Add-on saxagliptin improves glycemic status among uncontrolled type 2 diabetes mellitus

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) have multiple pathophysiologic defects contributing to hyperglycemia. T2DM patients have insulin resistance with progressive β-cell failure and progressive insulin secretion defect. Dipeptidyl peptidase-4 (DPP-4) inhibitors target the incretin system. saxagliptin is a DPP-4 inhibitor slowing the degradation of Glucagon-like peptide-1 (GLP-1) and Glucose-dependent insulinotropic peptide (GIP) sustain the incretin effects. Aim was to know the add-on effects of saxagliptin among uncontrolled T2DM.

Methods: A total of 71 uncontrolled T2DM patients on various antidiabetic therapies except incretin mimetic were consecutively selected for the study. Baseline fasting plasma glucose (FPG), 2hour postprandial glucose (PPG) and glycated hemoglobin (HbA1c) was measured. Saxagliptin orally 5mg/day was given after approval of ethical committee and FPG, 2hour PPG and HbA1c was measured at 12 weeks and 24 weeks. Data were collected and analyzed by ‘t’ test using SPSS software version 25.

Results: Baseline FPG, 2hour PPG and HbA1c was 158.4±13.9mg%, 252.6±24.4mg% and 8.6±1.3% respectively. Percentage of patients achieved HbA1c of <7% at 12 weeks was 16.9% and 43.6% at 24 weeks (P <0.05). Adjusted mean difference in HbA1c was 0.73% at 12 weeks and 1.2 % at 24 weeks (P <0.05). Reduction of mean FPG, 2hour PPG and HbA1c was 154.48±13.8mg%, 240.31±26.8mg% and 7.93±1.1% at 12 weeks and 151.15±13.7mg%, 231.7±27mg% and 7.38±1% at 24 weeks respectively (P <0.05). Patients on insulin were better responded.

Conclusions: Add-on saxagliptin improves all parameter of glycemic status in uncontrolled type 2 DM patients.

Keywords: Add-on, Type-2 Diabetes Mellitus, Saxagliptin, Uncontrolled

INTRODUCTION

Type 2 diabetes mellitus (T2DM) which is characterized by insulin resistance with a progressive insulin secretion defect and β-cell failure or loss accounts for more than 90% of all diagnosed cases.1 There is multiple pathophysiologic defects contributing to hyperglycemia and α-cell dysfunction has also been present.2 In health α-cell of pancreas has a guardian type of role in the islets to maintain body’s capacity to produce insulin, and the α-cell and β-cell regulate each other reciprocally and systemic glucose levels are maintained within narrow range. In T2DM absolute or relative excess of glucagon, which causes higher rate of hepatic glucose production than utilization favouring hyperglycaemia.3 The rate of hepatic glucose production has been correlated with the hyperglycemia in association with hyperglucagonemia.4

In T2DM, glucagon producing α-cells in the islets of pancreas remain relatively protected from the toxic environment created by metabolic stress i.e. glucotoxicity and lipotoxicity, while insulin secreting β-cells are not

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protected and die by apoptosis.\(^5\) Thus, the ratio of \(\beta\)-cells to \(\alpha\)-cells is increased. The impairment of insulin release and insulin resistance is often accompanied by absolute or relative increased levels of glucagon in the fasting and postprandial state.\(^6\) There is also lack of suppression of glucagon release in hyperglycemic condition contributing further to postprandial hyperglycemia in both type 1DM and T2DM. In this situation insulin is not effective as a negative feed back for hepatic glucose out put, while glucagon potentiate glucose mobilization from the liver, thus contributing to hyperglycaemia.\(^7\)

