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Original Research Article

Comparison of the Efficacy and Safety of Various Oral Antidiabetic Drug Regimens Used for Type - 2 Diabetes Mellitus - in a Tertiary Care Hospital in South Delhi

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Abstract

Objectives: Aim of this study was to evaluate efficacy and safety of various oral antidiabetic drugs/regimens used for Type-2 diabetes patients. The primary objectives were to compare fasting blood glucose (FBS), post prandial blood glucose (PPBS), and glycosylated haemoglobin (HbA1c). Secondary objectives were to compare Body weight (kg), vitals (blood pressure in mmhg) and to identify adverse drug reactions (if present) in all groups.

Methods: This is a prospective observational study conducted in Medicine OPD of a tertiary care Hospital in South Delhi over a period of 17 months. All the patients receiving oral anti diabetics were enrolled. The patients receiving injectable antidiabetic drugs were excluded. Patients were followed for 3 visits after the first visit, reviewed after every 12 weeks. All the necessary information were recorded in case record form that includes demographic details (age, gender etc), concomitant medication history, past medical history, vitals, physical examination (body weight[kg]) and relevant laboratory reports (FBS [mg/dl], PpBS [mg/dl], glycosylated haemoglobin [%]).

Results: A total of 248 patients were enrolled in our study and drugs received by the patients were found to be Biguanides(25%), Biguanides + Sulfonylureas (25.4%), Biguanides + Sodium Glucose co transporter (SGLT2) inhibitors (25.4%), Biguanides + Dipeptidyl peptidase (Dpp4) inhibitors (24.1%). A significant reduction in FBS, PPBS, and HbA1c was seen in all groups of patients. Adverse drug reactions were hypoglycemia, dizziness, urinary tract infections and Gastric side effects distributed in different groups. Maximum reduction in body weight in patients receiving B+SGLT2i was seen and weight increase was seen in the patient group receiving B+Su.

Conclusion: Overall, all classes of drugs showed efficacy in reducing glycemic parameters and body weight with SGLT2i showing maximum effect. Sulfonylureas were commonly associated with hypoglycemia and Sglt2i were associated with urinary tract infections.

Keywords: Type-2 Diabetes, Oral Antidiabetic Drugs.

Introduction

T2DM is a complex endocrine and metabolic disorder in which the interaction between genetic, environmental factors and behavioural factors, including a sedentary lifestyle and energy-rich, nutrient-poor diet, both of which predispose to obesity and hence generate a heterogeneous and progressive pathology with varying degrees of insulin resistance and dysfunction of pancreatic β cells and α cells, as well as other endocrine disturbances. The short-term as well as long-term benefits of improving glycaemic control results in delaying the onset and reducing the severity of diabetes-related complications, particularly retinopathy, nephropathy, neuropathy and cardiovascular disease. Metformin is the first treatment choice for T2DM patients, as standard treatment guidelines [1]. A combined approach using oral antidiabetic agents with different mechanisms of action is supposed to be adopted as monotherapy or increasing the therapeutic dose of metformin does not always effectively control blood glucose levels. The oral route of antidiabetic agents is widely used because of high patient adherence; the currently approved second-line oral antidiabetic agents include sodium-glucose co-transporter-2 (SGLT-2) inhibitors, dipeptidyl peptidase 4 (DPP-4) inhibitors, thiazolidinediones (TZDs), sulfonylureas (SUs), alpha-glucosidase inhibitors (AGIs), and meglitinides. Multiple factors are considered while selecting the second-line oral antidiabetic drug (OAD). To provide the most benefit of treatment to the patients, the attending clinician must balance the key factors such as patient compliance, glycemic control effect, drug-to-drug interactions, and other side effect profiles of the above-mentioned hypoglycemic agents. As it has become important to evaluate the benefits of oral antidiabetic drugs in patients, a comparative study is advantageous in choosing the right drug for the obese patient to reduce weight or put weight in control. The present study is aimed to analyse and compare the efficacy and safety of oral antidiabetic agent/agents in Type 2 Diabetes patients with or without being overweight. The objectives are to compare Fasting & Post prandial blood sugar levels (FBS & PPBS), to compare body weight in all groups, and to identify glycosylated haemoglobin levels (HbA1c) & adverse drug reactions (if present) in all the groups.

