Comparative study analyzing efficacy and safety of sitagliptin with metformin versus glimepiride with metformin on patients of type-2 diabetes mellitus

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Abstract
Introduction: Type 2 Diabetes Mellitus (T2DM) a serious, common chronic disease constituting a major public health issue worldwide. Yet no cure is available, education of populace is still the key to control this emerging epidemic. Novel drugs are being developed, some used as monotherapy or in-combination for effective glycaemic control.
Objective: Comparing the efficacy of Sitagliptin+Metformin versus Glimepiride+ Metformin on patients of T2DM.
Material and method: 30 weeks open labeled Randomized controlled study enrolling 80 patients of T2DM, divided into two groups with 40 patients in each. Group A given Metformin(500mg) with Sitagliptin(100mg) and group B given Metformin(500mg) with Glimepiride(1mg). HbA1c, FBG, PPBG were done at baseline, 15 and 30 weeks.
Results: Group A and Group B both leads to significant (<0.05) reduction in FBG, PPBG and HbA1c but group A leads to greater reduction in mean FBS, PPBS and HbA1c than group B (FBS -62.49±21.72 vs -55.46±31.69, -71.46±24.13 vs -68.26±32.57), (PPBS -106.18±30.48 vs -105.86±39.08, -118.64±29.64 vs -116.12±40.83), (HbA1c -1.20±0.42 vs -1.23±0.40, -2.44±0.59 vs -2.11±0.53) on statistically comparing both groups the difference was non-significant (>0.05) for FBG, PPBG at 15 and 30 weeks and HbA1c at 15weeks but was the difference was statistically significant (<0.05) for HbA1c at 30 weeks.
Conclusion: Sitagliptin with Metformin and Glimepiride with Metformin both causes efficient glycaemic control with no significant adverse reaction but the gylcaemic control of patients taking Sitagliptin with Metformin was slightly better as compared to patients taking Glimepiride with Metformin. Thus concluding Sitagliptin to be more efficacious than Glimepiride.

Keywords: Diabetes mellitus type II, Sitagliptin, Glimepiride, Metformin, HbA1c (glycosylated haemoglobin), Fasting blood glucose, Post-prandial blood glucose.

Introduction
Diabetes mellitus (DM) is probably one of the oldest diseases known to man. It was first reported in Egyptian manuscript about 3000 years ago.[1] The global prevalence of diabetes in adults (20-79 years old) according to a report published in 2013 by the IDF was 8.3% (382 million people), with 14 million more men than women (198 million men *vs* 184 million women), the majority between the ages 40 and 59 years and the number is expected to rise beyond 592 million by 2035 with a 10.1% global prevalence. With 175 million cases still undiagnosed, the number of people currently suffering from diabetes exceeds half a billion.[2] Two major concerns are that much of this increase in Diabetes will occur in developing countries and that there is a growing incidence of Type 2 Diabetes at a younger age including some obese children even before puberty. In developed countries most people with diabetes are above the age of retirement. In developing countries those most frequently affected are in the middle, productive years of their lives, aged between 35 and 64.[3] DM is characterized by chronic hyperglycemia and impaired carbohydrates, lipids, and proteins metabolism caused by complete or partial insufficiency of insulin secretion and/or insulin action.[4] Classification of diabetes mellitus is based on its aetiology and clinical presentation. As such, there are four types or classes of diabetes mellitus viz; type 1 diabetes, type 2 diabetes, gestational diabetes, and other specific types.[5] T2DM is the most common form of DM, which accounts for 90% to 95% of all diabetic patients, results from the interaction among genetic, environmental and other risk factors. Furthermore, loss of first-phase of insulin release, abnormal pulsatility of basal insulin secretion, and increased glucagon secretion also accelerate the development of T2DM.[4] The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries.[1] Moreover 85 to 95% of all diabetes in high-income countries are of type 2 accounting for an even higher dominance in developing countries.[5]

Genetic predisposition for type 2 DM is even stronger than for type 1 DM. Almost 40 percent of patients who have type 2 DM have at least one parent who has the disorder. The lifetime risk for a first-degree relative of a patient who has type 2 DM is 5 to 10 times higher than that of age and weight-matched patients without a family history of DM. Among monozygotic twin pairs with one affected twin, type 2 DM eventually develops in 60 to 90 percent of initially unaffected twins.[6]

The American Association of Clinical Endocrinologists (AACE)/American College of Endocrinology (ACE) recommends an initial HbA1c goal ≤6.5% for most patients on the basis of the trial results comparing intensive with standard glucose-lowering strategies. They stress the importance of individualizing therapy; thus, a goal of >6.5%, even 7% to 8%, may be appropriate for some patients, such as those with limited life expectancy, a history of severe hypoglycemia, or advanced comorbid disease.

