. The changes in Lipid Profile from baseline to week 12 improved in two study groups. **Conclusion:** Dapagliflozin significantly reduced body weight and insulin AUC levels and improved serum adiponectin levels without inducing hypoglycemia. These results suggest that along with metformin and DPP-4 inhibitors, SGLT2 inhibitors could be a viable first-line treatment option for drug-naïve Japanese patients with type 2 diabetes because of their optimum glucose-lowering properties, ability to avoid hypoglycemia or weight gain, and tolerability over a wide range of ages.

Keyword: Sitagliptin, Dapagliflozin, Adiponectin, Lipid Profile

Abstract

Introduction

Type 2 diabetes mellitus (T2DM) is an acquired form of diabetes often associated with being overweight and having an unhealthy lifestyle with respect to diet and exercise. [1] It also shows a stronger association of onset with increasing age and is more common in certain ethnic groups such as South Asian and Afro-caribbeans. [2-4] Prevalence is highest amongst South Asians and Afro-Caribbeans settled in westernized countries further highlighting the importance of lifestyle in the development of this disease. [5] T2DM typically develops later in life and hence is sometimes referred to as maturity onset diabetes, though diagnoses of the disease are becoming common at younger ages possibly, in part, due to increasing childhood obesity. [6]

T2DM has a slower rate of progression to severity, hence the majority of individuals are often diagnosed during routine screening and are often asymptomatic at diagnosis. Though the level of hyperglycaemia they experience may not be sufficiently severe to manifest in symptoms, it is still capable of inducing longer term organ damage. [7] These individuals do not require insulin immediately. However, depending on how well they manage the disease with lifestyle alterations and various non-insulin medications, they can often progress to needing insulin therapy at some stage in life. [8]

Based on these findings, in recent years, American and European diabetes and cardiology society guidelines and consensus reports recommend the use of SGLT2 inhibitors for patients with type 2 diabetes who have atherosclerotic cardiovascular disease (ASCVD) or those at risk. [8] Although SGLT2 inhibitors have become an early recommended drug for patients with type 2 diabetes at a high risk of cardiovascular events, its effectiveness as a first-line medication for patients with newly diagnosed type 2 diabetes with no history of cardiovascular events is unclear. [9]

Dapagliflozin is a selective inhibitor of SGLT2 and acts to reduce hyperglycemia independently of insulin secretion or action. Dapagliflozin reduces systemic glycemic load by inhibiting this transporter, allowing some filtered glucose to pass into the urine for elimination. [10] Reduction in HbA_{1c} with dapagliflozin was relatively consistent across randomized, controlled, clinical trials in a variety of settings from treatment-naive patients to first add-on to metformin, sulfonylurea, or pioglitazone, and to patients requiring insulin, with or without concomitant OADs. [11] The blood glucose–lowering effect of dapagliflozin after 6 months of treatment was similar to that of metformin-XR monotherapy and, after 1

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year of treatment, was similar to glipizide in patients poorly controlled on metformin monotherapy. [12]

Material and Methods:

This is a Prospective, randomized, Open-label was conducted in Type 2 DM patients attending the outpatient department of Medicine in Index Medical College and Hospital over a period of 2 years.

Inclusion Criteria:

- Male or female patients between 18 to 60 years of age.
- Patients with type 2 diabetes who had not used any glucose-lowering agents within 8 weeks before consenting, or those who had used only metformin;
- Patients those with HbA1c (NGSP values) levels of $\geq$ 7.1%.
- Patients willing to take medications as directed & willing to come for the follow-

Exclusion Criteria:

- Patients with history of Alcohol intake & Smoking.
- Patients with known history of Diabetes and hypertension.
- Patients with severe cardiac, liver and renal disease.
- Patients with GIT diseases.
- Patients with a history of lactic acidosis
- Patients with hypothyroidism and hyperthyroidism
- Patients taking vitamin B_{12}, folate, steroid, oral contraceptives & hormone replacement therapy
- Pregnant and breast-feeding females.
- Patients with polycystic ovarian disease.

Subjects:

- All the Type 2 DM patients attending outpatient department (OPD) of Medicine were randomly divided into Dapagliflozin Group and Sitagliptin Group.
- Subjects willing to participate and written informed consent was obtained from each participant before study.
- Permission from treating consultant was obtained for subjects to participate in the study.
- Subjects were screened for selection criteria. Baseline evaluation included recording of demographic details, BMI, medical history, general and systemic examination and laboratory investigations, which included complete haemogram, hepatic and renal function tests and routine urine analysis. The eligible patients were enrolled as randomization.

