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Original Research Article

A clinical investigational study on safety and effective management of type-2 diabetes mellitus patients by using sitagliptin

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ABSTRACT

Background: To study the health and efficiency of the more up to date oral hypoglycemic specialist sitagliptin in the executives of sort 2 diabetes mellitus patients. In our examination authors have enlisted 250 patients who met our investigation criteria of which authors ordered dependent on age and lab information, most of patients in the age bunch between 45-55 years (n=97, 39.2%), the RBS was diminished to Comparatively estimations of RBS, FBS, PPBS, HbA1C were decreased in follow up than benchmark esteem.
Methods: This simultaneous observational investigation was done when all is said in done department of General Medicine of Hi-Tech Medical College and Hospital, Bhubaneswar, Odisha for a time of 6 months in which type 2 diabetes mellitus patients were enrolled dependent on incorporation and avoidance criteria and were pursued to assess the adequacy and security of sitagliptin. Information was dissected by utilizing chart cushion crystal understudy T-test.
Results: Authors can presume that sitagliptin use was not related with any dangers and is compelling in the board of Type 2 diabetics, treatment with sitagliptin gave clinically significant decreases in HbA1C, RBS, FBS, PPBS by utilizing this investigation authors realize that gliptins are considerably more protected and powerful in the treatment of sort 2 diabetes mellitus.
Conclusion: Treatment with sitagliptin provided clinically meaningful reductions in HbA1C, RBS, FBS, PPBS by using this study authors know that sitagliptins are much more safe and effective in the treatment of type 2 diabetes mellitus.

Keywords: Diabetes mellitus, FBS, Glycosylated hemoglobin, Insulin, PPBS, RBS, Sitagliptin

INTRODUCTION

Diabetes mellitus refers to a group of diseases that affect how your body uses blood sugar (glucose). Glucose is vital to your health because it's an important source of energy for the cells that make up your muscles and tissues. It's also your brain's main source of fuel.[1]

The underlying cause of diabetes varies by type. But, no matter what type of diabetes you have, it can lead to excess sugar in your blood. Too much sugar in your blood can lead to serious health problems.[2]

Chronic diabetes conditions include type 1 diabetes and type 2 diabetes. Potentially reversible diabetes conditions include prediabetes - when your blood sugar levels are higher than normal, but not high enough to be classified

as diabetes - and gestational diabetes, which occurs during pregnancy but may resolve after the baby is delivered.[3]

Gliptins represent a novel class of agents that improve beta cell health and suppress glucagon, resulting in improved post-prandial and fasting hyperglycemia. Gliptins improve glycaemic control in type 2 diabetes and these are DPP-4 inhibitors. Sitagliptin, vildagliptin and saxagliptin are dipeptidyl peptidase-4 (DPP-4) inhibitors. Glucagon-like peptide-1 (GLP-1) and glucose dependent in sulinotropic polypeptide (GIP) are incretin hormones that stimulate insulin secretion and suppress glucagon.[4]

These incretin hormones are rapidly degraded by DPP-4. DPP-4 inhibitors enhance the effect of these incretin hormones by inhibiting DPP-4. A DPP-4 inhibitor may be used as monotherapy in the event of intolerance to metformin and is a useful second tier agent for use in combination therapy. DPP-4 inhibitors are not associated with weight gain. When used as monotherapy, hypoglycemia is rare with these agents. Dosage adjustments are required for renal insufficiency with Sitagliptin and Saxagliptin but not with Linagliptin.[5] DPP-4 inhibitor class of oral anti-diabetic agents selectively inhibits the DPP-4 enzyme that rapidly degrades two major incretin hormones, glucagon-like peptide-1 (GLP1) and glucose dependent insulinotropic polypeptide. DPP-4 inhibitors in 2011, analyzing the similarities and differences among members of the DPP-4 inhibitor class of oral anti-diabetic agents including their efficacy and safety profiles as monotherapy or in combination with metformin a sulfonylurea (SU) and/or a thiazolidinedione, and insulin.[6]

The review demonstrated that, although DDP-4 inhibitors produce a similar reduction in glycosylated hemoglobin (HbA1c) levels compared with other existing classes of oral glucose-lowering agents sitagliptin is an orally active, potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor in development for the treatment of patients with type 2 diabetes mellitus16. Sitagliptin acts through increasing active incretin hormone concentrations.[7]