Likewise, the ADA recommends an HbA1c goal <7% for most nonpregnant adults.[7]

Diabetes and its associated complications lower the quality of people's lives and generate enormous economic and social burdens.[4] Despite the morbidity and mortality associated with retinopathy, nephropathy, and neuropathy, cardiovascular disease remains the leading cause of death in type 2 diabetes mellitus. Consequently, the treatment of confounding risk factors of obesity, hypertension, and hyperlipidemia assumes major importance and must be coordinated with good glycemic control for reduction in total mortality in type 2 diabetes mellitus.[8] The UK Prospective Diabetes Study (UKPDS) found that every 1% reduction in glycated haemoglobin (HbA1c) was associated with a 37% decrease in microvascular disease and a 14% reduction in myocardial infarction (MI).[9] So, Early diagnosis, correct treatment, and effective follow-up are essential in any health care system to prevent complications of diabetes and ensure patient's well being.[10]

No cure has yet been found for the disease; however, treatment modalities include lifestyle modifications, treatment of obesity, oral hypoglycemic agents, include biguanide, non-sulfonylurea secretagogues, thiazolidinediones, alpha glucosidase inhibitors, glucagon-like peptide 1 analogoues: dipeptidyl peptidase-IV inhibitors, inhibitors of the sodium-glucose co-transporter 2 and 11ß-hydroxysteroid dehydrogenase 1, insulin-releasing glucokinase activators and pancreatic-G-protein-coupled fatty-acid-receptor agonists, glucagon-receptor antagonists, metabolic inhibitors of hepatic glucose output, quick-release bromocriptin and insulin.[1] Although T2DM patients are generally independent of exogenous insulin, they may need it when blood glucose levels are not well controlled with diet alone or with oral hypoglycemic drugs.[4]

Biguanides, of which metformin is the most commonly used in overweight and obese patients, suppresses hepatic glucose production, increases insulin sensitivity, enhances glucose uptake by phosphorylating GLUT-enhancer factor, increases fatty acid oxidation, and decreases the absorption of glucose from the gastrointestinal tract.[1]

Sulphonylureas act directly on the islet β cells to close ATP-sensitive K+ channels and stimulate insulin secretion.[4] Glimepiride is a second-generation sulfonylurea that stimulates pancreatic β cells to release insulin. This agent mainly stimulates insulin secretion, but has also been shown to have additional extra-pancreatic effects.[11] It is most preferred and frequently used with metformin for control of blood glucose levels. The second drug added to metformin has most of the times been sulfonylureas.[12]

Dipeptidyl peptidase-4 (DPP-4) inhibitors exhibit antidiabetic effects by stimulating insulin secretion through highly selective inhibition of DPP-4, an enzyme that inactivates incretins such as glucagon-like peptide 1 and gastric inhibitory polypeptide via a mechanism different from that of conventional hypoglycemic drugs.[13] They are effective as monotherapy in patients inadequately controlled with diet and exercise and as add-on therapy in combination with metformin, thiazolidinediones, and insulin. The DPP-4 inhibitors are well tolerated, carry a low risk of producing hypoglycemia and are weight neutral. However, they are relatively expensive.[1] Many reports have demonstrated the superior efficacy and safety of DPP-4 inhibitors, among which sitagliptin was the first to gain approval in Japan in 2009.[13] Sitagliptin, a once-daily, oral, potent and highly selective DPP-4 inhibitor, inhibits plasma DPP-4 activity ≥80% over 24 h with single doses of ≥100 mg.[14]

In this study we are evaluating and comparing the efficacy of sitagliptin with metformin and glimepiride with metformin as oral hypoglycaemic agent.

