



## COMPARISON OF THE EFFICACY AND SAFETY PROFILE OF SITAGLIPTIN AND GLIMEPIRIDE IN TYPE 2 DIABETIC PATIENTS.

Mazhar Hussain<sup>1</sup>, Muhammad Amir Rafique<sup>2</sup>, Abdul Qudoos Arain<sup>3</sup>, Shoaib Akhtar<sup>4</sup>,  
Muhammad Bilal Ghafoor<sup>5</sup>, Lubna Akhtar<sup>6</sup>

1. MBBS, M.Phil (Pharmacology)  
Associate Professor Pharmacology  
Sheikh Zayed Medical College,  
Rahim Yar Khan.
2. MBBS, M.Phil (Pharmacology)  
Assistant Professor Pharmacology  
Islam Medical, Sialkot.
3. MBBS, M.Phil (Pharmacology)  
Associate Professor Pharmacology  
HBS Medical & Dental College,  
Islamabad.
4. MBBS, FCPS (Medicine)  
Senior Registrar Medicine  
Sheikh Zayed Hospital, Rahim Yar  
Khan.
5. MBBS, M.Phil (Hematology)  
Associate Professor Hematology  
Sheikh Zayed Medical College,  
Rahim Yar Khan.
6. MBBS, FCPS (Gynae & Obs)  
Senior Demonstrator Pharmacology  
Sheikh Zayed Medical College,  
Rahim Yar Khan.

### Correspondence Address:

Dr. Mazhar Hussain  
House No 214/C Satellite Town,  
Rahim Yar Khan.  
mazharhussain214@gmail.com

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**ABSTRACT... Objectives:** To compare the efficacy and safety profile of sitagliptin vs. glimepiride in type 2 diabetic patients. **Study Design:** Comparative study. **Setting:** Medical Unit, Islam Centarl Hospital Sialkot. **Period:** September to December 2018. **Material & Methods:** In which Type 2 diabetic patients (n=220) were randomly placed into interventional groups to prescribed either sitagliptin or glimepiride for an interval of 16 weeks. A blood sugar level was maintained by dose titration in both groups. The main end point was change in FBG & HbA1C while additional end point was change in body weight, hypoglycemic episodes and gastrointestinal adverse effects from baseline by using SPPS 16. **Results:** After 16 weeks of treatment both sitagliptin and glimepiride caused a significant improvement ( $P < 0.001$ ) in glycemic control by reducing FBG ( $-22 \pm 3.2$  &  $-33.5 \pm 4.4$ ) & HbA1c ( $0.78 \pm 0.3$  &  $1.12 \pm 0.25$ ) respectively. However when comparison was done between two group, glimepiride has more pronounced effect on glycemic control as compared to sitagliptin ( $P < 0.001$ ). Net BMI reduced to  $0.8 \pm 0.68$  in sitagliptin group while net BMI increased to  $1.1 \pm 0.78$  in glimepiride treated group with ( $P < 0.001$ ). There were no adverse effects reported in sitagliptin treated group while 25 hypoglycemic episodes were noticed in glimepiride treated group. **Conclusion:** Glimepiride has more pronounced effect on glycemic control as compared to sitagliptin. However this pronounced effect was associated with more hypoglycemic episodes and weight gain. Euglycemic effect and weight reducing property of sitagliptin precludes that it has better safety and tolerability profile in comparison with glimepiride.

**Key words:** Body Weight, BMI, Glimepiride, HbA1c, Sitagliptin.

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## INTRODUCTION

Type 2 diabetes mellitus is rising at an alarming rate all across globe. Out of every 11 adults, 1 has diabetes mellitus now. The number of diabetic patients and its associated complications increases day by day more in Asians countries because of strong genetic predisposition. Moreover developing countries far behind in controlling diabetes related risk factors such as obesity, dyslipidemia, physical inactivity, sedentary life style, urbanization and stress.<sup>1</sup> Therefore a self management education and support is required in order to prevent and control diabetes associated risk factors and complications. This will reduce social and economic burden of diabetes on public health system.<sup>2</sup>

Life style modifications usually consider first in the management of type 2 diabetes. Oral hypoglycemic agents and insulin are other options if glycemic control can be achieved within therapeutic range in spite of life style modification. Antidiabetic drugs act through various mechanisms to counteract the increase level of glucose in diabetic patients. They inhibit glucose absorption from intestine, decrease glucose production from liver, increase insulin release from pancreas, inhibit glucose reabsorption from proximal tubules and increase insulin sensitivity.<sup>2-3</sup>

