Comparative Evaluation of DPP-IV Inhibitors and other Oral Hypoglycaemic Agents used Either Alone or in Combination with Reference to Glycemic Targets in Patients with Type 2 Diabetes Mellitus

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ABSTRACT

Introduction: This study assumes significance as it compares head on DPP-IV inhibitors along with other oral hypoglycemic agents with respect to glycemic and non-glycemic targets. Study was done to evaluate the DPP-IV inhibitors and other oral hypoglycemic agents (OHA) either alone or in combination, with reference to glycemic targets like fasting plasma glucose (FPG), post prandial glucose (PPG) and glycosylated hemoglobin (HbA_{1c}) in type 2 diabetes mellitus.

Material and Methods: This was an open labelled comparative study and included 90 patients with Type 2 DM. These patients were divided into 3groups: Each group was containing 30 patients i.e. Group A: DPP-IV inhibitors (n= 30); Group B: Oral hypoglycemic agents other than DPP-IV inhibitors (n= 30) and Group C: DPP-IV inhibitors + other oral hypoglycemic agents (n= 30). The patients were given drugs on the basis of physician's discretion, depending upon the glycemic of the patients at the time of presentation. A detailed history regarding age, sex, profession, duration of disease, treatment history, family history and personal history was taken for each patient. After stabilization patients observed at 0 weeks, 6 weeks, 12 weeks and 24 weeks.

Results: Mean duration of diabetes was 5.35±0.53 years, and the mean age of onset of diabetes was 46.98±0.91years. There was no significant difference between the study groups with respect to FPG, PPG, and HbA1c levels. The HbA1c showed significant improvement in each group at the end of study period.

Conclusion: In summary, this study showed that treatment with sitagliptin, either alone or in combination with other oral hypoglycemic agent led to clinically meaningful reductions in HbA1c, FPG and PPG over a 24 week period. Sitagliptin presents an alternative therapeutic strategy for patients with type 2 diabetes and, in general, showed significant improvements in glycemic control and is well tolerated, particularly with regard to weight change and hypoglycemia.

Keywords: Diabetes Mellitus, Oral Hypoglycemic Agents, DPP-IV Inhibitors, Glycaemic Control, Glycosylated hemoglobin

INTRODUCTION

Diabetes mellitus is a metabolic disorder with common denominator of hyperglycemia, arising from a variety of pathogenic mechanisms. It has emerged as an epidemic both in the developing and developed countries and shows no signs of regression.[1] India, the world's second most populous country, is also world's second most populous with reference to type 2 diabetes (≈61.3 million), first being China. Type 2 Diabetes mellitus is rapidly increasing and is a major public health problem globally with a prevalence of 6 % in 2007 which is expected to rise to 7.3% in 2025.This means there would be near 80 million diabetics by 2025. It poses a major health, social and economic burden on the society.[2]

Glycaemic management in type-2 diabetes mellitus has become increasingly complex and, to some extent, controversial, with a widening array of pharmacological agents now available.[3,4] It mounts concerns about their potential adverse effects and new uncertainties regarding the benefits of intensive glycaemic control on macrovascular complications.[5,6] The strict glycemic control is necessary to prevent diabetic complications. However strict glycemic control is associated with frequent hypoglycemic effects. It is even observed that it does not produce any cardiovascular benefits. This forms the rationale of using more than one pharmaco-therapeutic agent with varied mechanisms of action to not only target hyperglycemia but also non glycemic parameters.[7]

Treatment of type 2 diabetes is based on interplay of patient characteristics, severity of hyperglycemia and available therapeutic options. Metformin, sulfonylureas (SU) and thiazolidinediones (TZD) are the most studied of the oral