Materials and Methods

The present study was conducted in Pharmacology department in association with department of Medicine and Pathology, enrolling 80 patients of type II diabetes mellitus coming to outdoor department of medicine. The patients were selected in the study on the basis of the following inclusion and exclusion criteria.

Inclusion criteria

Patients with newly diagnosed type II diabetes mellitus, age >20 years of either sex, having symptoms of diabetes mellitus plus fasting plasma glucose ≥126md/ dL, post-prandial plasma glucose ≥ 200mg/dL or HbA1c ≥6.5% levels were included.

Exclusion criteria

Patients with type I, secondary or gestational diabetes mellitus, hepatic/renal/bleeding disorders, any history of allergy to given medication, pregnant or lactating females and those taking any other treatment which can alter the glycaemic control were excluded.

An open labeled prospective randomized study of 30 weeks duration consisting of screening period (1–2 weeks), titration period (2–10weeks), maintenance period (20 weeks), enrolling 80 patients of type II diabetes mellitus, fulfilling the inclusion criterias and having none of the exclusion criteria, after taking written informed consent was conducted with the permission of the institutional ethical committee and required procedures were performed according to the declaration of Helsinki. A detailed history and clinical examination of all the patients was done and recorded and later on a watch was kept on any undesirable new symptoms that might appear during the study period. Patients were advised to stop the drug and report immediately if he/she feels any undesirable symptoms during the course treatment.

These patients were randomly divided into age and sex matched two groups i.e. Group A and group B of 40 patients each and were advised to have low fat diet, avoid alcohol intake and follow lifestyle modification like regular exercise and quit smoking. Baseline characteristics i.e. gender was statistically analysed using chi-square test ($\chi 2$) and for age group, anthropometric parameters and body mass index (BMI) unpaired student 't' was used. Group A was given Metformin (500mg) with Sitagliptin (100mg) and group B was given Metformin (500mg) with Glimepiride (1mg). The

patients were stabilized for two weeks and followed up every 2 weeks for 30 weeks. Fasting Plasma Glucose (FPG) and Postprandial Plasma Glucose (PPPG) were measured at every follow-up; glycosylated hemoglobin (HbA1c) was measured at baseline, 15 weeks and then at the endpoint i.e. 30 weeks of starting the treatment.

Primary and Secondary Endpoints: The endpoints were monitored by change in HbA1c, FPG and PPPG from baseline to 30 weeks of the study period.

The results are presented in frequencies, percentages and mean±SD. The Chi-square test was used to compare categorical variables between the groups. Students Unpaired and Paired *t*-test was used to continuous variables between the groups. The $p<0.05$ was considered significant.

Results

According to gender/age

19(47.50%) females and 21 (52.50%) males in group A and, 22 (55.0%) females and 18 (45.0%) males in group B were included. For group A mean age of patients was 56.37±6.22 years and for group B patients was 54.87±7.33 years. Statistical analysis of both age and gender showed that the difference between the two groups was not statistically significant (p>0.05) hence comparable. (Table 1)

Anthropometric parameters

Mean of height in cms (160.36±9.95 vs 162.06±8.10), weight in Kgs (62.44±8.89 vs 63.99±6.67)and BMI in Kg/mtr^2 (24.88±3.13 vs 24.51±4.0)of patients of group A and group B respectively when compared, difference was found to be non-significant. (p> 0.05). (Table 1)

Duration of diabetes

The duration of diabetes in Group A and Group B was 2.24±0.98 and 2.36±1.22 years respectively. There was no significant (p>0.05) difference in the duration of diabetes between the groups. (Table 1)

Table 1: Baseline characteristic comparison

Group	Mean age (years)	Gender		Anthropometric parameters			Duration of Diabetes mellitus (years)
		Male	Female	Height (cms)	Weight (Kgs)	BMI (Kg/mtr^2)	
Sitagliptin+ Metformin **Group A N=40**	56.37±6.22	21	19	160.36±9.95	62.44±8.89	24.88±3.13	2.24±0.98
Glimepride+ Metformin **Group B N=40**	54.87±7.33	18	22	162.06±8.10	63.99±6.67	24.51±4.0	2.36±1.22
p value	>0.05	>0.05		>0.05			>0.05

