www.jmscr.igmpublication.org
Index Copernicus Value: 79.54
ISSN (e)-2347-176x ISSN (p) 2455-0450
crossrefDOI: https://dx.doi.org/10.18535/jmscr/v7i3.06

IGM Publication
Journal Of Medical Science And Clinical Research
An Official Publication Of IGM Publication

Safety and Effective Management of Type-2 Diabetes Mellitus Patients by using Sitagliptin

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Abstract
Objectives: *To study the safety and efficacy of the newer oral hypoglycemic agent sitagliptin in management of type-2 diabetes mellitus patients.*
Methods: *This concurrent observational study was carried out in general medicine department of Rajiv Gandhi Institute Of Medical Sciences for a period of 6 months in which type 2 diabetes mellitus patients were recruited based on inclusion and exclusion criteria and were followed to evaluate the efficacy and safety of sitagliptin. Data was analyzed by using graph pad prism-student T-test.*
Results: *In our study we have recruited 41 patients who met our study criteria of which we categorized based on age and laboratory data, the majority of patients in the age group between 56-65 years (n=14, 34.15%), the RBS was reduced to Comparatively values of RBS, FBS, PPBS, HbA1C were reduced in follow up than base line value. RBS was reduced from 195.5 mg/dl to 155.68 mg/dl. FBS was 167.43 mg/dl at the base line, and then decreased to 135.21 mg/dl after follow-up. Likewise PPBS and HbA1C at base line were 196.6 mg/dl and 6.78 % respectively. Both were decreased to 157 mg/dl and 6.04 % respectively.*
Conclusion: *Based on results we can conclude that sitagliptin use was not associated with any risks and is effective in management of Type 2 diabetics, treatment with sitagliptin provided clinically meaningful reductions in HbA1C, RBS, FBS, PPBS by using this study we know that gliptins are much more safe and effective in the treatment of type 2 diabetes mellitus.*
Keywords: *Diabetes mellitus; Sitagliptin; Insulin.*

Introduction

Diabetes mellitus (DM) comprises a group of common metabolic disorders that share the phenotype of hyperglycemia. Depending on the etiology of the diabetes mellitus, factors contributing to hyperglycemia may include reduced insulin secretion, decreased glucose utilization, and increased glucose production.[1] Diabetes mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia, as

opposed to earlier criteria such as age of onset or type of therapy. The two broad categories of diabetes mellitus are designated type 1 and type 2. Individuals with type1 diabetes mellitus lack immunologic markers indicative of an autoimmune destructive process of the beta cells. Type 2 diabetes mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production.[2] Approximately 85% of patients with the diabetes disorder are overweight or obese and nearly 75% have hypertension.[3] Additionally, obesity is a shared risk factor for diabetes and hypertension[4].

Prior to 1995, the use of SU was the most popular anti-diabetic therapy in the USA (United States). SU's act by increasing insulin secretion in a glucose-independent manner, thereby risking severe unpredictable hypoglycemia, particularly if the meal is delayed or if its carbohydrate quantity reduced. It only makes sense that they continue to remain mainstay therapy as despite their problems. This was particularly true since there was no agent that could help improve health of the beta cell and cause insulin release in a glucose dependant manner and it was inevitable to use SUs and biguanides as there are no efficient substitutes to these agents. But all changed once it was learnt that the incretin system was involved in the pathogenesis of T2DM. Failure of this incretin system has been implicated in progression of beta-cell failure and therefore any therapy that can augment this system has been shown to promote beta cell health and insulin release in a glucose-dependent manner[5-9].

Even though the metformin therapy has been known for its advantages (non-hypoglycemic, weight-loss promoting, anti-ischemic to cardiac tissue, improvement in non-alcoholic hepatosteatosis, anti-neoplastic etc), its use has been associated with gastrointestinal adverse effects, precluding or limiting its use, particularly in the non-overweight patient[10]. Use of SU's on the other hand although effective in lowering plasma glucose can be associated with variable severities of hypoglycemia, weight gain, beta-cell death, and possibly adverse cardiac outcomes as proposed originally by the UKPDS and later by other groups[11].

