Acute and long-term effects of saxagliptin on a set of cardiovascular targets measured at fasting and post-prandially in obese patients with impaired glucose tolerance: A placebo-controlled study

Amel Rezki, Emmanuel Cosson, Marinos Fysekidis, Sabrina Chiheb, Eric Vicaut, Paul Valensi

▶ **To cite this version:**

Amel Rezki, Emmanuel Cosson, Marinos Fysekidis, Sabrina Chiheb, Eric Vicaut, et al.. Acute and long-term effects of saxagliptin on a set of cardiovascular targets measured at fasting and post-prandially in obese patients with impaired glucose tolerance: A placebo-controlled study. Nutrition, Metabolism and Cardiovascular Diseases, 2021, 31 (10), pp.2945-2958. 10.1016/j.numecd.2021.06.017 . hal-03500288

HAL Id: hal-03500288

https://hal-cnam.archives-ouvertes.fr/hal-03500288

Submitted on 24 Apr 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Copyright

Version of Record: https://www.sciencedirect.com/science/article/pii/S0939475320305512
Manuscript_086adf1b4a0e2200d8ad564ccd858978

Acute and long-term effects of saxagliptin on post-prandial glycemic response in obese patients with impaired glucose tolerance

Amel Rezki[1,2], Marinos Fysekidis[1,2], Sabrina Chiheb[1], Eric Vicaut[3], Emmanuel Cosson[1,2], Paul Valensi[1]

1. Department of Endocrinology, Diabetology, Nutrition, Jean Verdier Hospital, AP-HP, CRNH-IdF, CINFO, Paris Nord University, Sorbonne Paris Cité, Bondy, France

2. Sorbonne Paris Cité, UMR U1153 Inserm/U1125 Inra/Cnam/Université Paris 13, Bobigny, France

3. Clinical Research Unit, Lariboisière-St Louis, Fernand Widal Hospital, APHP, Paris, France

Corresponding author: Professor Paul Valensi

Department of Endocrinology-Diabetology-Nutrition

Jean Verdier Hospital

Avenue du 14 Juillet

93143 Bondy cedex. France

☎ (Int) +33 (0)148026580

(Int) +33 (0)148026579

paul.valensi@aphp.fr

Short running head: Saxagliptin on glycemic homeostasis in obese patients with impaired glucose tolerance

© 2020 published by Elsevier. This manuscript is made available under the CC BY NC user license
https://creativecommons.org/licenses/by-nc/4.0/

Abbreviations

ACCES: “ACute and Chronic Effects of Saxagliptin”

ANOVA: one-way analysis of variance

AUC glucose: area under curve glucose

BMI: body mass index

CGM: continuous subcutaneous glucose monitoring

CRP: C reactive protein

CV%: coefficient of variation of glucose

DPP-4i: dipeptidyl peptidase-4 inhibitor

FFA: free fatty acids

FPG: fasting plasma glucose value

GIP: glucose dependent insulinotropic peptide

GLP-1: glucagon-Like Peptide 1

IGT: impaired glucose tolerance

IL6: interleukin 6

T2D: type 2 diabetes

OGTT: oral glucose tolerance test

SD: standard deviation

Word count text: 3827

Word count abstract: 250

Number of references: 31

Number of tables: 4 tables

Number of figures: 2 figures

1 figure as supplementary material

Abstract

Background and aims

Dipeptidyl-peptidase inhibitors might be useful in type 2 diabetes prevention. ACCES (ACute and Chronic Effects of Saxagliptin) was a randomized, placebo-controlled, double-blind, controlled phase 2, pilot study aiming to examine in obese patients with impaired glucose tolerance (IGT) the acute effects and the effects after 12 weeks of treatment by saxagliptin on glucose levels at fasting and postprandially after a standard breakfast, and on glucose tolerance.

Methods and results

We included 24 obese patients with IGT. Patients were randomized to receive saxagliptin 5mg or placebo in the morning. The treatment was taken on Visit 1 before breakfast, then continued for 12 weeks. Biochemical measurements were performed before, one, two and three hours after a standard breakfast including 75g of carbohydrates, during Visit 1 and Visit 2 (12 weeks). Glucose variability (GV) was evaluated at Visit 1 from 24-h continuous glucose monitoring including the breakfast. A second OGTT was performed at Visit 3 (3-5 days after Visit 2).

Compared with placebo-treated patients, saxagliptin-treated patients had lower 1h and 2h post-meal plasma glucose levels at Visit 1 and similar changes at Visit 2 ($p<0.01$ to $p<0.004$), with lower GV indexes after breakfast at Visit 1. At Visit 3, all patients but one in saxagliptin group and only 4 patients in placebo group turned to normal glucose tolerance. Lower glucose response to breakfast at Visit 1 was predictive of recovery of glucose tolerance.

Conclusion

Saxagliptin has metabolically beneficial effects in glucose-intolerant obese patients by significantly lowering postprandial blood glucose levels.

Clinical Trial Registration number: NCT01521312:

https://clinicaltrials.gov/ct2/show/NCT01521312

Key-words: Impaired glucose tolerance. Obesity. Saxagliptin. DPP-4 inhibitors. OGTT. CGMS. Glucose variability

Introduction

In obese patients glucose regulation is often altered. Prediabetes is a metabolic disorder characterized by insulin resistance, reduction of insulin secretion and a reduction of incretin effect, which increases the risk of incident type 2 diabetes (T2D) [1,2]. Impaired glucose tolerance (IGT) is a prediabetic state whose progression results from the deterioration of beta-cell function and aggravation of insulin resistance. IGT is associated with increased cardiovascular risk and might have harmful effects on other organs including the kidney [3-6]. The growing prevalence of T2D makes the prevention of the disease a major public health issue. IGT is an attractive stage for intervention, allowing the possibility of slowing down or preventing progression to T2D. Various intervention trials have shown the efficacy of lifestyle programs and pharmacological agents to prevent or delay the progression from IGT to T2D [7,8].

Standardized meals have been suggested as a more physiological way than oral glucose tolerance test (OGTT) to diagnose glycemic disorders [9,10]. In recent years, techniques have been developed for continuous subcutaneous glucose monitoring (CGM). These tools make it possible to evaluate interstitial glucose levels throughout the day and to precisely analyze postprandial glucose excursions. Using CGM data, we recently showed in obese patients that glucose response to a standard breakfast including 75g carbohydrates shows strong similarities with the response to 75g OGTT (Rezki et al. submitted). In addition, CGMS allows to analyze more accurately daily glucose variability. The acute effects of glycemic control on glucose variability have never been studied specifically in IGT patients.