METHODS

A concurrent observational study was carried out in outpatient and inpatient units of general medicine department of Hitech Medical College and Hospital, Bhubaneswar, Odisha, India the research protocol has been prepared. The study duration was six months. Approximately 250 patients were taken as sample size. The criteria for inclusion was patients between the age of 18 to 80 years, newly diagnosed with diabetes mellitus patients, those who are on irregular treatment with currently available OHAs and Patients who are not responded to current OHAs (or) not controlled their blood glucose levels with current drugs.[8] The type 1 diabetes, Diabetics with other co-morbid conditions, pregnant population, those who are on steroid and immunosuppressive therapies was excluded from our study. After enrolling the subjects, the history taking from the patients was performed, the data was collected on self-prepared data collection case note. The data collected was demographic details, past medical history, family history and personal history like dietary habits, socioeconomic status.[9]

Also the base line values of RBS, FBS, PPBS and HbA1C were collected at the initial recruitment of subjects and after treatment administration follow ups were done at ingestion of a meal, incretins, including glucagonlike peptide-1 (GLP-1) and glucose-dependent insulin otrophic polypeptide (GIP), reduce fasting glucose concentrations. Both GLP-1 and GIP are rapidly inactivated by the enzyme DPP-4. In patients with type 2 diabetes, treatment with single doses of sitagliptin provided sustained 24- hour inhibition of DPP-4 enzyme activity and increased active GLP-1 and GIP concentrations, leading to increases in insulin and C-peptide, reductions in glucagon's and improvements in oral glucose tolerance.[10]

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The data collected was demographic details, past medical history, family history and personal history like dietary habits, socioeconomic status. Also the base line values of RBS, FBS, PPBS and HbA1C were collected at the initial recruitment of subjects and after treatment administration follow ups were done at 2nd, 4th and at the end of 6th month[12]. At the time of follow up the values of RBS, FBS, PPBS and HbA1C were collected along with the safety profile of the drug. The collected data was entered and documented in excel sheets for retrieval. The Statistical analysis of data was analyzed by using graph pad prism-student T-test.

RESULTS

Total of 280 patients were interviewed for participation in the study and 250 patients were enrolled as per inclusion and exclusion criteria. Altogether 62 patients were participated in this study, and the response was 100%. Table 1 shows the participants were divided into 3 groups by age: 25-35 years (n=6927.4%), 35- 45 years (n=84, 33.4%), 45-55 years (n=97, 39.2%). The majority of

patients in the age group between 45-55 years (n=97, 39.2%).

Table 1: Age wise distribution of patients.

Age	No. of patients	Percentage
25-35	69	27.4
35-45	84	33.4
45-55	97	39.2

Table 2 shows the participants were divided into 3 follow-ups and authors have estimated the average value of RBS in patients at each follow-up i.e., at baseline (192.52), 1st follow- up (163.14), second follow-up (163.58), third follow-up (152.65), respectively, which has been observed in three months of duration, extremely statistical significance difference was observed in 3rd follow-up, P-value between baseline Vs first follow-up (0.198), second follow-up(0.041*), third follow-up (0.0005*) of RBS.

Table 2: Distribution of patients by RBS (Random blood sugar) levels (mg/dl).

Baseline	1st Follow up	2nd follow up	3rd follow up
192.525±51	163.14±38	163.58±41	152.65±27
p - value	0.198	0.041*	0.0005*

Table 3 shows the participants were divided into 3 follow-ups and authors have estimated the average value of FBS in patients at each follow-up i.e. at baseline (168.23), 1st follow- up (152.69), second follow-up (137.64), third follow-up (131.32), respectively, which has been observed in three months of duration, extremely statistical significance difference was observed in 3rd follow-up, P-value between baseline Vs first follow-up (0.0752), second follow-up(0.0068*), third follow-up (0.0003*) of FBS.

Table 3: Distribution of patients by FBS (fasting blood sugar) levels (mg/dl).

Baseline	1st Follow up	2nd Follow up	3rd Follow up
168.23±56	152.69±42	137.64±32	131.32±19
P- value	0.0752	0.0068*	0.0003*

Table 4 shows the participants were divided into 3 follow-ups and authors have estimated the average value of PPBS in patients at each follow-up i.e., at baseline (186.24), 1st follow- up (173.62), second follow-up (157.42), third follow-up (148.32), respectively, which has been observed in three months of duration, extremely statistical significance difference was observed in 3rd follow-up, P-value between baseline Vs first follow-up (0.124), second follow-up(0.0135*), third follow-up (0.0006*) of PPBS.