This can be relevant in the context of impairment of insulin secretion or action. Another defect in glucagon secretory response of \(\alpha\)-cells to low glucose concentration is impaired in type 1 DM and long-lasting T2DM increasing risk of episodes of sever hypoglycemia, especially in patients treated with insulin.\(^8\) The lack of glucagon response to hypoglycemia has been associated with multiple failures in \(\alpha\)-cell regulation including defective glucose sensing, loss of \(\beta\)-cells function, insulin resistance or autonomic malfunction. Paradoxical increase in glucagon secretion following carbohydrate meals leads to postprandial hyperglycemia as the response of \(\alpha\)-cell to hyperglycemia is blunted or vanishing and plasma glucagon remains inappropriately excessive at comparable blood glucose levels. A relative increase in ratio of \(\alpha\)-cells to \(\beta\)-cell mass in pancreatic islets occurs owing to decrease in \(\beta\)-cells mass , but the \(\alpha\)-cell mass is similar to that of non-diabetic individuals.\(^9\) In context of hyperglycemia and hyperglucagonemia that the glucagon levels are relatively high to the ambient glucose levels, as the glucagon levels might not be increased in absolute term in early phase of T2DM.\(^10\) After meal ingestion hepatic glucose production is still remain near fasting levels in diabetic subjects and contribute to the postprandial hyperglycemia and hyperglucagonemia responsible for as much as 50% of the pathological increase in glucose.\(^11\)\(^,\)\(^12\)

There is evidence that \(\beta\)-cell dysfunction could contribute to \(\alpha\)-cell dysfunction. The glucagon secretion by \(\alpha\)-cells is under paracrine control by insulin (the switch-off hypothesis) for the architectural proximity between \(\alpha\)-and \(\beta\)-cells. Insulin represses glucagon secretion in a pulsatile manner in non-diabetic subjects, but this coordination is disrupted in patients with advanced T2DM and it could be potentially contribute to glucagon dysregulation.\(^13\) Defective counter regulation in advance T2DM with hyperglycemia occurs and the counter regulatory effects of glucagon to hyperglycemia is impaired and the degree of \(\alpha\)-cell dysregulation is related with lack of \(\beta\)-cell function in diabetes.

There is a well-established correlation between hyperglycemia, as measured by elevated glycated hemoglobin (HbA1c) levels and an increased risk for microvascular and macrovascular complications. Elevated 2hour PPG in patients with T2DM even in absence of fasting hyperglycemia and HbA1c <7% also increased the risk of cardiovascular disease (CVD). Thus, there is interrelationship among fasting hyperglycemia, postprandial hyperglycemia and raised HbA1c levels exist, the higher the fasting hyperglycemia the higher the postprandial hyperglycemia and vice versa.\(^14\) A reduction in the risk of T2DM complication was observed for every 1% decrease in HbA1c. The lower the risk for disease related complications was observed in patients with HbA1c level bellow 6.0%.\(^15\) Therefore, attaining good glycemic control by triad model of diabetic management strategies in which all the three parameters i.e. HbA1c, PPG and FPG levels are considered that may help prevent or delay long-term complications of T2DM, especially microvascular complications.

There is wide array of medications available to treat T2DM. Aside from insulin, most medications are expected to reduce HbA1C levels by 0.5 to 2% when administered as monotherapy. A reduction in HbA1c of 0.5% is generally considered to be a clinically meaningful and therapeutic response. DPP-4 inhibitors are a new class of antihyperglycemic therapy that targets the incretin system. The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinoentrant peptide (GIP), which are released from the intestinal tract, facilitate postprandial insulin secretion from the pancreas and accounts for 50% of the postprandial insulin response.

