EFFECTS OF SITAGLIPTIN ON HBA1C LEVELS IN UNCONTROLLED HYPERGLYCEMIA IN DIABETICS USING CONVENTIONAL OAD'S.

Amar Nazir¹, Fida Muhammad Sheikh², Sheraz Saleem³

ABSTRACT... Objectives: The study anticipates to appraise HbA1c levels after three months of sitagliptin addition (100mg/day) to patients already using conventional oral antidiabetics in patients of type II diabetes mellitus who have a meager retort to these existing anti diabetics. Study Design: Cross sectional prospective study. Setting: Department of Medicine University medical diagnostic center & District Head Quarter Hospital Sargodha. Period: January 2017 to June 2017. Material & Methods: 100 inadequately controlled diabetics using different types of oral anti diabetics were chosen and an especially designed performa was accomplished. In our study we gave preference to those patients who were on preexisting oral anti diabetics and now dipeptidyl peptidase 4 inhibitors were added for the first time. The patients were instructed (at the baseline visit) to report during the subsequent visit about glycemic control. Patients were not clued-up that glycosylated hemoglobin control was the main seek of the study, so there was no chance for Pygmalion effect. Results: Levels of glycosylated hemoglobin were significantly reduced after three months of treatment compared to baseline, with a mean alteration in HbA1c level from baseline of −0.77% (range, −0.68 to −0.86%) in the entire study population at three months. The percentage of patients who achieved an HbA1c level of <6.9% significantly increased after three months of treatment, reaching 58.1%. Conclusion: HbA1c significantly lowered in patients with type 2 diabetes mellitus on conventional OADs after adding sitagliptin.

Key words: Conventional OAD's, Sitagliptin HbA1c.

Article Citation: Nazir A, Sheikh FM, Saleem S. Effects of Sitagliptin on HbA1c levels in uncontrolled hyperglycemia in diabetics using conventional OAD's. Professional Med J 2020; 27(5):963-967. DOI: 10.29309/TPMJ/2020.27.05.3940

INTRODUCTION
Since its discovery in 1960’s serine proteasedipeptidyl peptidase 4 inhibitors has been a prevalent focus of study.¹ Oral dipeptidyl peptidase 4 inhibitors are drugs used for management of type II diabetes mellitus with hyperglycemia. Natural substances like incretins are increased in diabetics using sitagliptin. Especially incretins escalates post meal insulin release and overwhelms glucagon secretion which facilitates to control blood sugar levels among diabetics. They too reduce the liver sugar manufacturing.²,³ About 65% to 75% diabetics at present are being treated with conventional anti diabetic drugs. Tiresome administration, inefficiency, gaining body weight, petite-lasting consequences are commonest diverse snags of these conventional anti diabetics. Admissibility, protection, improved effectiveness and diversity is shown by these new drugs due to their endeavor mechanism. Sitagliptin incapacitates incretins such as gastric inhibitory polypeptide and glucagon like peptide-1 by extremely selective inhibition of dipeptidyl peptidase- 4 inhibitor through a mechanism diverse from that of traditional oral anti diabetics thought provoking insulin secretion. First time in Japan, sitagliptin gained endorsement in 2009 and the loftier efficiency and safety of dipeptidyl peptidase 4 inhibitors have been established in numerous research studies.⁴,⁵,⁶ There is lot of published literature on sitagliptin and in present study we got preexisting treatment groups and started sitagliptin for scrutinizing its effects in these groups. Due to uncontrolled diabetes mellitus and frequent assorted hitches these diabetics often
cuddle additional anti diabetic medications.\textsuperscript{7,8} In this study we intend to explore the stirring effect of Sitagliptin on HbA1c and blood sugar levels in patients with meagerly reactive to existing anti diabetic drugs.

**MATERIAL & METHODS**
Mainly cross sectional prospective multicenter, open labeled study of 100, well oriented & cooperative diabetic patients (age 30-75 years) presented in outpatient department (OPD), admitted in teaching medical unit of DHQ Hospital Sargodha and University medical and diagnostic center Sargodha.

Criteria for poor blood glucose: Patients having fasting blood sugar level $\geq 130$ mg/dl and HbA1c level $\geq 6.9\%$ were included in the study. Afterward sitagliptin (100mg) was given in addition to these pre-existing treatment groups of type 2 diabetes (combination therapy). Treatment was not altered throughout the study period explicitly of three months after the addition of sitagliptin. The alteration in HbA1c level at 3 months from baseline was the primary end point. The diabetics on diet, exercise therapy, biguanides, sulfonylureas, $\alpha$-glucosidase inhibitors or two or more of these drugs in combinations and patients reluctant to insulin were included in this study.