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medications used worldwide. They play a prominent initial role in the type 2 diabetes treatment algorithm recommended by the American Diabetes Association (ADA) and the European Diabetes Association for the Study of Diabetes (EASD).[8] Metformin is considered first-line therapy unless not tolerated or contraindicated. Second-line therapy then includes SUs, TZDs, dipeptidyl peptidase-IV (DPP-4) inhibitors, glucagon-like polypeptide-1 (GLP-1) agonists or insulin. DPP-4 inhibitors are relatively newer and are the only oral agent in the incretin family of therapeutic targets. In addition, multiple oral medications have been approved for the treatment of type 2 diabetes that is less widely used.[9] The American Diabetes Association / European Society for the Study of Diabetes consensus algorithm for the treatment of type 2 Diabetes mellitus endorses the use of newer class of drugs, the incretins or incretin based therapies, either alone or in combination. Incretin based therapy, specially DPP-IV inhibitors is a unique class of drugs, which prevent the rapid degradation of endogenous Glucagon like Peptide-1(GLP-1) and Glucose dependent insulinotropic polypeptide (GIP) and increase the level of intact active form of endogenous GLP-1.[10] The DPP-IV (Dipeptidyl peptidase) inhibitors increase insulin concentrations in a glucose dependent fashion. Other advantages are little or no hypoglycemia, improvement in Fasting and Post Prandial hyperglycemia, no weight gain, decrease in appetite, reduced HbA1C level by an average of 0.8% and an improved β-cell function.[1]

For anti-hyperglycaemic management of type 2 diabetes, the comparative evidence basis to date is relatively lean, especially beyond metformin monotherapy.[11] There is a significant need for high-quality comparative effectiveness research, not only regarding glycaemic control, but also regarding non glycaemic parameters. As new medications are introduced for type 2 diabetes, their benefit and safety should be demonstrated in studies to provide meaningful data on meaningful outcomes. This study assumes significance as it compares head on DPP-IV inhibitors along with other oral hypoglycemic agents with respect to glycemic.

MATERIAL AND METHODS

This study was carried out in the departments of Pharmacology and Medicine at Shri Guru Ram Rai Institute of Medical and Health Sciences (SGRRIM and HS), Dehradun, Uttarakhand, India. Prior to initiation of study approval of institutional ethics/research committee and written informed consent from the patient/legal guardian of the patient were obtained after full explanation of elements contained in the research protocol. All Type-2 DM patients diagnosed as per ADA criteria, attending the medicine outpatient department and inpatient department were included in the study. The duration of the study was one year from January 2013 to December 2013.

Inclusion Criteria

- Patients aged between 18-70 years
- Either sex
- Established diagnosis of Type 2 Diabetes mellitus

Exclusion Criteria

- Age less than 18 years or more than 70 years
- Type 1 Diabetes mellitus
- Secondary Diabetes mellitus
- History of hypersensitivity/ allergy to any drug
- Gestational Diabetes mellitus
- Pregnancy and lactation
- Patient with impaired renal or hepatic function.
- History of any other severe systemic illness.

Study Groups

This was an "Open labelled comparative trial" and included 90 patients with Type 2 DM. These patients were divided into 3groups: Each group containing 30 patients.

- Group A: DPP-IV inhibitors (n= 30)
- Group B: Oral hypoglycemic agents other than DPP-IV inhibitors (n= 30)
- Group C: DPP-IV inhibitors + other oral hypoglycemic agents (n= 30)

The patients were given drugs on the basis of physician's discretion, depending upon the glycemic and non-glycemic parameters of the patients at the time of presentation. A detailed history regarding age, sex, profession, duration of disease, treatment history, family history and personal history was taken for each patient. Thorough clinical examination was done in each case including weight, height, waist circumference and hip circumference. Patients were stabilized initially for a period of 2 weeks with the drugs and doses mentioned below:

Group **A**: DPP-IV inhibitors (Sitagliptin 100mg) once daily 30 minutes before breakfast.	Group **B:** Oral hypoglycemic agents other than DPP-IV inhibitors (Metformin 500mg+ Glimepiride 1mg) once daily 30 minutes before breakfast.	**Group C:** Combination of DPP-IV inhibitors+ other oral hypoglycaemic agents (Metformin 500mg+ Sitagliptin 50mg) once daily 30 minutes before breakfast.

After stabilization patients observed at 0 weeks, 6 weeks, 12 weeks and 24 weeks. Fasting plasma glucose (FPG), post prandial plasma glucose (PPG), body mass index, waist circumference, hip circumference, and waist: hip ratio was measured in every visit. HbA1c (glycosylated hemoglobin), lipid profile was measured at -2 and 24 weeks. For FPG patients were fasted for at least 8 hours. Levels were estimated by hexokinase glucose-6-phosphate dehydrogenase (by micro slide vitros-250). PPG readings were taken after 2 hours of standard meal. Levels were estimated by hexokinase glucose-6-phosphate dehydrogenase (by micro slide vitros-250). HbA1c was measured by HPLC method with glycosylated hemoglobin kit.

