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COMPARE THE EFFICACY AND SAFETY OF DIPEPTIDYL PEPTIDASE-4 INHIBITORS WITH OTHER ORAL HYPOGLYCEMIC AGENTS IN TYPE 2 DIABETES MELLITUS PATIENTS

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Diabetes Mellitus (DM), Dipeptidyl peptidase 4 inhibitors (DPP), Sulfonylureas (SU), Thiazolidinediones (TZ), Fasting blood sugar (FBS), Post prandial blood sugar (PLBS), Adverse events (AE)

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ABSTRACT: Background: The incidence of Diabetes Mellitus has increased dramatically in recent decades. Di Peptidyl Peptidase 4 inhibitors (DPP-4) have their role in glycemic control. An impaired 'incretin effect', occurs in patients with type 2 Diabetes Mellitus in response to glucose intake. **Objectives:** The main objective of the study is to compare therapeutic outcomes and adverse drug reactions among commonly prescribed anti diabetic drug combinations in adults with type 2 diabetes mellitus. **Methodology:** A retrospective and prospective study experimental study was carried out for a period of one year at care diabetes centre. **Results:** FBS and PLBS were found to be significantly lower in DPP group when compared with SU and TZ. Adverse events such as itching, abdominal pain, constipation and weight loss are more in DPP when compared with other groups. Data from this study indicated that DPP-4 inhibitors are superior to sulfonylureas (SU) and thiazolidinediones (TZ) when used in combination with metformin (B) in glycemic control. **Conclusion:** DPP inhibitors provide an effective therapeutic option for individuals with Type 2 Diabetes along with obesity.

INTRODUCTION: According to World health organization (WHO) Diabetes Mellitus (DM) describes 'a metabolic disorder of multiple etiologies characterized by varying degrees of insulin hypo-secretion and/or insulin insensitivity leading to hyperglycemia' [1]. WHO estimated that, by 2025 about 300 million people will have Diabetes across the World [2]. Uncontrolled diabetes mellitus results in chronic microvascular complications such as diabetic retinopathy, diabetic cataracts, macular edema, glaucoma, diabetic neuropathy and diabetic nephropathy and macrovascular complications Coronary artery disease, Peripheral artery disease, Cerebro vascular disease and various other complications like gastro paresis, diarrhea, uropathy / sexual dysfunction and various infections [3]. Most of these complications are preventable through proper diet, exercise, and medication. Various classes of oral anti-diabetic drugs are available which acts on different sites to show their actions, but these available treatments fail to maintain effective glycemic control in long term as β-cell function declines overtime.

Biguanides, sulfonylureas or thiazolidinediones are most commonly prescribed oral antidiabetic drugs. Risks of hypoglycemia and weight gain are increased with sulfonylureas and thiazolidine-diones. Weight loss is seen with biguanides, although hypoglycemia is rare. Most of the patients with DM start their treatment with single oral ant diabetic drugs [4]. As disease progresses two or more antidiabetic drugs should be used where newer drugs are beneficial.

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New therapies in addition to maintaining glycemic control, could reduce body weight and hypoglycemia risk. In particular, incretin-based therapies (Glucogon like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors specifically) can help to meet these new targets by offering weight reduction, blood pressure reduction, and reduced hypoglycemia risk in addition to glycemic control [5].

After meal ingestion, secretion of active GLP-1 and glucose dependent insulinotropic peptide (GIP) occurs. And these GLP-1 and GIP are responsible for increased insulin release from β-cells of pancreas and thereby increases cellular glucose uptake [6]. GLP-1 alone acts on α-cells on pancreas and suppress glucagon release which decreases glucose production from liver *i.e.,* hepatic glucose output is reduced. DPP-4 inactivates GLP-1 and GIP. DPP-4 inhibitors are incretin enhancers. Sitagliptin and vildagliptin are most widely used DPP-4 inhibitors may stimulate GLP-1 secretion directly from intestine [7, 8].

