



SITAGLIPTIN; SITAGLIPTIN AS ADD ON THERAPY TO PATIENTS ON INSULIN.

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Article received on:

21/07/2017

Accepted for publication:

23/09/2017

Received after proof reading:

03/11/2017

ABSTRACT... The objective of this study is to compare the mean reduction of HbA1c in patients taking sitagliptin insulin combination with insulin alone in patients of type II Diabetes mellitus. **Study Design:** Randomized control trial (RCT). **Setting:** Medicine Department, Allied Hospital, Faisalabad. **Period:** August 2013 to February 2014. **Methodology:** Patients of both genders with ages between 18 and 60 years having uncontrolled type 2 diabetes mellitus with HbA1c taking insulin were included in the study while Pregnant or lactating mothers, patients with chronic liver disease and patients with renal insufficiency (creatinine >3.0mg/dl) were excluded from study. Patients were randomly divided into two groups (A & B) using computer generated random number table. Group A was given Sitagliptin 50mg per day and dose was increased to 100mg per day after 2 weeks if fasting blood sugar was more than 110mg/dl or 2 hours postprandial blood sugar more than 140mg/dl. Dose of insulin in group A remained same as before start of study. Group B was kept on same regimen of insulin they were already taking and dose remained same. HbA1c was done at start of study and after 24 weeks. Primary outcome measure was mean reduction in HbA1c levels at 24 weeks from baseline. **Results:** 60 patients were included in the study. Mean age was 52.7 ± 8.43 years. 36(60%) were male and 24(40%) were female. Mean HbA1c at baseline was $8.361 \pm 0.523\%$ in Group A on Sitagliptin-insulin combination and $8.187 \pm 0.432\%$ in group B on insulin alone. Mean HbA1c at 24 weeks was $7.767 \pm 0.428\%$ in group A on Sitagliptin-insulin combination and $7.69 \pm 0.407\%$ in group B on insulin alone. Independent sample t-test was applied to change in HbA1c in Group A and B during 24 weeks of treatment. Mean change in HbA1c after 24 weeks in Group A was 0.600 ± 0.315 and 0.49 ± 0.19 in Group B after 24 weeks treatment (p-value 0.002) which is highly significant. Paired sample t-test was applied to HbA1c at baseline and 24 weeks of treatment in group A and group B. There was a significant change in both groups after 24 weeks of treatment in both groups (p-value <0 .000) which is highly significant. Chi Square test was applied on efficacy in group A and B. 22(73.33%) patients in group A and 14(46.67%) patients in group B which achieved significant reduction in HbA1c. 8(26.67%) patients in group A and 16(53.33%) patients in group B failed to achieve significant reduction in HbA1c. (P-value < 0.032). **Conclusion:** It has been concluded from this study that insulin and sitagliptin-insulin combination both significantly reduce HbA1c in type 2 diabetes mellitus. However addition of sitagliptin to uncontrolled diabetic patients already taking insulin, is more effective than insulin for glycemic control of patients with type 2 diabetes mellitus.

Key words: Type 2 Diabetes Mellitus, Insulin, Sitagliptin.

Article Citation: Ahmed Z, Fareed H, Musharraf MU. Sitagliptin; as add on therapy to patients on insulin. Professional Med J 2017;24(11):1755-1760.

DOI:10.17957/TPMJ/17.4444

INTRODUCTION

Diabetes Mellitus (DM) is the most common chronic conditions prevalent worldwide Type-II DM constitutes 90% of all DM cases.¹ Glycemic control maintenance is the primary treatment goal for type-II DM. Japanese Kumamoto study² and UKPDS study³ which are the land trials in DM, have established the fact that excellent glycemic

control with insulin therapy decreases risk of microvascular complications, in people with type-II DM. DM is a rising epidemic, especially type-II DM in Pakistan and is putting an unbearable burden on economy and adversely affecting quality of life of people with DM due to poor glycemic control and resultant high rates of complications. Resource utilization is unacceptably high. Society,