Table 2: FBG levels group A (Sitagliptin) at different time interval

Time interval	Mean ± SD	Mean change ± SD	%age reduction at 30 weeks from baseline	p	Sig.
Baseline	174.03±19.19	-	41.06%	-	-
15 weeks	111.54±12.53	-62.49±21.72		0.000	HS
30 weeks	102.57±11.52	-71.46±24.13		0.000	HS

Table 3: FBG level group B (Glimepride) at different time interval

Time interval	Mean ± SD	Mean change ± SD	%age reduction at 30 weeks from baseline	p	Sig.
Baseline	176.06±32.56	-	38.77%	-	-
15 weeks	120.60±14.01	-55.46±31.69		0.000	HS
30 weeks	107.80±12.41	-68.26±32.57		0.000	HS

Table 4: Comparing FBG levels of group A versus Group B

Time interval	Group	Mean ± SD	Mean change ± SD	p	Sig.
Baseline	**A**	174.03±19.19	-	-	-
	B	176.06±32.56	-	-	-
After 15 weeks	**A**	111.54±12.53	-62.49±21.72	0.77	NS
	B	120.60±14.01	-55.46±31.69		
After 30 weeks	**A**	102.57±11.52	-71.46±24.13	0.96	NS
	B	107.80±12.41	-68.26±32.57		

Table 5: PPBG level Group A (Sitagliptin) at different time interval

Time interval	Mean ± SD	Mean change ± SD	%age reduction at 30 weeks from baseline	p	Sig.
Baseline	274.64±31.70		43.19%	-	-
15 weeks	168.46±16.30	-106.18±30.48		0.000	HS
30 weeks	156.00±14.99	-118.64±29.64		0.000	HS

Table 6: PPBG level group B (Glimepride) at different time interval

Time interval	Mean ± SD	Mean change ± SD	%age reduction at 30 weeks from baseline	p	Sig.
Baseline	272.34±39.89	-	42.63%	-	-
15 weeks	166.48±17.97	-105.86±39.08		0.000	HS
30 weeks	156.22±14.59	-116.12±40.83		0.000	HS

Table 7: Comparison of PPBG of group A versus group B

Time interval	Group	Mean ± SD	Mean change ± SD	p	Sig.
Baseline	**A**	274.64±31.70	-	-	-
	B	272.34±39.89	-	-	-
After 15 weeks	**A**	168.46±16.30	-106.18±30.48	0.33	NS
	B	166.48±17.97	-105.86±39.08		
After 30 weeks	**A**	156.00±14.99	-118.64±29.64	0.25	NS
	B	156.22±14.59	-116.12±40.83		

Table 8: HbA1c level group A (Sitagliptin) at different time interval

Time interval	Mean ± SD	Mean change ± SD	%age reduction at 30 weeks from baseline	p	Sig.
Baseline	8.97±0.34	-	27.20%	-	-
15 weeks	7.77±0.47	-1.20±0.42		0.01	S
30 weeks	6.53±0.37	-2.44±0.59		0.01	S

Table 9: HbA1C level group B (Glimepiride) at different time interval

Time interval	Mean ± SD	Mean change ± SD	%age reduction at 30 weeks from baseline	p	Sig.
Baseline	8.89±0.53	-	23.73%	-	-
15 peeks	7.66±0.51	-1.23±0.40		0.01	S
30 weeks	6.78±0.27	-2.11±0.53		0.01	S

Table 10: Comparison of HbA1c group A versus group B

Time interval	Group	Mean ± SD	Mean change ± SD	p	Sig.
Baseline	**A**	8.97±0.34	-	-	-
	B	8.89±0.53	-	-	-
After 15 weeks	**A**	7.77±0.47	-1.20±0.42	0.25	NS
	B	7.66±0.51	-1.23±0.40		
After 30 weeks	**A**	6.53±0.37	-2.44±0.59	0.001	S
	B	6.78±0.27	-2.11±0.53		

Table 11: Comparison of safety parameters between the groups

Efficacy parameters	Group A (n=40)		Group B (n=40)		p-value[1]
	No.	%	No.	%	
Edema	2	5	3	7.5	0.11
Headache	4	10	3	7.5	
Elevated liver enzyme	2	5	2	5	
Symptomatic hypoglycaemia	1	2.5	8	20	
Abdominal discomfort	2	5	1	2.5	
Diarrhea	5	12.5	2	5	
Chest discomfort and dyspnoea	2	5	2	5	

