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Effectiveness of DPP-IV Inhibitors versus Sulphonylureas in Management of Uncontrolled Type-II Diabetes Mellitus- A Comparative Study

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ABSTRACT:

Objective: To evaluate effectiveness and tolerability of DPP-IV inhibitors versus Sulphonylureas in treatment of Type-II Diabetes Mellitus (T2DM) patients, uncontrolled with Metformin alone. Methods: 50 patients suffering from T2DM and receiving treatment with Metformin were recruited for the study based on inclusion and exclusion criteria after obtaining their informed consent. Recruited patients were randomly prescribed combination of Sulphonylurea + Metformin and DPP-IV inhibitors + Metformin. Blood glucose levels were checked every month and HbA1c was checked at the end of three months treatment. Results and Discussion: Sulphonylureas as well as DPP-IV inhibitors when given in combination with Metformin reduced RBG, FBG and PP2BG after one month treatment, without any significant difference as compared with baseline values. Comparing the PP2BG and HbA1c values in both treatment groups after three months, the difference was found to be statistically significant. Also incidence of adverse effects was observed to be higher in Sulphonylurea + Metformin group. Conclusion: Results of the study lead to the conclusion that both treatment groups are equally effective in management of T2DM uncontrolled with Metformin alone. However, looking at tolerability aspect DPP-IV inhibitors seem to be more safe and tolerable as compared to Sulphonylureas.

KEYWORDS: DPP-IV Inhibitors, Metformin, Type-2 Diabetes Mellitus, Sulphonylureas

INTRODUCTION:

Diabetes Mellitus (DM), a major lifestyle disorder, has transitioned from being a class disease to a mass epidemic and poses a rapidly emerging global threat to public health with a worldwide prevalence of 366 million.[1] It is a group of metabolic disease characterized by hyperglycaemia resulting from defects in insulin secretion, insulin action or both.[2] It is a lifelong disorder which is markedly affected by day to day variation in the diet, exercise, infection and stress.[3]

India, once known as the diabetes capital of the world, [4] was home to 61.3 million patients with Type II Diabetes Mellitus (T2DM) in 2011 and this figure is expected to rise to 101.2 million by 2030. [5] The global increase in the prevalence of diabetes is due to population growth, aging, urbanization and increase of obesity and physical inactivity. [6]

Diabetes Mellitus is a chronic disease, for which there is no known cure except in very specific situations. Management concentrates on keeping blood glucose levels as close to normal as possible, without causing hypoglycemia. This can usually be accomplished with diet, exercise and use of appropriate medications like Insulin or Oral hypoglycemic agents such as Sulphonylureas, Biguanides, Thiazolidinediones, DPP-IV inhibitors etc.[7]

Metformin, a member of Biguanide class has long been considered the initial drug therapy of choice in treatment of T2DM.[8] It is one of the oldest and indeed one of the safest medications used in the treatment of T2DM. It exerts its effect by decreasing hepatic glucose output. [9] Patients may initially receive Metformin but may not be able to tolerate common side effects, mainly its gastrointestinal adverse effects. Also its use is contraindicated in various categories of patients and thus such patients may not get adequate glycemic control.[10]

The American Diabetes Association & European Association for the study of Diabetes recommend use of a Sulfonylurea, Meglitinide, Pioglitazone or Dipeptidyl peptidase 4 (DPP-IV) Inhibitor when Metformin cannot be used.[11] Association of Clinical Endocrinologists state that GLP-1 agonists, DPP-4 inhibitors, and Alpha-glucosidase inhibitors are acceptable alternatives to metformin.[12] Although monotherapy with an oral hypoglycemic agent is initially effective, glycemic control deteriorates in most patients which requires the addition of a second agent.