Methodology

A prospective observational study was carried out at a tertiary care hospital in South Delhi after getting approval from the Ethical committee for a period of 17 months. Patients with Type 2 Diabetes Mellitus of all sexes and age >18 years and are on oral anti-diabetic agents were included in the study. Patients with Type 1 Diabetes Mellitus and patients with insulin therapy or any other injectable anti-diabetic medication were excluded from this study. All patients visiting the Medicine OPD were reviewed on a daily basis and those who met our study criteria were enrolled in our study. An informed consent was obtained from the patients if they agreed to be part of our study. Patient demographics, past medical history, and current treatment charts were recorded in case record form. Investigations at baseline that were relevant such as Fasting Blood Glucose (FBS), Post Prandial Blood Glucose (PPBS), and Glycosylated Haemoglobin (HbA1c) along with the physical examination and vitals examination were done and noted initially, and later on, were reviewed in next 3 visits (each visit 12 weeks± 5 days). Patients were also interviewed regarding any kind of adverse drug reaction throughout the study. Based on the pharmacotherapy received, patients were divided into 4 groups, Group 1 using only Biguanides (B), Group 2 using

Biguanides + Sulfonylureas(Su), Group 3 using Biguanides + Sodium Glucose co Transporter 2 inhibitors (SGLT2i), and Group 4 using Biguanides + Dipeptidyl Peptidase 4 inhibitor (DPI). Efficacy parameters (FBS, PPBS, HbA1c), Safety Parameters (adverse drug reactions) and Body weight changes are compared in three visits. To determine the level of significance in treatment groups before and after follow up ANOVA was used using SPSS 29. To determine the burden of adverse drug reactions, incidence rates were calculated. Follow up chart is given in Table 1

Table1: Patients follow-up chart

Monitoring Parameters	Visits			
	Baseline	1 (12 weeks)	2 (24 weeks)	3 (36 weeks)
Body weight	√	√	√	√
FBS	√	√	√	√
PPBS	√	√	√	√
HbA1c	√	√	√	√
ADR collection	√	√	√	√

Results

In our study a total of 1080 patients were reviewed, out of which 110 were excluded (10.1%) due to Type 1 Diabetes, 587(54.3%) were excluded due to switching to injectable anti-diabetic drugs and 135 (12.5%) were excluded due to loss to follow-up. Finally, 248 (22.9%) patients were enrolled in the study out of which 140 (56.4%) were males and 108 (43.5%) were females.

These 248 patients were divided into four groups based on the oral anti-diabetic regimen received. Out of these, 140 (56.4%) were males and 108 (43.5%) were females.

62 (25%) patients were receiving only Biguanides, 63 (25.4%) patients were prescribed with the combination of Biguanides and Sulfonylureas, 63 (25.4%) patients were receiving a combination of Biguanides and Sodium-Glucose cotransporter (SGLT2) inhibitors and 60 (24.1%) patients were prescribed with a combination of Biguanides and Dipeptidyl Peptidase 4 (DPP4) inhibitors. Details are given in Table 2

Table 2: Patient distribution according to oral antidiabetic agents prescribed

Group	Number of Patients	Percentage
1. Biguanides (Metformin)	62	25%
2. Biguanides+ Sulfonylureas	63	25.4%
3. Biguanides+Sodium Glucose co-transporter (SGLT2) inhibitors	63	25.4%
4. Biguanides + Dipeptidyl peptidase -4 (DPP4) inhibitor	60	24.1%

Body weight (kg) was measured in all 3 visits. Laboratory findings such as FBS levels(mg/dl), PPBS levels(mg/dl) and HbA1c(%) were recorded and mean was calculated and the standard deviation was measured in all four groups. These were compared using the ANOVA test using SPSS29.

