RESEARCH ARTICLE

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A Study Involving Indian Subpopulation of Sikkim for the Effect of Sitagliptin, in Control of Diabetes Mellitus Type-2

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ABSTRACT

Introduction
There is a growing worldwide epidemic of Type - 2 Diabetes mellitus and it is now a common and serious global health problem. The population in and around Sikkim, a state in north eastern part of Indian province has never been studied for anti-diabetic drugs and thus was thought to take one. This is a community based, case - control prospective study involving adult population residing at Sikkim, reporting to Secondary Care Hospital and receiving treatment for diabetes.

Methods
A standardized random sample of 500 patient's was considered. Pretested proforma was filled after detailed examination and taking informed consent of the patients after adding Sitaglipitin100 mg daily for 48 weeks. Data was then compiled and statistical analysis was done using Carl Pearson's correlation, chi square test, odds ratio, students't' test and correlation coefficients as applicable.
Parameters for analysis
- Glycosylated Haemoglobin (HbA_1c)
- Plasma glucose (Fasting and Postprandial**)**

Results
The drop in the blood sugar during the entire study, it was seen that in the Sitagliptin group, the drop was persistent and steady after 8-12 weeks while in the controls, though there was an initial drop of blood glucose, the glycemic control was not continuous but intermittent.

Conclusions
In patients with Type-2 Diabetes, Sitagliptin 100 mg/day was well tolerated and provided good glycemic control and none of the cases had relapse of hyperglycemia. Effective blood sugar control was seen after 36 weeks of commencement of therapy.

Keywords: Serum Glucose, HbA_1c, Hyperglycemia, Metformin, OHAs.

INTRODUCTION

There is a growing worldwide epidemic of Type - 2 Diabetes mellitus (DM) and it is now a common and serious global health problem.[1,2] Type - 2 diabetes is a complex metabolic disorder characterized by increased blood glucose levels resulting from defects in insulin secretion, insulin action, or both.[3]In recent years treatment options have increased with the development of new oral anti-diabetic therapies, but the ability of these agents to lower blood glucose levels and sustain glycemic targets is limited.[4,5]Although monotherapies such as sulfonylureas, thiazolidinediones and biguanides have been shown to slow the progressive loss of glycemic control in patients with Type - 2 diabetes, in the A Diabetes Outcomes Progression Trial (ADOPT) at the 4-year evaluation of HbA_1c goal attainment only 40% of rosiglitazone, 36% of metformin, and 26% of glyburide-treated patients achieved HbA_1c levels of <7%. This indicates that monotherapy with these agents was not able to maintain glycemic control for a majority of patients over time.[7]Existing monotherapies also have safety and tolerability issues which can limit their utility.[5,8]Reports of suboptimal glycemic control in the vast majority of patients suggest that there is an urgent need for new approaches to antidiabetic therapy.[6,7,9]There is a need

for more comprehensive approaches to help patients establish and maintain glycemic control, with anti-hyperglycemic agents that are not limited by safety and tolerability issues such as weight gain and hypoglycemia.[6,8,10,11]

MATERIALS & METHODS

This is a community based, case - control prospective study involving resident population of Sikkim, a state of India in north east part of country, reporting to a Secondary Care Hospital and receiving treatment at this hospital for diabetes care. With a National Rural Prevalence of NIDDM at about 2.4 %, an urban prevalence of 7.8% and a national average of 5.1%, with an alpha allowable error of 20%, the sample size for this study was 488 subjects. However with existing morbidity in the clientele covered by this hospital, a sample size of 500 was considered for this study. Parameters for analysis-

- Glycosylated Haemoglobin (HbA_1c)
- Plasma glucose (Fasting & Postprandial**)**

Inclusion criteria

- Patients aged between 18 -70 years.
- Diagnosed case of Type - 2 Diabetes mellitus.
- Poor Glycemic control (HbA_1c : 7.0 – 9.0)
- Patients on one or more OHAs

Exclusion criteria

- Patients on β- blockers
- Patients on Insulin therapy
- Patients with end organ involvement like
    a. Cardiac failure
    b. Stage 2 or more Diabetic Nephropathy
    c. Hepatic failure

Thus samples (cases) were drawn from 500 consecutive cases of Type -2 DM visiting this North East Zonal Hospital for their health care needs while an equal number of controls were enrolled based on the criteria detailed above.