Dipeptidyl peptidase-4 inhibitors (DDP-4is) improve blood glucose regulation by increasing the active levels of incretins, glucagon-like peptide 1 (GLP-1) and glucose dependent insulinotropic peptide (GIP). By preventing the deactivation of GLP-1 and GIP, they increase insulin release and decrease glucagon levels [11]. These drugs may reduce beta cell apoptosis

and preserve beta cell function [12], and might thus prevent the progression from prediabetes to T2D. Furthermore, these drugs were shown to offer a good safety profile.

The ACCES (ACute and Chronic Effects of Saxagliptin) Glucose pilot study aimed to explore in obese patients with IGT the effects of saxagliptin *versus* placebo on glycemic status with the objectives to determine: *(i)* the acute effects of saxagliptin on plasma glucose levels after a standardized breakfast and evaluate the interaction with indexes of glucose variability; *(ii)* the effects of a 12-week treatment with saxagliptin on plasma glucose levels before and after a standardized breakfast and on HbA1c; *(iii)* the effects of a 12-week treatment with saxagliptin on the results of OGTT and IGT status; and *(iv)* the acute and 12-week treatment effects of saxagliptin on inflammatory parameters.

Methods

Study design

ACCES is a randomized, placebo-controlled, double-blind, controlled phase 2, pilot study, conducted at Jean Verdier University Hospital (Bondy, France). The study was approved both by the local ethics committee (Comité de Protection des Personnes, Reference Number: JLD/AP-protocole 27-2011), by the French National Agency for Drug Security (Agence Nationale de Sécurité du Médicament, Number: A110912-14) and was registered as a clinical trial (Number EudraCT: NCT01521312). There were two parts in the study: *(i)* the acute and chronic effects of saxagliptin *vs* placebo on glucose tolerance (ACCES-Glucose study) which are described in the current article; *(ii)* the acute and chronic effects of saxagliptin *vs* placebo on micro and macrovascular parameters (ACCES-Vasc study), which will be reported in another article.

Study population

The inclusion criteria were the following: patients with IGT according to an OGTT performed less than 3 weeks before the inclusion, age between 18 and 70 years, body mass index (BMI) ranging from 30 to 40 kg/m^2. The major exclusion criteria were the following: known diabetes (defined as fasting plasma glucose (FPG) ≥7 mmol/L or 2-h post-glucose ≥11.1 mmol/L) [13], uncontrolled hypertension, dyslipidemia (total cholesterol > 6.5 mmol/l or triglycerides > 2.3 mmol/l), renal failure (glomerular filtration rate < 60 ml/min), hepatic failure (prothrombin time < 70%), chronic respiratory disease, anemia (hemoglobin level < 10 g/dl), cardiac failure (from grade 2 of the NYHA classification), lower limb arterial disease, cardiac arrhythmia, anti-hypertensive or current lipid-lowering treatment initiated after the diagnosis of glucose intolerance, patients who have previously experienced a severe hypersensitivity reaction to a DPP-4i. Smoking was defined as present if patient continued to smoke or had stopped less than 3 years ago.

The methods used were non-invasive. All patients gave us their agreement and signed the informed consent according to the European directives.

The anticipated effect size (Δ/σ) for our study was estimated at 1.1, the power level was 80% and the probability level was set at 0.05. The estimated minimum sample size for a two-tailed hypothesis was calculated at 12 persons per group.

Screening and global procedure

Patients were screened during their routine checkup for obesity in our department. The OGTT was performed within one to three weeks before inclusion with 75g of glucose after a 12-hour fasting. IGT was defined as 2h post-OGTT glucose value ≥7.8 mmol/L and <11.1mmol/L, with FPG <7 mmol/L [13]. During the pre-inclusion period, participants received dietary advices. A CGM device was placed on the day prior to Visit 1 and removed after breakfast. Patients were

randomly assigned to a treatment with saxagliptin 5 mg in the morning or placebo for 12 weeks. At Visit 1, treatment by saxagliptin or placebo was taken after the fasting blood sampling, 30 minutes before eating the standardized breakfast (supplementary Figure 1). For the rest of the study, treatment was taken immediately before breakfast. Participants were contacted every month during the 12-weeks experimental treatment by phone for any side effects. Patients were advised not to modify their daily physical activity during the study period. Patients came for a second visit after 12 weeks of treatment and then stopped treatment. The study ended after Visit 3, which occurred 3 to 5 days after Visit 2. During Visit 3, the participants had an OGTT (supplementary Figure 1).

Procedures during visit 1 and visit 2

Standard breakfast test

A standard breakfast prepared at hospital and consisting of unsweetened coffee or tea (200 ml), 200 ml of orange juice and 60 g of white bread with 30 g of jam was offered to the patient who was asked to eat it in 10 minutes. This meal of 400 kcal contained 75g of carbohydrates. The breakfast test was performed at study Visits 1 and 2.

Biochemical measurements

Participants remained at rest in the supine position throughout the morning tests. Measurements were performed at fasting and 1, 2 and 3 hours after the standard breakfast.

Plasma glucose was measured by the glucose oxidase method (colourimetry, Kone Optima, Thermolab System, Paris La Défense, France), serum insulin by luminescent immunological assay (Diagnostic Products Corporation, Los Angeles, CA, USA) and HbA1c by agarose electrophoresis (HYRYS, HYDRASYS, Sebia, Evry, France). The HbA1c level was standardized according to the Diabetes Control and Complications Trial. Fructosamine, total

cholesterol, HDL-cholesterol and triglycerides were measured by enzymatic colourimetry (Hitachi 912, Roche Diagnostics, Meylan, France), and LDL cholesterol was calculated by Friedwald formula. Free fatty acids (FFA) were measured with enzymatic colorimetry (Wako Chemicals, GmBH). Serum samples were centrifuged at - 4 °C and stored at - 80 °C. These samples were used for an enzyme-linked immunosorbent assay (R&D Laboratory Systems, Minneapolis, Minnesota) to measure interleukin 6 (IL6), leptin, adiponectin and C reactive protein (CRP) according to the manufacturer's instructions.

For all women of childbearing age, a pregnancy blood test was performed at Visit 1 and 2, and also urinary pregnancy tests at the hospital every month and at any time during the study in case of late menstruation.

Glucose variability indexes

The CGM system "Medtronic ipro2®" was used to analyse glucose variability at study Visit 1. Interstitial glucose was measured by glucose oxidase method. Interstitial glucose readings were validated with three to four capillary glucose measurements a day, following the manufacturer's guidelines. Glucose data were collected every 5 minutes. The 24h data including the standard breakfast was analyzed by the Easy GV software, a spreadsheet that calculates various indexes of glucose variability: mean glucose value, standard deviation (SD glucose), coefficient of variation (CV% = (SD-glucose / Mean glucose) *100), continuous overall net glycemic action (CONGA) and mean amplitude of glycemic excursions (MAGE) [14]. During 3 hours after breakfast, mean glucose, the area under the curve of glucose (AUC glucose), SD glucose and CV% were calculated using CGM data.