Patients having (i) Diabetic nephropathy (having serum creatinine levels $\geq 1.5$ mg/dl) (ii) Severe infections or injury (iii) Gestation or breast feeding (iv) Past history of spartan ketosis, diabetic unconsciousness or pre-coma within the past 3 months (v) Patients using insulin (vi) Patients on nateglinide, rapaglinide and using sulfonylureas other than 1-2mg glimepride (vii) Allergic to sitagliptin were excluded from the study.

**RESULTS**
In general adding sitagliptin 100mg one time daily to diabetics using conventional oral anti diabetics considerably abridged HbA1c from preliminary of $-0.77\%$ (range, $-0.68$ to $-0.86\%$) in the whole cram diabetics at three months. The percentage of diabetics who accomplished an HbA1c echelon of $<6.9\%$ drastically augmented subsequent to 30 days of management, achieving maximum (58.1\%) at 3 months. In the amalgamation group taking sitagliptin and metformin (preliminary mean HbA1c=7.4\%), the reduction in glycosylated hemoglobin was $0.68\pm0.72\%$ (0.70\%). In the medley group of sulfonylurea (glimepride 1-2mg), sitagliptin and biguanides (preliminary mean HbA1c=7.7\%), the diminution in HbA1c was $0.73\pm0.79\%$ (0.76\%). In the combination group of sitagliptin, $\alpha$-glucosidase inhibitors, sulfonylurea (1mg glimepride) and biguanides (preliminary mean HbA1c=8.1\%), the reductions in HbA1c was $0.83\pm0.86\%$ (0.85\%). Relatively more HbA1c reductions were observed in abundant drug combination group.
DISCUSSION
Pancreatic beta cells dysfunction is the main reason for type II diabetes mellitus rather than impaired insulin sensitivity. Characteristically, the time a patient is diagnosed with type II diabetes mellitus, islet function has previously been declined by around half. Partially impaired islet function is due to abridged pancreatic beta cell mass which is chiefly due to accelerated apoptosis of these pancreatic cells. Sulfonylureas lowers blood glucose levels by provoking insulin secretion, although using high dose sulfonylureas for long time persuade apoptosis in beta cell lines and islet pancreatic cells. Seemingly beta cells discrimination, propagation and conservation is increased by dipeptidyl peptidase 4 inhibitors and they augment islet architecture, remodeling and inhibits glucagon secretion. Sitagliptin could maintain and perhaps overturn the escalating riddance of pancreatic beta cells and insulin secretory failure attribute of type II diabetes mellitus as advocated by tentative and scientific studies. To display the clinical implication of these conclusions, however enduring studies in persons with type II diabetes mellitus are required.

Influence of DPP-4 inhibitor (sitagliptin 100mg daily) on glycosylated hemoglobin levels among type 2 diabetics was observed in this cross sectional study. When sitagliptin added to these hyperglycemic patients on previous antidiabetics mean HbA1c was ominously lower in these diabetics. Related to an aforementioned transnational research study by Scott et al., the decline in HbA1c was alike in the biguanides and sitagliptin coalescence group (HbA1c amend, -0.72% vs. -0.73. Another trial by Charbonnel et al. obtained comparable results for sitagliptin effects on HbA1c like our study. Tomoya hamaguchiet al. revealed a bit higher HbA1c reduction as compare to this study which may be due to longer duration of study, large patients group and a Japanese race.

In biguanides, α-glucosidase inhibitor, sulfonylurea and sitagliptin integration group initial mean HbA1c was 8.1%, in sulfonylurea, biguanides and sitagliptin combination group initial denote HbA1c was 7.7% and the decline in glycosylated hemoglobin was significant. In our study using identical medications it was known that the superior was the reduction in HbA1c levels in groups of high early HbA1c levels. Even though in abundant drug combination group the early levels of HbA1c were higher compared to biguanides and sitagliptin group, this nor has outcome in lesser diminution in the HbA1c levels of diabetics using multiple drugs in comparison to that in scarce. It’s also important that shifting from sulfonylureas to sitagliptin can be considered for diabetics with alternating hypoglycemic episodes and near blot HbA1c. Prevalence of GIT troubles, hypoglycemia and other side effects were not raised with sitagliptin addition. There are some limitations in our study as it is impossible to authenticate that the given modifications in lifestyle as exercise or diet were adopted by our patients or not. Therapeutic acquiescence by the registered diabetics was not assured and considering figures were attained from side to side review of management reports, reports of hypoglycemia occurrences or the frequency of GIT system nuisances. Summing up, this study shows that adding 100mg once daily sitagliptin to conventional antidiabetics is effective and well endured in Pakistani patients with type II diabetes mellitus who experience persistent hyperglycemia on conventional oral anti diabetics.