On the inclusion of a person to this study (i.e., those who fulfill the inclusion criteria) the following was undertaken:

(a) Recording of informed consent

(b) Recording of detailed history, age, sex, period of follow up, past medication for NIDDM, relevant details like anthropometry, demographic details and presence of any co-morbid medical/surgical conditions.

(c) The benefits involved with Sitagliptin mono therapy were discussed with all the patients.

(d) Detailed clinical examination.

All the data was noted in a pre-tested data recording proforma sheet for compilation and statistical analysis. All the patients were reminded about the requirement of dietary changes and other lifestyle modifications prior to enrolment for this study. The patients who have already been diagnosed as diabetics and on medication in the form of Biguanides and/or Sulfonylureas and whose $HbA_1c > 7.0$, were followed up after adding Sitagliptin (100 mg daily) for a total duration of 48 weeks. Patients were subjected to a 4 weekly testing of fasting & post prandial plasma glucose levels while HbA_1c estimation was performed at 12-weekly intervals. The entire numerical data was entered in a MS EXEL spreadsheet for statistical evaluation. The efficacy of Sitagliptin in lowering the blood glucose was calculated by obtaining the percentage decrease of blood glucose. The categorical variables were compared for 'outcome' (of euglycemia) using Carl Pearson's Correlation / Chi square, to test the statistical significance. Thus the strength of association of Sitagliptin on glycemic control at 48 weeks by Chi-square test, Odds ratio(OR), for evaluation of the appropriate treatment regimen at 95% Confidence Intervals (CI) was estimated. The efficacy of glycemic control by estimating the HbA_1c level, was tested using the paired Students 't' test. Finally the correlation coefficient for glycemic control at 48 weeks was attempted by framing the mathematical relation between HbA_1c and fasting blood glucose. The relevant graphical representations based on the above mentioned calculations were then plotted.

RESULTS

The average decrease in HbA_1c to acceptable levels was seen after 36-weeks - if based on the National Health and Nutritional examination survey (NHNES) studies and by 24-weeks if based on the American Diabetes Association (ADA) recommendations. The 50% drop in cases to desirable levels was seen in 24-weeks in cases while in the controls it took much longer - justifying the efficacy. Assuming a cut off of blood glucose level of 120 and 140 mg (fasting and post prandial respectively as level of glycemic control), it is seen that with Sitagliptin the levels were reached / achieved by 8 weeks after initiation of treatment while without Sitagliptin it took an additional 4 weeks more, i.e., by 12 weeks to achieve the onset of glycemic control. On comparing the efficacy of the glycemic control, the addition of Sitagliptin showed marked changes when added either to the two / three drug regimen rather than while being treated with sulfonylurea or biguanide (without Sitagliptin). On comparing the drop in HbA_1c since onset by a paired t test, it was seen to be statistically significant ($p<0.001$) after 24-weeks, as well as between the 4-weekly intervals of monitoring for the same. The t-test was significant w.r.t. the baseline values from 24-weeks onwards, while the comparative decrease was noted from 24 to 36 weeks, indicating a probable stabilization after 36 weeks. The strength of association of Sitagliptin in glycemic control was evident both with two / three drug regimen with statistically significant 95% confidence intervals (Table - 4). On comparing the correlation between the FBS and HbA_1c of cases vs controls it was seen that it had positive correlation with significant coefficient values. On comparing the drop in blood sugar during the entire study it was seen that in the cases (Sitagliptin group), the drop was persistent and steady

after 8-12 wks while in the controls, though there was an initial drop, the glycemic control was not continuous but intermittent.

	HbA_{1c} values at				
	Onset	12 weeks	24 weeks	36 weeks	48 weeks
Average value of HbA_{1c}	7.74	7.37	6.66	6.499	6.493
No of cases with HbA_{1c}<6.5*	Nil	5	225	285	305
% increase in efficacy	-	1%	44%	12%	4%
No of cases with HbA_{1c}<7.0 #	Nil	30	285	310	325
% increase in efficacy	-	6%	51%	5%	3%

*Based on the US-based National Health and Nutritional Examination Survey recommendations. #Based on the American Diabetes Association recommendations.