Resource constraints, lack of medical insurance system and insufficiently allocated health funds are major reasons for deficient quality care. Most of the people with Type-II DM are not able to afford the high cost of treatment.⁴

DM is an ever increasing epidemic that is adding to so many chronic diseases like Cardiovascular, Cerebrovascular, End Stage Kidney Disease and Retinopathies. If treated earlier, the dreaded consequences of these complications can be avoided. These complications have a broad spectrum and attributable largely to chronically elevated glycemic levels resulting in damage to intima of the blood vessels. In diabetes, the resulting complications are grouped under “microvascular disease” (due to damage to small blood vessels) and “macrovascular disease” (due to damage to the arteries).⁵ Glycemic control tends to deteriorate over time because of beta cell loss which occurs over time in type-II DM.⁶ Patients must be started on combination therapy at this stage of disease.⁷

DPP-IV Inhibitors were introduced in 2006 and these have shown promising results in glycemic control in type-II DM.⁸ Six different DPP-IV inhibitors are available: sitagliptin, alogliptin, vildagliptin, teneligliptin, linagliptin and anagliptin. Sitagliptin is most commonly used among these and its safety profile and efficacy are proven in many trials.⁹ Sitagliptin might be more effective for glycemic control in some ethnic populations as well.¹⁰ In many trials, HbA1c improvement ranged from 0.5% to 1.4%.¹¹ Sitagliptin can be used in combination with sulfonylureas, insulin and metformin.^{12,13,14} Sitagliptin combination has shown the advantage of better glycemic control, less hypoglycemic events and a decrease in number of units of insulin in patients who were already taking insulin.¹⁵ There is no increase in hypoglycemia incidence when used alone or in combination with euglycemic drugs such as metformin and thiazolidinediones but there can be hypoglycemia in combination with sulfonylureas or insulin.¹⁶ It can also be used in patients with liver disease¹⁷ and kidney disease.¹⁸ Sitagliptin dosage can be adjusted based on renal function. These properties make this medication an

attractive option for the treatment of diabetes in renal disease as well.¹⁹

Addition of sitagliptin to insulin is quite safe and it results in decreased episodes of hypoglycemia,²⁰ better glycemic control and decreased requirement of insulin unit in patients with type-II DM.²¹

Keeping in view the potential advantages of Sitagliptin like better Glycemic control and less hypoglycemic events, we will compare the Sitagliptin-insulin combination with insulin alone. This will provide us a better insight into efficacy in patients taking Sitagliptin and insulin and this will help us formulate recommendations for patients who require combination of Sitagliptin with insulin.

OBJECTIVE

I compared the mean reduction of HbA1c in patients taking Sitagliptin-insulin combination with insulin alone in patients of Type 2 Diabetes Mellitus.

MATERIALS & METHODS

It was a RCT done at Medicine Department, Allied Hospital, Faisalabad from August 2013 to February 2014. Approval from hospital ethical review committee was taken after formulation of synopsis. Patients fulfilling the inclusion criteria were enrolled in the study. Total 60 patients were enrolled in study. Sample size was calculated using WHO sample size calculator for two proportions (2-sided) using following values: Test value of population mean = 0.6, Anticipated population mean = 0.2, Pooled standard deviation = 0.1, Power of study = 90%, Level of Significance = 5%, Sample size = 60 (30 in each group). Non-probability consecutive sampling technique was used. Both male and female patients between 18 and 60 years of age having uncontrolled type 2 diabetes mellitus with HbA1c taking insulin were included in the study. Chronic liver disease, nephropathy (creatinine >3.0mg/dl) and Pregnant or lactating mothers were excluded from study. Informed consent was obtained from each participant. Patients were randomly divided into two groups (A & B) using computer generated random number table. Group A was

given Sitagliptin 50mg per day and dose was increased to 100mg per day after 2 weeks if fasting blood sugar(FBS) was ≥ 110 mg/dl or 2 hours postprandial blood sugar (PPBS) ≥ 140 mg/dl. Dose of insulin in group A remained same as before start of study. Group B was kept on same regimen of insulin they were already taking and dose remained same. HbA1c was done at start of study and after 24 weeks.