The National Institute of Health and Clinical Excellence (NICE) suggests adding DPP-4 inhibitors instead of sulfonyl urea as second line treatment to metformin, if there is considerable risk of hypoglycemia or if sulfonyl urea is contraindicated [9]. Proper control of type 2 DM is not adequate till now in spite of well planned dosage regimens. This work discusses the rationale behind newly available DPP-4 inhibitors and compares efficacy and safety with other oral hypoglycemic drug regimes. The main objective of the study is to compare therapeutic outcomes and adverse drug reactions among commonly prescribed anti diabetic drug combinations in adults with type 2 diabetes mellitus.

METHODOLOGY: A prospective observational study was performed at care diabetes center in Telangana region after getting approval from institutional human ethical committee (file no: 0733/2) for a period of 1 year. Patients with type 2 diabetes mellitus of both sex and age group >18 years, diagnosed with diabetes ≥ 1 year ago without proper glycemic control and whose medication was changed to combination therapy as required recently (in past three months) were included in the study. Patients with type 1 or secondary forms of diabetes mellitus, patients with severe hepatic or renal impairment and patients with any change in medication during follow up were excluded from the study.

All the patients visiting diabetic center were reviewed on daily basis and those who meet our study criteria were enrolled into the study and inform consent was obtained from the subjects if he/she agrees to participate in to the study. Demographics details, past medication history, current treatment charts were recorded in data collection form. Baseline relevant investigations such as Fasting blood sugar (FBS), Post prandial blood sugar (PPBS), HbA1c were noted initially; patients were followed for next three months. FBS, PLBS were reviewed in next three visits (each visit 30 ± 5 days) and HbA1c was rechecked only in third visit to compare efficacy. Patients are also interviewed for any type of adverse reactions throughout the study. Based on medication received, patients were divided into three groups, group 1 using biguanides (B) + Sulfonylureas (SU), Group 2 on B + Thiazolidinediones (TZ), Group 3 using B + Dipeptidyl peptidase inhibitors (DPP). Efficacy parameters (FBS, PLBS and HbA1c) and safety parameters (adverse drug reactions, body weight changes (atleast 3% change from baseline value) are compared in three visits. Unpaired t-test was performed using graph pad prism 6 to determine the level of significance in treatment groups before and after follow up. Incidence rate was calculated to determine burden of adverse drug reactions in treatment groups.

RESULTS: During our study period, 2800 patients were reviewed. We identified a total of 700 (40%) patients eligible for inclusion in the study, Among these 700 patients, 170 patients had change in medication during follow up and248 patients did not attend reviews in next three visits. 282 (10.07%) patients were enrolled into the according to the inclusion criteria.

TABLE 1: NUMBER OF PATIENTS IN 3 GROUPS

Number of patients	Groups		
	B+SU	B+TZ	B+DPP
n = 282	149	66	67
Percentage %	52.83%	23.4%	23.75%

Of 282 subjects with DM, 149 (52.83%) patients were treated with B + SU, 66 (23.4%) were treated with B + TZ and 67(23.75%) were treated with B + DPP.

TABLE 2: COMPARISONS OF FBS, PLBS, HbA1c IN TWO GROUPS

Groups		Baseline	P value	Follow up (Visit 3)	P value
1. SULFONYL UREAS *vs.* DIPEPTIDYL PEPTIDASE-4 INHIBITORS					
FBS	B+SU	178.3 ± 30.22		149.1 ± 39.98	
	B+DPP	177.2 ± 33.23	>0.05	128.1 ± 25.43	<0.001
	B+SU	267.3 ± 59.13		207.2 ± 63.55	
PLBS	B+DPP	266.2 ± 53.1	>0.05	187.2 ± 65.75	<0.001
	B+SU	9.45 ± 0.15		8.93 ± 1.53	
HbA1c	B+DPP	9.45±0.12	>0.05	7.73 ± 0.36	>0.05
2. THIAZOLIDINE DIONES *vs.* DIPEPTIDYL PEPTIDASE-4 INHIBITORS					
FBS	B+ TZ	176.4 ± 29.56		156.4 ± 54.78	
	B+DPP	177.2 ± 33.23	>0.05	128.1 ± 25.43	<0.001
PLBS	B+TZ	263.2 ± 47.11		206.0 ± 63.28	
	B+DPP	266.2 ± 53.12	>0.05	187.2 ± 65.75	<0.05
HbA1c	B+TZ	9.45 ± 0.18		8.91 ± 1.26	
	B+DPP	9.45 ± 0.12	>0.05	7.73 ± 0.36	>0.05