Beside, GLP-1 has multiple physiologic benefits including stimulating glucose-dependent insulin secretion, decreasing glucagon secretion and slowing of gastric emptying.\(^16\)\(^,\)\(^18\) Native GLP-1 and GIP however, are degraded within minutes by the DPP-4 enzymes.DPP-4 expression and activity is higher in T2DM patients compared to healthy control. By slowing the degradation of GLP-1 and GIP, DPP-4 inhibitors, thus sustain the incretin effects of increasing postprandial insulin secretion and suppressing glucagon production.\(^16\) Current guideline support the addition of DPP-4 inhibitors for patients experiencing suboptimal glycemic control with metformin alone or as a first line alternative, if metformin monotherapy can not be tolerated.\(^19\)\(^,\)\(^20\) Saxagliptin in a once-daily (QD) orally administered potent competitive and reversible DPP-4 inhibitor, currently approved by US FDA in July 2009 and European Medicine Agency (EMA) in October 2009 as adjunct to diet and exercise to control hyperglycemia in T2DM. In clinical trials, saxagliptin was shown to be efficacious in lowering fasting glucose, 2hour PPG and glycated HbA1c when used as monotherapy, in combination with metformin, with sulfonylurea with Thiazolidinediones and with insulin.\(^21\)\(^\)\(^,\)\(^26\)

This study was undertaken to know the effects of saxagliptin as an add-on therapy to uncontrolled T2DM patients in terms of glycemic control and any adverse reactions with different oral OAD singly or in combinations OADs and with insulin alone or insulin with other OADs, except patients on incretin mimic.
METHODS

It was an open label, observational, prospective, interventional, single centre comparative study. A total of 100 T2DM patients were selected for the study from November 2015 to November 2017 from OPD and indoor department of medicine of VIMSAR, Burla (India), with history of uncontrolled glycemcic status either singly or multiple parameters of hyperglycemia, i.e. FPG >140mg%, 2hour PPG >240mg% and HbA1c >7.5%, who were on stable doses of OADs in singly or in combinations and/or on stable doses of basal or premixed insulin for ≥8 weeks without any incretin mimetic.

Exclusion criteria were severe hyperglycemia i.e. FPG >250mg%, diabetic ketoacidosis, hyperosmolar nonketotic states, acute and chronic pancreatitis, women of child bearing ages, pregnancy, lactating mothers, severe co-morbidities i.e. congestive heart failure, myocardial infarction, angina, multi-vascular heart disease, CABG, and angioplasty, cerebrovascular accidents, severe sepsis, pulmonary TB, acute and chronic liver disease, unstable renal diseases, anemia, hemoglobinopathies, major psychosis, immunocompromized state and repeated use of corticosteroids. After approval of ethical committee, Saxagliptin orally 5mg daily was given as an add-on and SMBG was advised weekly for detection of hypoglycemia or need for dose reduction of existing secretogauge or insulin and patients were advised to attain the study centre at 12 weeks and 24 weeks for measurement of FPG and 2 hour PPG and HbA1c. Data were collected and analyzed by ‘t’ test using SPSS software version 25.

RESULTS

After drop out of 29 cases, 71 cases remained in the study. 69% patients were male and 31% female. Age of patients ≤55 years were 18% and ≥65 years were >55 years of age. The mean age of patients was 60.8±8.2 years. BMI was >25 in 66% cases and ≤25 in 43% cases. Baseline FPG, 2hour PPG and HbA1c was 158.4±13.9mg%, 252.6±24.2mg% and 8.6±1.3% respectively. The reduction in mean FPG, 2hour PPG and HbA1c at 12 weeks were 154.48±13.8mg%, 240.31±26.8mg% and 7.93±1.1% respectively (P<0.05) and after 24 weeks it was 151.15±13.7mg%, 231.07±27mg% and 7.38±1% respectively (P<0.05) (Table 1 and Figure 1).

| TABLE 1: Changes in mean FPG, 2hr PPG & HbA1c over 12 weeks and 24 weeks. |
|-----------------|--------|--------|--------|--------|--------|
| **mg/dl**       | **Baseline** | **SD** | **12 weeks** | **SD** | **P Value** | **24 weeks** | **SD** | **P value** |
| FPG             | 158.41 | 13.3   | 154.48 | 13.8   | <0.05    | 151.15 | 13.7   | <0.05    |
| 2 hr PPG        | 252.65 | 24.3   | 241.31 | 26.8   | <0.05    | 231.07 | 27     | <0.05    |
| HbA1c%          | 8.60   | 1.3    | 7.93   | 1.1    | <0.05    | 7.38   | 1      | <0.05    |

Table 2: Changes in mean FPG, 2hr PPG & HbA1c over 12 weeks and 24 weeks with insulin.