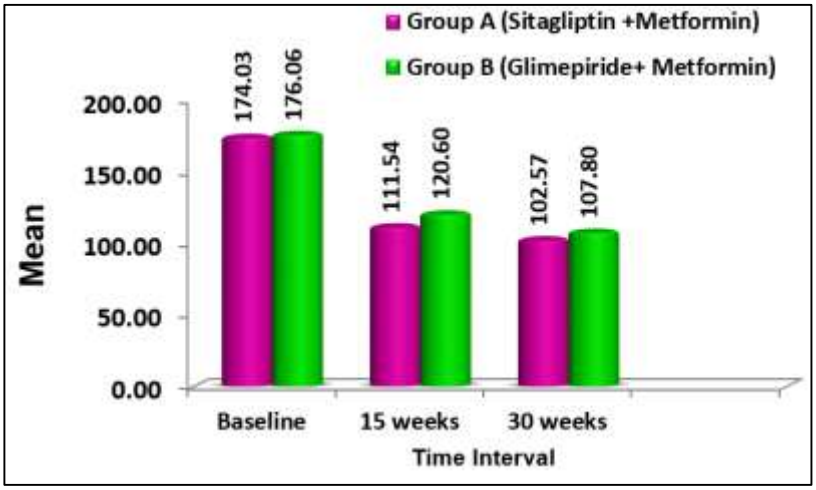

Fig. 1: mean FBG levels at different visits both the groups

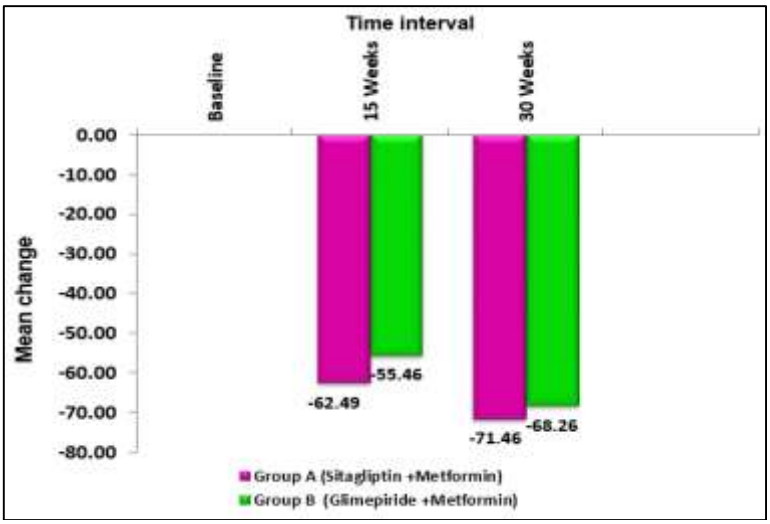

Fig. 2: Comparison of mean change FBG level both groups

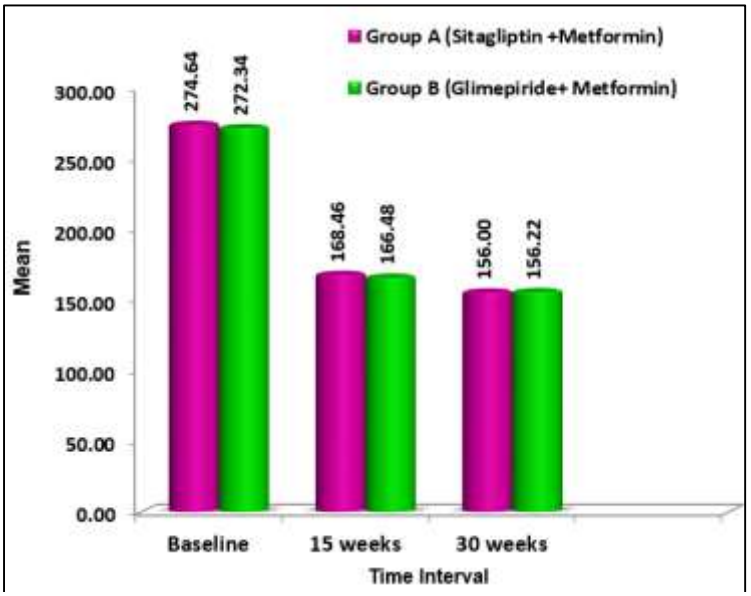

Fig. 3: Mean PPBG levels at different visits both the groups

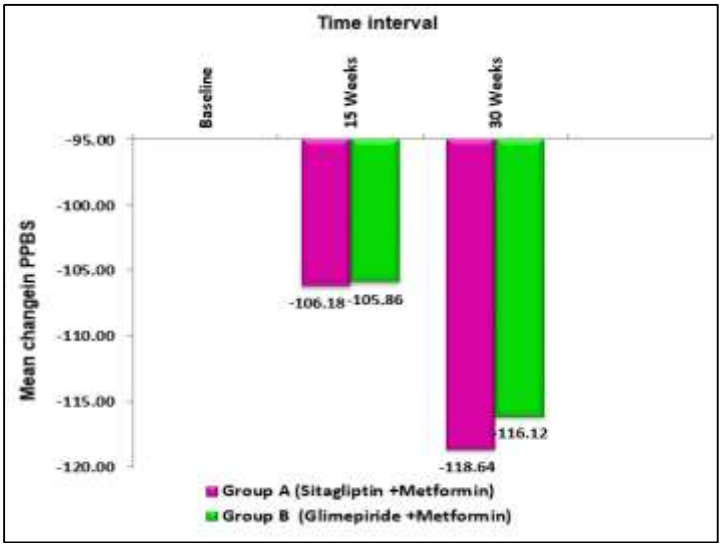

Fig. 4: Comparison of mean change PPBG level both groups

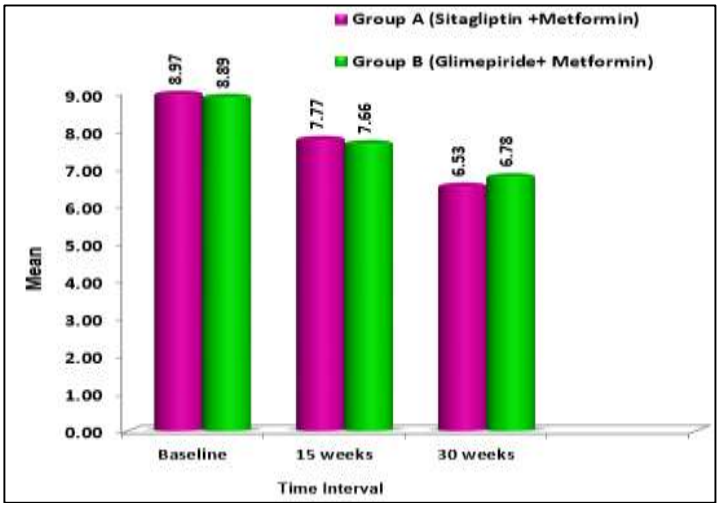

Fig. 5: Mean HbA1c levels at different visits both the groups

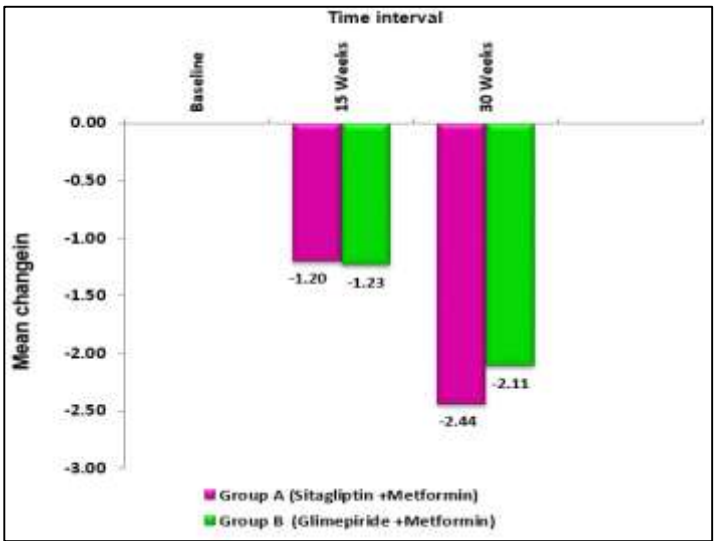

Fig. 6: Comparison of mean change HbA1c level both groups

Discussion

Type 2 diabetes mellitus (DM) prevalence has been increasing steadily all over the world, fast becoming an epidemic in some countries, with the number of people affected expected to double in the next decade due to increase in ageing population, thereby adding to the already existing burden for healthcare.[1] There have been no effective measures to fully cope with the diseases. The main cause of the diabetes epidemic is the interaction between genetic and environmental risk. A number of other factors are also attributable to the diseases. Whereas most antidiabetic agents have shown beneficial effects when used as monotherapy or combination therapy, they are also associated with negative effects, such as weight gain, hypoglycemia, gastrointestinal effects or cardiovascular disease. So, searching an ideal therapy becomes one of the top priorities in combating this disease.[4] In the view of previous reports on efficacy of sitagliptin (DPP-4 inhibitor), the present study was designed evaluating and comparing the hypoglycemic efficacy of sitagliptin with glimepride given in combination with metformin in patients of type II diabetes mellitus.