Statistical analysis

The data so obtained was evaluated in terms of comparison of HbA1c, FBG, and PPG. The treatment groups were compared

and results were analyzed by paired t test. Intergroup comparison was done using Analysis of Variance (ANOVA) test. P value ≤ 0.05 was considered to be significant.

RESULTS

The present study was done for comparative evaluation of DPP-IV inhibitors and other OHAs either alone or in combination, with reference to glycemic targets like FPG, PPG, and HbA1c in type 2 diabetes mellitus in a tertiary health care setup. The study was conducted in SGRRIM and HS, Patel Nagar Dehradun.

All the consecutively diagnosed patients, aged between 18 to 70 years, attending the medicine OPD of SGRRIM and HS, over a period of one year, starting from January 2013 to December 2013 were included in the study. The patients were diagnosed as having type 2 diabetes mellitus based on the diagnostic guidelines laid down by the American Diabetic Association and recruited in the study as per the research protocol. A total of 90 patients were included in the study which was divided into 3 groups of 30 patients each:

Group A: DPP-IV inhibitors (sitagliptin 100mg) (n= 30)

Group B: Oral hypoglycemic agents other than DPP-IV inhibitors (metformin 500mg+ glimepiride 1mg) (n= 30)

Group C: DPP-IV inhibitors+other OHAs (metformin 500mg+ sitagliptin 50mg) (n= 30)

The enrolled patients were stabilized for a period of 2 weeks. After stabilization, the patients were continued the same treatment as per their respective group. Patients were assessed for both efficacy and safety of these drug groups at the end of the study period. All the included patients completed the study and were statistically analyzed. All the results were expressed in Mean ±SEM. Total no of patients included were 90 with a mean age of 52.3±0.95 years. All values expressed in Mean ± SEM. Mean duration of diabetes was 5.35±0.53 years, and the mean age of onset of diabetes was 46.98±0.91years. Male: Female ratio was 43:47 (47.78%, 52.22%). Positive family history of diabetes mellitus was present in 35 (38.89%) patients [Table 1].

The baseline values of FPG, PPG, HbA1c, waist hip ratio (WHR), body mass index (BMI) and lipid profile were comparable in all the groups. All the values were expressed in Mean ± SEM. The mean FPG at the start of study in group A was 179.87±1.41 mg/dL, in group B was 180.70 ±

Total No. of Patients		**90**
Sex	Male	43 (47.78%)
	Female	47 (52.22%)
Mean age [Yrs]		52.3±0.95
Mean duration of diabetes [Yrs]		5.35±0.53
Mean age of onset of diabetes [Yrs]		46.98±0.91
Positive family history of diabetes mellitus		35 (38.89%)

Table-1: Demographic profile of patients included in the study

Parameters	**Group A (n=30)**	**Group B (n=30)**	**Group C (n=30)**
FPG (mg/dL)	179.87 ± 1.41	180.70 ± 5.49	185.86 ± 5.99
PPG (mg/dL)	225.93 ± 3.54	235.60 ± 6.25	239.37 ± 7.52
HbA1c	8.91 ± 0.11	8.79 ± 0.11	8.98 ± 0.13

(Group A- DPP-4 inhibitors, Group B -OHA, Group C-DPP-4 inhibitors+ OHA)
(FPG- Fasting blood glucose, PPG- Postprandial blood glucose, HbA1c- Glycosylated hemoglobin, OHA- Other oral hypoglycemic agents)

Table-2: Baseline characteristics of the patients in the study drug groups (-2 week) (All the values are expressed in Mean ± SEM)

Groups (n=30)	**FPG**		**p value**	**FPG**		**p value**
	-2 weeks (mg/dL)	**0 weeks (mg/dL)**		**-2 weeks (mg/dL)**	**0 weeks (mg/dL)**	
A	179.87±1.41	166.60±1.20	< 0.001	225.93±3.54	211.83±3.35	< 0.001
B	180.70±5.49	164.40±5.09	< 0.001	235.60±6.25	209.90±8.29	< 0.001
C	185.86±5.99	167.30±5.69	< 0.001	239.37±7.52	214.53±5.64	< 0.001

