

A Retrospective Comparison Study between the Effectiveness and Safety of Fixed Dose Combination of Vildagliptin versus Sitagliptin with Metformin in Type 2 Diabetes Mellitus Patients

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ABSTRACT

Aim: To compare the effectiveness and safety of fixed dose combination of vildagliptin 50mg versus sitagliptin 50mg with metformin 500mg in Type 2 Diabetes Mellitus patients. **Method:** Retrospectively 160 subjects were divided into two groups: A and B, in group A 80 subjects received a fixed dose combination of sitagliptin 50mg with metformin 500mg and 80 subjects in group B received a fixed dose combination of vildagliptin 50mg with metformin 500mg for a period of 24 weeks. Glycated hemoglobin, fasting plasma glucose, postprandial glucose, bodyweight, potassium, microalbuminuria and creatinine were evaluated as outcomes parameters while safety was evaluated by reporting adverse event including hypoglycemic effect. **Results:** Both groups have shown a greater reduction in plasma glucose parameter: glycated hemoglobin reduced up to 0.97% ($P < 0.000$) for vildagliptin group versus 0.928% ($P < 0.000$) in sitagliptin group, fasting plasma glucose reduced up to 27.46mg/dl ($P < 0.000$) in vildagliptin group versus 20.925mg/dl ($P < 0.019$) for sitagliptin and postprandial glucose reduced up to 42.25mg/dl ($P < 0.000$) for vildagliptin versus 35.260mg/dl ($P < 0.000$) for sitagliptin. There were no significant alteration in kidney parameters in both groups: potassium, creatinine, micro albuminuria, body weight was increased by one kilogram (1.02kg) in sitagliptin group whereas it was reduced by 0.47kg in vildagliptin group. The incidence of hypoglycemic effect were comparable less in both group 6.25% in vildagliptin group versus 5% in sitagliptin group other adverse drug reactions GIT was mild in both group did not require any alteration or discontinuation of the drugs. **Conclusion:** Both drugs are effective and safe in the management of type 2 diabetes mellitus. These drugs improve plasma glucose and are safe from hypoglycemic effect and they are not associated with the increase of body weight. However, vildagliptin offer a superior benefit over sitagliptin in the management of type 2 diabetes mellitus

Key words: Type 2 Diabetes Mellitus, Sitagliptin, Vildagliptin, Metformin.

DOI: 10.5530/ijopp.11.4.37

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INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a chronic metabolic disorder occur due to the body does not respond to the insulin produced from pancreas¹ or due to a decreased secretion of insulin^{2,3} (or) sometime a combination of the two.⁴ It is characterized by rised of blood glucose level,⁵ increased thirst, frequent urination, increased hunger, retardation of wound healing etc.⁶ according to the data International Diabetes Federation (IDF)

in the last three decades the incidence of diabetes mellitus has boosted from 30 million in 1985 to 425 million in 2018, and it is set to reach 629 million by 2045 When it is not appropriately managed^{7,8} the management of diabetes require a combination of drug therapy and life style modifications.⁹ British National Institute for Health and Care Excellence (NICE), the American Diabetes Association (ADA) and the European



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Association for the Study of Diabetes (EASD) along with life style modification: recommend early intervention with single oral monotherapy antidiabetic agents¹⁰ In Types 2 diabetes mellitus although monotherapy may be adequate initially, a large number of patients do not achieve adequate glycemic control.¹¹ Dose adjustment and progression to multiple diabetes therapies are required to maintain target HbA1c levels. Metformin is the first line drug for management of hyperglycemic recommended by NICE, ADA and EASD which can be used as single or in combination therapy.^{10,12} metformin works by increasing glucose uptake and improving sensitivity of body tissues to insulin^{13,14} which helps the insulin produced by body to be efficaciously used to control blood sugar and it also acts by suppressing hepatic glucose production. Nausea, abdominal discomfort, vomiting and diarrhea are possible side effects of metformin.¹⁵ In addition to metformin therapy a health care practitioner also recommends lifestyle changes: such as losing weight, eating healthy diet.¹⁶ Only a single drug therapy is suggested when HBA1c is less than 7.5% whereas if glycated hemoglobin is above 9% a combination of two or more drug therapy^{17,18} are required. After metformin (a Biguanide) prescribed as first-line drug; sulfonylurea, DPP-4 inhibitors, SGLT2 inhibitors, Meglitinides, GLP-1 analogues or insulin can be added to metformin. However, in the current clinical practice the American Diabetes Association/European Association for the Study of Diabetes consensus algorithm for the treatment of Type 2 DM endorses the use of newer class of drugs, the incretins or incretin-based therapies such as DPP-4 inhibitors, either alone or in combination.¹⁹