Type-II DM was defined as fasting blood sugar (FBS) ≥ 126 mg/dl or 2 hours' postprandial blood sugar ≥ 200 mg/dl measured on two different occasions. Patients having HbA1c more than 7% were classified as inadequately controlled diabetes mellitus. Primary outcome measure was mean reduction in HbA1c levels at 24 weeks from baseline.

Information collected comprised age, sex, address, HbA1c at start of study and HbA1c at 24 weeks. HbA1c was done at start of study and after 24 weeks. All the collected information transferred to SPSS version 20 and analyzed accordingly. Mean and standard deviation were calculated for all quantitative variables like age, HbA1c at baseline and 24 weeks and reduction in HbA1c at 24 weeks. Frequency and percentage were calculated for all qualitative variables like gender. Paired sample t test, Independent sample t test and chi square test were applied to compare. P value of <0.05 was taken as significant.

RESULTS

60 patients were included in the study. Mean age was 52.7 ± 8.43 years (Table-I). 36(60%) were male and 24(40%) were female. (Figure-1).

Mean HbA1c at base was $8.361 \pm 0.523\%$ in Group A on Sitagliptin and insulin and $8.187 \pm 0.432\%$ in group B on insulin alone. Mean HbA1C at 24 weeks was $7.767 \pm 0.428\%$ in group A on Sitagliptin and insulin and $7.69 \pm 0.407\%$ in group B on insulin alone (Table-V). Independent sample t-test was applied to change in HbA1C in Group A and B during 24 weeks of treatment. Mean change in HbA1C after 24 weeks in Group A was 0.600 ± 0.315 and 0.49 ± 0.19 in Group B after 24 weeks treatment (p-value 0.002) which is

highly significant (Table-II).

Paired sample t-test was applied to HbA1C at baseline and 24 weeks of treatment in group A and group B. there was a significant change in both groups after 24 weeks of treatment in both groups (p-value <0.000) which is highly significant (Table-II).

Chi Square test was applied on efficacy in group A and B. 22(73.33%) patients in group A and 14(46.67%) patients in group B achieved significant reduction in HbA1C. 8(26.67%) patients in group A and 16(53.33%) patients in group B failed to achieve significant reduction in HbA1C. (P-value < 0.032) which is also highly significant (Table-III).

Age	All	Group A	Group B
N	60	30	30
Mean	52.73	53.27	48.32

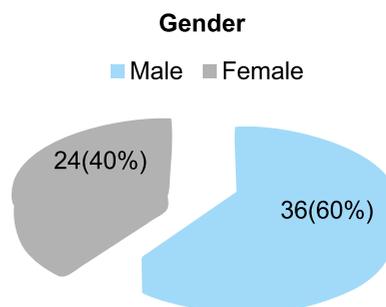


Figure-1. Gender Distribution of Study Population

Std. Deviation	8.43	9.028	6.345
Minimum	34	37	34
Maximum	69	69	65

Table-I. Demographics of the study population

DISCUSSION

Diabetes mellitus is a rapidly increasing epidemic of the modern times. Several drugs are available to treat type 2 diabetes mellitus but eventually diabetic control deteriorates over time. Novel drugs are always needed to improve diabetic control.