(Group A- DPP-4 inhibitors, Group B -OHA, Group C-DPP-4 inhibitors+ OHA)

Table-3: Changes in FPG and PPG (mg/dL) during titration period

Groups (n=30)	**-2 weeks (mg/dL)**	**0 weeks (mg/dL)**	**6 weeks (mg/dL)**	**12 weeks (mg/dL)**	**24 weeks (mg/dL)**
FPG (mg/dL)					
A	179.87±1.41	166.60±1.20	154.30±1.18	144.60±1.19	136.90±1.25
B	180.70±5.49	164.40±5.09	143.80±4.30	138.20±3.35	127.30±2.31
C	185.86±5.99	167.30±5.69	145.70±4.88	133.06±3.88	125.16±2.48
PPG (mg/dL)					
A	225.93±3.54	211.83±3.35	188.43±3.39	173.20±2.68	164.43±2.34
B	235.60±6.25	209.90±8.29	186.57±6.90	170.50±5.96	160.83±4.40
C	239.37±7.52	214.53±5.64	177.90±4.15	164.40±2.86	156.93±2.10

Table-4: Progressive change in FPG & PPG (mg/dL) over the study period in different groups (All the values are expressed in Mean ± SEM)

Groups (n=30)	FPG		p value Intragroup	p value Inter-group 24 weeks	PPG		p value Intra-group	p value Inter-group 24 weeks
	0 week (mg/dL)	24 weeks (mg/dL)			0 week (mg/dL)	24 weeks (mg/dL		
A	166.60±1.20	136.90±1.25	< 0.001	A vs B= <0.01	211.83±3.35	164.43±2.34	< 0.001	A vs B= <0.01
B	164.40±5.09	127.30±2.31	< 0.001	B vs C= >0.05	209.90±8.29	160.83±4.40	< 0.001	B vs C= <0.05
C	167.30±5.69	125.16±2.48	< 0.001	C vs A= <0.001	214.53±5.64	156.93±2.10	< 0.001	C vs A= <0.001
p value Inter-group (A vs B vs C	>0.05	< 0.001			>0.05	< 0.001		

Table-5: Comparison of FPG and PPG at 0 weeks and 24 weeks

Groups (n=30)	-2 weeks	24 weeks	p value Intragroup	p value Intergroup at 24 weeks
A	8.91±0.11	7.93±0.10	< 0.001	A vs B= <0.01
B	8.79±0.11	7.32±0.11	< 0.001	B vs C= >0.05
C	8.98±0.13	7.09±0.13	< 0.001	C vs A= <0.001
p value Intergroup (A vs B vs C)	>0.05	< 0.001		

Table-6: Comparison of HbA1c between - 2 weeks and 24 weeks (all the values are expressed in Mean ± SEM)

Groups	Hypoglycemia Symptoms	Weight loss	Weight gain	Nausea/ Vomiting	Abdominal discomfort	URTI	Weakness/ Fatigue	Allergic reactions	Total number of adverse events
A	-	2	-	1	3	2	1	-	09 [30%]
B	3	1	2	2	3	-	1	-	12 [40%]
C	4	3	-	2	4	1	1	-	15 [50%]
Total	7	6	2	5	10	3	3	-	36 [40%]

Table-7: Adverse effects profile with the study drug groups over the study period

5.49 mg/dL and in group C was 185.86 ±5.99 mg/dL. The mean post prandial plasma glucose (PPG) at the start of study in group A was 225.93±3.54 mg/dL, in group B was 235.60±6.25 mg/dL and in group C 239.37±7.52 mg/dL. The mean glycosylated hemoglobin (HbA1c) at the start of the study in group A was 8.91 ± 0.11%, in group B was 8.79 ± 0.11% and in group C was 8.98 ± 0.13% [Table 2]. There was no significant difference between the study groups with respect to FPG, PPG, and HbA1c levels [Table 3, 4].

