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## Original Research Article

## Assessment of safety of Saxagliptin in patients of type 2 diabetes mellitus who were previously on metformin monotherapy with uncontrolled diabetes

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## ABSTRACT

**Introduction:** Dipeptidyl peptidase-4 are a relatively new class of oral antihyperglycemic agent that enhance insulin secretion by reducing degradation of endogenous glucagon-like peptide 1. Currently, sitagliptin, vildagliptin, saxagliptin, linagliptin and alogliptin are approved in India, USA and Europe for the use in patients with type 2 diabetes. In this study we have tried to assess the safety of saxagliptin used in patients of type 2 DM who were previously on metformin monotherapy.

**Materials and Methods:** A total of 35 patients who were previously on metformin monotherapy with uncontrolled diabetes were enrolled. Patients were started with saxagliptin (2.5 mg OD) and were followed up at 1st, 3rd and 6th months for the estimation of Liver Function Test (SGOT, SGPT, Bilirubin direct & indirect), Renal Function Test (BUN and Sr. Creatinine). During the follow up period patients were also assessed for the adverse drug reactions.

**Results:** Male and female patients mean age  $\pm$  SD (61.42 yrs  $\pm$  6.99 and 55.93 yrs  $\pm$  5.74 respectively). The mean significant decrease in values from baseline at 24 weeks were seen for SGOT, SGPT, Blood urea nitrogen and serum creatinine.

**Conclusion:** The combination of saxagliptin plus metformin for the treatment of type 2 diabetes offers an oral treatment regimen that is safe and well tolerated.

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## 1. Introduction

Type 2 Diabetes Mellitus (T2DM) is the most common form of diabetes mellitus and accounts for about 95% of all diabetes cases.<sup>1</sup> Several oral agents have been approved for type 2 diabetes management. There are various established adverse effects related to the use of OHA (oral hypoglycemic agents) including hypoglycemia, weight gain, gastrointestinal disturbance, lactic acidosis, and fluid retention.<sup>2</sup> Adverse drug reactions may reduce the patient compliance (poor patient adherence towards the therapy). From a clinical/economic viewpoint, patient's poor-adherence towards OHA is associated with

reduced treatment benefits and significant financial burden. Also it can cause prolonged uncontrolled diabetes with microvascular and macrovascular complications.<sup>3</sup>

In one of the study, Patients with moderate or worse symptoms of hypoglycemia reported poorer adherence (46% versus 67%;  $P < 0.01$ ) compared with patients with no or mild symptoms.<sup>4</sup>

Dipeptidyl peptidase-4 (DPP-4) inhibitors are a class of oral diabetic medications approved both as monotherapy as well as in combination with metformin.<sup>5</sup> They were introduced for the treatment of type 2 diabetes in 2006. DPP-4 is a ubiquitous enzyme that acts on incretin hormones, mainly GLP-1 (glucagon-like peptide-1) and GIP (gastric inhibitory peptide), which maintain glucose homeostasis by increasing insulin secretion and decreasing

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glucagon secretion. GLP-1 and GIP is a hormone secreted by small intestine, which lowers blood glucose by stimulation of insulin secretion, lowering glucagon concentrations, and delay in gastric emptying. These incretins get released within a very short time after the intake of food. DPP-4 enzyme is responsible for the degradation of these hormones. DPP-4 inhibitors increase the levels of incretins (GLP & GIP) by inhibiting DPP-4 enzyme, which increase insulin secretion in the pancreas, and helps to reduce post meal and fasting blood glucose level.<sup>6,7</sup>

Saxagliptin is a DPP4 inhibitor, was approved in India in 2009 as an adjunct to diet and exercise to improve glycemic control in adults with type-2 diabetes mellitus and in 2011 as add on therapy to metformin.<sup>8</sup> The recommended dose for Saxagliptin is 2.5 mg or 5 mg once daily. Following 5 mg of oral saxagliptin  $C_{max}$  for saxagliptin and its metabolite are 24 ng/mL and 47 ng/mL respectively and  $T_{max}$  for saxagliptin and its metabolite are 2 hrs and 4 hrs respectively. The metabolism of saxagliptin is primarily mediated by cytochrome P450 3A4/5 (CYP3A4/5) and eliminated by both renal and hepatic pathways.<sup>9</sup>

## 2. Materials and Methods

After taking the permission from Protocol review committee and institutional ethics committee the study was conducted in the department of pharmacology and medicine in Dr Rajendra Prasad Government medical college and hospital.