Sulfonylureas *vs*. Dipeptidyl Peptidase-4 Inhibitors: Mean baseline FBS in B+TZ group is 178.3 ± 30.22 and in B+DPP group is 177.2 ± 33.23, unpaired t test was performed and it symbolizes that, at 95% CI, there is no significant difference in baseline FBS among two groups (P value > 0.05). Mean FBS in B+SU group after follow up is 149.1 ± 39.98 and in B+DPP group is 128.1 ± 25.43, which showed significant difference (P<0.001).

Baseline mean PLBS in B+SU and B+DPP groups are 267.3 ± 59.13 and 266.2 ± 53.12 respectively, this brings out that at 95% CI there is no significant difference in both treatment groups (P value> 0.05), whereas mean PLBS values in both groups are 207.2 ± 63.55 and 187.2 ± 65.75 respectively, which revealed that mean PLBS levels were significantly higher in B+SU group (P value <0.001).

Mean baseline HbA1c values in B+SU and B+ DPP groups are 9.45 ± 0.15 and 9.45 ± 0.12 respectively, which did not show any difference (P>0.05), in revisit these values were 8.93 ± 1.53 and 7.73 ± 0.36 respectively, which did not show any difference in two treatment groups.

Thiazolidinediones *vs.* Dipeptidyl Peptidase-4 Inhibitors: Mean baseline FBS in B+TZ group is 176.4 ± 29.56 and in B+DPP group is 177.2 ± 33.23, unpaired t test was performed to determine the level of significance, at 95% CI, there is no significant difference in baseline FBS among two groups (P value). Mean FBS in B+TZ group after follow up is 156.4 ± 54.78 and in B+DPP group is 128.1 ± 25.43, which symbolized that mean FBS is significantly reduced in B+DPP group (P<0.001).

Baseline mean PLBS in B+SU and B+TZ groups are 263.2 ± 47.11 and 266.2 ± 53.12 respectively, this brings out that at 95% CI there is no significant difference in both treatment groups (P value > 0.05), whereas mean PLBS values in both groups are 206.0 ± 63.28 and 187.2 ± 65.75 respectively, which revealed that mean PLBS levels were significantly higher in B+TZ group (P value <0.05).

TABLE 3: IDENTIFICATION OF ADVERSE DRUG REACTIONS

ADR	Total	B+SU Incidence (%)	B+TZ Incidence (%)	B+DPP Incidence (%)
Hypoglycemia	21	16 (10.7%)	03 (4.54%)	02 (2.98%)
Diarrhea	7	04 (2.68%)	---	03 (4.47%)
Constipation	2	---	---	02 (2.98%)
Itching	6	---	---	06 (8.95%)
Abdominal pain	9	03 (2.01%)	02 (3.03%)	04 (5.97%)
Dizziness	14	09 (6.04%)	04 (6.06%)	01 (1.49%)
Pedal edema	8	02 (1.34%)	06 (9.09%)	---
GI disturbances	5	05 (3.35%)	---	---
Cough	1	---	---	01 (1.49%)
Weight gain	26	22 (14.76%)	04 (6.06%)	---
Weight loss	15	02 (1.34%)	01(1.51%)	12 (17.91%)
Total		63 (42.28%)	20 (30.3%)	29 (43.28%)

Mean baseline HbA1c values in B+TZ and B+DPP groups are 9.45 ± 0.18 and 9.45 ± 0.12 respectively, which did not show any difference (P>0.05), in revisit these values were 8.93 ± 1.53 and 7.73 ± 0.36 respectively, which did not show any difference in two treatment groups.