Statistical analyses

Variables were expressed as mean ± SD or as percentages. Comparisons between groups at baseline were performed for continuous variables by analysis of variance or the Mann–Whitney test as appropriate and by Chi-square test for categorical variables. Quantitative variables were analyzed by different mixed models of ANOVA for longitudinal data including factor treatment (saxagliptin and placebo) and factor time with 2 levels when comparing changes between visits (i.e. V1 and V2) or four levels when analyzing the test meal response (0, 60,120 and 180 min after breakfast). Interaction between the 2 factors was used to test possible effect of treatment on time-dependent changes in studied parameters. Normalizing transformations were made if necessary. All tests were two-sided at 5% significance level. Statistical analyses were performed with SAS version 9.4.

Results

Patients' characteristics

From September 2012 to September 2014, we included 24 obese patients with IGT, 12 in saxagliptin group and 12 in placebo group. We had to stop the study tests for one patient at Visit 2 due to an atypical chest pain. The baseline characteristics are summarized in Table 1. Overall, mean BMI was 36.8±4.9 kg/m^2, one third of the patients had hypertension, 8.3% were smokers and 8.3% had obstructive sleep apnea syndrome. The two groups (placebo *vs* saxagliptin) did not show any significant difference for age, BMI, gender and blood pressure levels.

Anthropometric changes and side effects

During the study, body weight decreased between Visit 1 and 2 (p=0.007), from 107.5±18.5 kg to 106.1±20.2 kg in the saxagliptin group and from 97.2±14.5 to 93.5±16.6 kg in the placebo group (no significant treatment effect, p=0.153, nor time*treatment interaction, p=0.171). Waist

circumference decreased during the study (p=0.026), from 114±13 cm to 109±13 cm in saxagliptin group and from 108±9 to 102±11 cm in placebo group (no significant treatment effect, p=0.165, nor time*treatment interaction, p=0.07). Changes in body weight and waist circumference did not differ significantly between the two groups**.** No adverse effect occurred in any patient during the trial.

Effect of saxagliptin treatment on metabolic parameters at fasting

At fasting, there was no significant difference between the two groups at Visit 1 or Visit 2, for any of the metabolic parameters including FPG, HbA1c, fructosamine, lipid parameters; for hormone levels including leptin and adiponectin; and for renal function (Table 2).

Effect of saxagliptin treatment on metabolic parameters after the standard breakfast

At Visit 1 (acute effect), plasma glucose levels after breakfast differed significantly between the two treatment groups. Glucose response was lower in saxagliptin group ($p<0.02$) with a significant interaction time*treatment effect (p=0.0003) (fig 1A). At Visit 2 (chronic effect), the same effect was observed with a significantly lower glycemic increase after breakfast in saxagliptin group ($p<0.01$) and a significant interaction time*treatment effect (p=0.009) (fig 1B). At Visit 1 and 2, plasma insulin increased after breakfast until 2 hours and decreased at 3 hours with no difference between treatment groups (fig 1 C and D).

Triglycerides decreased at Visit 1 postprandially without treatment effect at any visit (Fig 1 E and F). During both visits, FFA levels decreased markedly 2 hours after breakfast (time effect, $p<0.0001$) without treatment effect (fig 1 G and H).

Acute saxagliptin effect on glucose variability indexes

None of the indexes of 24h glucose variability differed between saxagliptin and placebo groups (Table 3). No hypoglycemic episode occurred during 24h recordings.

The 3h period after breakfast analysis showed that SD glucose and CV% were reduced significantly after the first saxagliptin tablet (p=0.003 and 0.006, respectively) (Table 3).

Effect of saxagliptin treatment on glycemic status

During the OGTT performed before inclusion, FPG at fasting and 120 minutes was very similar in the two groups. OGTT was again performed at Visit 3 in 10 saxagliptin-treated patients and 9 placebo-treated patients. Compared to OGTT results at baseline, OGTT at Visit 3 showed a decrease in plasma glucose at 120 minutes in both groups, which was greater for the saxagliptin-treated group (saxagliptin: -3.45 ± 1.40 mmol *vs* placebo: -1.58 ± 0.59 mmol/l, p<0.008) (figure 2). Nine of the 10 patients treated by saxagliptin were no longer glucose intolerant and 5 out of the 9 placebo-treated patients still had IGT (p<0.01).

When comparing 3h CGM data after the standard breakfast during Visit 1 in the patients who recovered a normal glucose tolerance and those who did not, whatever they were treated by saxagliptin or placebo, mean glucose, glucose peak, SD glucose and AUC glucose were significantly lower in the former (p<0.05 for all indexes) (Table 4).

Effect of saxagliptin treatment on inflammatory parameters measured at fasting and after the standard breakfast

IL-6 and CRP levels did not change significantly after breakfast at any visit, and there was no treatment effect on IL-6 and CRP levels (figure 1 I to L).

Discussion

Several epidemiological studies have shown that high post-challenge (2-h post-OGTT) or post-prandial glucose values, independent of FPG, are associated with greater cardiovascular risk [3,4,15,16]. Various mechanisms may be involved, particularly post-prandial activation of oxidative stress and impairment of endothelial function [17].

Several prospective randomized studies have demonstrated that dietary and physical activity programs can reduce the incidence of T2D by 30-60% over 3-6 years in individuals with prediabetes [for review, 8 and 18]. However, lifestyle interventions require significant resources from the community [19], and adherence to lifestyle interventions is often poor despite extensive support [8]. Pharmacological interventions with glucose-lowering agents including metformin, acarbose or glitazones have shown a 25 to 60% reduction in the incidence of diabetes over 2.5 to 6 years [8]. Patients could be more compliant to drug therapy even if this option is less effective than lifestyle changes. Ultimately pharmacological intervention combined with diet and exercise counseling may be a realistic option for actually reducing T2D incidence [18].

In the current randomized study, we examined the effects of saxagliptin compared to placebo on glucose and other metabolic parameters, oxidative stress and inflammatory parameters in obese patients newly diagnosed with IGT. By the first day of saxagliptin treatment, plasma glucose levels were significantly reduced after the standard breakfast and the same changes were confirmed after 12 weeks of treatment with a conversion to normal glucose tolerance in 90% of the patients, while body weight decreased similarly as in the control group. FPG was not changed by saxagliptin treatment. Insulin response to breakfast was not modified, suggesting an improvement in insulin secretion. Lipid parameters and inflammatory parameters were also unchanged.