In the present study group A (Sitagliptin+Metformin) and Group B (Glimepiride + Metformin) both leads to significant (<0.05) reduction in FBS,PPBS and HbA1c levels but group A leads to greater reduction in mean FBS, PPBS and HbA1c level than group B (FBS levels -62.49±21.72 vs -55.46±31.69, -71.46±24.13 vs -68.26±32.57), (PPBS levels -106.18±30.48 vs -105.86±39.08, -118.64±29.64vs -116.12±40.83), (HbA1c levels -1.20±0.42 vs-1.23±0.40, -2.44±0.59 vs -2.11±0.53) on statistically comparing the data of both the groups the difference was non-significant (>0.05) for FBS PPBS levels and HbA1c level at 15weeks but was the difference was statistically significant (<0.05) for HbA1c at 30 weeks.

Jothydev Kesavadev et al[15] in their 24 weeks study with sitagliptin 100mg vs glimepiride 1-3mg as add on therapy with metformin +insulin, concluded that the two groups having similar HbA1c values at baseline (P = 0.36). Showed significant differences in the change in HbA1c with sitagliptin (100 mg) and glimepiride (1–3 mg) (P <0.001), with greater reductions in HbA1c seen with sitagliptin regimen compared to glimepiride regimen. Moreover at 24 weeks, the patients achieving target HbA1c of <7.0% with sitagliptin (100 mg) (59.62%) were significantly higher (P = 0.0003) compared to glimepiride (1–3 mg) (41.95%) therapy. Similarly, for a target HbA1c of <6.5% at 24 weeks, the percentage of patients attaining