Body weight (in kg) was monitored in all 3 visits including baseline. Details are given in Table 3. In the patient group receiving only Biguanides baseline body weight was 73.3 ± 13 (kg), visit 1 Body weight 73.1 ± 12.8 (kg), visit 2 Body weight 72.6 ± 11.9 (kg), visit 3

body weight 72.3 ± 11.9 (kg) showed a statistically significant decrease of 1kg from baseline ($p<0.05$); In Biguanides + Su group baseline body weight 69.9 ±14.2 (kg), visit 1 body weight 70.2 ±14 (kg), visit 3 body weight 71 ± 13.6 (kg), also showed a statistically significant increase of 2kg from baseline ($p<0.02$); In Biguanides + SGLT2i group baseline body weight was 71.6 ± 11.3 (kg), visit 1 Body weight 71 ± 10.6 (kg), visit 2 Body weight 70.6 ± 10.4 (kg), visit 3 body weight 79.3 ± 9.1 (kg) showed a statistically significant decrease of 2.3kg from baseline ($p<0.01$); In Biguanides + DPP4i baseline body weight visit 1 72 ± 12.3 (kg) Body weight 71.9 ± 12.2 (kg), visit 2 Body weight 71.8 ± 12.1 (kg), visit 3 body weight 71.7 ± 11.9 (kg) did not show any statistical significance.

Table 3: Mean Bodyweight (kg) at each visit

Group	Baseline	Visit 1 (12 weeks)	Visit 2 (24 weeks)	Visit 3 (36 weeks)	Change from baseline
B	73.3 ± 13	73.1 ± 12.8	72.6 ± 12.3	72.3 ± 11.9*	- 1 kg
B + Su	69.9 ± 14.2	70.2 ± 14	71.07 ± 13.6	71.9 ± 13.2*	+ 2kg
B + SGLT2i	71.6 ± 11.3	71.03±10.63	70.6 ± 10.4	69.3 ± 9.1*	- 2.3kg
B + DPP4i	72 ± 12.3	71.9 ± 12.2	71.8 ± 12.1	71.7 ± 11.9	- 0.3kg

Data is represented as Mean±SD; ANOVA was performed using SPSS 29 to determine the level of significance in treatment groups before and after follow-up.; * $p < 0.05$ (comparison between before treatment and after treatment in each group)

Evaluation and Comparison of FBS in four groups and FBS at each visit is given in Table 4. In the patient group receiving Biguanides baseline FBS level was 135.1±13.2 (mg/dl), visit 1 FBS 132.2 ± 4.2 (mg/dl), visit 2 FBS 131.4 ± 5.6 (mg/dl), visit 3 FBS 128.9 ± 5.9 mg/dl showing the highly significant statistical difference of - 6.2 mg/dl ($p<0.001$) from baseline. In the patient group receiving Biguanides + Su baseline FBS level was 184.2±18.9 (mg/dl), visit 1 FBS 179.9 ± 17.3 (mg/dl), visit 2 FBS 173.4 ± 15.4 (mg/dl), visit 3 FBS 165.9 ± 15.2 mg/dl showing the highly significant statistical difference of - 18.3 mg/dl ($p<0.01$) from baseline. In the patient group receiving Biguanides+SGLT2i baseline FBS level was 181.8±18.9 (mg/dl), visit 1 FBS 175.8 ± 10.3 (mg/dl), visit 2 FBS 169±10.2 (mg/dl), visit 3 FBS 157.9 ± 12.9 mg/dl showing the highly significant statistical difference of - 23.9 mg/dl ($p<0.001$) from baseline. In the patient group receiving Biguanides+DPP4i baseline FBS level was 168.2±26.5 (mg/dl), visit 1 FBS 161.3 ± 23.6 (mg/dl), visit 2 FBS 157.9 ±21.3 (mg/dl), visit 3 FBS 152.8 ± 19 mg/dl showing the highly significant statistical difference of - 15.4 mg/dl ($p<0.04$) from baseline.