The incretin pathway is attenuated in T2D and in prediabetes [2]. Mechanism of the progression from prediabetes to diabetes state may be related to the lack of incretin secretion in the intestine [20]. Therefore, DPP-4is can effectively improve GLP-1 levels. In patients with T2D, DPP-4is reduce FPG by 1.1 mmol/l in means and reduce more 2h postprandial glucose value by 2.7 mmol/l on average, with an average HbA1c decrease by approximately 0.8% [21]. Meanwhile, body weight remains stable or modestly decreased and the risk of hypoglycemia is not enhanced [21]. Early intervention with incretin drugs might prevent the progression of prediabetic into diabetic state. Among prediabetic subjects, due to the predominant effect of incretin therapies on postprandial glucose levels, the major benefit is expected in subjects with IGT. In a 24-week, randomized controlled trial conducted in 25 Chinese obese subjects with newly diagnosed pre-diabetes, saxagliptin 5 mg resulted in a significant decrease in fasting and 2h postprandial plasma glucose and HbA1c values compared with the control group, with a reduction of insulin resistance [22]. Twelve weeks of sitagliptin treatment was recently shown to improve glucose tolerance and lipid profile in overweight individuals with prediabetes [23]. Similarly, after an acute coronary syndrome, sitagliptin was tested in patients with IGT or T2D detected by OGTT. In the sitagliptin-treated patients, beta-cell function was improved and significantly more patients improved post-load glucose metabolism compared with the placebo group [24]. Likewise, liraglutide 3.0 mg a day was compared to placebo as an adjunct to a reduced-calorie diet and increased physical activity in individuals with obesity and prediabetes and was shown to reduce significantly the risk of incident T2D together with a greater weight loss [25].

Our current results showed that saxagliptin was able to reduce postprandial glucose levels without affecting FPG levels, which were normal at baseline. This effect occurred by the first day of treatment and remained with the same magnitude after 12 weeks of treatment. In addition, the second OGTT performed while the patients had stopped treatment three to five days before showed an improvement of 2h-glucose and even a normalization of glucose

tolerance in 90% of the saxagliptin-treated patients. Looking at CGM data after the first tablet of experimental treatment, glucose peak, mean glucose, SD glucose and AUC glucose during the 3 hours after the standard breakfast were lower in the patients who recovered a normal OGTT at Visit 3. These results suggest that the effect of saxagliptin may be appreciated as soon as the first tablet is given, as the improvement of glucose after the standard breakfast is predictive for the improvement of glucose tolerance after 12 weeks of treatment.

The effect of DPP-4is on weight loss is usually modest as compared to a significant decrease commonly occurring with GLP-1 receptor agonists [26]. In our study, body weight and waist circumference decreased similarly in saxagliptin and placebo treated patients as the result of dietary advice given before study entry in both groups. Improvement of glucose profile may not be attributed to such changes.

Standardized meals have been suggested as a more physiological way than OGTT to diagnose glycemic disorders [9,10]. We recently showed in obese patients that glucose response to a standard breakfast including 75g carbohydrates shares strong similarities with the response to 75g OGTT. In particular, the magnitude of the response evaluated by 2h AUC-glucose, glucose peak and glucose value 60 min after OGGT or standard breakfast were similar. Additionally this breakfast offers good diagnostic performances for the detection of IGT or T2D (Rezki et al. submitted). We used in the present study the same standard breakfast. It was well accepted by our patients and easy to provide, since it contained the usual components of the French breakfast. The present study further supports the role of this standard breakfast as an interesting tool to explore glucose metabolism in real life.

Greater glucose variability generates a growing interest as an additional target for the overall management of glucose control [27]. We previously reported that glucose variability is increased by prediabetic stages, albeit modestly, in subjects with normal or slightly elevated HbA1c levels [28]. Glucose variability was here simply explored after the breakfast and showed

an improvement after the first saxagliptin tablet. An improvement of glucose variability was also reported after eight weeks of treatment by sitagliptin or vildagliptin [29].

Recent cardiovascular outcomes trials performed in large populations of patients with T2D and high cardiovascular risk provided evidence for cardiovascular safety except in the Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus (SAVOR-TIMI 53) study where the risk of hospitalization for heart failure was increased with saxagliptin mostly in patients with heart failure history or elevated plasma N-terminal pro-B-type natriuretic peptide levels without clear explanation for that [30]. Our patients were free of any cardiovascular disease. The saxagliptin treatment was well tolerated and no hypoglycemia event occurred during the trial. CGM after the first tablet did not detect any hypoglycemia. Saxagliptin had no significant effect on lipid profile and inflammatory parameters at fasting or postprandially, neither in acute condition nor after long-term treatment. In the same line, the effect of saxagliptin on adipose tissue inflammation was tested in overweight or obese people without diabetes and reported to be relatively modest, with many inflammatory markers unchanged [31]. Thus, saxagliptin appears to be safe in patients with IGT and might therefore be used to prevent T2D in this population.

Our study has some strengths. We evaluated glucose changes both in acute and long-term conditions, using both a standard breakfast close to real life and OGTT, in an homogenous population of obese patients with IGT. The study also has some limitations. The sample size was relatively modest, 24 patients, and thus the study did not have the power to detect any smaller effects among treatment groups. The study duration was only 12 weeks. Further studies in large cohorts, testing the effect of saxagliptin and other DPP-4is in delaying or preventing the progression from prediabetes to T2D are necessary.

Conclusion

Saxagliptin has a metabolically beneficial effect in obese glucose-intolerant patients by significantly lowering postprandial plasma glucose levels without affecting body weight. Saxagliptin improved glycemic status of patients with IGT after 12 weeks of treatment and turned it to normal glucose tolerance status in the majority of patients. The benefit of saxagliptin may be seen after taking the first tablet, as the improvement of glucose after the standard breakfast is predictive for the recovery of a normal glucose tolerance after 12 weeks of treatment. This study may add to the armamentarium of agents that may be used for the management of prediabetes.

Authors' contributions

PV conceived the study. EC and PV designed the study protocol. AR and MF organized and performed the study investigations. AR, EC, SC, MF and PV supported the recruitment of the patients. EV managed statistical analyses. PV and AR wrote the first draft of the manuscript. All authors critically revised the manuscript for important intellectual content. They all read and approved the final manuscript.

Acknowledgments

The authors are grateful to Chantal Cyrille for her contribution as study nurse, Angela Sutton for biochemical measurements and Jean-Jacques Portal for statistical analyses.