Results showed that, incidence of hypoglycemia highest in B+SU group (10.7%), whereas (4.54%) in B+TZ and (2.98%) in B+DPP group *i.e.* patients using SU are 3.6 times more risk of developing hypoglycemia and patients using TZ are 1.5 times higher risk than DPP. Incidence of diarrhea is 2.68% in B+SU group and 4.47% in B+DPP, which shows DPP users are 1.6 times greater risk of developing diarrhea than SU. Diarrhea is not reported in B+TZ group. Constipation is reported only in DPP group (2.98%). Itching is reported only in B+DPP (8.95%). Incidence of abdominal pain is highest (5.97%) in B+DPP group, followed by 3.03% in B+TZ and 2.01% in B+SU group. DPP users are 3 and 2 times increased risk of developing abdominal pain than SU and TZ respectively. Incidence of dizziness is more (6.04%) and (6.06%) in B+SU and B+TZ groups respectively, and (1.49%) in B+DPP group *i.e.* SU and TZ are 4 times higher risk than DPP. Incidence of pedal edema is highest in B+TZ group. Pedal edema and GI disturbances are not reported in such as Nausea, vomiting and indigestion are seen only in B+SU group (3.35%). Shortness of breath is not observed in any patient; whereas only one case of cough has been reported in B+DPP group (1.49 %).

Incidence of weight gain is higher in patients using B+SU (14.76%), 6.06% in B+TZ group. Patients using SU are 14.76 times more likely to gain weight than DPP. Incidence of weight loss is highest (17.91%) in B+DPP group, 1.51% in B+TZ and 1.34% in B+SU group *i.e.* only 2 cases developed weight loss, among them one patient was found to be effected with Tuberculosis during the follow-up. This would be the reason for weight loss and this shows that DPP users are 13 times and 11 times more likely to loss their weight than SU and TZ users respectively.

TABLE 4: WHO PROBABILITY SCALE

Scale	B+SU	B+TZ	B+DPP
Probable	37	6	9
Possible	23	11	16
Unlikely	3	3	4

To assess the adverse drug reaction (Adr), WHO probability scale was used. Among adverse drug reactions observed in B+SU group, 37 were probable, 23 were possible and 3 were unlikely ADR's where as in B+TZ group 6 were probable, 11 possible and 3 were unlikely. In B+DPP group, 9 were probable, 16 were possible and 4 were unlikely adr's.

TABLE 5: SEVERITY ASSESSMENT SCALE

Scale	B+SU	B+TZ	B+DPP
Mild	45	13	17
Moderate	18	7	12

Severity was assessed for Adr's, in B+SU group, 45 were mild and 18 were moderate. In B+TZ group, 13 ADR's were found to be mild and 7 ADR's were moderate, whereas in B+DPP 17 were mild and 12 were moderate.

DISCUSSION: This study demonstrates that, there was a significant decline in FBS and PLBS from baseline to end of treatment in B+DPP group when compared to B+SU and B+TZ groups (P values <0.001). HbA1c reduction is almost similar in three groups and did not show any significant difference. This suggests that, Dipeptidyl peptidase inhibitors are superior to Sulfonylureas and Thiazolidine-diones in efficacy parameter i.e. glycemic control. In a study conducted by Hyun JJ *et al.,* 2011, the vildagliptin + metformin treatment showed an HbA1c reduction comparable to that of the glimepiride + metformin treatment over a 32 week period [10]. Our study period was limited to three months; this would be the reason for HbA1c difference in 2 studies. This difference might be due to limited study period in our study.

Where safety parameters are concerned, results showed that, patients using SU are 3.6 times more risk and patients using TZ are 1.5 times higher risk of developing hypoglycemia than DPP. Incidence of diarrhea, itching and abdominal pain are highest in B+ DPP group. DPP users are 1.6 times greater risk of developing diarrhea than SU. Diarrhea is not reported in B+TZ group. Constipation is reported only in DPP group. Itching is reported only in B+DPP. DPP users are 3 times and 2 times increased risk of developing abdominal pain than SU and TZ respectively, this could be a signal for pancreatitis. However, follow up is required to confirm this hypothesis.