DPP-IV inhibitors are newer class of drugs and sitagliptin is most commonly used among this group. The present study has made a comparison

HbA1C	Group A	Group B	Independent sample t-test P-Value
At start of study	8.36±0.523	8.187±0.432	0.002
After 3 months of study	7.767±0.4286	7.690±0.407	0.002
Change in HbA1C after 24 weeks of treatment	0.6000±0.3151	0.496±0.190	0.002
Paired sample t-test (p value)	0.000	0.000	

Table-II. Independent sample t-test and paired sample t-test

		Efficacy		Total
		Yes	No	
Group	A	22(73.33%)	8(26.67%)	30
	B	14(46.67%)	16(53.33%)	30
Total				60
Chi Square Value		4.444		
p-value		0.032		

Table-III. Chi square test for comparison of efficacy:

of sitagliptin-insulin combination with insulin alone in the treatment of type-II DM for glycemic control in patients uncontrolled on insulin alone. The study has shown that sitagliptin as add on therapy to patients already taking insulin and still uncontrolled significantly improved glycemic control by reducing HbA1C after 6 months as compared to patients taking insulin alone (p value= 0.002). There was a significant reduction of HbA1C in type-II DM P-Value = 0.0001).

In 2013, Shimoda S et al conducted a study in Japanese population to evaluate the effects of addition of sitagliptin, an oral DPP-IV inhibitor, in people with type-II DM inadequately controlled on complex insulin regimens. HbA1c was significantly reduced during the first 12 weeks ($-0.64 \pm 0.60\%$), and was maintained over 24 weeks ($-0.69 \pm 0.85\%$). This is comparable to the results of our study in which adding sitagliptin also improved glycemic control significantly by decreasing HbA1C.⁹

Giampetro O et al found out that in type-II DM, the combination of insulin and sitagliptin improved lipid profile and metabolic control and significantly decreased insulin requirements. It is the same as in our study which also showed similar results.²²

In one study by Katsuno T et al, addition of sitagliptin to people with type-II DM on insulin improved HbA1C significantly from $8.1 \pm 1.2\%$ to

$7.6 \pm 1.1\%$ over a 12 weeks of therapy with addition of sitagliptin ($p < 0.01$), and the insulin dosage was reduced from 27.3 ± 15.8 Units /day to 24.5 ± 16.5 Units /day ($p < 0.001$). The results of this investigation confirmed that addition of sitagliptin to insulin can improve glycemic control without increasing risk of hypoglycemia and/or weight gain. It also confirms the results of our study which shows that sitagliptin improves glycemic control when added to patients on insulin.²³

A study done by HariKumar KV et al showed that the exenatide and/or sitagliptin addition significantly decreases insulin dosage without increase in endogenous insulin production or hypoglycemic episodes. This result is also supportive of the results of my study that sitagliptin improves diabetic control in patients on insulin alone.²⁴

Mori Y et al conducted a similar study in 2013 in Japanese population and he found that the addition of sitagliptin significantly decreases in 24 hour mean glucose levels measured by continuous glucose monitoring (CGM) ($P < 0.01$).²⁵

It was a small study with a sample size of 60 with non-randomized sampling and no double blinding. Large randomized controlled trials are needed to further validate these results.

CONCLUSIONS AND RECOMMENDATIONS

It has been concluded from this study that insulin and sitagliptin-insulin combination both significantly reduce HbA1C in type 2 diabetes mellitus.

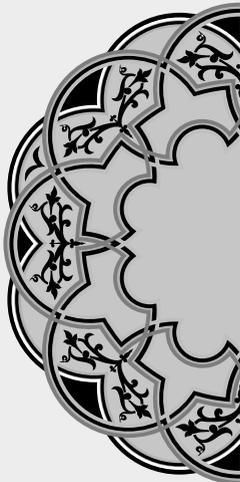
However addition of sitagliptin to patients already taking insulin and uncontrolled, is more effective than insulin for glycemic control of patients with type 2 diabetes mellitus.

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*“Don't think outside the box.
Think like there is no box.”*

Unknown

AUTHORSHIP AND CONTRIBUTION DECLARATION

Sr. #	Author-s Full Name	Contribution to the paper	Author=s Signature
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3	M. Usman Musharraf	Data collection	