Funding source

This research work was conducted with the financial supports from Assistance Publique-Hôpitaux de Paris and Bristol-Myers-Squibb and AstraZeneca companies. The companies

agreed with the study design and encouraged the authors to submit this article for publication, but were not involved in the collection, analysis and interpretation of data.

Declaration of conflicting interests

Amel Rezki, Marinos Fysekidis and Sabrina Chiheb declare they do not have any conflict of interest in relation with this manuscript.

Eric Vicaut declares counseling activities for Abbott, Boston, Genomichealth, Celgen, CEMKA, Bristol-Myers-Squibb, CreativPharmaceuticals, Genomic health, and having received research grants from Astra-Zeneca, Bristol-Myers-Squibb and Pfizer.

Emmanuel Cosson declares counseling activities for Abbott, AlphaDiab, Ascencia, Lilly, Medtronic, Merck-Sharp-Dohme, Novartis, Novo-Nordisk, Roche Diagnostics, Sanofi-Aventis, YpsoMed; having given lectures for Abbott, Astra-Zeneca, Bezins, Bristol-Myers-Squibb, LifeScan, Lilly, Merck-Sereno, Novartis, Novo-Nordisk, Roche Diagnostics, Sanofi-Aventis; and received research grants from Abbott, Air Liquide, Astra-Zeneca, Lilly, Novo-Nordisk, Roche diagnostics, Sanofi-Aventis, Ypsomed.

Paul Valensi declares having given lectures for Abbott, AstraZeneca, Bayer, Eli-Lilly, Hikma, Merck-Sharp-Dohme, Novo-Nordisk, Novartis, Pfizer, Sanofi ; received research grants from Abbott, Bristol-Myers-Squibb-AstraZeneca, Novo-Nordisk ; and participated to Expert Committees for Astra Zeneca, Boehringer Ingelheim, Merck-Serono, Novo-Nordisk, Daiichi-Sankyo, Sanofi, Servier.

References

[1] Alberti KG. The clinical implications of impaired glucose tolerance. Diabet Med 1996;13:927-37.

[2] Foghsgaard S, Vedtofte L, Andreasen C, Andersen ES, Bahne E, Bagger JI, Svare JA, Holst JJ, Clausen TD, Mathiesen ER, Damm P, Knop FK, Vilsbøll T. Women with prior gestational diabetes mellitus and prediabetes are characterised by a decreased incretin effect. Diabetologia 2017;60:1344-53.

[3] Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. *Lancet* 1999;354:617-621.

[4] Balkau B, Shipley M, Jarrett RJ, Pyörälä K, Pyörälä M, Forhan A, Eschwège E. High blood glucose concentration is a risk factor for mortality in middle-aged nondiabetic men. 20-year follow-up in the Whitehall Study, the Paris Prospective Study, and the Helsinki Policemen Study. Diabetes Care 1998;21:360-367.

[5] Wang H, Song Y, Tang X, Xu J, Jiang P, Jiang L, et al. Impact of unknown diabetes and prediabetes on clinical outcomes in "nondiabetic" Chinese patients after a primary coronary intervention. Nutr Metab Cardiovasc Dis 2020;30:644-651.

[6] Markus MRP, Ittermann T, Baumeister SE, Huth C, Thorand B, Herder C, et al. Prediabetes is associated with microalbuminuria, reduced kidney function and chronic kidney disease in the general population: The KORA (Cooperative Health Research in the Augsburg Region) F4-Study. Nutr Metab Cardiovasc Dis 2018;28:234-242.

[7] Davies MJ, Tringham JR, Troughton J, Khunti KK. Prevention of Type 2 diabetes mellitus. A review of the evidence and its application in a UK setting. Diabet Med 2004;21:403-14.

[8] Paulweber B, Valensi P, Lindström J. A European evidence-based guideline for the prevention of type 2 diabetes. Horm Metab Res 2010;42 Suppl 1:S3-36.

[9] Wolever TM, Chiasson JL, Csima A, Hunt JA, Palmason C, Ross SA, Ryan EA: Variation of postprandial plasma glucose, palatability, and symptoms associated with a standardized mixed test meal versus 75 g oral glucose. Diabetes Care 1998;21:336-340.

[10] Meier JJ, Baller B, Menge BA, Gallwitz B, Schmidt WE, Nauck MA. Excess glycaemic excursions after an oral glucose tolerance test compared with a mixed meal challenge and self-

measured home glucose profiles: is the OGTT a valid predictor of postprandial hyperglycaemia and vice versa? Diabetes Obes Metab 2009;11:213-222.

[11] Holst JJ, Deacon CF. Inhibition of the activity of dipeptidyl-peptidase IV as a treatment for type 2 diabetes. Diabetes 1998;47:1663-1670.

[12] Crepaldi G, Carruba M, Comaschi M, Del Prato S, Frajese G, Paolisso G. Dipeptidyl peptidase 4 (DPP-4) inhibitors and their role in Type 2 diabetes management. J Endocrinol Invest 2007;30:610-614.

[13] American Diabetes Association. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2018. Diabetes Care 2018;41(Suppl 1):S13-S27.

[14] Danne T, Nimri R, Battelino T et al. International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 2017;40:1631-1640.

[15] Cavalot F, Petrelli A, Traversa M, Bonomo K, Fiora E, Conti M, et al. Postprandial blood glucose is a stronger predictor of cardiovascular events than fasting blood glucose in type 2 diabetes mellitus, particularly in women: lessons from the San Luigi Gonzaga Diabetes Study. J Clin Endocrinol Metab 2006;91:813-819.

[16] Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, et al. Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. Diabetologia 1996;39:1577-1583.

[17] Ceriello A, Colagiuri S, Gerich J, Tuomilehto J, Guideline Development Group. Guideline for management of postmeal glucose. *Nutr Metab Cardiovasc Dis* 2008;**18**:S17-33.

[18] Valensi P, Schwarz E, Hall M, Felton AM, Maldonato A, Mathieu C. Pre-diabetes essential action: a European perspective. Diabetes Metab 2005;31:606-620.

[19] Hernan WH, Brandle M, Zhang P, Williamson DF, Matulik MJ, Ratner RE, Lachin JM, Engelgau MM; Diabetes Prevention Program Research Group. Costs associated with the

primary prevention of type 2 diabetes mellitus in the diabetes prevention program. Diabetes Care 2003;26:36-47.

[20] DeFronzo RA. Current issues in the treatment of type 2 diabetes. Overview of newer agents: where treatment is going. Am J Med 2010;123(3):S38–48.

[21] Amori RE, Lau J, Pittas AG: Efficacy and safety of incretin therapy in type 2 diabetes: systematic review and meta-analysis. Jama 2007; 298:194-206.