Sitagliptin is an oral antidiabetic agent that is used as monotherapy or combination therapy in diabetes patients. It increases the physiological concentration of two gastrointestinal hormones

glucagon like peptide (GLP) and gastric inhibitory peptide (GIP) in body. It increases these enzyme concentrations by inhibiting another enzyme called dipeptidyl peptidase 4 (DPP-4) Sitagliptin control blood sugar through various actions such as suppression of appetite, increase insulin release from pancreas, inhibits glucagon production and increases insulin sensitivity towards peripheral tissues. Sitagliptin has an excellent glycemic control profile with no risk of hypoglycemia. Moreover sitagliptin has a mild decrease or neutral effect on body weight.<sup>4-5</sup> Moreover sitagliptin has many useful effects on other body system such as blood pressure, inflammation, lipid profile, oxidative stress, endothelial and myocardial dysfunction.<sup>6</sup>

Glimepiride is one of the 2<sup>nd</sup> generation sulfonylurea groups of oral antidiabetic drug. Glimepiride is prescribed mostly in type 2 diabetic patients either alone or in combination therapy. It acts as an insulin secretagogue and increases insulin production from the beta cells of pancreas. Glimepiride has also good glycemic control profile in most of the type 2 diabetic patients. However in comparison with first generation sulfonylurea, glimepiride is associated with low risk of hypoglycemia. Moreover it is associated with increase in body weight in most of the type 2 diabetic patients.<sup>7</sup>

The present study was conducted to compare the effects of sitagliptin and glimepiride in terms of HbA1C, body weight, hypoglycemic episodes and gastrointestinal adverse effects over a period of 16 weeks.

## MATERIAL & METHODS

This 16 weeks comparative clinical trial was conducted at Islam Central Hospital at its medical outdoor from September to December 2018. An ethical permission and informed consent was taken before start of study. In the beginning, 350 patients of type 2 diabetes were screened at medical outdoor over a period of 6 months. From which 220 were recruited for the study in terms of inclusion and exclusion criteria. The inclusion criterion was type 2 diabetic patients aged 42-65 with HbA1c 7.5-9% and BMI 27-29.

The exclusion criteria include detailed history, clinical examination and routine test to rule out any diabetes related complication in the form of neuropathy, nephropathy and retinopathy. In addition patients with history of type 1 diabetes, smoking, alcohol, hypertension, cardiac diseases, renal and hepatic disorders were excluded from the study. In addition those patients whose glycemic level should not be controlled within 4 weeks of study were excluded from the study.

These patients were randomly divided in a ratio of 1:1 in two groups. These patients had inadequate glycemic control and were switched from metformin routine to sitagliptin and glimepiride over a washout period of 2 weeks. Patients in Group A were given tablet sitagliptin 50mg while patients in group B were given tablet glimepiride 1mg initially. The doses of both drugs were adjusted according to their blood sugar level. Most of the patients were adjusted on sitagliptin 100mg and glimepiride 2mg daily after 04 weeks of treatment. Treatment was continued over a period of 16 weeks. A digital weight machine was used to measure body weight. A microtoise was used to measure height. Measurements were done by wearing light clothes and without shoes. A standard formula, weight in kg divided by height in meter square ( $\text{kg/m}^2$ ) was used to calculate BMI. A 5ml overnight fasting blood sample was taken from cephalic vein through aseptic technique. After clotting and centrifugation, serum was separated and stored at 4 °C for 1 hour until analyzed for HbA1c and serum lipid profile. A glucose oxidase peroxidase method was used to estimate blood sugar while liquid chromatography and enzymatic end point method was used to determined HbA1c and serum lipid profile respectively.

Statistical package for social sciences (SPSS-16) was used to analyze data. Parametric data such as body weight, BMI, blood sugar and HbA1c were expressed as mean  $\pm$  SD from baseline. The adverse effects and hypoglycemic episodes were expressed as numbers. The comparison among group and between groups was done by paired t test and student t-test. P value <0.01 were seemed to be statistically significant.