Treatment:

The treatment drug (dapagliflozin 5.0 mg/day and sitagliptin 50 mg/day) was administered for 12 weeks.

Follow-up Visits:

Follow-up visits were scheduled at the end of every month for 12 weeks for assessment, including measurement of weight and general and systemic examination.

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Biochemical Parameters:

The following laboratory investigation was performed on sample of Type 2 DM patients before and after Dapagliflozin and Sitagliptin therapy.

Adiponectin was estimated by DRG Diagnostic adiponectin Enzyme linked immune sorbent assay (ELISA) Kit. (B-Bridge International Inc., San Jose, CA, USA) with range of assay between 83-104 pg/Ml.

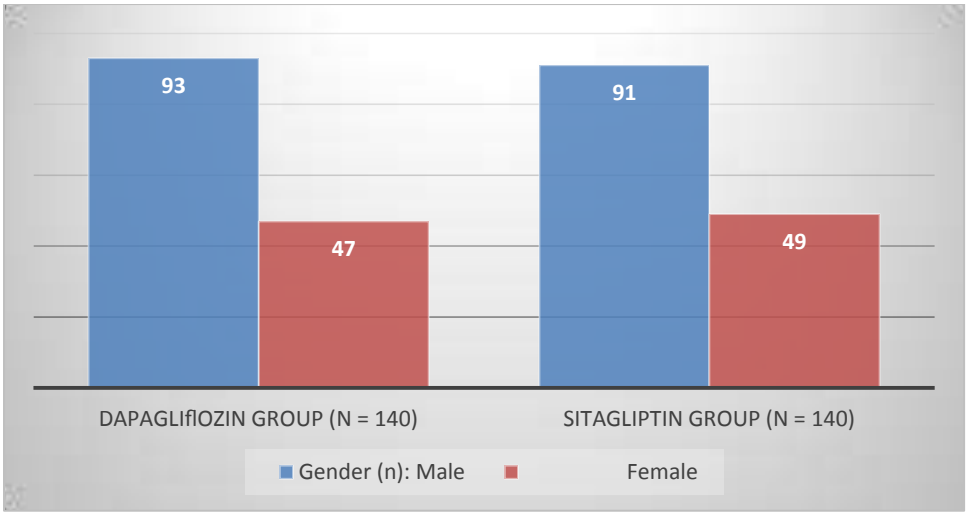
Statistical Analysis:

The collected data was compiled in MS Excel sheet for analysis in Statistical Package for the Social Sciences (SPSS) version 25th was applied. The qualitative data was represented in the form of frequencies and percentage also represented in visual impression like bar diagram, pie diagram etc. For quantitative data was represented in the form of mean and standard deviation. To check significance difference between baseline and after three months effect of Dapagliflozin and Sitagliptin group on various parameters level in Type 2 DM patient. A paired 't' test was applied and also quantitative data was represented in the form of pie diagram and bar diagram. p value was check at 0.05 % level of significance.

Results

Patient were randomly assigned to receive dapagliflozin 5 mg (n = 140), sitagliptin 50 mg (n = 140).

Graph 1 Baseline characteristics of the study participants



In **Graph** 1, Mean age among Dapagliflozin group was 57.7 ± 7.3 years and Sitagliptin group 55.9 ± 6.6 years. Whereas, there were no significant differences between two groups. parameters among the two study groups. In our study 93 were male and 47 were female among Dapagliflozin group and in Sitagliptin group was 91 was male and 49 were female.