There was a significant improvement in FPG and PPG in all the study drug groups over the study period. Comparison was done in FPG and PPG values between 0 weeks and 24 weeks. In group A the FPG was changed from 166.60±1.20mg/dL to 136.90±1.25 mg/dL (p< 0.001) and in group B from 164.40±5.09 mg/dL to 127.30±2.31 mg/dL (p< 0.001) and in group C from 167.30±5.69 mg/dL to 125.16±2.48 mg/dL (p< 0.001). PPG was changed from 225.93±3.54 mg/dL to 164.43±2.34 mg/dL (p< 0.001) in group A, from 235.60±6.25 mg/dL to 160.83±4.40mg/dL (p< 0.001) in group B and from 239.37±7.52mg/dL to 156.93±2.10 mg/dL (p< 0.001) in group C [Table 4]. There was an extremely significant improvement in all the groups with respect to FPG and PPG at the end of the study period.

At the end of the study period, the three groups were compared for changes in FPG and PPG values. At 24 weeks FPG was in group A, B and C were 136.90±1.25mg/dl, 127.30±2.31mg/dl and 125.16±2.48 mg/dl. ANOVA test was used for intergroup comparison. There was a significant difference between the three groups (p< 0.001). The difference between group A and group B was highly significant (p< 0.01). The difference between group B and group C was insignificant (p>0.05) and between group A and group C was extremely significant (p <0.001) [Table 5].

PPG in groups A, B and C at 24 weeks were 164.43±2.34 mg/dl, 160.83±4.40mg/dl and 156.93±2.10 mg/dl respectively. There was a significant difference between the three groups (p< 0.001). The difference between group A and group B was highly significant (p< 0.01). The difference between group B and group C was significant (p< 0.05) and between group A and group C was extremely significant (p < 0.001) [Table 5].

The HbA1c showed significant improvement in each group at the end of study period. At the end of study period comparison was made in HbA1c values between -2 weeks and 24 weeks. In group A the HbA1c at -2 weeks was 8.91±0.1 and at 24 weeks was7.93±0.10 (p< 0.001). In group B at -2 and 24 weeks it was 8.79±0.11and 7.32± 0.11(p< 0.001) and in group C 8.97±0.13 and 7.09±0.13 (p< 0.001). Intergroup comparison of HbA1c was done at 24 weeks using ANOVA test and it was highly significant (p <0.001). In group A and B it was highly significant (p <0.01), between group A and C extremely significant (p <0.001) and between group B and C it was insignificant (p> 0.05) [Table 6].

All the patients were enquired for any adverse reactions due to study drugs throughout the study period. A total of 36 adverse drug reactions were observed during the study period (09 in group A, 12 in group B and 15 in group C. The predominant

adverse drug reactions were abdominal complaints like flatulence, bloating, diarrhoea and constipation (10 patients), followed by hypoglycaemia symptoms (7 patients), weight loss (6 patients), nausea /vomiting (5 patients), upper respiratory tract infection (URTI) and weakness/ fatigue in 3 patients each and weight gain in 2 patients [Table 7]. All the adverse drug reactions were mild and transient and did not require alteration or discontinuation of study drugs.

DISCUSSION

The prevalence of type 2 diabetes particularly in the Indian subcontinent is increasing enormously over the recent years. For the physicians to be able to use these new drugs for pharmacotherapy, clinical trials which evaluate the efficacy and safety of these drugs are important. Metformin is the most commonly used oral antihyperglycemic agent both as monotherapy and in combination with other agents. Combination of glimepiride with metformin is a well-established therapy for type 2 diabetes mellitus. In India there is a dearth of data regarding results of use of DPP-4 inhibitors in the Indian population.[12] Recent advances in the understanding of the physiological functions of incretins and their degrading enzyme dipeptidyl-peptidase (DPP)-4 have led to the 'discovery' of a new class of oral anti-diabetic drugs.