Demographic Characteristics	Sitagliptin (N=110)	Glimepiride (N=110)	P-Value
Age (years)	54.6±8.8	48.5±12.5	0.76
Gender(M/F)	71(64.5%)/39(35.4%)	64(58.1%)/46(41.9%)	0.32
Body weight (kg)	79±12.5	82±14.6	0.88
BMI (kg/m <sup>2</sup> )	28±5.3	27±3.8	0.12
Diabetes duration (years)	5.6±4.2	5.2±6.5	0.98
<b>Parameters Lab (mean ± SD)</b>			
Serum glucose F(mg/dl)	160±12.5	155±14.2	0.62
HbA1c (%)	8.4±0.9	8.2±0.82	0.42
Total Cholesterol(mg/dl)	186±34.56	170.5±30.5	0.77
Triglycerides(mg/dl)	157±20.76	166±24.8	0.23
LDL-Cholesterol(mg/dl)	110±14.6	118±18.3	0.43
HDL-Cholesterol(mg/dl)	43.5±4.62	44±4.26	0.82

**Table-I. Study parameters at the start in both groups**  
Values are given ±standard deviation

Group A Sitagliptin(n=110)				Group B glimepiride (n=110)			
Parameters	0 weeks	16 weeks	Mean Difference	Parameters	0 weeks	16 weeks	Mean Difference
BMI (kg/m <sup>2</sup> )	28±5.3	26.5±4.2	-0.8±0.68	BMI (kg/m <sup>2</sup> )	27±3.8	27.9±3.2	+1.1±0.78
FBG(mg/dl)	154±10.2	134±12.5	-22±3.2	FBG(mg/dl)	160.5±13.4	130±10.8	-33.5±4.4
HbA1c (%)	8.4±0.9	7.62±0.62	-0.78±0.3	HbA1c (%)	8.2±0.82	7.4±0.55	-1.12±0.25

## RESULTS

The compliance of both drugs was quite good and no patient was dropped out from the study. Demographic parameters (Table-I) at start of study showed no significant statistical difference in both study groups. There was significant improvement ( $P<0.001$ ) in glycemic control after 16 weeks treatment in both sitagliptin and glimepiride treated groups. HbA1c value was decreased from  $8.4\pm0.9$  to  $7.62\pm0.62$  with a net reduction of  $-0.78\pm0.3\%$  in sitagliptin treated group. While in glimepiride treated group HbA1C value was also decreased from  $8.2\pm0.82$  to  $7.4\pm0.55$  with a net reduction of  $1.12\pm0.25\%$ . Both groups showed a significant reduction ( $P<0.001$ ) in fasting blood sugar level. The mean fasting blood sugar level was reduced by  $22\pm3.2$  in sitagliptin and  $33.5\pm4.4$  in glimepiride treated group respectively. However comparison between two group revealed that glimepiride was statistically significant effect on glycemic control in comparison with sitagliptin ( $P<0.001$ ). The net reduction of BMI was  $0.8\pm0.68$  in sitagliptin treated group while BMI increased to  $1.1\pm0.78$

in glimepiride treated group with ( $P<0.001$ ). The safety and tolerability profile of sitagliptin and glimepiride was quite good with no major adverse effects were noted during the study. However 4 patients in sitagliptin group and 5 patients in the glimepiride group were complaint of abdominal distention at start of study which was settle down itself without any treatment. There was no single episode of hypoglycemia reported in sitagliptin group. On the other hand we have noticed 25 hypoglycemic episodes in the form of lightheadness, sweating, anxiety and confusion in glimepiride treated group.

## DISCUSSION

In this comparative study sitagliptin and glimepiride were assessed in terms of body weight, glycemic control, hypoglycemic episodes and gastrointestinal adverse effects over a period of 16 weeks. In our study both drugs improved glycemic control marked by significant reduction of FBG and HbA1c. This improvement in glycemic control was further accompanied by reduction in body weight with no hypoglycemic episode

in sitagliptin treated group while glimepiride treated group was associated with increase in body weight and increase risk of hypoglycemic episodes. However no gastrointestinal and other adverse effects were noted in both study groups.

The results of our study were in consistent with various studies in which sitagliptin improved glycemic control and reduced body weight with no risk of hypoglycemia. Sitagliptin reduced BMI  $0.8 \pm 0.68$  (kg/m) and HbA1C  $0.78 \pm 0.3\%$  in our study which were almost similar to study conducted by Yanai et al<sup>8</sup> which revealed that sitagliptin treatment significantly reduced body weight and HbA1c in type 2 diabetes over a period of 6 months. Sitagliptin reduced HbA1C 0.43 to 1.0% and body weight 0.2 to 2kg in various clinical studies.<sup>9-12</sup> However duration of these studies were 6 months or more. Aschner et al<sup>9</sup> also observed that sitagliptin has more pronounced effect on HbA1c > 8% as compared to HbA1c 7.2%. These studies also shown that sitagliptin either monotherapy or as combination therapy with metformin significantly reduced body weight. Moreover combination with metformin as additive effect on reducing body weight as metformin has well known for its weight reducing property.