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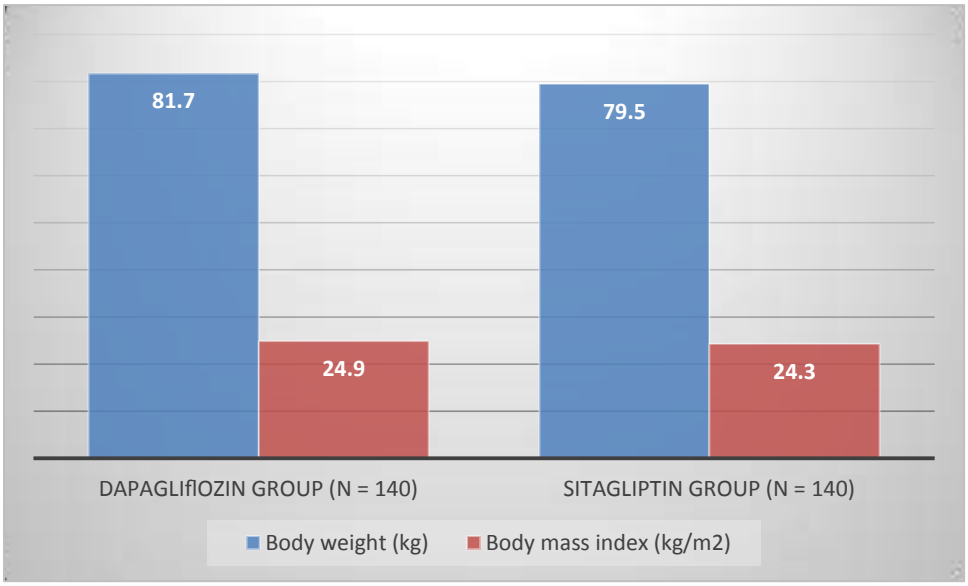
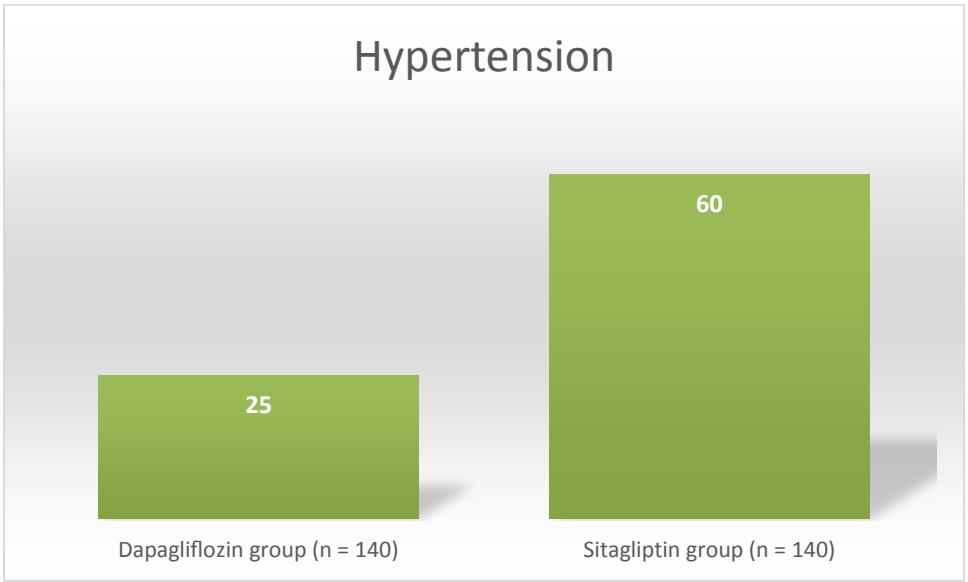
Graph 2 Baseline characteristics of the study participants of Body weight and BMI



In **Graph** 2 body weight was 81.7 ± 8.3 kg in Dapagliflozin group and Sitagliptin group was 79.5 ± 7.10 kg. However, there were no significant differences in the changes in these metabolic parameters among the two study groups. Body mass index (kg/m^2) was 24.9 ± 6.7 in Dapagliflozin group and Sitagliptin group was 24.3 ± 8.8.

Graph 3 Baseline characteristics of the study participants of Comorbidities



In **Graph** 3, Hypertension was seen in 25 (17.9%) in Dapagliflozin group and Sitagliptin group was 60 (42.9). However, there were no significant differences between among two study groups.