Table I: Efficacy of Sitagliptin on HbA_{1c} since onset

	HbA_{1c} values at				
	Onset	12 weeks	24 weeks	36 weeks	48 weeks
Average value of HbA_{1c}	7.72	7.45	7.17	6.82	6.76
No of cases with HbA_{1c} <6.5*	Nil	Nil	Nil	15	110
% increase in efficacy	-	-	-	3%	19%
No. of cases with HbA_{1c} <7.0 #	Nil	Nil	Nil	50	62
% increase in efficacy	-	-	-	50%	8%

*Based on the US-based National Health and Nutritional Examination Survey recommendations.
#Based on the American Diabetes Association recommendations.

Table II: Efficacy on HbA_{1c} since onset of treatment amongst controls

Category	Periodicity	Plasma Blood Glucose (mg%)	
		Fasting	PP
Cases	Onset	160.8	231.3
	4 weeks	126.9	195.7
	8 weeks	118.4	139.7
	12 weeks	117.7	138.7
Controls	Onset	159.6	224.7
	4 weeks	135.7	201.2
	8 weeks	134.9	200.3
	12 weeks	127.4	171.8

Table III: Onset of glycemic control after initiation of treatment

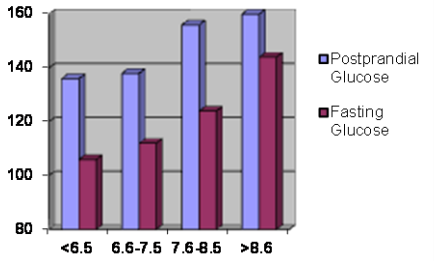

Figure 1 (A): Glycemic control as shown by HbA_{1c} values (without Sitagliptin)

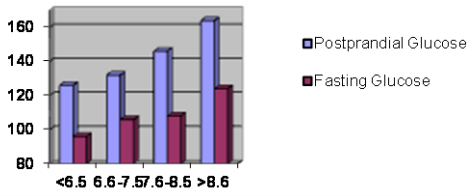

Figure 1 (B): Glycemic control as shown by HbA_{1c} values (on addition of Sitagliptin)

S. No.	Group	Reduction in HbA_{1c} (%)	Reduction in Blood Sug (F) (mg/dl)
(a)	Cases	16.1	42
(b)	Controls	8.2	28
(c)	Patients on Sitagliptin, Metformin and Glimiperide (n=180)	13.6	41
(d)	Patients on Sitagliptin, Metformin, Pioglitazone and Glimiperide (n=140)	17.4	39
(e)	Patients on Sitagliptin, Metformin (n=180)	16.2	39
(f)	Patients on Metformin and Glimiperide (n=240)	6.8	36
(g)	Patients on Metformin, Pioglitazone and Glimiperide(n=160)	11.9	27

Table IV: Comparative efficacy in glycemic control at 36 weeks

Paired t-test Onset vs 12 wks	Paired t-test Onset vs 24 wks	Paired t-test Onset vs 36 wks	Paired t-test Onset vs 48 wks
2.3(p<0.1) N.S	22.9(p<0.001)	25(p<0.001)	24.5(p<0.001)

NS = Not significant

Table V: Comparison of efficacy (HbA_{1c}) as per periodicity

Paired t-test 12 wks vs 24 wks	Paired t-test 24wks vs 36 wks	Paired t-test 36wks vs 48 wks
15(p<0.001)	8.8(p<0.001)	0.32(p<0.1) NS

NS = Not significant

Table VI: Comparison of efficacy based on serial monitoring of HbA_{1c}

Sitagliptin, Metformin and Glimipride vs Sitagliptin, Metformin, Pioglitazone and Glimiperide			Sitagliptin and Metformin vs Sitagliptin, Metformin, and Glimiperide			Sitagliptin group vs Controls		
X^2	O.R	95% CI	X^2	O.R	95% CI	X^2	O.R	95% CI
0.32 *	0.7	0.19 to 2.5 *	0.1 *	1.12	0.61 to 1.9 *	26.1#	13.2	4.95 to 35.18