Hence in patients with T2DM uncontrolled with Metformin alone, the combination of Metformin and Sulphonylurea is one of the most commonly used combination and can attain a greater reduction in HbA1c (0.8-1.5%) than either drug alone. Sulphonylureas act on beta cells to increase insulin release. [10]

DPP-IV inhibitors are the newest class of oral agents for treatment of T2DM which act by inhibiting enzymatic degradation of glucagon like peptide (GLP-1) which suppresses glucagon release and increases glucose stimulated insulin release. The mechanism of DPP-IV Inhibitors is complementary to that of Metformin, making this combination very useful for achieving adequate glycemic control. [9] Metformin has also been found to increase plasma GLP-1 levels, probably by either direct inhibition of DPP-IV or by increased secretion, leading to reduced food intake and weight loss, thus giving better glycemic control then either drug alone. [13]

Hence the present study was undertaken with the aim to evaluate effectiveness and tolerability of DPP-IV Inhibitors versus Sulphonylureas in management of patients with T2DM, uncontrolled with Metformin alone.

MATERIALS AND METHODS:

Subject recruitment procedure:-

Inclusion criteria: 50 patients of either sex in the age range of 18-60 years suffering from T2DM and receiving treatment with Metformin alone were recruited for the study.

Exclusion criteria: Patients having history of hypersensitivity to any drug, having history of disease conditions such as pancreatitis and hepatic impairment, having high SGPT or Serum Creatinine level (>1.5) and pregnant and nursing woman were excluded from the study.

Procedure:

Approval was obtained from Safe Search Independent Ethics Committee, Ahmedabad. Patients who were selected for the study based on inclusion and exclusion criteria were screened for their Blood Glucose Levels (BGL) and HbA1c levels. Patients having FBG > 126 mg/dl, PP_2BG > 200 mg/dl and HbA1c > 7% were finally recruited in the study after obtaining their **informed consent**. Recruited patients were randomly prescribed a combination of Sulphonylurea + Metformin and DPP-IV inhibitors + Metformin by the treating doctor.. Blood Glucose levels were checked every month and HbA1c level was checked after completion of 3 months treatment. All the demographic, clinical data and data of drugs prescribed as standard care of treatment of T2DM were collected from records of patients and documented in Case Record Form(CRF).

Statistical analysis:

The scientific data collected were analysed using Frequency distribution and Independent T-test. Results were expressed as Mean ± SEM and p value < 0.05 was considered to be statistically significant.

Results:

1. Patient demographic characteristics:

The present single centred, randomized, prospective study was carried out at Ahmedabad, under the supervision of a physician.

Of the 50 patients recruited in the study 23 were male and 27 were female. All the patients were in the age range of 33 to 60 years with mean age of 51.72 ± 1.57 years. Body weight of patients ranged between 49-86 kg with average body weight of 63.58 ± 1.69 kg

The physician randomly prescribed DPP-IV inhibitors and Sulphonylureas in combination with Metformin to the recruited patients. Table 1 shows demographic characteristics of the patients prescribed Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin

Table 1. Demographic characteristics of patients prescribed Sulphonylurea + Metformin and DPP-IV inhibitors + Metformin:

Characteristics of Patients	Mean Age Range (Years)	Sex		Mean Body Weight (Kg)
		(Male)	(Female)	
Patients prescribed Sulphonylurea + Metformin	53.44 ± 1.41	11 (44%)	14 (56%)	61.84 ± 1.77
Patients prescribed DPP-IV Inhibitors + Metformin	50.00 ± 1.72	12 (48%)	13 (52%)	65.32 ± 1.60
Mean of Total Patients (50)	51.72 ± 1.57	23 (46%)	27 (54%)	63.58 ± 1.69

Values are represented as Mean ± SEM.

2. Baseline Mean Blood Glucose Level of all 50 patients recruited in the study:

Normal values of RBG, FBG and PP_2BG in non-diabetic individuals are **70-130 mg/dl, 110-125 mg/dl, and 140-199 mg/dl** respectively. Table 2 shows the baseline mean blood glucose levels of the 50 patient recruited in the study**.**

Table No. 2: Baseline Mean Blood Glucose Level of all 50 patients recruited in the study

Parameter	RBG (mg/dl)	FBG (mg/dl)	PP_2BG (mg/dl)
Mean ± SEM	252.88 ± 5.10	199.36 ± 4.20	262.68 ± 6.33

Values are represented as Mean ± SEM.