DPP-4 inhibitors represent a novel therapeutic approach for the treatment of patients with type 2 diabetes. In larger clinical trials, DPP-4 inhibitors provide clinically meaningful reductions in HbA1C and in fasting and postprandial glucose concentrations and were well tolerated either as monotherapy or as add-on therapy to metformin or glimepiride.[13,14] Trial by Bennett et al reviewed one 12-week moderately-sized double blind RCT compared high dose sitagliptin with maximum dose glipizide and found similar reductions in HbA1c, -0.77% versus -1.00%, for DPP-4 inhibitor and SFU respectively.[15] Additional studies comparing sitagliptin or sulfonylurea add-on therapy to metformin have shown similar results for reduction of HbA1c, but not favouring either agent.[16,17]

On the basis of previous observations, we compared DPP-4 inhibitors either alone or in combination with other oral hypoglycaemic agents with reference to glycemic and non-glycemic targets in patients with type 2 diabetes mellitus. A total of 90 patients suffering from type 2 diabetes mellitus were included in the study which were randomly divided into three groups each consisting of 30 patients at the time of enrolment: Group A patients were put on sitagliptin, Group B were put on metformin + glimepiride and Group C patients were given a combination of sitagliptin and metformin.

The efficacy of oral hypoglycemic agents used in our study was assessed in terms of glycemic control using various tests like fasting and post prandial glucose levels and glycosylated hemoglobin. In addition the non-glycemic parameters like lipid profile and anthropometric changes were also measured.

Type 2 diabetes mellitus is commonly seen in middle age individuals especially after 50 years of age (Table 1).[18] The mean age in our study was 52.3 years which was seen in collaboration with previous studies where the average age was 53.51 years and 58.3 years respectively. In this study the male: female ratio was 43:47. Females outnumber males which may be due to their more sedentary and diabetogenic lifestyle. This was similar to previous studies by Bennett P et al and Howteerakul et al which showed higher prevalence of type-2 diabetes in women than in men.[19,20] In the present study 35 patients had a positive family history indicating either one or both the parents had type 2 diabetes which was at one stage or the other transferred from one generation to another.[21]

The average duration of diabetes mellitus in the present study was 5.35 years which was seen in collaboration with previous study by Hyun et al where the mean duration was 5.89 years. The mean changes in FPG in group A, B and C during titration phase were 13.27, 16.3 and 18.56 mg/dl respectively. The mean changes in PPG were 14.1, 25.7 and 24.84 mg/dl respectively. All the three groups showed a good control in glycemic index measured by fasting and post prandial glucose levels during the titration phase which was highly significant ($p < 0.001$). This was in accordance with previous studies where efficacy of oral antidiabetics has been well documented.[22-25]

The total study period of 24 weeks showed a good control in FPG, PPG and HbA1C in all the three study groups. The mean changes in FPG from 0 to 24 weeks in groups A, B and C were 29.7mg/dl, 37.1mg/dl and 42.14 mg/dl respectively. The improvement was highly significant for all three groups ($p < 0.001$). The mean changes in PPG were 47.4mg/dl, 49.07mg/dl and 57.6 mg/dl respectively. This was highly significant for all the three groups ($p<0.001$). This was in accordance with previous studies by Goldstein B J et al[25] and Hermansen K et al[26] where the effects of sitagliptin either alone or in combination with other oral hypoglycemic have been well documented. The mean changes in HbA1c from baseline to 24 weeks in the three groups were 0.98%, 1.47% and 1.89% respectively. This was highly significant in all study groups ($p<0.001$). Previous studies by Raz I et al[23], Bennett et al[19] and Hermansen K et al[26] have proven the improvement in HbA1C by Sitaglipitn either alone or in combination with other oral hypoglycemic agents. The present study supported the use of Sitagliptin as monotherapy as the improvement in all glycemic parameters was comparable with other oral hypoglycemics.

At the end of study period, the intergroup comparison between groups A, B and C were done for FPG, PPG and HbA1c which were highly significant ($p < 0.001$) indicating that the group where combination of sitagliptin and metformin was given, had a better glycemic control as compared to groups where sitagliptin and metformin + glimepiride were used. This was comparable with previous study by Goldstein BJ et al. where combination of sitagliptin and metformin had better glycemic control with respect to FPG, PPG and HbA1c.[25]