Table 4: Distribution of patients by PPBS(post prondial blood sugar) levels (mg/dl).

Baseline	1st Followup	2nd Follow up	3rd Follow up
186.24±46	173.62±38	157.42±32	148.32±28
P- value	0.124	0.0135*	0.0006*

Table 5: Distribution of patients by HbA1C (glycated hemoglobin) levels.

Baseline	Follow up
5.892±1.3	5.468±0.7
P- Value	0.0181

Table 6: Distribution of Subjects Based on values of FBS, PPBS and HbA1C at the start of the study.

Parameters	Range	No. of subjects	Percentage
FBS	≤145 mg/dl	86	34.34
	146-180 mg/dl	99	39.47
	>180 mg/dl	65	26.19
PPBS	≤180 mg/dl	124	49.61
	180-250 mg/dl	66	26.54
	>250 mg/dl	60	23.85
HbA1C	≤ 6.5%	11	4.36
	6.6-7.0%	207	82.99
	>7.0%	32	12.65

Table 7: Distribution of Subjects Based on values of FBS, PPBS and HbA1C- At the end of sixth month.

Parameters	Range	No. of subjects	Percentage
FBS	≤145 mg/dl	165	65.8
	146-180 mg/dl	49	19.51
	>180 mg/dl	36	14.63
PPBS	≤180 mg/dl	189	75.6
	180-250 mg/dl	30	12.19
	>250 mg/dl	30	12.19
HbA1C	≤ 6.5%	140	56.09
	6.6-7.0%	104	41.46
	>7.0%	6	2.43

Table 5 shows the participants were divided into baseline and follow-up and authors have estimated the average value of HBA1C in patients at follow-up i.e, at baseline (5.892), follow-up (5.468) which has been observed in three months of duration because HBA1C was investigated 3 months once, statistical significance difference was observed in follow-up group, P-value between baseline Vs follow-up (0.0181*) of HbA1C.

The number of subjects with FBS >180mg/dl was 65 (26.19%) and number of subjects with PPBS >250mg/dl was 60 (23.5%). 9.7% i.e. 32 subjects were having

HbA1C >7 %, which was decreased to 2.43% at the end of follow up as shown in Table 6.

Table 7 shows distribution of subjects depending on the values of FBS, PPBS and HbA1C at the end of the study where the number of subjects falling in upper limit has been decreased. The no. of subjects in >180mg/dl of FBS has been reduced to 36 (14.63%), likewise the number of subjects in >250 mg/dl of PPBS was decreased to 6 (2.43%).

DISCUSSION

In the total of 280 sample size, 250subjects were enrolled in our study as remaining were dropped out due to reasons like absconding, shifting to ICU or received corticosteroid therapy. Among 250 patients who met the inclusion criteria, n=97, (39.2%)subjects were present in 45-55 years age group. The mean age is 48.29 years±12. The females were predominant (n=134, 53.6%) than males (n=116, 46.34%). This finding was in correlation with findings of Sharma et al study.[13]

The normal ranges of HbA1C according to ADA are less than 5.7%, if it is 5.7% to 6.4% it is considered as prediabetic and 6.5% or higher is diabetic. The normal ranges of FBS are less than 100mg/dl, prediabetic is 100mg/dl to 125mg/dl and diabetic is greater than 126mg/dl. The normal limit of OGTT is less than 140mg/dl, prediabetic is 140mg/dl to 199mg/dl and diabetic is greater than 199mg/dl.[14]

In our study sitagliptin alone is well tolerated, exhibited better efficacious outcome in type 2 diabetes mellitus subjects who are uncontrollable hyperglycemic with other existing OHAs. Comparatively values of RBS, FBS, PPBS, HbA1C were reduced in follow up than base line value Thus our study supported the fact that usage of sitagliptin in type 2 diabetes mellitus resulted in reduction of RBS, FBS, PPBS, HbA1C. At base line the random blood glucose value was 195.53±58mg/dl which was decreased to 182.63±42 mg/dl at 1st follow up, 172.45±35 mg/dl at 2nd follow up and at third follow up it was 155.68±29mg/dl as shown in Table 2.

With sitagliptin administration the Fasting Blood Glucose levels were better controlled and from 167.43±5 mg/dl, it reached 135.21±21mg/dl at the end of sixth month. The similar finding was also reported by srivastav et al.[15] Similarly Post Prandial Blood Glucose and HbA1C were also fallen to normal ranges by using DPP-4 inhibitor sitagliptin as shown in tables 4 and 5. Sitagliptin can also be designed to add-on therapies to sulpfonylureas and biguanides as it gives excellent improvements in FBS and PPBS values.