the target HbA1c was higher (P = 0.0001) with sitagliptin (25.82%) than with glimepiride (10.73%) therapy. This result was in concordance with our study showing significant difference in decrease in HbA1c in both the groups with sitagliptin (100 mg) (p=0.01) and glimepiride (1mg) (P =0.01), with greater reductions in HbA1c seen with sitagliptin regimen (27.20%) compared to glimepiride regimen (23.73%). On statistically comparing both the groups the difference was non-significant at 15 weeks but was significant at 30 weeks. Viewing the safety parameters their study showed that only 2.13% patients on sitagliptin had hypoglycaemia and none has severe hypoglycaemia whereas 27.80% patients on glimepride had hypoglucaemia, out of which 3.90% has severe hypoglycaemia. Similarly our study also showed concordance with their study as more number of patients had hypoglycaemia taking glimepride (20%) as compared to patients taking sitagliptin (2.5%).

Manuj Sharma et al [16] in their comparitive study of 18 weeks with sitagliptin 100mg and glimepiride 2mg per day as add on drug with metformin concluded that both the groups showed significant improvement in HbA1c, FBG and PPG values, with greater fall in the sitagliptin group, though intergroup comparison showed no significant difference in all the parameters. These findings are in accordance with our study except that our study showed significant difference on intergroup comparison of HbA1c levels at end point. This may be due to our longer study duration (30weeks) and less dose of glimepride (1mg) used in comparison to their study.