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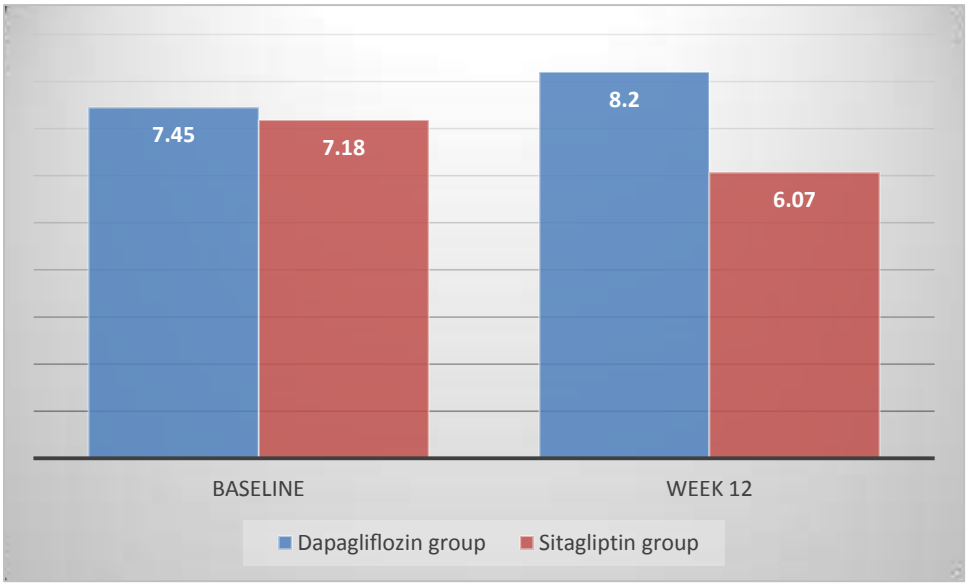
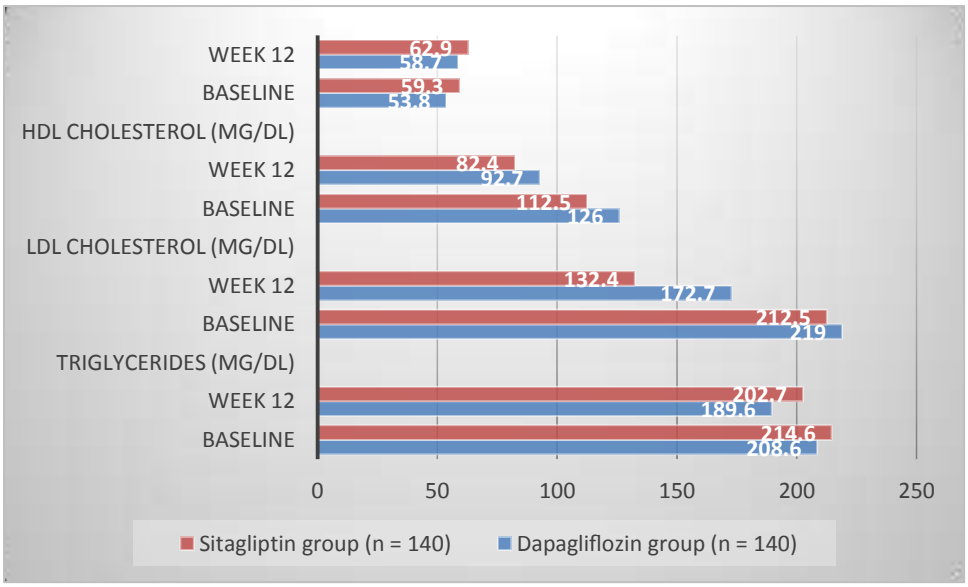
Graph 4 Effects of dapagliflozin and sitagliptin on Serum adiponectin at 12 weeks



The change in serum adiponectin level from baseline to week 12 increased significantly only in the dapagliflozin group (P = 0.004) (Table 4). The mean ± SD change in Serum adiponectin at 12 weeks from baseline to 12 weeks were 0.75 ± 1.03 and 0.11 ± 0.05 in the dapagliflozin and sitagliptin groups, respectively.

Graph 5 Effects of dapagliflozin and sitagliptin on Lipid profile at 12 weeks



In **Graph** 5 shows the subgroup analysis results for patients categorized according to their Lipid Profile at baseline into two groups. The changes in Lipid Profile from baseline to week 12 improved in two study groups.