3. Mean Blood Glucose Level of patients prescribed Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin after one month treatment:

Treatment with Sulphonylurea + Metformin or DPP-IV Inhibitor + Metformin for one month reduced the mean blood glucose values as compared to the baseline values. However the difference between the two treatment groups was not found to be statistically significant. (Table: 3)

Table 3: Mean Blood Glucose Level (BGL) of patients prescribed Sulphonylureas + Metformin or DPP-IV inhibitor + Metformin after one month treatment:

Parameter	Baseline mean blood glucose levels	Mean BGL in patients prescribed Sulphonylurea + Metformin after one month treatment	Mean BGL in patients prescribed DPP-IV Inhibitor + Metformin after one month treatment
RBG (mg/dl)	252.88 ± 5.10	182.80 ± 5.17	178.40 ± 4.86
FBG (mg/dl)	199.36 ± 4.20	142.88 ± 5.96	145.88 ± 5.07
PP_2BG (mg/dl)	262.68 ± 6.33	189.04 ± 8.47	183.76 ± 5.73

Values are represented as Mean ± SEM.

4. Mean Blood Glucose Level of patients prescribed Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin after three months treatment:

Table 4. shows mean blood glucose levels of patients prescribed Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin after three months treatment. Though both categories of drugs reduced RBG and FBG after 3 months treatment, the difference was not found to be statistically significant. However, the reduction in mean PP_2BG in the patient's prescribed DPP-IV inhibitor + Metformin was significantly higher than the reduction in PP_2BG in patient's prescribed Sulphonylurea + Metformin.

5. Mean Percentage decrease in Blood Glucose Level over a period of three months treatment

Compiled data of mean percentage decrease in Blood Glucose Level after treatment with Sulphonylurea + Values are represented as Mean ± SEM., *p < 0.05 statistically significant by T-test.Metformin or DPP-IV

Table 4: Mean Blood Glucose Level of patients prescribed Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin after three months treatment.

Parameter	Baseline mean blood glucose levels	Mean BGL in patients prescribed Sulphonylurea + Metformin after 3 months treatment	Mean BGL in patients prescribed DPP-IV Inhibitor + Metformin after 3 months treatment	p value	
RBG (mg/dl)	252.88 ± 5.10	148.16 ± 2.34	141.84 ± 2.66	0.08	0.08
FBG(mg/dl)	199.36 ± 4.20	132.04 ± 2.25	136.48 ± 2.30	0.17	0.17
PP_2BG(mg/dl)	262.68 ± 6.33	145.32 ± 2.70	*158.16 ± 2.79	*0.0018	*0.0018

Table 5: Mean Percentage decrease in Blood Glucose Level over a period of three months treatment:

Parameter	Sulphonylureas + Metformin			DPP-IV inhibitor + Metformin		
	Decrease in BGL after one month	Decrease in BGL after two months	Decrease in BGL after 3 months	Decrease in BGL after one month	Decrease in BGL after two months	Decrease in BGL after 3 months
RBG(mg/dl)	29.05 ± 2.75	35.99 ± 2.05	39.33 ± 2.30	29.65 ± 1.72	40.77 ± 2.09	43.17 ± 2.17
FBG(mg/dl)	32.17 ± 4.10	33.99 ± 2.19	32.55 ± 2.30	25.92 ± 2.43	28.37 ± 1.99	30.20 ± 1.76
PP_2BG(mg/dl)	31.68 ± 3.99	37.50 ± 2.01	42.59 ± 2.38	29.74 ± 2.08	37.43 ± 1.89	38.86 ± 2.35

Values are Mean ± SEM

inhibitors + Metformin, over a period of 3 months is shown in Table.5

5. HbA1c Estimation:

HbA1c known as Glycated Hemoglobin has a normal value of 4-7 % in non-diabetic individuals.