The desired goal in all is to control blood glucose levels and to prevent microvascular and macrovascular complications²⁰ When a fixed dose combination of metformin with DPP-4 inhibitors is used it increases compliance in patients rather than taking a free drug combination of metformin with other oral anti-diabetic agents; Under this category of dipeptidyl peptidase-4 inhibitors:²¹ Sitagliptin was approved by FDA in 2006, vildagliptin approved in 2008, saxagliptin approved in 2009 and Alogliptin in year 2010 and last Linagliptin was approved by FDA in year 2011. DPP-4 Inhibitor are incretin-based therapy which reduce blood sugar by promoting insulin secretion, decreasing glucagon production,²² delaying gastric emptying, increasing satiety without inducing hypoglycemia and there are also not associated with weight gain²³ among the diabetes mellitus patients. Sitagliptin has a good oral bioavailability, which goes up to 87 percent,²⁴ Its half-life is 14.4 hrs there is dose dependent inhibition of DPP-4 activity and approximately 80 percentage of enzyme activity is inhibited for 24 hr at 100mg.¹² Studies have shown that

Sitagliptin has no clinical significant interactions with other medications.²⁵ The drug is excreted through the urine by the tubular secretions. Hence, renal function should be monitored in case of renal insufficiency dose can be reduced to 50mg and 25mg for a creatinine clearance of 30 to 50mL/minute and less than 30mL/min respectively.²⁶ Vildagliptin is quickly absorbed and the maximum plasma concentration can be achieved between 1 hour and 1.5 hr²⁷ and almost 85% of the drug is absorbed the final half-life is 2.8 hr²⁸ but the complete removal from the body can last up to 7 days and it is mostly excreted from the urine while a remaining least fraction of absorbed drug is eliminated through feces.²⁹ Due to its short half-life when it is used as monotherapy or in combination with other anti-diabetes drugs a daily required dose is 100mg which is given as single or in divided doses.

This study is aimed to compare the efficacy and safety of Vildagliptin 50mg versus Sitagliptin 50mg fixed dose combination with metformin 500mg in Types 2 diabetes mellitus patients.

METHODOLOGY

Retrospectively data were collected from medical record department, a total number of 160 subjects were divided into two group: Group A and B respectively, 80 patients from group A received Sitagliptin in fixed dose combination with metformin 500mg whereas 80 patients from group B received Vildagliptin 50mg in fixed dose combination with metformin 500mg. the study was conducted at PSG Hospitals a tertiary care hospitals in both group patient with Type 2 Diabetes Mellitus prescribed with either only a fixed dose combination of vildagliptin 50mg with metformin 500mg or a fixed dose combination of sitagliptin 50mg with metformin 500mg in age ranging from 30-75 year old who visited hospital at least two times within 6 months study period were included, patient who took other antidiabetic drugs were excluded Glycated hemoglobin, fasting plasma glucose, postprandial glucose, bodyweight, potassium and creatinine, microalbuminuria were evaluated as outcomes parameters while safety was evaluated by reporting adverse event including hypoglycemic effect in both group selected for the study.

RESULTS

During the six month period of follow-up the results of the fixed dose combination of either vildagliptin or sitagliptin with metformin in group A and group B: Both groups have shown a greater reduction in plasma

Table 1: Patient characteristic before and after 24 weeks of the study.