The prevalence of diabetics in Indian adults was found to be 2.4% in rural and 4-11.6% in urban dwellers. India is presently estimated to have 41 million individuals affected by this deadly disease, with every fifth diabetic in the world being an Indian. The current oral blood glucose lowering agents and dietary measures only partially correct the multiple metabolic defects in type 2 diabetes mellitus with insulin resistance remaining relatively impervious to treatment hypoglycemia and secondary failure are common with presently available sulphonyl lureas and pioglitazone are associated with bladder cancer have largely been allayed by subsequent evidence. These agents tend to cause weight gain and peripheral oedema and have been shown to increase the incidence of heart failure.[16] They also increase the risk of bone fractures, predominately in women. Hence there is a need for newer blood glucose lowering drugs.

Herman et al. conducted a multicenter, randomized, double-blind, placebo-controlled, crossover study comparing PPG levels 2 hours after administration of a sitagliptin dose. Secondary efficacy endpoints included 24-hour PPG levels in patients who received a standardized meal (578 kcal) or a 75-g glucose solution.[17,18] Fifty-eight patients with type 2 diabetes (27.6% women), a mean age of 50 years (range, 33–60 years), and a mean BMI of 29.5 kg/m^2 were randomized to receive once-daily oral sitagliptin 25 or 200 mg or placebo, with a seven-day washout period between each crossover (additional demographic data not provided). Patients were instructed to consume >150 g of carbohydrates daily for three days before their scheduled visit, during which the study drug was administered followed by measurement of PPG levels 2 hours after dose administration.

Scott et al. assessed the efficacy and tolerability of sitagliptin monotherapy in a multinational, double-blind, randomized, placebo- and active-controlled, parallel-group, dose-ranging study. Patients with type 2 diabetes mellitus and inadequate glycemic control with diet and exercise (n = 743, 54.5% women) were randomized after a 6-week diet and exercise run-in period to one of six treatment groups: placebo (n = 125), sitagliptin 5 mg twice daily (n = 125), sitagliptin 12.5 mg twice daily (n = 123), sitagliptin 25 mg twice daily (n = 123), sitagliptin 50 mg twice daily (n = 124), or glipizide 5 mg twice daily (n = 123) (glipizide dosages were adjusted based on protocol-specific criteria, up to 20 mg twice daily).[19]

Raz and colleagues conducted a multinational, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and tolerability of sitagliptin mono therapy in men and women with type 2 diabetes. After a run-in period of ≤12 weeks, 521 patients (45.6% women) were randomized to receive placebo or sitagliptin 100 or 200 mg once daily for 18 weeks.[20] Patients were required to discontinue treatment with oral antidiabetic agents up to 12 weeks before study initiation.

Naucket al. conducted a multinational, parallel-active-controlled, double-blind, 52-week study to compare the efficacy and safety of sitagliptin versus glipizide when added to metformin therapy in patients with type 2

diabetes. Patients (40.8% women) having a mean BMI of 31.3 kg/m^2, a mean FPG concentration of 164.7 mg/dL, mean ages of 56.8 and 56.6 years, mean HbA_{1c} values of 7.7% and 7.6%, and mean durations of diabetes of 6.5 and 6.2 years were randomized to receive sitagliptin 100 mg daily (n = 588) or glipizide 5 mg daily (n = 584), respectively; the dosage of glipizide could be adjusted upward according to a protocol to a maximum dosage of 20 mg daily.[21] Patients in both groups continued to receive their standard metformin hydrochloride dosage (>1.5 g daily).

Rosenstock et al. conducted a multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group study to evaluate the change in HbA_{1c} values at week 24 with add-on treatment with sitagliptin 100 mg (n = 175) versus placebo (n = 178) to pioglitazone 30 or 45 mg daily.[22] Patients (44.4% women) who did not achieve glycemic targets throughout the study period received rescue therapy with metformin. The investigators did not indicate whether patients received counseling regarding diet and exercise.