From the above data it seems clear that existing popular therapies are not only ineffective but are associated with a significant amount of morbidity (weight gain and hypoglycemia). There is scarcity of refreshing class of drugs whose effects on hyperglycemia can be sustained, without adversely affecting the survival of beta-cells, and are weight neutral and free of hypoglycemia, a true class of anti-hyperglycemics. Gliptins might be better substitutes to the current OHAs.

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 insulinotropic polypeptide (GIP) are incretin hormones that stimulate insulin secretion and suppress glucagon. 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[12]. 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[13]. 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 (GLP-1) and glucose dependent insulinotropic polypeptide[14]. 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[15]. 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 mellitus[16]. Sitagliptin acts through increasing active incretin hormone concentrations. Following ingestion of a meal, incretins, including glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotrophic polypeptide (GIP), reduce fasting glucose concentrations. Both GLP-1 and GIP are rapidly inactivated by the enzyme DPP-4[17]. 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[18].

Research Methodology

A concurrent observational study was carried out in outpatient & inpatient units of general medicine department of Rajiv Gandhi Institute of Medical Sciences (RIMS), a 750 bedded tertiary care teaching hospital, Kadapa. Research protocol has been prepared and got ethical approval by the ethical committee of Rajiv Gandhi institute of Medical Sciences (RIMS) with registered number RC. No. 4226/Acad./2015.

The study duration was six months from april 2015 to September 2015.Approximately 60 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. 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. 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 2^{nd}, 4^{th} and at the end of 6^{th} month. 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 81 patients were interviewed for participation in the study and 41 patients were enrolled as per inclusion and exclusion criteria. Altogether 41 patients were participated in this study, and the response was 100%.

Table 1 shows the participants were divided into 5 groups by age: 25-35 years (n=7, 17.07%), 35-45 years (n=11, 26.82%),.45-55 years (n=7, 17.07%), 55-65 years (n=14, 34.15%), 65-75 years (n=2, 4.8%). The majority of patients in the age group between 55-65 years (n=14, 34.15%).

Table 1: Age wise distribution of patients

n=41	No of patients	Percentage
25-35 years	7	17.07%
35-45 years	11	26.82%
45-55 years	7	17.07%
55-65 years	14	34.15%
65-75 years	2	4.8%

Table 2 shows the participants were divided into 3 follow-ups and we have estimated the average value of RBS in patients at each follow-up i.e, at baseline (195.53), 1^{st} follow- up (182.63), second follow-up (172.45), third follow-up (155.68), 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 (0.2168), second follow-up(0.0311), 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
195.53±58	182.63±42	172.45±35	155.68±29
P-Value	0.2168	0.0311	0.0005
	Not statistically significant	Statistically significant	Extremely statistically significant

Table 3 shows the participants were divided into 3 follow-ups and we have estimated the average value of FBS in patients at each follow-up i.e. at baseline (167.43), 1st follow- up (153.56), second follow-up (146), third follow-up (135.21), 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 (0.0911), second follow-up(0.0073), 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
167.43±54	153.56±47	146±33	135.21±21
P-Value	0.0911	0.0073	0.0003
	Not statistically significant	Statistically significant	Extremely statistically significant

Table 4 shows the participants were divided into 3 follow-ups and we have estimated the average value of PPBS in patients at each follow-up i.e, at baseline (196.60), 1st follow- up (180.12), second follow-up (168.31), third follow-up (157), 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 (0.1393), second follow-up(0.0125), third follow-up (0.0007) of PPBS.

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

Baseline	1st follow up	2nd follow up	3rd follow up
196.60±48	180.12±40	168.31±33	157±26
P-Value	0.1393	0.0125	0.0007
	Not statistically significant	Statistically significant	Extremely statistically significant

Table 5 shows the participants were divided into baseline and follow-up and we have estimated the average value of HBA1C in patients at follow-up i.e, at baseline (6.78), follow-up (6.04) 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 (0.0165) of HbA1C.