### 2.1. Inclusion criteria

Patients of age between 18 to 80 years with non-insulin dependent diabetes mellitus, taking metformin in the doses of 1500mg having HbA1c (between 7% to 10%), FPG ( $\geq 126$  mg/dl), 2hPG ( $\geq 200$  mg/dl) were enrolled in the study.

### 2.2. Exclusion criteria

Patients with -

1. Acute complications of diabetes
  - a. Hyperglycemic hyperosmolar state
  - b. Diabetic ketoacidosis
2. Renal or liver disease.
3. Congestive heart failure.
4. Acute coronary syndrome.
5. Pregnancy

### 2.3. Sample size

Total 35 male and female patients with type 2 DM attending in Medicine OPD of Dr RPGMC hospital on Saturday were screened and enrolled in the study.

## 2.4. Methods

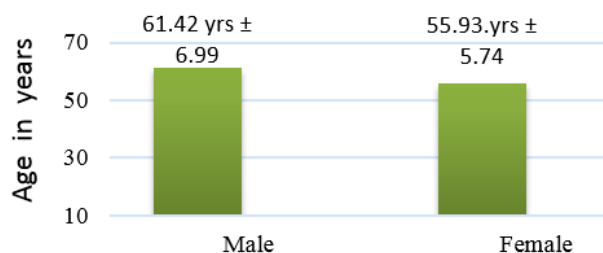
Patients were screened for diabetes status with the help of HbA1C, FPG, and PPG. Also detailed history taking, clinical examination, and lab investigation (Lipid profile, Liver function test and Kidney function test) of all the patients were done before enrolling the patients. Patients were prescribed metformin 500 mg twice a day + saxagliptin 2.5 mg (onglyza) once a day. In patients with uncontrolled diabetes dose escalation was done with saxagliptin up to 5 mg once a day. Patients who were having uncontrolled diabetes even after the increase in the doses on follow up visits, he / she was considered failure of therapy and was managed with alternative treatments. The patients were followed up on 1st, 3rd and 6th month, Liver Function Test (SGOT, SGPT, Bilirubin direct & indirect) and Renal Function Test (BUN and Sr. Creatinine) were repeated at all the follow up visits. All the patients were assessed for the adverse drug reactions during the follow up visits. Also patients were contacted telephonically at regular interval to check the adverse drug reactions if occurring in between the follow up period.

### 2.5. Statistical analysis

Microsoft excel version 2013 and Graph pad online software were used for the analysis of data.

## 3. Results

Out of the total 35 enrolled patients, 4 patients were couldn't report for the follow up and 1 patient after starting with saxagliptin, reported with the side effect of bilateral knee joint pain so she was discontinued from the treatment. Total 30 patients, 14 males and 16 females completed the study duration of 6 months with saxagliptin as add on therapy to metformin. The mean age  $\pm$  SD for male was 61.42 yrs  $\pm$  6.99 and for female patients was 55.93 yrs  $\pm$  5.74.



**Fig. 1:** Mean age  $\pm$  SD of male and female patients in yrs.

A significant decrease in SGOT value has been seen from baseline to 24 weeks after treatment with saxagliptin.

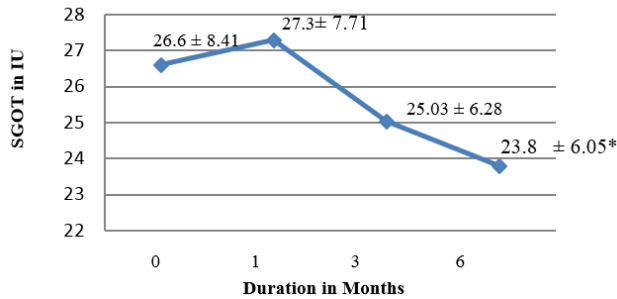
A significant decrease in SGPT value has been seen from baseline to 24 weeks after treatment with saxagliptin.

A decrease in direct Bilirubin value was seen from baseline to 24 weeks after treatment with saxagliptin.