[22] Wang Z, Xu D, Huang L, Zhang T, Wang J, Chen Q, Kong L, Zhou X. Effects of saxagliptin on glucose homeostasis and body composition of obese patients with newly diagnosed pre-diabetes. Diabetes Res Clin Pract 2017;130:77-85.

[23] Nahon KJ, Doornink F, Straat ME et al. Effect of sitagliptin on energy metabolism and brown adipose tissue in overweight individuals with prediabetes: a randomised placebo-controlled trial. Diabetologia 2018;61:2386-2397.

[24] Hage C, Brismar K, Efendic S, Lundman P, Rydén L, Mellbin L. Sitagliptin improves beta-cell function in patients with acute coronary syndromes and newly diagnosed glucose abnormalities--the BEGAMI study. J Intern Med 2013;273:410-421.

[25] le Roux CW, Astrup A, Fujioka K, Greenway F, Lau DCW, Van Gaal L, Ortiz RV, Wilding JPH, Skjøth TV, Manning LS, Pi-Sunyer X; SCALE Obesity Prediabetes NN8022-1839 Study Group. 3 years of liraglutide versus placebo for type 2 diabetes risk reduction and weight management in individuals with prediabetes: a randomised, double-blind trial. Lancet 2017;389(10077):1399-1409.

[26] Pratley RE, Nauck M, Bailey T, Montanya E, Cuddihy R, Filetti S, Thomsen AB, Søndergaard RE, Davies M; 1860-LIRA-DPP-4 Study Group. Liraglutide versus sitagliptin for patients with type 2 diabetes who did not have adequate glycaemic control with metformin: a 26-week, randomised, parallel-group, open-label trial. Lancet 2010;375(9724):1447-1456.

[27] Ceriello A, Monnier L, Owens D. Glycaemic variability in diabetes: clinical and therapeutic implications. Lancet Diabetes Endocrinol 2018.

[28] Fysekidis M, Cosson E, Banu I, Duteil R, Cyrille C, Valensi P. Increased glycemic variability and decrease of the postprandial glucose contribution to HbA1c in obese subjects across the glycemic continuum from normal glycemia to first time diagnosed diabetes. Metabolism 2014;63:1553-1561.

[29] Guerci B, Monnier L, Serusclat P, Petit C, Valensi P, Huet D, Raccah D, Colette C, Quéré S, Dejager S. Continuous glucose profiles with vildagliptin versus sitagliptin in add-on to metformin: results from the randomized Optima study. Diabetes Metab 2012;38:359-366.

[30] Scirica BM, Braunwald E, Raz I, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Heart failure, saxagliptin, and diabetes mellitus: observations from the SAVOR-TIMI 53 randomized trial. Circulation 2014;130:1579-1588.

[31] Koska J, Osredkar T, D'Souza K, Sands M, Sinha S, Zhang W, et al. Effects of saxagliptin on adipose tissue inflammation and vascular function in overweight and obese people: a placebo-controlled study. Diabet Med 2019;36:1399-1407.

Legends of figures

Figure 1: Effect of saxagliptin treatment on metabolic parameters and inflammatory parameters after standard breakfast

Data are mean ± SD

A) Plasma glucose at fasting and after breakfast during Visit 1: between groups, p<0.02; time effect, p<0.0001; time*treatment interaction, p=0.0003; and during Visit 2: between groups, p<0.01; time effect, p<0.0001; time*treatment interaction, p=0.009.

B) Insulin at fasting and after breakfast during Visit 1: between groups, p=0.74; time effect, p<0.0001; time*treatment interaction, p=0.30); and during Visit 2: between groups, p=0.72; time effect, p<0.0001; time*treatment interaction, p=0.36.

C) Triglycerides at fasting and after breakfast during Visit 1: between groups, p=0.71; time effect, p<0.02; time*treatment interaction, p=0.15; and during Visit 2: between groups, p=0.70; time effect, p=0.32; time*treatment interaction, p=0.78.

D) Free fatty acids (FFA) at fasting and after breakfast during Visit 1: between groups, p=0.16; time effect, p<0.0001; time*treatment interaction, p=0.30; and during Visit 2: between groups, p=0.50; time effect, p<0.0001; time*treatment interaction, p=0.81.

E) Interleukin 6 (IL 6) at fasting and after breakfast during Visit 1: between groups, p=0.20; time effect, p=0.27; time*treatment interaction, p=0.39; and during Visit 2: between groups, p=0.19; time effect, p=0.99; time*treatment interaction, p=0.70.

F) CRP us at fasting and after breakfast during Visit 1: between groups, p=0.89; time effect, p<0.004; time*treatment interaction, p=0.12; and during Visit 2: between groups, p=0.71; time effect, p<0.002; time*treatment interaction, p=0.47

Figure 2: Results of oral glucose tolerance test before inclusion and at the end of study (Visit 3)

