Sitagliptin *versus* saxagliptin in decompensated type 2 diabetes mellitus patients

Antonio Asti,[1] Alessandra D'Alessandro,[2] Francesco Paolo Zito,[2] Salvatore Nardi,[1] Giovanni Sarnelli,[2] Giorgio Maresca,[1] Giuseppe D'Alessandro[1]

[1]Department of Clinical Medicine and Emergency, S. Maria di Loreto Nuovo Hospital, Napoli; [2]Department of Clinical Medicine and Surgery, Gastroenterology Unit, Federico II University, Napoli, Italy

ABSTRACT

Sitagliptin and saxagliptin are oral hypoglycemic agents inhibitors of DPP-4, indicated in the treatment of type 2 diabetes mellitus in combination with metformin, in patients who have not achieved adequate glycemic control. In our study we enrolled 128 decompensated type 2 diabetes patients while on metformin maximum dosage. At time 0' we have detected, body mass index (BMI), total cholesterol, high- and low-density lipoproteins (HDL and LDL), triglycerides, transaminases and pancreatic amylase; patients were randomized to receive sitagliptin or saxagliptin; follow-up was performed after 4 months with the revaluation of the same variables and adverse events. In both sitagliptin and saxagliptin groups we observed a significant reduction in fasting glucose, glycated hemoglobin, weighing, BMI, triglycerides, while the reduction in total cholesterol, LDL cholesterol did not reach statistical significance. There was no suspension of therapy, adverse events appeared minor and temporary. In conclusion, our observations highlight the almost identical efficacy of sitagliptin and saxagliptin. These data reinforce even more the idea that we should think about this class of drugs as the next step in patients failing therapy with metformin.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic and progressive disease, characterized by persistent hyperglycemia, due to both a decline of β-pancreatic insulin production and an increased peripheral insulin resistance. The incidence of this pathology is increasing rapidly, indeed, it was estimated that the number of diabetics will arise from 371 million (2012) to 552 million (2030), representing one of the major challenge to health care worldwide.[1]

Traditional therapies can be still considered suboptimal, since there are no treatments able to guarantee a perfect glycemic control and a stable prevention of diabetic complications, without the risk of hypoglycemia.[2] For these reasons, the finding that particular hormones, called glucon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide, are able to induce a greater secretion of insulin only in the presence of high level of glucose, has quickly attracted the attention of scientists.[3,4]

GLP-1 is a polypeptide, secreted by endocrine cells of small intestine during the digestive phase; the glucose in the intestinal lumen acts as a trigger and induces the release of this hormone. Through the circulation, GLP-1 reaches its receptor on β-pancreatic cells, stimulating the secretion of insulin in relation to the amount of glucose concentration. Physiologically, the half-life of endogenous GLP-1 is around 2 min; this hormone, indeed, is quickly degraded by a specific peptidase, the dipeptdyl-peptidase 4 (DPP-4).[5]

In addition to the stimulus of insulin secretion, the hypoglycemic effect of this substance is enhanced by the inhibition of glucagon release. Moreover, this hormone stimulates the transcription of insulin and

Correspondence: Alessandra D'Alessandro, Department of Clinical Medicine and Surgery, Gastroenterology Unit, Federico II University, via Pietro Castellino 141, 80131 Napoli, Italy.
Mobile: +39.333.5021090 - Fax: +39.081.7462751.
E-mail: alessa.dalessandro@gmail.com

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induces β-cells neogenesis and proliferation, improving insulin reservoir.[6]

Interestingly, the positive effect of GLP-1 seems not to be limited to glycemic control,[5] in fact it delays gastric emptying, inducing satiety with a consequent reduction in food intake and it seems to have a cardio-, vaso- and nephroprotective effect.[7-10]