**Table 1:** Changes in SGOT levelsover a period of 6 months

Investigation	Duration (Month)	(Mean ± SD)
SGOT	0	26.6 ± 8.41
	1	27.3 ± 7.71
	3	25.03 ± 6.28
	6	23.8 ± 6.05*

Unit – IU, Normal value: 5-34IU, \* p value < 0.05

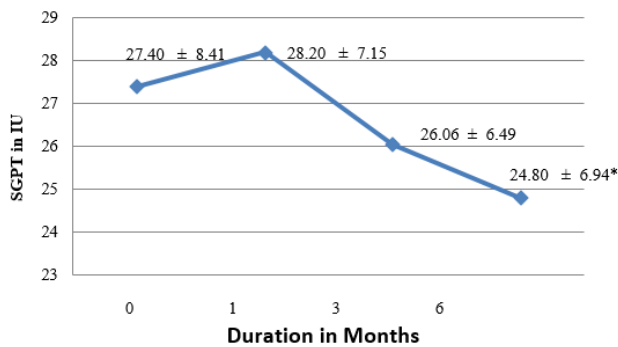


**Fig. 2:** Changes in SGOT levels over a period of 6 months

**Table 2:** Changes in SGPT levels over a period of 6 months

Investigation	Duration (Month)	(Mean ± SD)
SGPT	0	27.40 ± 8.41
	1	28.20 ± 7.15
	3	26.06 ± 6.49
	6	24.80 ± 6.94*

Unit – IU, Normal value: 6-40 IU, \* p value < 0.05

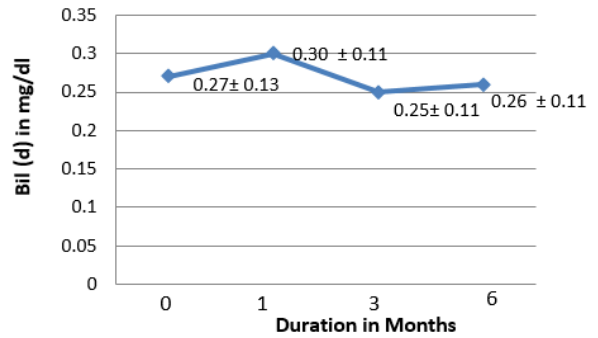


**Fig. 3:** Changes in SGPT levelsover a period of 6 months

**Table 3:** Changes in Bil.(d)levels over a period of 6 months

Investigation	Duration (Month)	(Mean ± SD)
Bil (d)	0	0.27 ± 0.13
	1	0.30 ± 0.11
	3	0.25 ± 0.11
	6	0.26 ± 0.11

Unit – mg/dl, Normal value: 0 - 0.3 mg/dl

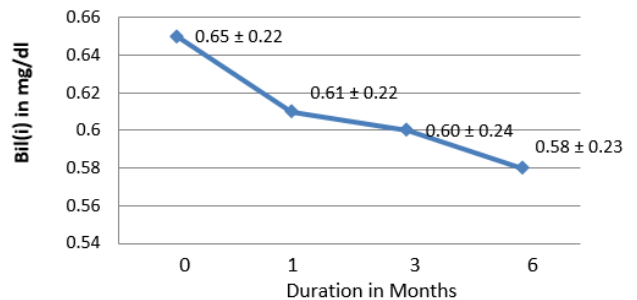


**Fig. 4:** Changes in Bil(d) levels over a period of 6 months

**Table 4:** Changes in Bil.(i)levels over a period of 6 months

Investigation	Duration (Month)	(Mean ± SD)
Bil (i)	0	0.65 ± 0.22
	1	0.61 ± 0.22
	3	0.60 ± 0.24
	6	0.58 ± 0.23

Unit – mg/dl, Normal value: 0.2-0.5 mg/dl



**Fig. 5:** Changes in Bil (i) levels over a period of 6 months

A decrease in indirect Bilirubin value was seen from baseline to 24 weeks after treatment with saxagliptin.