	Vildagliptin Group (N=80)		Sitagliptin Group (N=80)	
	Before	After	Before	After
AGE (Year)	59.22 ± 8.50		56.80 ± 10	
GENDER(F/M)	38/42		24/56	
FPG (in mg/dl)	169.72±55.47	142.26±33.26	171.31±67.17	150.38±52.38
PPG(in mg/dl)	233.90±50.77	191.65±40.11	234.41±60.95	199.15±55.74
HBA1C percentage	8.64±2.09	7.67±0.97	9.02±2.20	8.09±1.36
CREATININE(in mg/dl)	1.35±1.19	1.22±0.95	1.04±0.86	1.07±0.92
POTASSIUM(meq/dl)	4.57±0.5	4.55±0.48	4.36±0.61	4.35±0.53
ALBUMINE(in mg/dl)	3.95±0.29	3.96±0.30	4.11±0.47	4.05±0.44
BODY WEIGHT (in Kg)	70.41±12.85	69.94±12.39	68.28±13.24	69.3±12.88

F: Female, M: male, Kg=kilogram, mg/dl = milligram per deciliter meq/dl= miliequivalent per deciliter N= Total Number ± = Mean SD

glucose parameter as Table 1: glycated hemoglobin reduced from 8.64 % ± 2.09 % to 7.67% ± 0.97% up to 0.97% ($P<0.000$) was reduced for vildagliptin group versus a change from 9.02% ± 2.20% to 8.09% ± 1.36% a total number of 0.928% ($P<0.000$) was reduced in sitagliptin group, fasting plasma glucose reduced up to 169.72±55.47mg/dl to 142.26±33.26mg/dl a total reduction of 27.46mg/dl ($P<0.000$) in vildagliptin group versus 171.31± 67.17 to 150.38 ± 52.38mg/dl a total reduction of 20.925mg/dl ($P<0.019$) for sitagliptin and postprandial glucose reduced from 233.90 ± 50.77 mg/dl to 191.65 ± 40.11 mg/dl a total reduction of 42.25mg/dl ($P<0.000$) for vildagliptin was seen versus a reduction from 234.41± 60.95mg/dl to 199.15 ± 55.74mg/dl a total reduction of 35.260mg/dl ($P<0.000$) for sitagliptin.

There were no significant alteration in kidney parameters in both groups: potassium, creatinine, microalbuminuria were remained near closer to the baseline for the period of the study which indicate that both drugs have a renal protection in the management of Type 2 diabetes mellitus patients, creatinine has reduced from 1.35 ± 1.19 to 1.22± 0.95 in vildagliptin whereas it has changed from 1.04± 0.86 to 1.07 ± 0.92, potassium changed from 4.57 ± 0.5 to 4.55 ± 0.48 in Vildagliptin versus to 4.36 ± 0.61 to 4.35 ± 0.53 in sitagliptin, microalbuminuria changed from 3.95 ± 0.29 to 3.96 ± 0.30 in Vildagliptin to 4.11 ± 0.47 to 4.05 ± 0.44 in Sitagliptin.

Body weight was increased from 68.28± 13.24Kg to 69.30 ± 12.88 kg near weight increased by one kilogram (1.02kg) from the baseline in sitagliptin group whereas it was reduced from 70.41 ± 12.85kg to 69.94± 12.39 kg a total of 0.47 kg was reduced from the baseline in vildagliptin group. The hypoglycemic effect and other adverse effect during the period of study patients who had co-morbidities such as hypertension, coronary artery diseases, myocardial infarction, cerebrovascular accident

(strokes), dyslipidemia and microvascular complications such as nephropathy, retinopathy and neuropathy didn't show any potential effect for discontinuations of the treatment or alterations of drug therapy during the period of the Study. 6.25% of patient who took 50mg Vildagliptin in fixed dose combination with metformin have developed hypoglycemic effect whereas there were 5% cases was found in the Sitagliptin group. The other minor adverse effect such as nausea and vomiting were comparable less for both groups.

DISCUSSION

Type 2 Diabetes Mellitus is commonly seen in middle age individuals especially after 50 years of age³⁰ in our study the mean average in age was 59.22 ± 8.50 in Vildagliptin group and 56.8 ± 10 in Sitagliptin group which show collaboration with previous study where the mean average age was 58.3 years,^{31,32} A difference of 0.04% in glycated hemoglobin was seen in Vildagliptin group over Sitagliptin which is comparable to a comparison study of the randomized trials conducted in Japan by signorovitch *et al.* showed a difference of 0.3% of reduction shown by Vildagliptin over sitagliptin.³³ in their study entitled efficacy and safety of Vildagliptin in clinical practice results of Vildagliptin-study demonstrated an average reduction of 0.9% in mean glycated hemoglobin after a six months of the treatment by Vildagliptin and Metformin which almost similar to the results of this study. Previous studies conducted by Reasner *et al.*³⁴ Pérez-Monteverde *et al.*³⁵ and Weinstein *et al.*³⁶ have proven that combination of Sitagliptin and metformin produces significant improvement in glyceic parameters such as FPG, PPG and HbA1c and also improve adherence in type 2 diabetes mellitus patient.