Table 4: Comparison of fasting blood sugar (in mg/dl) in four groups
Mean FBS (mg/dl) at each visit

Group	Baseline	Visit 1 (12 weeks)	Visit 2 (24 weeks)	Visit 3 (36 weeks)	Change from baseline
B	135.1 ± 13.2	132.2 ± 4.2	131.4 ± 5.6	128.9± 5.9*	-6.2 mg/dl
B + Su	184.2 ± 18.9	179.9 ± 17.3	173.4 ± 15.4	165.9± 15.2*	-18.3 mg/dl
B + SGLT2i	181.8 ± 9.4	175.8 ± 10.3	169 ± 10.2	157.9± 12.9*	-23.9 mg/dl
B + DPI	168.2 ± 26.5	161.3 ± 23.6	157.9 ± 21.3	152.8 ± 19*	-15.4 mg/dl

Data is represented as Mean±SD; ANOVA was performed using SPSS 29 to determine the level of significance in treatment groups before and after follow-up.; * $p < 0.05$ (comparison between before treatment and after treatment in each group).

Evaluation and Comparison of PPBS in four groups and PPBS at each visit is given in Table 5. In the patient group receiving Biguanides baseline PPBS level was 193.1± 20 (mg/dl), visit 1 PPBS 185.5 ± 14.5 (mg/dl), visit 2 PPBS 174 ± 11.5 (mg/dl), visit 3 PPBS 167.6 ± 8.7 mg/dl showing the highly significant statistical difference of - 25.5 mg/dl ($p<0.001$) from baseline. In the patient group receiving Biguanides + Su baseline PPBS level was 235.4±23 (mg/dl), visit 1 PPBS 226.9 ± 18.4 (mg/dl), visit 2 PPBS 215 ± 19 (mg/dl), visit 3 PPBS 208.1 ± 21.2 mg/dl showing the highly significant statistical difference of - 27.3 mg/dl ($p<0.005$) from baseline. In the patient group receiving Biguanides+SGLT2i baseline PPBS level was 281.5 ± 13.1 (mg/dl), visit 1 PPBS 268.7 ± 17.4 (mg/dl), visit 2 PPBS 247.2 ± 21.5 (mg/dl), visit 3 PPBS 227.3 ± 20.6 mg/dl showing a good significant statistical difference of - 54.2 mg/dl ($p<0.001$) from baseline. In the patient group receiving Biguanides+DPP4i baseline PPBS level was 239.3 ±41.9 (mg/dl), visit 1 PPBS 230 ± 35.4 (mg/dl), visit 2 PPBS 219.1 ± 27 (mg/dl), visit 3 PPBS 210.9 ±25.6 mg/dl showing a significant statistical difference of - 28.4 mg/dl ($p<0.02$) from baseline.

Table 5: Comparison of post prandial blood sugar (in mg/dl) in four groups

Group	Baseline	Visit 1 (12 weeks)	Visit 2 (24 weeks)	Visit 3 (36 weeks)	Change from baseline
B	193.12 ± 20	185.5 ± 14.5	174 ± 11.5	167.6± 8.7*	-25.5 mg/dl
B + Su	235.4 ± 23	226.9 ± 18.4	215 ± 19	208.1± 21.2*	-27.3 mg/dl
B + SGLT2i	281.5 ± 13.1	268.7 ± 17.4	247.2 ± 21.5	227.3± 20.6*	-54.2 mg/dl
B + DPI	239.3 ± 41.9	230 ± 35.4	219.1 ± 27	210.9 ± 25.6*	-28.4 mg/dl

Mean PPBS (mg/dl) at each visit

Data is represented as Mean±SD; ANOVA was performed using SPSS 29 to determine the level of significance in treatment groups before and after follow-up.; * $p < 0.05$ (comparison between before treatment and after treatment in each group)