Safety assessment in study drug groups: Few adverse drug reactions were noted during the study period which were mild and did not require any alteration or discontinuation of study drugs. A total of 36 adverse drug reactions were

noted during the entire study period. The most common reactions were hypoglycemia, abdominal discomfort, weight loss, weight gain, nausea/vomiting, upper respiratory tract infections and weakness/fatigue. Abdominal discomfort was commonly seen with most of the antidiabetic drugs which has been well documented in previous studies.[25] Hypoglycemia was seen in 3 patients in group B and 4 patients in group C. No patients complained of hypoglycemia in the group which received DPP-4 inhibitors alone. Hypoglycemia is an uncommon complication of DPP-4 inhibitors. In a meta-analysis of clinical trials by Drucker DJ et al[27] and Amori RE et al[28] there were lower incidences of hypoglycemia with DPP-4 inhibitors. The incidence of hypoglycemia with other oral hypoglycemicshas been proven in many previous studies. Other adverse drug reactions were similar in all the study groups which were similar to the study by Goldstein et al.[25]

The efficacy and safety of Sitagliptin either alone or in combination with other oral hypoglycemics was assessed in his 24 week study in patients with type 2 diabetes mellitus. By inhibiting the degradation of active incretins, sitagliptin increases active incretin concentrations, thereby enhancing their glucoregulatory effects.[29]

In the present study all the three groups showed improvement in HbA1c, FPG, PPG and Lipid profile at the end of study period. The group with a combination of Sitagliptin and Metformin provided a greater reduction in all glycemic targets relative to other groups. DPP-4 inhibitors and other oral hypoglycemics have different mechanisms, thus predicting a potential complementary effect on lowering glucose levels.[30]

Study limitations: This was an open label study. The patients and the doctor were aware of the prescribed drugs. Hence there are more chances of errors. Secondly the sample size was small. Only 90 patients were included in the study which may not be sufficient enough to demonstrate intergroup differences in efficacy of study drugs. Thirdly the duration of follow up was just upto 24weeks. A longer follow up period may have yielded different results. Hence keeping these limitations in view, further studies with larger sample size and longer duration are needed to evaluate the magnitude of the antidiabetic effects of DPP-4 inhibitors.

CONCLUSION

Type 2 Diabetes mellitus affects middle aged patients and is more prevalent in males than females. There was an improvement in FPG, PPG and HbA1c in all the study drug groups at the end of study period. At the end of study period, the intergroup comparison showed highly significant improvement in FPG, PPG and HbA1c, indicating that the patients receiving DPP-4 inhibitors+ other oral hypoglycemic agents had a better glycemic control than the patients receiving DPP-4 inhibitors alone or other oral hypoglycemic agents. The study drug groups were similar with respect to the safety profiles. No patient discontinued the study or changed the treatment because of the adverse effects.

To conclude, all the patients showed improvement in glycemic parameters like FPG, PPG and HbA1c at the end of study period. Intergroup comparison revealed better glycemic control in patients receiving DPP-4 inhibitors+ other oral hypoglycemic agents. But further larger studies with more number of patients are needed to evaluate the magnitude of antidiabetic effects of DPP-4 inhibitors.

REFERENCES

1. Powers AC, D'Alessio D. Endocrine Pancreas and Pharmacotherapy of Diabetes Mellitus and Hypoglycemia. In: Brunton LL, Chabner BA, Knollman BC, editors. Goodman and Gilman's The Pharmacological Basis of Therapeutics 12th ed. New York: McGraw-Hill; 2011:p.1237-1273.
2. IDF Diabetes Atlas 5th Edi. (www.idf.org/print/diabetesatlas/5e/the-globalburden).
3. Bolen S, Feldman L, Vassy J et al. Systematic review: comparative effectiveness and safety of oral medications for type 2 diabetes mellitus. Ann Intern Med 2007; 147:386–99.
4. Bergenstal RM, Bailey CJ, Kendall DM. Type 2 diabetes: assessing the relative risks and benefits of glucose-lowering medications. Am J Med 2010;123:e9–e18.
5. Greenfield S, Billimek J, Pellegrini F et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study. Ann Intern Med 2009; 151:854–60.
6. Matthews DR, Tsapas A. Four decades of uncertainty: landmark trials in glycaemic control and cardiovascular outcome in type 2 diabetes. Diab Vasc Dis Res 2008; 5:216–18.
7. Hyun JJ, Tae OK. Comparison of vildagliptin-metformin and glimepride-metformin treatments in type 2 diabetic patients. Diabetes Metab J 2011; 35:529-35.
8. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycaemia in type 2 diabetes: A patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2012; 55:1577–96.
9. Stein S A, Lamos EM, Davis SN. A review on efficacy and safety of oral antidiabetic drugs. Expert Opin Drug Safety 2013;12:153-75.
10. Cobble M. Differentiating among incretin-based therapies in the management of patients with type 2 diabetes mellitus. Diabetology and Metabolic Syndrome 2012;4:1-10.
11. Bennett WL, Maruthur NM, Singh S et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med 2011; 154:602–13.
12. Srivastava S, Saxena GN, Keshwani P. Comparing the Efficacy and Safety Profile of Sitagliptin Versus Glimepiride in Patients of Type 2 Diabetes Mellitus Inadequately Controlled with Metformin alone. JAPI 2012;60:27-30.
13. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Khatami H. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in