However two studies also showed that sitagliptin increased body weight +0.4 and +0.28kg. This increase in body weight was mainly caused by as add on therapy with pioglitazone and glimepiride. The increase in body weight by both of these drugs is already well understood.<sup>13-14</sup> However a study conducted by Nonaka et al<sup>15</sup> revealed that sitagliptin reduced HbA1C 0.65% without any hypoglycemic episodes but had no effect on body weight in contrast to our study.

A tight glycemic control was achieved by glimepiride in our study as compared to sitagliptin. This tight glycemic control was associated with more hypoglycemic attacks in glimepiride versus sitagliptin group. Similar results were observed in other studies revealing that glimepiride although has an excellent glycemic control profile but associated with more hypoglycemic episodes in comparison with sitagliptin. Further there was

increase in body weight by glimepiride which was similar to various studies that concluded that average weight gain by glimepiride was +1 to 2kg in type 2 diabetic patients over a period of 12 weeks to 2 years.<sup>16-18</sup>

There were limited studies about comparison between sitagliptin and glimepiride in terms of glycemic control, body weight and tolerability profile. Similar to our study Srivastava et al<sup>19</sup> revealed that although glimepiride had more beneficial effect on glycemic control but it was also associated with more hypoglycemic attacks and weight gain as compared to sitagliptin. Two another studies<sup>20-21</sup> pointed out that DPP-4 inhibitors, sitagliptin and saxagliptin showed a better tolerability and safety profile as compared to glimepiride in elderly type 2 diabetic patients with inadequate glycemic control. However multicentre randomized control trial conducted by ferrannini et al<sup>22</sup> demonstrated that DPP-4 inhibitor displayed a comparable efficacy but more safety profile in comparison with glimepiride over a period of 52 weeks in type 2 diabetic patients. Similarly meta analysis of 10 randomized control trial showed that there were no difference between sitagliptin and glimepiride in terms of clinical efficacy when added to patients who were inadequately controlled with metformin monotherapy. Body weight decreased by 2.2kg and only one hypoglycemic episode were recorded over a follow up in 10,616 patients of type 2 diabetes.<sup>23</sup> While a systematic review and meta analysis of 16 randomized trial showed that both drugs can be used as an add on therapy in type 2 diabetic patients whose blood sugar was inadequately controlled with metformin. However glimepiride was associated increase risk of hypoglycemia and weight gain in comparison with sitagliptin which was associated with no risk of hypoglycemia and weight loss.<sup>24</sup> Another meta analysis of 41 randomized controlled trial concluded that sitagliptin has excellent safety profile with a mean reduction of HbA1c 0.6 to 0.8% lesser than sulphonylureas but without gaining weight and low risk of hypoglycemia similar to our study.<sup>25</sup> (monami). A systematic review and meta analysis of 19 studies yield similar result in sense that DPP-4 inhibitors lower HbA1C in

same way as sulphonylureas or pioglitazone with neutral effect on body weight and without hypoglycemia.<sup>26</sup> (Karagiannis).

Moreover DPP-4 inhibitors have additional benefits as compared to glimepiride on risk factors in type 2 diabetic patients. They reduce blood pressure, inflammatory markers, apoptosis and oxidative stress. They also improve lipid profile, postprandial lipaemia, endothelial and myocardial dysfunction. Seeing these pleiotropic effects, sitagliptin has strong potential against ischemic, atherosclerotic and hypertensive cardiovascular diseases.<sup>27-29</sup>

## CONCLUSION

Glimepiride has more pronounced effect on glycemic control as compared to sitagliptin. However this pronounced effect was associated with more hypoglycemic episodes and weight gain. Euglycemic effect and weight reducing property of sitagliptin precludes that it has better safety and tolerability profile in comparison with glimepiride.

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**AUTHORSHIP AND CONTRIBUTION DECLARATION**

Sr. #	Author(s) Full Name	Contribution to the paper	Author(s) Signature
1	Mazhar Hussain	Conceived the idea, Search literature & wrote the paper.	
2	M. Amir Rafique	Designed the study and Collected clinical data.	
3	Abdul Qudoos Arain	Preparing the manuscript, data analysis and interpretation of discussion.	
4	Shoaib Akhtar	Search the literature, manuscript editing and drafting of the manuscript.	
5	M. Bilal Ghafoor	Manuscript review, Proof reading and laboratory data analysis.	
6	Lubna Akhtar	Final editing, plagiarism and assisted in final writing of manuscript.	