**Table 5:** Changes in BUN levels over a period of 6 months

Investigation	Duration (Month)	(Mean ± SD)
BUN	0	14.46 ± 3.21
	1	13.63 ± 2.76*
	3	12.8 ± 2.41**
	6	11.43 ± 2.59**

Unit – mg/dl, Normal value: 7- 20 mg/dl, \* p value < 0.05, \*\* p value < 0.001

A significant decrease in Blood urea nitrogen value was seen from baseline to 24 weeks after treatment with saxagliptin.

A significant decrease in serum creatinine value was seen from baseline to 24 weeks after treatment with saxagliptin.

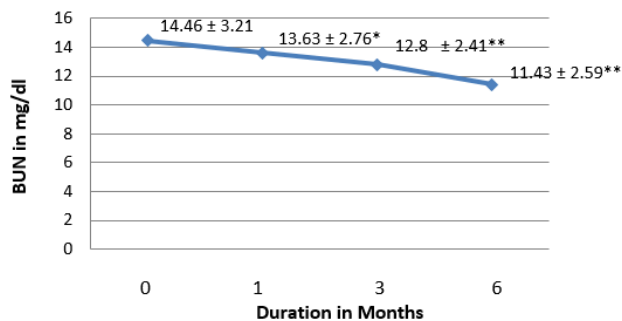


Fig. 6: Changes in BUN levels over a period of 6 months

Table 6: Changes in Sr. creat. levels over a period of 6 months

Investigation	Duration (Month)	(Mean ± SD)
SR Creatinine	0	0.89 ± 0.28
	1	0.89 ± 0.24
	3	0.77 ± 0.19*
	6	0.73 ± 0.20*

Unit – mg/dl, Normal value: 0.6-1.2 mg/dl, \* p value < 0.05

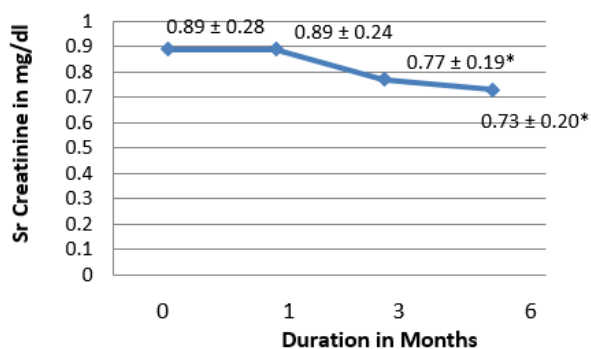


Fig. 7: Changes in Sr creatinine levels over a period of 6 months

### 3.1. Adverse drug reaction assessment

All the patients were assessed during the follow up period at 1<sup>st</sup>, 3<sup>rd</sup> and 6<sup>th</sup> for the serious and non serious adverse drug reactions, also patients were contacted telephonically at regular interval to get the information about adverse drug reactions.

In 2015, US FDA has issued a warning against saxagliptin for knee joint pain, one of the patient in our study who were on saxagliptin 5 mg once a day treatment developed bilateral knee joint pain. All the necessary investigations were done to rule out the necessary causes for knee joint pain. The joint pain resolved after the drug was stopped.

No incidence of hypoglycemia was reported in any of the patient after treatment with saxagliptin during the study period.

## 4. Discussion

The current study evaluated the safety of saxagliptin as add-on therapy to metformin for the duration of 6 months in the patients of type 2 diabetes mellitus who were previously on metformin monotherapy with inadequate glycemc control.

We found that a significant reduction in the liver function test (SGOT and SGPT) and liver function test (BUN and Sr. Creatinine) were seen during the study period of 6 months. No significant change in bilirubin (direct and indirect) values were seen during the 6 months of treatment.

Saxagliptin do not increase liver function test and renal function test parameters and do not cause liver and renal toxicity.

No incidence of hypoglycemia was reported in patients taking saxagliptin. Only one patient reported with bilateral knee arthralgia which was immediately shifted to alternative therapy and the case was reported to the NCC-PvPI. No serious adverse drugs reactions were reported during the study.

Saxagliptin was well tolerated and there was no increased risk of overall and serious adverse events in combination therapy with metformin.

## 5. Conclusion

The combination of saxagliptin plus metformin for the treatment of type 2 diabetes offers an oral treatment regimen that is safe and well tolerated.

## 6. Conflicts of Interest

All contributing authors declare no conflicts of interest.

## 7. Source of Funding

None.

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