<table>
<thead>
<tr>
<th><strong>mg/dl</strong></th>
<th><strong>Baseline</strong></th>
<th><strong>SD</strong></th>
<th><strong>12 weeks</strong></th>
<th><strong>SD</strong></th>
<th><strong>P Value</strong></th>
<th><strong>24 weeks</strong></th>
<th><strong>SD</strong></th>
<th><strong>P value</strong></th>
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<tr>
<td>FPG</td>
<td>162.15</td>
<td>14.4</td>
<td>157.06</td>
<td>14.0</td>
<td>&lt;0.05</td>
<td>153.42</td>
<td>14.8</td>
<td>&lt;0.05</td>
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<tr>
<td>2 hr PPG</td>
<td>253.39</td>
<td>25.9</td>
<td>240.7</td>
<td>25.7</td>
<td>&lt;0.05</td>
<td>229.21</td>
<td>25.5</td>
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<tr>
<td>HbA1c%</td>
<td>9.40</td>
<td>1.5</td>
<td>8.53</td>
<td>1.3</td>
<td>&lt;0.05</td>
<td>7.8</td>
<td>1.1</td>
<td>&lt;0.05</td>
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</tbody>
</table>

Table 3: Changes in mean FPG, 2hr PPG & HbA1c over 12 weeks and 24 weeks without insulin.

<table>
<thead>
<tr>
<th><strong>mg/dl</strong></th>
<th><strong>Baseline</strong></th>
<th><strong>SD</strong></th>
<th><strong>12 weeks</strong></th>
<th><strong>SD</strong></th>
<th><strong>P Value</strong></th>
<th><strong>24 weeks</strong></th>
<th><strong>SD</strong></th>
<th><strong>P value</strong></th>
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</thead>
<tbody>
<tr>
<td>FPG</td>
<td>155.16</td>
<td>12.9</td>
<td>152.24</td>
<td>12.8</td>
<td>&lt;0.05</td>
<td>149.18</td>
<td>12.5</td>
<td>&lt;0.05</td>
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<tr>
<td>2 hr PPG</td>
<td>252.00</td>
<td>23</td>
<td>241.84</td>
<td>28.1</td>
<td>&lt;0.05</td>
<td>232.68</td>
<td>28.4</td>
<td>&lt;0.05</td>
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<tr>
<td>HbA1c%</td>
<td>8.02</td>
<td>0.68</td>
<td>7.42</td>
<td>0.67</td>
<td>&lt;0.05</td>
<td>7.00</td>
<td>0.63</td>
<td>&lt;0.05</td>
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</table>

Adjusted mean difference in HbA1C at 12 weeks was 0.73% and at 24 weeks 1.2%. The percentage of patients achieved HbA1c <7% was 16.9% at 12 weeks and 43.6% at 24 weeks (P<0.05). In subgroup of 33 (46.47%) patients who were on insulin alone and 38 (53.52%) on insulin with other OADs combination had also reduction of all parameters of glycemia. T2DM patients on insulin alone had more significant reduction in all parameters of glycaemia (Table 2 and Figure 2), than insulin with other OADs combination (Table 3 and Figure 3).
The adjusted mean difference of HbA1c was 0.5% (P<0.05). Patients with history of shorter duration of diabetes of <5 years (45 %) had more significant reduction of HbA1c than patients with longer duration of >5 years (55%), with adjusted mean HbA1c difference of 0.55% (P<0.05). Hypoglycaemia was confirmed in 2.8% cases, one patient with insulin alone and one with sulfonylurea combination. Dose reduction of sulfonylurea and insulin was required in 37 (52%) cases at 24 weeks of the study to avoid hypoglycaemia. There was no any other adverse reaction associated in this study.