Evaluation and Comparison of HbA1c in four groups and HbA1c at each visit is given in Table 6. In the patient group receiving Biguanides baseline HbA1c level was 7.82 ±0.60 (%), visit 1 HbA1c 7.62 ± 0.36 (%), visit 2 HbA1c 7.46 ± 0.32 (%), visit 3 HbA1c 7.06 ± 0.32 (%) showing a statistical difference of - 0.76 % ($p<0.01$) from baseline. In the patient group receiving Biguanides + Su baseline HbA1c, the level was 8.25±0.39 (%), visit 1 HbA1c 7.99 ± 0.23 (%), visit 2 HbA1c 7.82 ±0.22 (%), visit 3 HbA1c 7.43 ± 0.36 (%) showing the significant statistical difference of -0.82% ($p<0.05$) from baseline. In patient group receiving Biguanides+SGLT2i baseline HbA1c level was 8.86 ±0.24(%), visit 1 HbA1c 8.31 ± 0.37 (%), visit 2 HbA1c 7.88 ±0.55(%), visit 3 HbA1c 7.48 ± 0.33(%) showing significant statistical difference of - 1.38% ($p<0.01$) from baseline. In the patient group receiving Biguanides+DPP4i baseline HbA1c level was 8.44 ±0.57 (%), visit 1 HbA1c 7.90 ± 0.51 (%), visit 2 HbA1c 7.73 ± 0.37 (%), visit 3 HbA1c 7.44±0.42 (%) showing a significant statistical difference of - 1% ($p<0.05$) from baseline.

Table 6: Comparison of HbA1c (%) in four groups

Group	Baseline	Visit 1 (12 weeks)	Visit 2 (24 weeks)	Visit 3 (36 weeks)	Change from baseline
B	7.82 ± 0.60	7.62 ± 0.36	7.46 ± 0.32	7.06 ± 0.32*	0.76%
B + Su	8.25 ± 0.39	7.99 ± 0.23	7.82 ± 0.22	7.43 ± 0.36*	0.82%
B + SGLT2i	8.86 ± 0.24	8.31 ± 0.37	7.88 ± 0.55	7.48 ± 0.33*	1.38%
B + DPI	8.44 ± 0.57	7.90 ± 0.51	7.73 ± 0.37	7.44 ± 0.42*	1%

Mean HbA1c at each visit

Data is represented as Mean±SD; ANOVA was performed using SPSS 29 to determine the level of significance in treatment groups before and after follow-up.; * $p < 0.05$ (comparison between before treatment and after treatment in each group)

A total of 57 Adverse drug reactions were seen in our study. Biguanides + Su group of patients showed 22 (38.5%) ADRs of the total ADRs. In our study, the maximum number of ADRs reported were Hypoglycemia (8 patients), Dizziness (8 patients), & Urinary Tract Infection (8 patients). Gastrointestinal Side effects were seen such as Nausea (7 patients), Vomiting (5 patients), Diarrhoea (4 patients), Constipation (1 patient), Abdominal Pain (3 patients), Metallic Taste (4 patients) and Dyspepsia (3 patients). Apart from these other side effects reported were Itching (2 patients) and Respiratory Tract Infections (3 patients). Group wise distribution of ADRs are tabulated below in Table 7 and shown in a graph form for better understanding.

Table 7: Incidence reporting of ADRs in each group

ADR	Biguanides	Biguanides + Sulfonylureas	Biguanides + SGLT2i	Biguanides + DPI
Hypoglycemia	0	7	0	1
Hyperglycemia	0	0	1	0
Urinary Tract Infection	0	1	6	1
Nausea	3	2	2	0
Vomiting	3	2	0	0
Diarrhoea	2	1	0	1
Constipation	1	0	0	0
Dyspepsia	2	1	0	0
Itching	0	0	0	2
Abdominal Pain	0	1	0	2
Respiratory Tract Infection	0	0	2	1
Dizziness	0	7	0	1
Metallic Taste	2	0	1	1
Total	13	22	12	10