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

Baseline	Follow up
6.78±1.2	6.04±0.9
P-value = 0.0165 (Statistically significant)	

Distribution of Subjects Based on values of FBS, PPBS and HbA1C

At the start of the study

Table no.6 Distribution of Subjects Based on values of FBS, PPBS and HbA1C at the start of the study

Parameter	Range	No. of subjects	Percentage
FBS	≤ 145 mg/dl	14	34.14%
	146-180 mg/dl	15	36.58%
	> 180 mg/dl	12	29.26%
PPBS	≤ 180 mg/dl	22	53.65%
	180-250 mg/dl	12	29.26%
	> 250 mg/dl	07	17.07%
HbA1C	≤ 6.5 %	01	2.43%
	6.6-7.0 %	36	87.8%
	> 7.0 %	04	9.7%

The number of subjects with FBS > 180mg/dl was 12 (29.26%) and number of subjects with PPBS > 250mg/dl was 7 (17.07%). 9.7% i.e. 4 subjects were having HbA1C > 7 %, which was decreased to 2.43% at the end of follow up as shown in table

no.7. Table no. 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 6 (14.63%), likewise the number of subjects in > 250 mg/dl of PPBS was decreased to 1 (2.43%).

Table no.7 Distribution of Subjects Based on values of FBS, PPBS and HbA1C- At the end of sixth month

Parameter	Range	No. of subjects	Percentage
FBS	≤ 145 mg/dl	27	65.85%
	146-180 mg/dl	08	19.51%
	> 180 mg/dl	06	14.63%
PPBS	≤ 180 mg/dl	31	75.6%
	≤180-250 mg/dl	05	12.19%
	> 250 mg/dl	05	12.19%
HbA1C	≤ 6.5 %	23	56.09%
	6.6-7.0 %	17	41.46%
	> 7.0 %	01	2.43%

Discussion

In the total of 60 sample size, 41 subjects were enrolled in our study as remaining were dropped out due to reasons like absconding, shifting to ICU or received corticosteroid therapy. Among 41 patients who met the inclusion criteria, 14 (34.15%) subjects were present in 55-65 years age group. The mean age is 48.29 years ± 12. The females were predominant (n=22, 53.6%) than males (n=19, 46.34%). This finding was in correlation with findings of Sharma et al study[19].

Despite the availability of numerous pharmacotherapies targeting different and complementary pathways associated with glucose homeostasis, diabetes remains a major global health issue and is amongst the four most common non-communicable diseases, affecting an estimated 415 million people in 2015 and predicted to affect 642 million individuals by 2040[20].

American diabetes association (ADA) and National Institute for Health and Clinical Excellence (NICE) has recommended DPP-4 inhibitors as the second and third line treatment option as an alternative to well established therapy[21,22]. 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[23].

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 no.2. With sitagliptin administration the Fasting Blood Glucose levels were better controlled and from 167.43±54 mg/dl, it reached 135.21±21mg/dl at the end of sixth month. The similar finding was also reported by srivastav et al[24]. 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 sulpfonyl ureas and biguanides as it gives excellent improvements in FBS and PPBS values. Anjoom et al, reported significant improvement in both the values of FBG and PPG after 24 weeks of follow up in both the groups ($p < 0.001$)[25]. Another study done by Hayati et al with 95 T2DM patients, who were previously taking metformin and glimepiride and adding sitagliptin as a third agent significantly reduced HbA1c by 0.41% ($P<0.007$) as compared to dual therapy alone, about 18.27% achieved their HbA1c targets[26].

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[16].

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 sulphonylureas 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. They also increase the risk of bone fractures, predominately in women. Hence there is a need for newer blood glucose lowering drugs[27].

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 we know that gliptins are much more safe and 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.

Limitations

Sample size is very less (41 patients). The complete pharmacology especially to study the dynamic parameters of the drug in special populations this data is sufficient. To know the optimal usage and safety issues associated with newer oral hypoglycemic agents, a large sample size is required. Limited study period (6 months). The long term side effects and therapeutic activity of the drug could be studied to a higher degree if study duration is longer.

Source of funding

The study was funded by a Short-term Grant from Rajiv Gandhi institute of medical sciences (RIMS).

Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval and consent to participate:

Approval to conduct this study was obtained from the Rajiv Gandhi institute of medical sciences (RIMS) Govt. Hospital, IEC (**RC. No. 4226/Acad./2015**). Permission to conduct this study was also obtained from the Director of Hospital RIMS.

Authors' contributions

AS and CT designed the study, conducted data collection and performed data analysis. AS and CT provided logistical support and performed the final review of results. AS wrote the initial and final draft of the article. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Acknowledgment

Special thanks to all patients who participated in this study, as well as the nurses of the Hospital RIMS who assisted us in making the research successful.

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