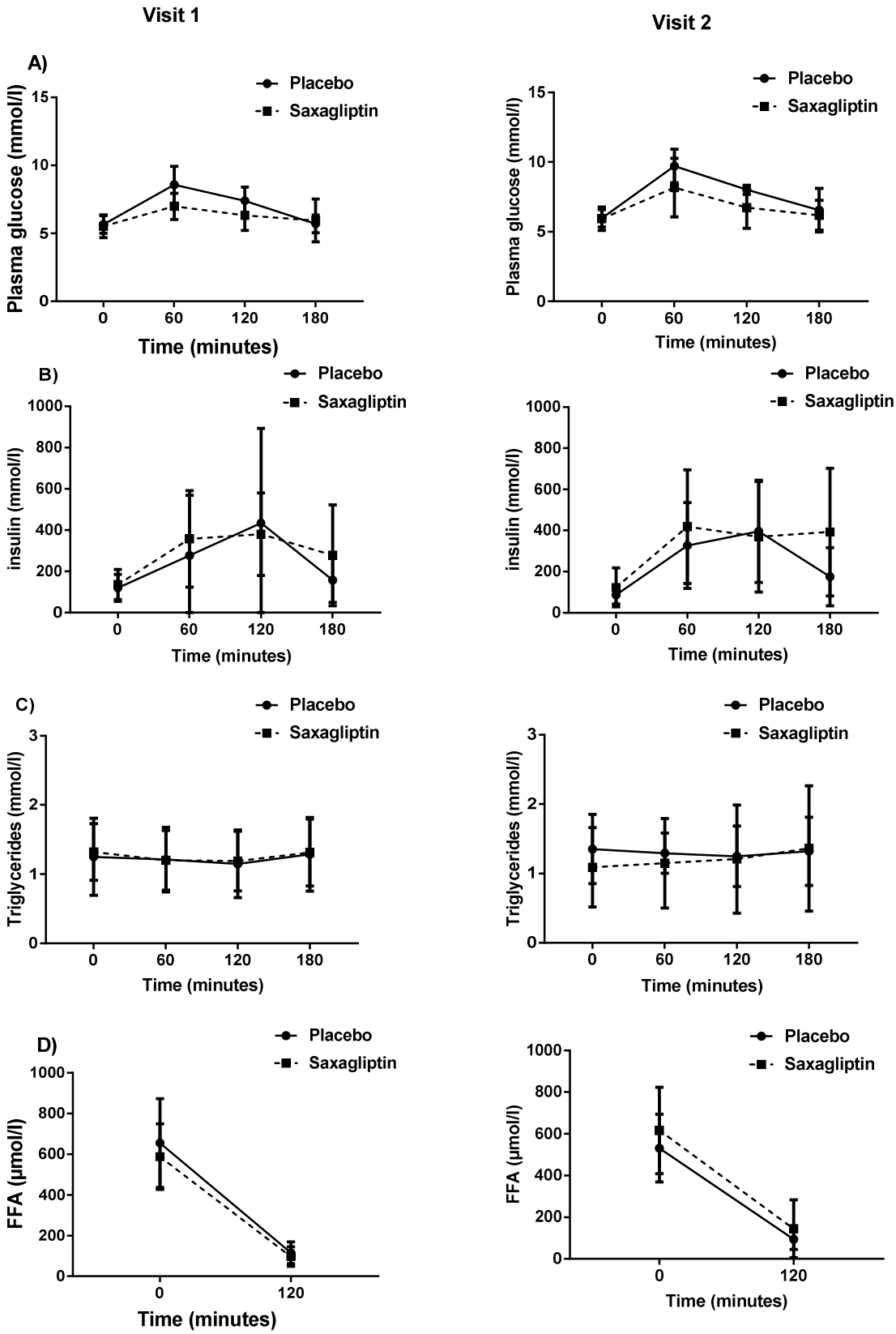
Data are mean ± SD

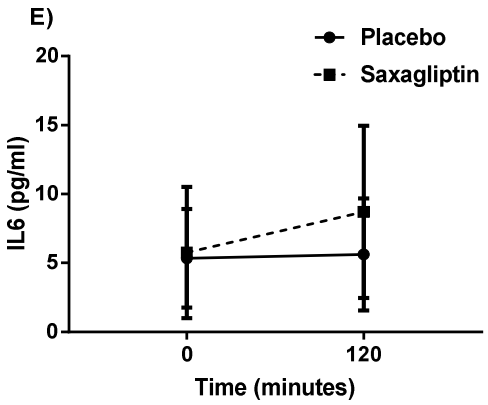
A) Plasma glucose response to OGTT before inclusion: between groups, p=0.88

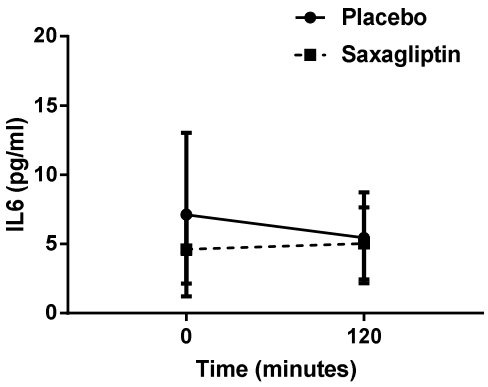
B) Plasma glucose response to OGTT after 12 weeks of saxagliptin or placebo: between groups, $p<0.05$

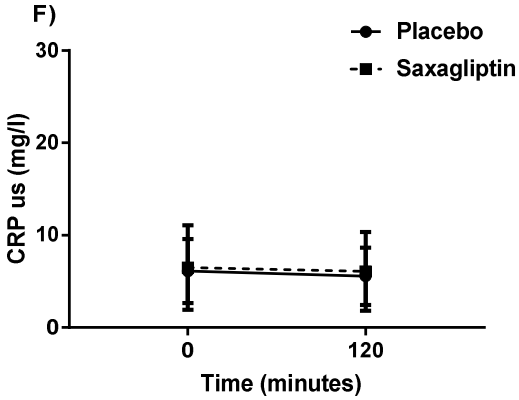
Supplementary Figure 1: ACCES glucose, study protocol

OGTT: oral glucose tolerance test. IGT: impaired glucose tolerance


Visit 1
Visit 2
A)
Placebo
Saxagliptin
Plasma glucose (mmol/l)
Time (minutes)
B)
insulin (mmol/l)
C)
Triglycerides (mmol/l)
D)
FFA (µmol/l)
0
60
120
180


E)
Placebo
Saxagliptin
IL6 (pg/ml)
20
15
10
5
0
0
120
Time (minutes)


Placebo
Saxagliptin
IL6 (pg/ml)
20
15
10
5
0
0
120
Time (minutes)


F)
Placebo
Saxagliptin
CRP us (mg/l)
30
20
10
0
0
120
Time (minutes)

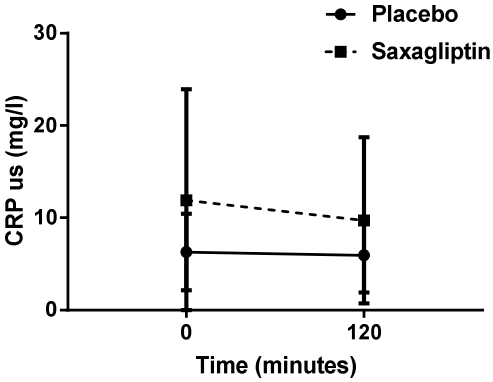

Placebo
Saxagliptin
CRP us (mg/l)
30
20
10
0
0
120
Time (minutes)