Present study data also revealed that sitagliptin was well tolerated as compared to glimepiride as 2.5% patients felt hypoglycemia in sitagliptin group as compare to 20% in glimepiride group. Almost similar results were documented by Manuj Sharma et al.[16]

Devarajant. V et al[17] in their 12 week study with sitagliptin 50 mg/metformin 500 mg twice daily versus glimepiride 1 or 2 mg/sustained-release metformin 1000 mg once daily concluded that at 12 weeks, both treatment groups exhibited an improvement in HbA1c, FBG, PPG from baseline, which was statistically significant (Student's *t*-test, P = 0.001). However, the mean reduction in HbA1c from baseline in the glimepiride group was significantly more as compared to the sitagliptin group (0.42± 0.24% vs. 0.30 ± 0.20% respectively, Student's *t*-test P= 0.001), the mean reduction in FPG (12.41 vs.7.45 mg/dl) and PPG (21.01 vs. 12.09 mg/dl) was also significantly more in the glimepiride group as compared to sitagliptin group, respectively, P = 0.008. These results are only partially in concordance with our study, as our data also showed that HbA1c, FBG, PPBG levels are significantly decreased in both the treatment groups but the mean change was more in patients taking Sitagliptin. This may be due to that our study was of longer duration and the dose of sitagliptin used in our study is higher as compare to their study and dose of Glimepiride used by them is variable (1-3mg).

Preeti Singh et al[12] in the 24 week study with glimepiride 5mg BD + metformin 500mg TDS and sitagliptin 100mg OD + metformin 500mg TDS, concluded that both the groups had significant fall in HbA1c, FBG, PPBG levels, these findings are accordance with our study. On intergroup comparison the significant fall in FBG and HbA1c levels was seen in glimepride group at 12 weeks, this disparity with our results may be due to very higher dose of glimepiride used in their study as compare to our study

Aschner Pablo et al[14] in their 24 week study with sitagliptin 100 mg or 200mg or placebo, reported that patient taking sitagliptin showed a significant decrease in fasting blood glucose, post prandial glucose and HbA1c

levels as compared to placebo, similarly our study also reported significant decrease in these three parameters at 30 weeks.

Liu Dan et al[18] in their analysis showed that during a mean follow-up time period ranging from 52 to 152 weeks, the primary endpoint (cardiovascular death/non-fatal myocardial infarction (MI)/non-fatal stroke) was not significantly different in the treatment of T2DM patients with versus without DPP-4 inhibitors (OR: 0.95, 95% CI: 0.86–1.04; P = 0.26). Our study at 30 week also concluded that there is no significant cardiovascular event occurred in both the groups. 2 Patients (5%) of each groups had mild complaint of chest discomfort and dyspnoes and the difference was again statistically non-significant (p=0.11).

Fewer limitations of this study are smaller sample size and shorter study period, as larger sample size and longer duration study could lead to varied results. However in this study none of the patient had drop out from the study.

Conclusion

30 weeks open randomized comparative study compared the effect of sitagliptin with Metformin versus Glimepiride with metformin on FBG, PPBG and HbA1c levels in patients with type II diabetes mellitus. It was found that both groups significant reduction in FBS, PPBS and HbA1c levels at all the visits. Improvement was more with group A and when the effects of both the drugs were compared, the difference was observed to be non-significant for FBG and PPBG at the end of 15 and 30 weeks of starting the treatment but was statistically significant for HbA1c at 30weeks. It was thus concluded that both sitagliptin and Glimepiride with metformin were very effective hypoglycaemic agents but sitagliptin had a slight edge over Glimepiride as it showed greater reduction in HbA1c levels and was found to be safe and well tolerated.

Abbreviations

T2DM: Type 2 Diabetes Mellitus
DM: Diabetes Mellitus
FBG: Fasting Blood Glucose
PPBG: Post Prandial Blood Glucose
HbA1c: Glycosylated haemoglobin
DPP-4: Dipeptidyl peptidase-IV inhibitors
BMI: Body mass index
IDF: International diabetic federation
AACE: American Association of Clinical Endocrinologists
ACE: American College of Endocrinology

Source of Funding

Nil.

Conflict of Interest

Nil.

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