Pleiotropic effects of sitagliptin versus voglibose in patients with type 2 diabetes inadequately controlled via diet and/or a single oral antihyperglycemic agent: a multicenter, randomized trial

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ABSTRACT

Purpose: A step-up strategy for diet therapy and/or single oral antihyperglycemic agent (OHA) regimens has not yet been established. The aim of this study was to evaluate hemoglobin A1c (HbA1c) as a primary end point, and the pleiotropic effects on metabolic and cardiovascular parameters as secondary end points, of sitagliptin versus voglibose in patients with type 2 diabetes with inadequate glycemic control while on diet therapy and/or treatment with a single OHA.

Methods: In this multicenter, randomized, open-label, parallel-group trial, a total of 260 patients with inadequately controlled type 2 diabetes (HbA1c levels $>$6.9%) were randomly assigned to receive either sitagliptin (50 mg, once daily) or voglibose (0.6 mg, thrice daily) for 12 weeks. The primary end point was HbA1c levels.

Results: Patients receiving sitagliptin showed a significantly greater decrease in HbA1c levels (-0.78 $\pm$0.69%) compared with those receiving voglibose (-0.30$\pm$0.78%). Sitagliptin treatment also lowered serum alkaline phosphatase levels and increased serum creatinine, uric acid, cystatin-C and homeostasis model assessment-$\beta$ values. Voglibose increased low-density lipoprotein-cholesterol levels and altered serum levels of several fatty acids, and increased $\Delta$-5 desaturase activity. Both drugs increased serum adiponectin. The incidence of adverse events (AEs) was significantly lower in the sitagliptin group, due to the decreased incidence of gastrointestinal AEs.

Conclusions: Sitagliptin shows superior antihyperglycemic effects compared with voglibose as a first-line or second-line therapy. However, both agents possess unique pleiotropic effects that lead to reduced cardiovascular risk in Japanese people with type 2 diabetes.

Trial registration number: UMIN 00003503.

Key messages

- This study directly compared a hemoglobin A1c and the pleiotropic effects of sitagliptin with voglibose added to concurrent treatment in Japanese patients with type 2 diabetes who could not achieve adequate glycemic control through diet therapy or a single OHA. Compared to voglibose, sitagliptin was superior to voglibose in lowering Hb1Ac levels in monotherapy and in combination therapy.
- Sitagliptin, but not voglibose, might impair renal function. Sitagliptin significantly increased serum Cr and cys-C decreased estimated glomerular filtration rate average.
- Sitagliptin significantly decreased polyunsaturated fatty acids, especially e6 fatty acids, whereas voglibose altered serum levels of many kinds of fatty acids. Voglibose, but not sitagliptin, increased $\Delta$-5 desaturase activity. Both sitagliptin and voglibose exert significant unique pleiotropic effects on surrogate cardiovascular risks.

INTRODUCTION

Recent large-scale clinical trials have suggested that intensive antidiabetic therapies that cause unnecessary hyperinsulinemia do not achieve satisfactory cardiovascular outcomes in people with type 2 diabetes, as they may lead to hypoglycemia and weight gain.1 To avoid these problems, incretin-based agents that do not provoke unnecessary hyperinsulinemia have been developed, and are generally used as second- or third-line therapies, in addition to metformin, in Western countries.2 However, to date, limited
clinical evidence is available regarding incretin-based agents as first-line or second-line antihyperglycemic therapies.

Sitagliptin is an inhibitor of dipeptidyl peptidase-4 (DPP-4), which subsequently prevents enzymatic inactivation of endogenous glucagon-like peptide-1 (GLP-1) and thus improves glycemic control in type 2 diabetes. Sitagliptin has proven effective both as a monotherapy and in combination with other oral antihyperglycemic agents, although it is thought to be more effective in Asian patients than in Caucasian patients. However, the majority of studies on sitagliptin monotherapy and combination therapy are based on non-Japanese patients, and its pleiotropic effects have not been investigated extensively, especially in Japanese patients.