CONCLUSION

This study was performed to provide an assessment of the efficacy and tolerability of sitagliptin at doses of 50mg twice daily in patients with type 2 diabetes with inadequate glycemic control on diet and exercise. Treatment with sitagliptin provided clinically meaningful reductions in HbA1C, RBS, FBS, PPBS by using this study authors know that sitagliptins are much safer and more effective in the treatment of type 2 diabetes mellitus. These agents are very superior to the existing OHAs in terms of efficacy and safety as they maintain the survival of beta cells unlike other agents.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Diabetes Blue Circle Symbol. International Diabetes Federation. 17 March 2006. Available at: http://www.diabetesbluecircle.org. Accessed on 11 Aug 2016.
2. Diabetes Fact sheet N°312. WHO. October 2013. Available at: http://www.who.int/mediacentre/factsheets/fs312/en/ 26 August 2013. Accessed on 06 Sep 2019.
3. Kitabchi AE, Umpierrez GE, Miles JM, Fisher JN. Hyperglycemic crises in adult patients with diabetes. Diabetes Care. 32(7):1335-43.
4. Chiang JL, Kirkman MS, Laffel LMB, Peters AL Type 1 Diabetes Through the Life Span: A Position Statement of the American Diabetes Association. Diabetes Care. 37(7):2034-54.
5. Causes of Diabetes. National Institute of Diabetes and Digestive and Kidney Diseases. June 2014. Accessed on 10 February 2016.
6. Ripsin CM, Kang H, Urban RJ. Management of blood glucose in type 2 diabetes mellitus. Am Fam Physician. 2009 Jan 1;79(1):29-36.
7. Brutsaert EF. Albert Einstein College of Medicine, Drug Treatment of Diabetes Mellitus, January 2019 by Erika F. Brutsaert, MD.
8. Bell DS. A Comparison of agents used to manage type 2 diabetes mellitus: Need for reappraisal of traditional approaches. Treat Endocrinol. 2004;3(2):67-76.
9. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy: A consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2006;29(8):1963-72.
10. De Fronzo RA, Goodman AM. Efficacy of metformin in patients with non-insulindependent diabetes mellitus. The Multicenter Metformin Study Group. N Engl J Med. 1995;333(9):541-9.
11. UKPDS 28: A randomized trial of efficacy of early addition of metformin in sulfonylurea-treated type 2 diabetes. U.K. Prospective Diabetes Diabetes Study Group. Diabetes Care. 1998;21(1):87-92.
12. Shah SK, Saikia M, Burman NN, Snehalatha A. Risk factors of type 2 diabetes in urban population in north eastern India. Int J Diabetes Dev Countries 1999;19:144-7.
13. Kashyap SR, Bhatt DL, Wolski K, Watanabe RM, Abdul-Ghani M, Abood B, et al., Moderate Obesity and Type 2 Diabetes: Analysis of a randomized control trial comparing surgery with intensive medical treatment. Diabetes Care. 2013 Aug 1;36(8):2175-82.
14. International Diabetes Federation. Diabetes and Cardiovascular Disease. 2016. Available at; www.idf.org/cvd. Accessed on 27 Oct 2016.
15. Srivastava S, Saxena GN, Keshwani P, Gupta R. 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(2):27-30.
16. Anjoom M, Dutta S, Beg MA, Varma A, Bawa S, Kant R. Comparative evaluation of combination of metformin and glimepiride with that of metformin and sitagliptin in type 2 diabetes mellitus with respect to glycemic targets. Int J Med Sci Public Health. 2015;4(4):476-80.
17. Hayati F, Hazim A, Sasongko TH, Siew HG, Wan WMI, Daud J, et al. Efficacy and safety of sitagliptin as a third therapeutic agent in the treatment of type 2 diabetes mellitus. J Diab Res Clin Met. 2014;3(1):10.
18. Herman GA, Bergman A, Stevens C, Kotey P, Yi B, Zhao P, 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 Metabol. 2006 Nov 1;91(11):4612-9.
19. Scott R, Wu M, Sanchez M, Stein P. Efficacy and tolerability of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy over 12 weeks in patients with type 2 diabetes. Int J Clin Practice. 2007 Jan;61(1):171-80.
20. 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 Nov 1;49(11):2564-71.
21. Brazg R, Xu L, Dalla Man C, Cobelli C, Thomas K, Stein PP. Effect of adding sitagliptin, a dipeptidyl peptidase-4 inhibitor, to metformin on 24-h glycaemic control and β-cell function in patients with type 2 diabetes. Diabetes, Obesity and Metabolism. 2007 Mar;9(2):186-93.
22. Nauck MA, Meininger G, Sheng D et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, compared with the sulfonylurea, glipizide, in patients with type 2 diabetes inadequately controlled on metformin alone: a randomized, double-blind, non- inferiority trial. Diabetes Obes Metab. 2007;9(2):194-205.

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