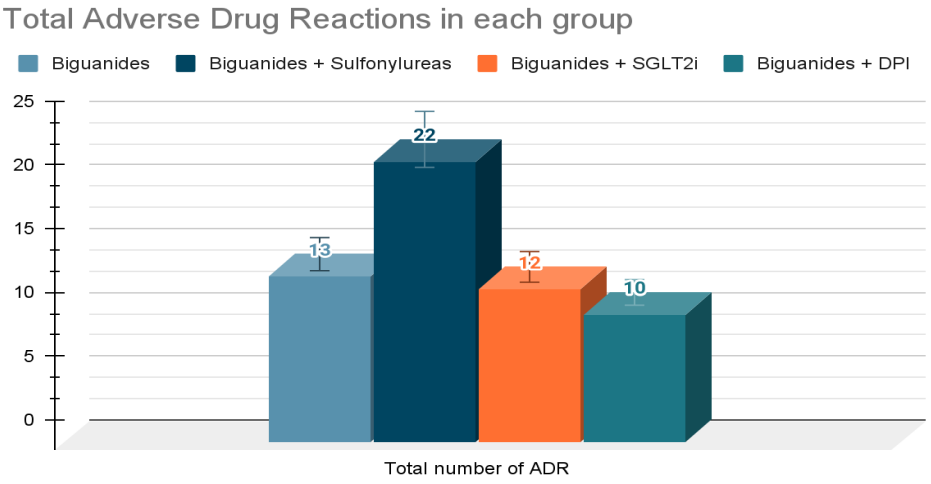

Figure 1: Total adverse Drug Reactions in each group

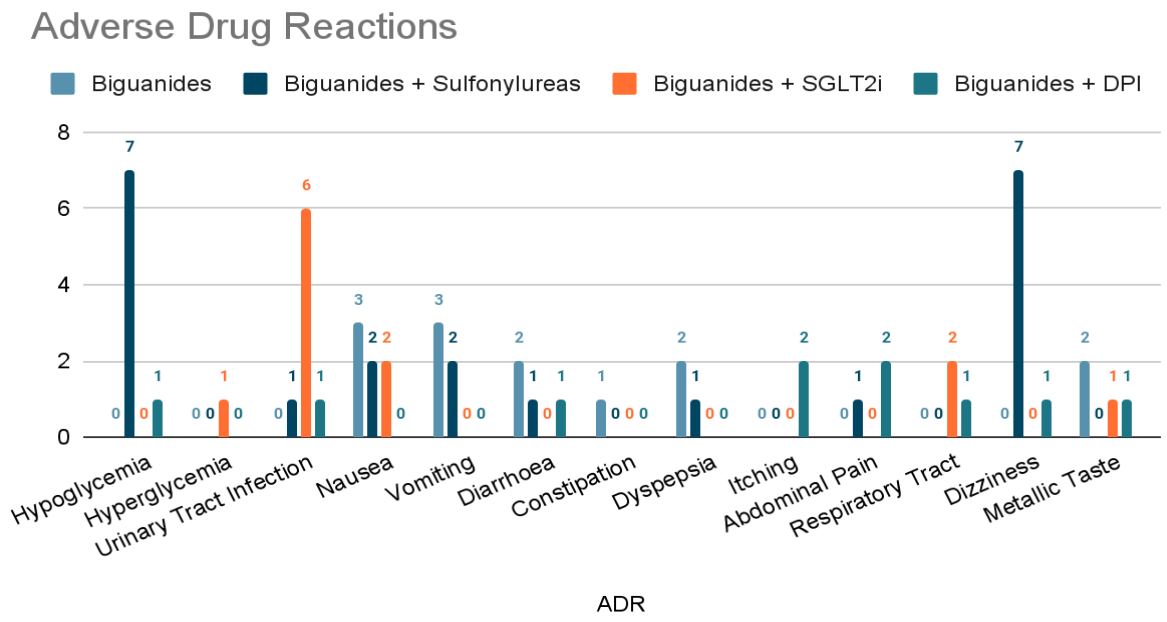

Figure 2: Adverse Drug Reactions

Discussion

In our study it was noted that the prevalence of diabetes was higher in men (56.4%) than women (43.5%), as known earlier, males are more likely to develop diabetes mellitus than women, which is similar to the study conducted by Gale and Gillespie [2]. This can be because men and women have a difference in insulin sensitivity and regional fat deposition.