Due to various favorable cardiometabolic and insulinotropic effects, GLP-1 is a very attractive candidate in the management of T2DM. Exogenous administration of GLP-1 analogues (exenatide, liraglutide) and the abatement of degradation by DPP-4 inhibitors (saxagliptin, sitagliptin, vildagliptin) are the two approaches used to obtain or maintain high levels of GLP-1.[11]

Sitagliptin and saxagliptin are potent, oral, selective DPP-4 inhibitors. These drugs are able to increase the concentration of endogenous incretin hormones, inducing insulin secretion from β cells in a glucose dependent manner. Differences in drug efficacy between these DPP-4 inhibitors have been investigated in few studies, hence the aim of our study is to compare the effectiveness and safety of saxagliptin and sitagliptin in patients who have not achieved adequate glycemic control with metformin.

Materials and Methods

Characteristics of patients

Two hundred and fourteen consecutive outpatients with type 2 diabetes mellitus were enrolled. Among them, we selected one hundred and twenty-eight patients, mean age 64.3 years [standard deviation (SD) ±8.4], with an average duration of diabetes of 6.5 years (SD±4.5), who have not achieved an adequate glycemic control while on therapy with maximum dosage of metformin.

We considered as decompensated, patients with glycated hemoglobin >7.5% and fasting glucose (FPG) >140 mg/dL.

Study design

After the enrollment, patients were randomly divided into two groups: 64 patients (33 F and 31 M) were put on therapy with metformin plus sitagliptin 100 mg/die and 64 (34 F and 30 M) on therapy with metformin plus saxagliptin 5 mg/die (Figure 1).

At time 0' we have detected glycated hemoglobin (HbA1c), FPG, weight, body mass index (BMI), total cholesterol, high- and low-density lipoproteins (HDL and LDL), triglycerides, transaminases and pancreatic amylase. Patients were instructed to maintain their previous eating habits. After four months (T4) all patients were evaluated and the same variables were analyzed. During the follow-up the onset of adverse effects was registered.

Statistical analysis

Paired Student's *t*-tests were performed to analyze the differences of each group between time 0 and time 4. Unpaired Student's *t*-tests were used to evaluate differences between sitagliptin and saxagliptin subgroups at time 0 and time 4.

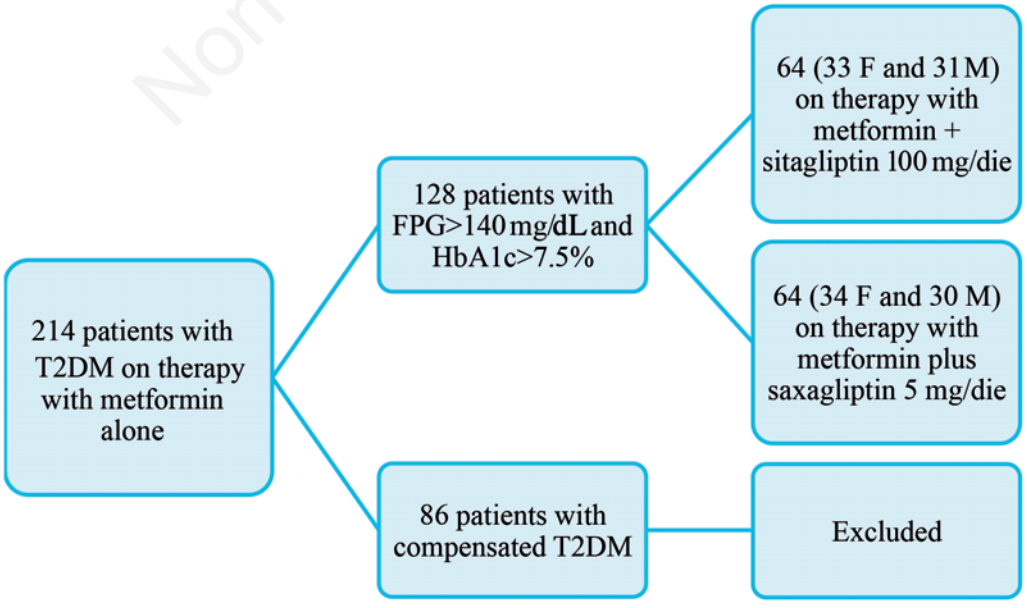

Figure 1. Flow chart demonstrating process of patients' enrollment. FPG, fasting glucose; T2DM, type 2 diabetes mellitus.