Incidence of dizziness is 4 times more in SU and TZ are than DPP, as hypoglycemia is common adverse effect of these 2 drugs when compared with DPP. Incidence of pedal edema is highest in B+TZ group, followed by B+SU group. Pedal edema is not reported in DPP group, TZ users are 6 times higher risk of developing edema than SU users.GI disturbances such as Nausea, vomiting and indigestion are seen only in B+SU group. Shortness of breath is not observed in any patient; whereas only one case of cough has been reported in B+DPP group. Incidence of weight gain is higher in patients using B+SU. Patients using SU are 14.76 times more likely to gain weight than TZ. Incidence of weight loss is highest in B+DPP group, making this drug beneficial for use in obese patients. DPP users are 13 times and 11 times more likely to loss their weight than SU and TZ users respectively. According to a study conducted by Williams Herman D *et al*., 2010; found overall adverse events were similar in sitagliptine and non exposed groups, except for an increased incidence of drug related adverse events in the non exposed group [11].

CONCLUSION: The results achieved with DPP inhibitors appear to be superior to those achieved with sulfonylureas and thiazolidinediones, with greater improvements in glycemic control.DPP inhibitors increase glycemic control in patients with type 2 diabetes with a low risk of hypoglycemia when compared with sulfonylureas and thiazolidinediones because DPP inhibitors have glucose-dependent mechanism of action. This drug class has also been demonstrated to promote weight loss, which could be of benefit to patients with type 2 diabetes with obesity, reducing their cardio-vascular risk. Furthermore, although abdominal pain is a common side effect with DPP inhibitors, it is very mild but this can also be a signal for pancreatitis on long term use. Thus, DPP inhibitors may provide an effective therapeutic option for individuals with type 2 diabetes and meet the hypothesis according to the National Institute of Health and Clinical Excellence (NICE) which suggests that adding DPP-4 inhibitors instead of sulfonyl urea as second line treatment to metformin is beneficial, if there is considerable risk of hypoglycemia or if sulfonyl urea is contraindicated. However more studies are needed to confirm these findings and to exclude any undesirable effects.

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CONFLICT OF INTEREST: There are no conflicts of interest.

REFERENCES:

1. Lawn A: Definition and Diagnosis AND Classification of Diabetes Mellitus and its complications. Internet
2. Ruth K, Anneli R and Margus L: Predictors of quality of life of patients with Type 2 diabetes. Patient Preferences and Adherence 2008; 2: 21-26.
3. Fauci AS, Kasper DL and Jameson JL: Harrisons principles of Internal Medicine. Unites States: McGraw Hill Edition 17th, 2008; 17: 942-946.
4. Garber AJ: Long-Acting Glucagon-Like Peptide 1 Receptor Agonists; A review of their efficacy and tolerability. Diabetes Care 2011; 34(2): 79-84.
5. Becker ML, Pearson ER and Tkáč I: Pharmacogenetics of Oral Antidiabetic Drugs. Int J Endocrinology 2013; 1-10.
6. Timothy R: Choosing GLP-1 receptor agonists or DPP-4 inhibitors: Weighing the clinical trial evidence. Clinical Diabetes 2013; 31(4): 148-156.
7. Tahrani A, Milan K, Kennedy A and Anthony H: Glycemic control in type 2 diabetes: targets and new therapies. Pharmacol Therapeut 2010; 125: 32861.
8. Perrin C, Chamberlain-Sheab H and Maria-Teresa M: Sitagliptin treatment of patients with type 2 diabetes does not effect CD^{4+} T-cell activation 2010; 24(3): 209-213.
9. Thomas K, Paschalis P and Konstantinos P: Apostolos-dipeptidyl peptidase-4 inhibitors for treatment of type 2 diabetes mellitus in the clinical setting: systematic review and meta analysis. BRIT MED J 2012; 12(3): 1-15.
10. Hyun JJ and Tae K: Comparision of vidagliptin-metformin and glimiperide- metformin treatments in type 2 diabetic patients. J Diabetes Metabolism 2011; 35: 529-35.
11. Williams-herman D, Elizabeth R and Arlene S: Safety and tolerability of sitagliptin in patients with type 2 diabetes: a pooled analysis. Biomedcentral Endocrine Disorders 2008; 8(14): 1-16.

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