Figure 2

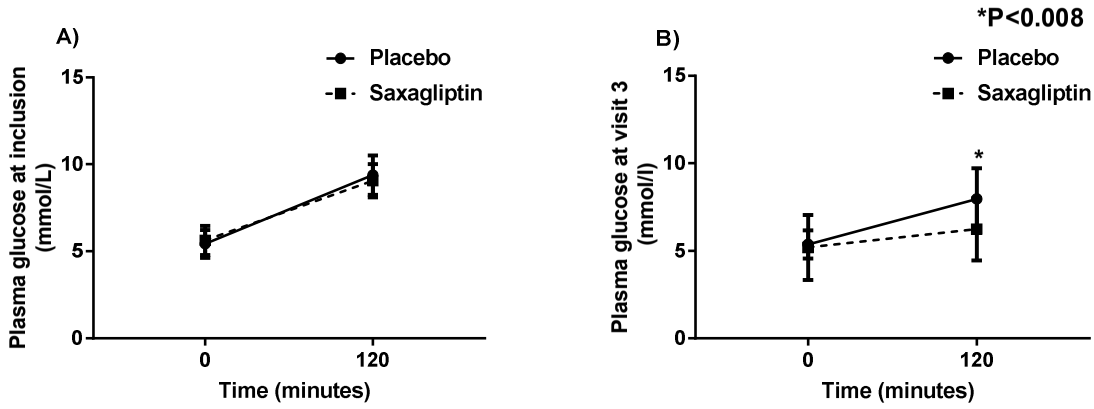

A)
Placebo
Saxagliptin
Plasma glucose at inclusion (mmol/L)
15
10
5
0
0
120
Time (minutes)
B)
*P<0.008
Placebo
Saxagliptin
Plasma glucose at visit 3 (mmol/l)
*
15
10
5
0
0
120
Time (minutes)

Table 1: Patients' characteristics at inclusion

	Placebo (n=12)	Saxagliptin (n=12)	Total (n=24)
Age (years)	49.8 ± 14.6	40.0 ± 10.7	44.9 ± 13.5
Female gender (%)	9 (75)	10 (83.3)	19 (79.2)
Body mass index (kg/m²)	36.2± 5.6	37.4 ± 4.1	36.8 ± 4.9
Weight (kg)	97.2 ± 14.5	107.5 ± 18.5	102.3 ± 17.1
Height (cm)	163.9 ± 6.5	169.0 ± 10.0	166.5 ± 8.6
Waist circumference (cm)	108.1 ± 9.1	114.3 ± 13.4	111.2 ± 11.7
Systolic Blood Pressure (mmHg)	125.6 ± 14.6	120.6 ± 11.0	123.1 ± 12.9
Diastolic Blood Pressure (mmHg)	75.3 ± 9.3	74.0 ± 7.1	74.6 ± 8.1
Hypertension (%)	3 (25)	5 (41.7)	8 (33.3)
Dyslipidemia (%)	1 (8.3)	0 (0)	1 (4.2)
Smokers (%)	2 (16.7)	0 (0)	2 (8.3)
Obstructive sleep apnea syndrome (%)	1 (8.3)	1 (8.3)	2 (8.3)

Data are n (%) or mean ± SD

Table 2: Metabolic and hormonal parameters at fast during Visit 1 and Visit 2, saxagliptin *vs* placebo

	Visit 1		Comparison at baseline	Visit 2		Treatment effect*
	Placebo	**Saxagliptin**	**p value**	**Placebo**	**Saxagliptin**	**p value**
HbA1c (%)	5.63 ± 0.38	5.70 ± 0.52	0.709	5.65 ± 0.41	5.73 ± 0.41	0.690
HbA1c (mmol/mol)	38±2.6	39±3.5	0.709	38±2.7	39±2.8	0.690
Fructosamine (µmol/L)	222 ± 21	221 ± 23	0.892	225 ± 18	222 ± 22	0.728
Total cholesterol (mmol/L)	4.99 ± 0.64	4.91 ± 0.71	0.772	4.91 ± 0.74	5.01 ± 0.99	0.818
HDL-c (mmol/L)	1.30 ± 0.26	1.24 ± 0.26	0.589	1.39 ± 0.24	1.34 ± 0.28	0.724
LDL-c (mmol/L)	3.15 ± 0.54	3.07 ± 0.62	0.731	2.94 ± 0.75	2.59 ± 0.79	0.345
Leptin (ng/ml)	36.7 ± 27.4	49.5 ± 18.1	0.208	36.0 ± 25.2	48.2 ± 18.5	0.208
Adiponectin (µg/ml)	4.2 ± 2.3	4.3 ± 2.1	0.906	5.0 ± 2.5	4.8 ± 2.2	0.821
Plasma creatinine (µmol/L)	73.1 ± 10.5	68.9 ± 13.5	0.439	69.6 ± 10.8	65.4 ± 13.1	0.499
Creatinine clearance* (ml/min)	89.8 ± 16.0	103.8 ± 28.9	0.190	95.8 ± 17.2	108.2 ± 20.7	0.203

Data are mean ± SD. HDL-c: high-density lipoprotein cholesterol; LDL-c: low-density lipoprotein cholesterol. * Modification of diet in renal disease formula

No significant differences for any parameter were found at fasting at Visit 1 and Visit 2, or between the 2 visits (all $p > 0.05$).

Table 3: Acute saxagliptin effect on 24h glucose variability indexes and glucose variability during 3 hours after breakfast during Visit 1

		Placebo (n=11)	Saxagliptin (n=12)	P
24-hour CGM data	**Mean glucose (mmol/L)**	5.5±0.5	5.8±0.9	0.355
	SD glucose (mmol/L)	0.8±0.3	1.0±0.4	0.336
	CV%	14.5±4.0	16.2±5.6	0.546
	CONGA	4.9±0.5	5.3±0.7	0.122
	MAGE	2.1±0.8	2.3±1.1	0.646
3-hour CGM data	**Mean glucose (mmol/L)**	7.4±1.7	6.7±1.3	0.223
	SD glucose (mmol/L)	0.9±0.2	0.5±0.2	0.003
	CV%	12.1±3.5	7.4±3.3	0.006
	AUC glucose	1275±300	112±210	0.313
	Peak glucose	8.8±1.8	7.7±1.6	0.147

Data are mean ± standard deviation (SD)

AUC: area under the curve; CGM: continuous glucose monitoring; CV%: coefficient of variation of glucose (CV% = (SD-glucose / Mean-glucose) *100); CONGA: continuous overall net glycemic action; MAGE: mean amplitude of glycemic excursions.

Table 4: Glucose variability during the 3 hours following standardized breakfast at Visit 1 by having recovered normal glucose tolerance or having still impaired glucose tolerance at the end of the study

	Patients who recovered a normal glucose tolerance at Visit 3 (n=13)	**Patients who had still impaired glucose tolerance at Visit 3 (n=6)**	**P**
Mean glucose (mmol/L)	6.8±1.2	8.5±1.8	0.042
SD glucose (mmol/L)	0.6±0.3	0.9±0.1	0.025
CV%	8.4±4.4	11.6±.2.6	0.131
AUC glucose	1166±208	1452±307	0.032
Glucose peak	7.9±1.6	9.9±1.6	0.030

Data are mean ± standard deviation (SD)

AUC: area under the curve; CV%: coefficient of variation of glucose (CV% = (SD-glucose / Mean-glucose) *100).