Results

Sitagliptin

In sitagliptin group we observed a significant reduction in fasting glucose from 187 mg/dL to 138 mg/dL (SD±38; P<0.0001) and in glycated hemoglobin from 8.2% to 7.1% (SD±1.2; P<0.0001). A significant lowering of weight from 88 kg to 85.4 (SD±13.9; P<0.0001), BMI from 32.2 to 31 (SD±3.6; P<0.0001) and triglycerides from 192 mg/dL to 156 mg/dL (SD±29.8; P=0.0003) was registered, as summarized in Figures 2 and 3. While the reduction in total and LDL cholesterol (P=0.3) and a slight increase in HDL cholesterol (P=0.3) did not reach statistical significance.

Saxagliptin

In saxagliptin group, as shown in Figure 2, we observed a significant reduction in fasting glucose from 191 mg/dL to 160 mg/dL (SD±31; P<0.0001) and in glycated hemoglobin from 8.1% to 7.5% (SD±1.5; P<0.0001). Similarly, as illustrated in Figure

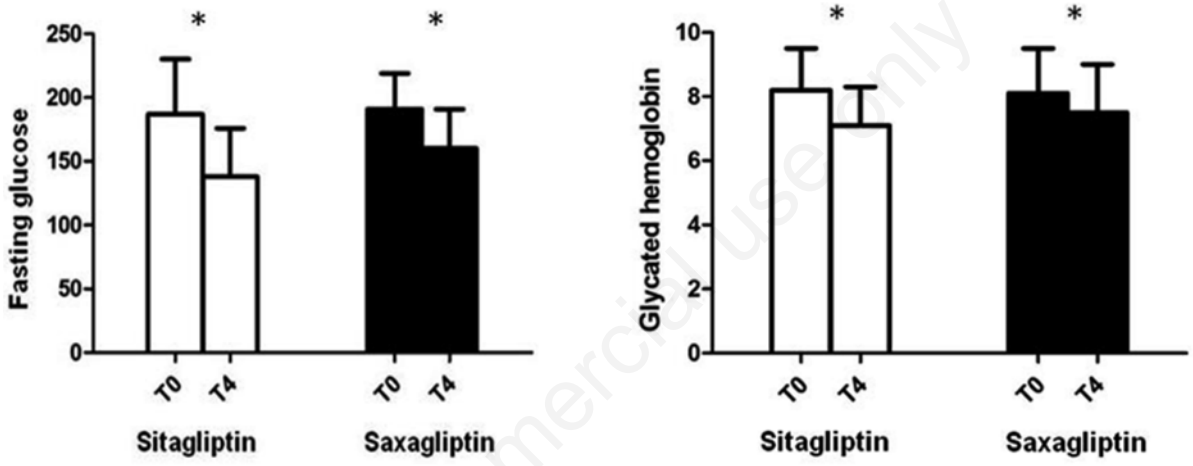

Figure 2. Sitagliptin and saxagliptin have induced a significant reduction of both fasting glucose and glycated hemoglobin in decompensated type 2 diabetes mellitus patients. No differences were found between sitagliptin and saxagliptin subgroups after 4 months. *P<0.05.