Mean initial HbA1c value of all 50 patients recruited in the study was **8.61 ± 0.10 %.** Comparing the value of HbA1c among male and female patients, it was observed that female patients had a higher HbA1c value of **8.79 ± 0.13 %** as against **8.46 ± 0.13 %** in male patients.

6. Mean and Precentage (%) Decrease in HbA1c value of patients prescribed Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin after three months treatment:

Table 6. shows initial and final mean HbA1c values and decrease in mean HbA1c values at the end of three months treatment with Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin. Comparing the reduction in HbA1c values produced by the two treatment arms the difference was found to be statistically significant. (**$p < 0.05$**)

Overall reduction in HbA1c value to near normal of ≤ 7% was achieved in **7(28%)** patients in Sulphonylurea + Metformin group and in **5(20%)** patients in DPP-IV inhibitor + Metformin group

7. Tolerability:

The most commonly observed adverse events in Sulphonylurea + Metformin group were: **Abdominal Pain (**12%**), Cough (**12%**), Constipation (**8%**), Nausea (**4%**), Hypoglycemia (**20%**)** and **Drowsiness (**4%**).** On the other hand, in DPP-IV inhibitor + Metformin group only one patient developed **Hypoglycemia (**4%**)** suggesting better tolerability of DPP-IV inhibitors.

DISCUSSION : T2DM is a progressive metabolic disorder that requires a range of treatment options.[14] National and International Treatment Guidelines suggest starting monotherapy with Metformin and if glycemic objective of HbA1c < 7% is not achieved, a second agent with a different mechanism of action is added which is usually a second generation Sulphonylurea.[15,16]However Sulphonylurea therapy is associated with weight gain and a substantial risk of hypoglycaemia.[17] Another agent recommended as second line therapy for T2DM uncontrolled with Metformin is DPP-IV inhibitor which is reported to be better tolerated and is not associated with weight gain or increased risk of hypoglycaemia.[18,19,20]

Hence the present study was designed to compare efficacy and tolerability of Sulphonylurea + Metformin and DPP-IV inhibitors + Metformin in treatment of T2DM patients uncontrolled with Metformin alone. As is evident, both the combinations decrease BGLs over a period of 3 months with almost comparable values of glucose at the end of the study. Our results are in correlation with other studies which have reported improvement in glycemia of

Table 6: Mean and Precentage (%) decrease in HbA1c value of patients prescribed Sulphonylurea + Metformin or DPP-IV inhibitor + Metformin after three months treatment:

Parameter	Sulphonylureas + Metformin			DPP-IV inhibitor + Metformin			p value
	Initial HbA1c	HbA1c after three months	Decrease in mean HbA1c	Initial HbA1c	HbA1c after three months	Decrease in mean HbA1c	
HbA1c (%)	8.68 ± 0.14	7.36 ± 0.015	1.32 ± 0.12	8.61 ± 0.13	7.58 ± 0.11	1.03 ± 0.02	*0.021

patients uncontrolled with Metformin monotherapy, given Sulphonylurea or DPP-IV inhibitor in combination[21,22,23]

Various studies have reported that Indian patients have higher mean HbA1c values. Our observation of mean HbA1c of 8.65 ± 0.093 % as against the normal of < 7% correlates with the report of a study which states that patients enrolled in India have a numerically higher baseline value of HbA1c of 8.6 ± 1.1 % [5]

Our result of better tolerability of DPP-IV inhibitors as compared to Sulphonylurea is consistent with results reported previously. [24,25]

CONCLUSION: Results of the study lead to the conclusion that both treatment groups Sulphonylurea + Metformin and DPP-IV inhibitors + Metformin are equally effective in management of T2DM uncontrolled with Metformin. However, looking at tolerability aspect DPP-IV inhibitors seem to be more safe and tolerable as compared to Sulphonylureas.

Also we observed that baseline mean BGLs as well as baseline HbA1c levels were higher in females as compared to males.

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