In this study, there was a mild reduction in body weight seen in the group receiving B+SGLT2i ($p<0.01$) of approx 2.3kg reduction, these findings were similar to a meta analysis done by Dan Qian *et al*[3]; whereas the group receiving B+Su showed an increase in mean body weight from baseline of 2kg ($p<0.02$), these finding suggested similar to a study done by Daniele Sola *et al*[4]. The group receiving only B showed a reduction in body weight from baseline of about 1kg ($p<0.05$)

SGLT2i appears to show maximum reduction in body weight, whereas Su are associated with weight gain and risk of hypoglycemia. Metformin reduces the risk of weight gain and shows no side effects such as hypoglycemia. DPP4i on the other hand are weight neutral. The results seen in our study regarding weight neutral effects of DPP4i are different from the results seen in a different study done by Jennifer green *et al* [5] that show weight reduction effects of DPP4i.

In our study there was significant reduction in FBS and PPBS in all four groups while the maximum reduction was seen in the group receiving B+SGLT2i -23.9mg/dl($p<0.001$) in FBS and -54.2mg/dl ($p<0.001$) in PPBS. The group receiving only B, FBS and PBS reductions were seen as -6.2mg/dl ($p<0.001$) and -25.5mg/dl ($p<0.001$) respectively. B+Su group showed significant reductions in FBS and PBS, -18.3mg/dl($p<0.01$) and -27.3mg/dl($p<0.005$) respectively. B+DPP4i showed their efficacy by reducing FBS and PPBS by -15.4mg/dl($p<0.04$) and -28.4mg/dl($p<0.02$). Similar results were found in the study conducted by Seon-Ah Cha *et al*[6] and meta analysis done by Dan Qian *et al*[3] with slight variation in the results.

According to the study, there was a significant reduction of HbA1c in all groups with

maximum reduction seen in B+SGLT2i group of -1.38% ($p<0.001$) from baseline followed by B+DPP4i showing reduction of -1% ($p<0.04$), B+Su with reduction of 0.82% ($p<0.05$) and least reduction in B only group of -0.76% ($p<0.01$). Similar results in glycemic control of these drugs/drug combinations with slight variation have been seen in studies conducted by Dan Qian *et al* [3], Ji *et al*[7] & Seon-Ah Cha *et al*[6].

All drug groups in our study showed significant reduction in glycemic parameters, maximum fasting blood glucose and postprandial blood glucose reduction were seen with patients receiving SGLT2 inhibitors along with metformin. Fasting blood glucose reduction was seen more with the group receiving sulfonylureas with metformin than with patients receiving DPP-4 inhibitors with metformin. Postprandial glucose reduction was more in patients receiving DPP4 inhibitors with metformin than the patients receiving Sulfonylureas with metformin.

A significant reduction in HbA1c was seen in all groups, with maximum reduction in the patient group receiving SGLT2 inhibitors with metformin.

Assessment of ADRs showed that maximum ADRs reported were Hypoglycemia (8,3.2%), Dizziness(8,3.2%) out of which maximum hypoglycemic events were reported in B+Su Group. B+SGLT2i group showed the occurrence of UTI in 6 (2.4%) patients. Gastrointestinal ADRs were reported in all drug groups.

Conclusion

This study was conducted on 248 patients, of which 140(56.4%) were males and 108(43.5%) were females. Significant reduction in glycemic parameters was seen in all four groups while the maximum reduction in FBS, PPBS and HbA1c was seen in the patient group receiving metformin + SGLT2i.

Adverse drug reactions observed were maximum in the patient group receiving metformin + Sulfonylureas and UTI was common among patients receiving metformin + SGLT2i.

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