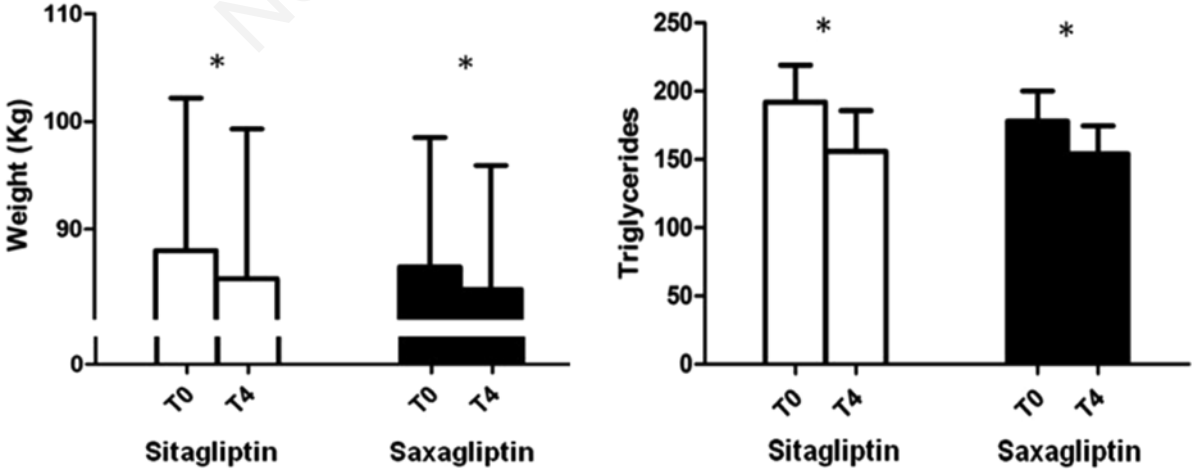

Figure 3. Sitagliptin and saxagliptin have induced a significant weight loss in association with a significant reduction of triglycerides after 4 months of therapy. No differences were found in these parameters between sitagliptin and saxagliptin. *P<0.05.

3, body weight, BMI and tryglicerides showed a significant diminution (from 86.5 kg to 84.4 kg with SD±11.5; P<0.0001, from 28 to 27.5 with SD±1.4; P<0.0001 and from 178 mg/dL to 154 mg/dL with SD±20.6; P=0.0003, respectively). Also in this subgroup the reduction in total cholesterol, LDL cholesterol (P=0.3) did not reach statistical significance, HDL cholesterol appeared virtually unchanged (P=0.5), as well as pancreatic amylase.

Sitagliptin *versus* saxagliptin

Sitagliptin and saxagliptin groups, at time 0, were comparable for mean age, duration of diabetes mellitus, fasting glucose, glycated hemoglobin, cholesterol, tryglicerides, transaminase and pancreatic amylase.

At time 4, a reduction of 49 mg/dL in fasting glucose was registered in patients on therapy with sitagliptin, while in saxagliptin group we evaluated a diminution of 31 mg/dL (P>0.05). Glycated hemoglobin has shown a reduction of 1.1% (SD±1.2) and 0.6% (SD±1.5) in sitagliptin and saxagliptin subgroups, respectively (P>0.05). A similar weight loss was observed in patients taking sitagliptin and saxagliptin ($\Delta_{T4\text{-}T0}$=2.6 kg and $\Delta_{T4\text{-}T0}$=2.1 kg, respectively). Also cholesterol, tryglicerides, transaminase and amylase have not shown significant differences between these subgroups.

Adverse effects

There was no suspension of therapy, adverse events appeared minor and temporary: in sitagliptin group we observed three cases of nausea and one case of nasopharyngitis, which resolved after ten days, in saxagliptin group two cases of nausea and one case of headache which resolved quickly (Table 1).

Discussion and Conclusions

In this study we have investigated the influence of the DPP-4 inhibitors sitagliptin (5 mg daily) and saxagliptin (100 mg daily) on glycemic control in decompensated T2DM patients.

Table 1. Description of adverse effects registered during the study.