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Discussion

In our study, body weight was 81.7 ± 8.3 kg in Dapagliflozin group and Sitagliptin group was 79.5 ± 7.10 kg. However, there were no significant differences in the changes in these metabolic parameters among the two study groups. Body mass index (kg/m^2) was 24.9 ± 6.7 in Dapagliflozin group and Sitagliptin group was 24.3 ± 8.8. Several reports on the effects of DPP-4 inhibitors on the glycaemic control of patients stratified by BMI suggest that patients with a lower BMI tend to have better glycaemic control than do those with a higher BMI. [13] In addition, a previous systematic review and metaanalysis suggested that DPP-4 inhibitors exhibit a better response to glucose-lowering efficacy in Indian populations than in other ethnic groups. Asian groups tended to have a lower BMI than other ethnic groups. [14]

In our study, dapagliflozin was more effective than sitagliptin not only regarding body weight reduction but also regarding the decrease in fasting plasma glucose level, and fasting plasma insulin level. These results are consistent with those of previous reports that SGLT2 inhibitors ameliorate hepatic steatosis and improve insulin sensitivity. [15] Both hepatic steatosis and insulin resistance are known risk factors of cardiovascular disease. [16] Taken together, these data suggest that dapagliflozin might indeed be superior to sitagliptin for the cardiometabolic effects. In addition, previous studies reported the preferable cardiometabolic effects regarding SGLT2 inhibitors. [17]

The change in serum adiponectin level from baseline to week 12 increased significantly only in the dapagliflozin group (P = 0.004) (Table 8). The mean ± SD change in Serum adiponectin at 12 weeks from baseline to 12 weeks were 0.75 ± 1.03 and 0.11 ± 0.05 in the dapagliflozin and sitagliptin groups, respectively. The present study revealed that dapagliflozin exerts a glucose-lowering effect comparable to that of the alternative first-line medications, metformin and sitagliptin. Besides its hypoglycemic action, dapagliflozin significantly lowered body weight and increased serum adiponectin levels in participants. It has also been suggested that dapagliflozin may protect pancreatic β cells by diminishing plasma insulin levels, which may be a pivotal feature to control type 2 diabetes patients for a long time.

Dapagliflozin also showed stronger therapeutic effects on other indices that might contribute to the prevention of cardiovascular events. For example, the increase in HDL cholesterol was significantly more pronounced in the dapagliflozin group than in the sitagliptin group. Previous studies reported that an increase in HDL cholesterol concentration is associated with a decrease in the risk of coronary artery disease. [18] The increase in hematocrit count was also significantly more pronounced in the dapagliflozin group. Ferrannini et al. indicated that SGLT2 inhibitors may increase hematocrit count by stimulating erythropoiesis, which increases oxygen transport to the tissues and protects from cardiovascular events. [19]

Our present study was the first to compare the efficacy of dapagliflozin and sitagliptin in terms of glucose fluctuation evaluated using the Freestyle device. Nevertheless, the change in HbA1c level was comparable between the groups and dapagliflozin provided a larger reduction in fasting plasma glucose. Taken together, these findings suggest that sitagliptin

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might predominantly lower postprandial blood glucose and suppress glucose fluctuation. As increased glucose variability was reportedly associated with increased risk of cardiovascular events, [20] sitagliptin might also contribute to the prevention of cardiovascular events through suppression of glucose variability, at least partly.

Furthermore, the glycemic response to DPP-4 inhibitors is larger in Asian subjects than in other races. [21] Therefore, our findings that HbA1c level reduction was comparable between the groups and that the improvement in glucose variability was better for sitagliptin may not apply fully to Caucasians.

Conclusion

In conclusion, to the best of our knowledge, this is the first study to directly compare the effects of sitagliptin and dapagliflozin on glycaemic control using Glucose stratified by BMI in Indian participants with early-stage type 2 diabetes. The response after 24 weeks of treatment was not significantly different between the sitagliptin and dapagliflozin groups. However, in the lower BMI subgroup, sitagliptin demonstrated superior efficacy in improving glycaemic variability than did dapagliflozin. Finally, our results demonstrated that, for the treatment of Indian patients with early-stage type 2 diabetes, patients should be stratified according to baseline BMI when selecting between sitagliptin and dapagliflozin.

Furthermore, dapagliflozin significantly reduced body weight and insulin AUC levels and improved serum adiponectin levels without inducing hypoglycemia. These results suggest that along with metformin and DPP-4 inhibitors, SGLT2 inhibitors could be a viable first-line treatment option for drug-naïve Japanese patients with type 2 diabetes because of their optimum glucose-lowering properties, ability to avoid hypoglycemia or weight gain, and tolerability over a wide range of ages.

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