OR = Odds Ratio,* - p<0.1 = not statistically significant, # - p<0.001 = statistically significant

Table VII: Strength of association of Sitagliptin (X^2) on glycemic control at 36 weeks

S. No.	Category	Correlation coefficient equation	R
(a)	Cases	Y = 3.42 + 0.02*x	0.94
(b)	Controls	Y = 4.63 + 0.02*x	0.96

y = HbA_{1c}, x = Fasting blood glucose

Table VIII: Correlation coefficients of cases Vs controls at 36 weeks

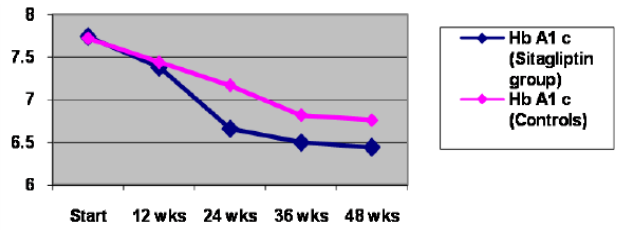

Figure 2: Effect on HbA_1c by Sitagliptin with OHAs and only with OHAs

DISCUSSION

With the availability of new treatment options as sequel to the development of new oral anti-diabetic therapies, the treating physician has a multitude of choices, but the ability of these agents to lower blood glucose levels and sustain glycemic targets is limited. In this case control study, on assortment of the data based on the prevalence of the age group distribution, it was seen that the youngest person was a 31 yrs old case and the eldest was 69 yrs old. The shift in the increased prevalence to a lower age group, i.e., to the 40-49 yrs shows a concurrence to the existing increased incidence of stress diseases in lower age groups.The average decrease in HbA_1c to acceptable levels was seen after 36 weeks - if based on the NHNES studies and by 24 weeks if based on the ADA recommendations. The 50% drop in cases to desirable levels was seen in 24 weeks in cases while in the controls in took much longer; justifying the efficacy. Assuming a cut off of blood glucose level of 120 and 140 mg (Fasting and Post prandial respectively as level of glycemic control), it is seen that with Sitagliptin the levels were reached / achieved by 8 weeks after initiation of treatment while without Sitagliptin it took an additional 4 weeks more, i.e., by 12 weeks to achieve the onset of glycemic control. On comparing the efficacy of the glycemic control, the addition of Sitagliptin showed marked changes when added either to the two / three drug regimen rather than while being treated with sulfonylurea or biguanide (without Sitagliptin). On comparing the drop in HbA_1c since onset by a paired t-test, it was seen to be statistically significant ($p<0.001$) after 24 weeks, as well as between the 4 weekly intervals of monitoring for the same. The t-test was significant w.r.t. the baseline values from 24 weeks onwards, while the comparative decrease was noted from 24 to 36-weeks, indicating a probable stabilization after 36 weeks.

CONCLUSION

In the present study, the efficacy and safety of this drug (100 mg OD) in patients with Type-2 Diabetes was evaluated on 500 consecutive patients over a period of 48 weeks. The response was monitored and side effects if any, noted.

(a)Drop in age of prevalence and onset of NIDDM among males.

(b)Achievement of glycemic control by 24-weeks of therapy was achieved with Sitagliptin whether it be based on the US-based National Health and Nutritional Examination Survey recommendations or on the American Diabetes Association recommendations.

(c)As a corollary HbA_1c also showed a drop to ideal levels by 24-weeks.

(d)There were no adverse/side effects noted during therapy or in the period under follow up.

It was thus concluded that Sitagliptin is an extremely effective therapy in cases of NIDDM over conventional OHAs. The drug was well tolerated and there were no reported adverse effects noted. The results were comparable with those carried out in the centers in the West, however long term prospective studies are recommended. In patients with Type- 2 diabetes, Sitagliptin 100 mg/day was well tolerated as mono therapy, as initial combination therapy, and as add-on therapy in clinical trials up to 48 weeks duration. The drug provided good glycemic control and none of the cases had relapses of hyperglycemia. Effective sustained blood sugar control was seen with a 100 mg daily dose after 36 weeks of commencement of therapy.

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