	Saxagliptin	Sitagliptin
Headache	1	0
Nausea	2	3
Nasopharyngitis	0	1
Hypersensitivity	0	0
Skin reactions	0	0

Our clinical study has demonstrated the efficacy of both saxagliptin and sitagliptin in the achievement of glycemic control in T2DM patients who have not reached this target with metformin alone. In fact, the addition of sitagliptin 5 mg/die induces a reduction in HbA1c of 1% (8.2 to 7.1%) and a lowering in FPG of 49 mg/dL; obtaining the adequate glycemic control in all patients. Even in the saxagliptin subgroup the glycemic control was reached in all patients, with a reduction in HbA1c of 0.6% and in FPG of 31 mg/dL.

In line with previous studies,[12] the addition of either sitagliptin or saxagliptin has shown similar reductions in HbA1c and FPG, confirming a comparable effectiveness in the treatment of T2DM patients with poor glycemic control with metformin alone.

Similarly, according to our data sitagliptin and saxagliptin share the same effects on lipid profile. In fact, a reduction in triglycerides without a significant lowering of cholesterol levels was demonstrated in both subgroups, likely as effect of a decrease of appetite. To date, a clear association between incretin-based drugs and reduction of BMI was demonstrated only for GLP-1 analogues, while the DPP-4 inhibitors are considered weight-neutral.[3,13] On the contrary, in this study, after four months of therapy a significant reduction in BMI was registered in patients treated with either saxagliptin or sitagliptin, however a long-tern follow-up is necessary to clarify the influence of these drugs on body weight.

Overall, DPP-4 inhibitors are considered well-tolerated drugs; the low risk of hypoglycemia depends on the glucose-dependent action of GLP-1. In fact, a key characteristic of this hormone is the ability to induce a reduction in blood glucose concentration only in the presence of hyperglycemia. Different minor adverse effects, including headache, nausea, nasopharyngitis, hypersensitivity and skin reactions, have been described.[3,14] Elashoff's study also linked incretin-based therapies with pancreatitis and pancreatic cancer in human patients,[15,16] in our study, although lipases were not detected, no change in pancreatic amylase and no clinical signs of pancreatitis were registered in both groups. The incidence of pancreatic cancer was not assessable due to the short follow-up. In a recent meta-analysis it was demonstrated that DPP-4 inhibitors and metformin combination therapy has a better efficacy than metformin monotherapy, without an increase in any adverse effect,[17,18] confirming the good safety profile of these drugs. In keeping with this, in our study there was no suspension of therapy and the adverse events appeared minor and temporary. In sitagliptin group we observed three cases of nausea and one case of nasopharyngitis, which resolved after ten days; while in saxagliptin group we detected two cases of nausea

and one case of headache, which resolved quickly. Although four months are not long enough to establish the long-term safety of these drugs, our data confirmed the high rate of tolerability of these medicaments. Lastly, in the SAVOR-TIMI 53 new data were published on the cardiovascular effects of DPP-4 inhibitors; in this study an higher risk of hospitalization for heart failure in patients on therapy with saxagliptin has been described, without a reduction in ischemic events.[19] Although we did not evaluated echocardiogram and cardiac biomarkers in our study, no cases of hospitalization for cardiac diseases were observed in both subgroups.

The impressive results achieved with incretin-based therapy have induced a rapid insertion of these drugs in the guidelines. In fact, according to the current American and European treatment algorithms for the management of T2DM, incretin-based therapies are considered, as thiazolidinedione and sulphonylurea, a second-line therapy in combination with metformin in patients with poor glycemic control with diet and metformin monotherapy.[20,21] Among incretin-based drugs, GLP-1RAs resulted stronger in the reduction of glycemia and BMI than DPP-4 inhibitors, however the oral administration, the lower incidence of gastrointestinal side effects and the minor cost of DPP-4 make them more manageable and cost-effective.[22-24]

In conclusion, DPP-4 inhibitors are effective, safe and manageable hypoglycemic drugs, and, considering, the lack of major side effects it is possible to hypothesize they will become the first-choice in the second line therapy for T2DM patients.

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