CONCLUSION
In patients who were poorly responsive to conventional oral anti diabetic drugs the target
control levels as blood sugars and glycosylated hemoglobin were well controlled in type II diabetics after sitagliptin 100 mg addition. Thus, sitagliptin showed its effectiveness for this patients group. Sitagliptin addition to other OAD’s remarkably could suppress glucose levels, fluctuations and HbA1c levels. Forthcoming studies with a large number of patients and with more frequent post meal self-glucose monitoring or with continuous glucose monitoring’s are warranted to confirm these findings.

Copyright © 03 Oct, 2019.

REFERENCES

1. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 2006; 29(12):2632–2637.

2. Results of “National health and nutrition survey”. Ministry of Health, Labour and Welfare. 2012.

3. Kahn SE, Haffner SM, Heise MA, et al. Glycemic durability of rosiglitazone, metformin, or glyburide monotherapy. N Engl J Med. 2006; 355:2427–43.

4. Wild S, Rosglic C, Green A, Sicree R, King H. Global prevalence of diabetes; estimates for the year 2000 and projections for 2030. Diabetes Care. 2004; 27:1047–1053.

5. Nathan DM. Finding new treatments for diabetes – how many, how fast … how good? New Engl J Med. 2007; 356:437–440.

6. Seino Y, Nanjo K, Tajima N, et al. Report of the Committee on the classification and diagnostic criteria of diabetes mellitus. Japan Diabet Soc. 2012; 52012; 55:485–504.

7. Ahren B. Dipeptidyl peptidase-4 inhibitors. Clinical data and clinical implications. Diabetes Care. 2007; 30:1344–1350.

8. Iwamoto Y, Taniguchi T, Nonaka K, et al. Dose-ranging efficacy of sitagliptin, a dipeptidyl peptidase-4 inhibitor, in Japanese patients with type 2 diabetes mellitus. Endocr J. 2010; 57:383.

9. Ahren B, Landin-Olsson M, Jansson PA, Svensson M, Holmes D, Schweizer A. Inhibition of dipeptidyl peptidase-4 reduces glycemia, sustains insulin levels, and reduces glucagon levels in type 2 diabetes. J Clin Endocrinol Metab. 2004; 89:2078–2084.

10. Aschner P, Kipnes MS, Lunceford JK, Sanchez M, Mickel C, Williams-Herman DE Sitagliptin Study 021 Group. Effect of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy on glycemic control in patients with type 2 diabetes. Diabetes Care. 2006; 29(12):2632–2637.

11. Raz I, Hanefeld M, Xu L, Caria C, Williams-Herman D, Katrami H Sitagliptin Study 023 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin as monotherapy in patients with type 2 diabetes. Diabetologia. 2006; 49:2564–2571.

12. Scott R, 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. Clin Pract. 2007; 61:171–180.

13. Nauck MA, Meiningerg G, Sheng D, Terranal L, Stein PP Sitagliptin Study 024 Group. 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; 9:194–205.

14. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or glimepiride and metformin. Diabetes Obes Metab. 2007; 9:733–745.

15. Hermansen K, Kipnes M, Luo E, Fanurik D, Khatami H, Stein P Sitagliptin Study 035 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor, sitagliptin, in patients with type 2 diabetes mellitus inadequately controlled on glimepiride alone or glimepiride and metformin. Diabetes Obes Metab. 2007; 9:733–745.

16. Scott R, 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. Clin Pract. 2007; 61:171–180.

17. Charbonnel B, Karasik A, Liu J, Wu M, Meiningerg G. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled on metformin alone. Diabetes Care. 2006; 29:2638–43.

18. Kubota A, Yabe D, Kanamori A, et al. Factors influencing the durability of the glucose-lowering effect of sitagliptin combined with a sulfonylurea. J Diabetes Investig. 2014; 5:445–8.
19. Kubota A, Yabe D, Kanamori A, et al. **Factors influencing the durability of the glucose-lowering effect of sitagliptin combined with a sulfonylurea.** J Diabetes Investig. 2014; 5:445–8.

---

### AUTHORSHIP AND CONTRIBUTION DECLARATION

| Sr. # | Author(s) Full Name          | Contribution to the paper | Author(s) Signature |
|-------|-----------------------------|---------------------------|---------------------|
| 1     | Amar Nazir                  | 1st Author                |                     |
| 2     | Fida Muhammad Sheikh        | 2nd Author                |                     |
| 3     | Sheraz Saleem               | 3rd Author                |                     |