Renal parameters such as creatinine, potassium and microalbuminuria were evaluated on both group i.e.

Sitagliptin and Vildagliptin and there was no marked change in both groups which is similar to a study conducted by Naoto Kamatani *et al.*³⁷

Body Weight has been increased by 1.02kg in Sitagliptin group and a decreased to 0.47kg in mean average which is insignificant from the baseline which was in accordance with a study done by Xiaoling *et al.*³⁸ in a meta-analysis entitled DPP-4I treatment in Chinese type 2 diabetes mellitus and Mousa Al Omar *et al.*³⁹ in their study entitled Vildagliptin efficacy in combination with metformin among Jordanian patients with type 2 diabetes mellitus inadequately controlled with metformin.

The incidence of hypoglycemia was almost similar in both the study groups that is 6.25% for Vildagliptin and 5% for Sitagliptin, which is similar to a previous study by Chun-Jun Li *et al.*¹ another study by Deacon CP *et al.* the expert's opinions on DPP-4I confirm that that Sitagliptin and Vildagliptin are well tolerated on hypoglycemic effect and body weight gaining.⁴⁰

There was no potential cardiovascular event reported during a total duration of this study and it is confirmed with a study by Edoardo Mannucci *et al.*⁴¹ on their systematic review of integrated analyses and RCT on the cardiovascular safety of incretin based therapies in type 2 diabetes. The incidence of adverse drug reactions was mild in both groups and did not require any alteration or discontinuation of study drugs.

CONCLUSION

This comparison study between a fixed dose combination of Sitagliptin and Vildagliptin with metformin show that both drugs are effective and safe in the management of Type 2 diabetes mellitus. These drugs improve plasma glucose and are safe from hypoglycemic effect and they are not associated with the increase of body weight. However, Vildagliptin offer a superior benefit over Sitagliptin in the management of Type 2 diabetes mellitus

ACKNOWLEDGEMENT

We are pleased to thank Dr. R. Senthil Kumar MD, MRCP, Assistant Professor, Department of Endocrinology, PSG Hospitals for granting us permission and necessary support to carry out this study in his department. We express our sincere thanks to DR. M. Ramanathan, M.Pharm, Ph.D., Principal of PSG College of Pharmacy, Coimbatore for providing the necessary facilities and amenities to carry out our study with great ease, we express our special note of thanks to Dr. Anshuman

A. Gandhi M.Pharm, PhD., Associate Professor, Department of Pharmacy Practice, PSG College of Pharmacy, Coimbatore for her advice, sharing her constrictive and valuable ideas for completion of this study. We thank Dr. Vimalkumar Govindan, MSc. FRCS., Director of Medical Record Department and his team for allowing us to use MRD and helping hand in data collection. We thank our friend for their comments and ideas which are more important for successful completion of this work

CONFLICT OF INTEREST

The authors announced that there is no conflict of interest regarding this work of study.

ABBREVIATIONS

ADA: American Diabetes Association; **BID:** Twice Daily; **CGM:** Continuous Glucose Monitoring; **DM:** Diabetes Mellitus; **DPP-4I:** Di Peptidyl Peptidase 4 Inhibitors; **EASD:** European Association for the Study of Diabetes; **FDA:** Food and Drug Administration; **FPG:** Fasting Plasma Glucose; **GLP-1:** Glucagon-Like Peptide 1 analogues; **HbA1c:** Glycated Hemoglobin; **IDF:** International Diabetes Federation; **NICE:** British National Institute for Health and Care Excellence; **PPG:** Post Prandial Glucose; **SGLT-2:** Sodium Glucose Co-Transporter -2; **T2DM:** Type 2 Diabetes Mellitus.

SUMMARY

A fixed dose combination of vildagliptin or sitagliptin with metformin controls plasma glucose in Type 2 diabetes mellitus patients. In addition to this it also increase patient compliance.

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