DISCUSSION

Management strategies of T2DM involves according to its pathophysiologic defects. The DPP-4 inhibitors acts in the incretin system is a new class of drug and efficacious in lowering all parameters of glycemia. In our study saxagliptin effectively reduced all parameters of glycemic control as an add-on to existing therapy other than incretin mimetic. Our study results are also consistent with other studies. Rosenstock J et al, have reported that saxagliptin reduces mean HbA1c by 0.7-0.9% from an average baseline of 7.9% vs (Placebo 0.3%) and FPG reduced by 14-15mg% and PPG at 60 minute by 24-41mg% in monotherapy.21

Jadzinski M et al, reported add-on saxagliptin 5mg and 10mg/day to metformin therapy reduce HbA1c by -2.5 and 2.5 vs 1.7 and 2.0% (placebo) and FPG by 60 and 60mg% vs 31 and 47mg%23 Proportion of patients achieved HbA1c of <7% was 60.3 and 59.7%. PPG AUC decreased by- 21080/min/dl and 21336mgxmin/dl. Depronzo RA et al, reported statistically significant decrease of HbA1c from baseline at 24 weeks vs placebo (0.59, 0.69, 0.58 with 2.5mg, 5mg and 10mg of saxagliptin as add-on to metformin (P<0.0001) and FPG by -14.31, -22.03, -20.50mg% vs 1.24mg% with placebo (P <0.0001) and PPG AUC (-8891-9586 and -8137 vs 3291mg .min/dl (P <0.0001) and more than twice as many patients achieved HbA1c < 7% with 2.5, 5 and 10mg saxagliptin vs placebo (37.44 and 44% vs 17% (P <0.0001).22 β-cell function and postprandial C-peptide , insulin and glucagon AUCs improves in all doses of saxagliptin in 24 weeks and incidence of hypoglycemia and weight gain was similar to placebo.

Chacra AR et al, added saxagliptin to suboptimal dose of sulfonylurea reported improved glycemic control compared with up titration of sulfonylurea in patients with type 2 diabetes and reduction of HbA1c by -0.645 and FPG by -10mg%.24 Proportion of patients achieving HbA1c <7% was 22% and PPG AUC by -5000mg.min/dl. Hollander P et al, as add-on to Thiazolidinediones reported statistically significant adjusted mean HbA1c reduction of -0.94% and FPG by-1mmol/L and proportion of patients achieved HbA1c <7% was 41.8% vs 25.6%.25 Barnet AH et al, reported effect of saxagliptin in T2DM patients with insulin alone and insulin combined with metformin had reduction in adjusted mean difference HbA1c of -0.47% (P< 0.0001) vs placebo and PPG AUCs were also reduced significantly at 180 and 120 minutes, and at 24 weeks adjusted mean FPG was -4.02mg/dl and achieved HbA1c <7% in 17.3% vs 6.7% placebo.26

CONCLUSION

In this study add-on saxagliptin among uncontrolled T2DM patients improved all parameters of glycemic control and achievement of mean HbA1c of <7% at 12 weeks in 16.5% patients and 43.6% at 24 weeks .The mean reduction of HbA1c, FPG and 2hour PPG was better in patients with insulin therapy, suggesting insulin sensitizing effect and shorter duration of diabetes than long duration of diabetes may be due to better preserved β-cell mass. It is conceivable that DPP-4 inhibitors may be considered in uncontrolled T2DM patients at multiple time points as add-on therapy or at initiation of therapy whether they are in any combination of antidiabetic therapy. Addition of saxagliptin to existing therapy, required dose reduction of existing secretagauge or insulin and may reduce glycemic variability and there is less risk of hypoglycaemia due to its unique mode of actions.

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