patients with type 2 diabetes mellitus. Diabetologia 2006; 49:2564–71.
14. Aschner P, Kipnes MS, Lunceford JK,Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2diabetes. Diabetes Care 2006; 29:2632–37.
15. Bennett WL, Wilson LM, Bolen S, Maruthur N, Singh S, Chatterjee R. Oral Diabetes Medications for Adults with Type 2 Diabetes: An Update [Internet]. Available at https://www.ncbi.nlm.nih.gov/pubmed/21735563
16. Arechavaleta R, et al. Efficacy and safety of treatment with sitagliptin or glimepiride in patients with type 2 diabetes inadequately controlled on metformin monotherapy: a randomized, double-blind, non-inferiority trial. Diabetes Obes Metab, 2011;13:160-8.
17. Goke B, et al. Saxagliptin is non-inferior to glipizide in patients with type 2 diabetes mellitus inadequately controlled on metformin alone: a 52-week randomised controlled trial. Int J Clin Pract 2010;64:1619-31.
18. JC Fredric, EC Jonathan. Recent antihyperglycemic prescribing trends for U.S. Privately Insured Patients with Type 2 Diabetes. Diabetes Care 2003; 26:1847-51.
19. Bennett P, Rewers M, Knowler W. Epidemiology of diabetes mellitus. In Porte D Jr, Sherwin RS, eds. Ellenberg & Rifkin's Diabetes Mellitus: Theory and Practice, 5th ed. New York, Elsevier Science 1997;373-400.
20. Howteerakul N, Suwannapong N, Rittichu C, Rawdaree P. Adherence to regimens and glycemic control of patients with type 2 diabetes attending a tertiary hospital clinic. Asia Pac J Public Health. 2007;19:43-9.
21. Mc Carthy M, Menzel S. The genetics of type 2 diabetes. Br J Clin Pharmacol 2001;51:195-99.
22. Zaman GS, Zaman FA, Arifullah M. Comparative risk of type 2 diabetes mellitus among vegetarians and non-vegetarians. Indian J Community Med 2010;35:441-2
23. Raz I, Hanefeld M, Xu L, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes mellitus. Diabetologia. 2006; 49:2564–71.
24. Gavin JR 3rd, Bohannon NJ.A review of the response to oral antidiabetes agents in patients with type 2 diabetes. Postgrad Med 2010;122:43-51.
25. Goldstein BJ, Feinglos MN, Lunceford JK, et al. Effect of initial combination therapy with sitagliptin, a dipeptidyl peptidase-4 inhibitor, and metformin on glycemic control in patients with type 2 diabetes. Diabetes Care 2007; 30:1979–87.
26. Hermansen K, Kipnes M, Luo E, et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor,sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or on glimepiride and metformin. Diabetes Obes Metab. 2007; 9:733–45.
27. Drucker DJ, Nauck MA The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. Lancet 2006; 368:1696–1705.
28. Amori RE, Lau J, Pittas AG. Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. JAMA 2007;298:194–206.
29. Herman GA, Bergman A, Stevens C, et al. Effect of single oral doses of sitagliptin, a dipeptidyl peptidase-4 inhibitor, on incretin and plasma glucose levels after an oral glucose tolerance test in patients with type 2 diabetes. J Clin Endocrinol Metab 2006; 91: 4612–4619.
30. Dicker D. DPP-4 inhibitors: Impact on glycemic control and cardiovascular risk factors. Diabetes Care 2011;34:276-78.

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