Voglibose is an α-glucosidase inhibitor widely used to improve postprandial hyperglycemia. The antidiabetic actions of voglibose may be mediated, at least in part, by endogenous incretins because an α-glucosidase inhibitor may increase GLP-1 levels both by inhibiting DPP-4 activity and by delaying intestinal absorption of a meal. However, the differences between sitagliptin and voglibose are unknown from the perspective of understanding pleiotropic effects.

The aim of this study was to evaluate hemoglobin A1c (HbA1c) as a primary end point, and the pleiotropic effects on metabolic and cardiovascular parameters as secondary end points, of sitagliptin versus voglibose in Japanese patients with type 2 diabetes who were unable to achieve adequate glycemic control via diet therapy and/or OHA monotherapy. Notably, dynamic randomization was used to adjust for demographic differences between the groups.

**RESEARCH DESIGN AND METHODS**

**Overview**

This was a randomized, parallel-group study conducted on Japanese patients. The study was designed in accordance with the principles stated in the Declaration of Helsinki, and the protocol was reviewed and approved by the appropriate institutional review board for each study site. All patients provided written informed consent before participation.

A total of 260 type 2 diabetes patients who were unable to achieve adequate glycemic control via diet therapy and/or OHA monotherapy were recruited from 19 centers in Japan between May 2011 and August 2012. Type 2 diabetes was diagnosed according to WHO criteria, based on a 2 h plasma glucose value of >11.1 mmol/L. Inadequate disease control was defined as having a HbA1c level >6.9%. The trial was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (registration number UMIN000003503).

**Patient eligibility**

Participants were eligible if they were at least 20 years old, had type 2 diabetes mellitus, poorly controlled diabetes (HbA1c levels >6.9% within 12 weeks before screening), and had been treated with diet therapy and/or a single OHA, such as sulfonylurea (SU), biguanide (BG) or thiazolidinedione (TZD) class drugs, for 12 weeks or longer.

Exclusion criteria were: (1) hypersensitivity or a contraindication to sitagliptin or voglibose; (2) history of type 1 diabetes; (3) history of ketoacidosis; (4) having experienced symptoms of hypoglycemia; (5) treatment with sitagliptin or voglibose within 12 weeks before screening; (6) treatment with insulin within 12 weeks before screening; (7) concomitant corticosteroid therapy; (8) poorly controlled or unstable diabetes (the state with ketoacidosis or with an increase in HbA1c >3% in the 12 weeks before screening); (9) alanine aminotransferase and/or aspartate aminotransferase levels more than 2.5-fold the upper limit of normal; (10) poorly controlled hypertension or systolic blood pressure >160 mm Hg or diastolic blood pressure >100 mm Hg; (11) presence of a severe health problem not suitable for the study; (12) pregnancy or breastfeeding; or (13) inability to participate in the study due to psychiatric or psychosocial status as assessed by the investigators.

**Efficacy endpoints**

A computer-generated randomization sequence was used to assign participants in a 1:1 ratio to either the sitagliptin or voglibose treatment group. Dynamic randomization was used to adjust for demographic differences (age, previous treatment for type 2 diabetes and HbA1c level) between the groups. In this active-comparator, parallel-group trial, eligible patients received either sitagliptin or voglibose in addition to their previous treatment for 12 weeks. Sitagliptin (Merck & Co, Inc, New Jersey, USA) was initiated and maintained at 50 mg once daily. Voglibose (Takeda Pharmaceutical Company Limited, Osaka, Japan) was initiated and maintained at 0.6 mg (0.2 mg with each meal). Other medications were unchanged during the study period.

The primary efficacy end point was the change in Hb1Ac levels from baseline over the 12-week period. Secondary end points recorded at baseline and week 12 included: fasting plasma glucose (FPG); serum creatinine (Cre); uric acid; alkaline phosphatase (ALP); bone alkaline phosphatase (BAP); cystatin-C (cys-C), 1,5-anhydroglucitol (1,5-AG), fasting serum insulin (IRI), fasting serum proinsulin, fasting C-peptide immunoreactivity (CPR), factors related to fasting lipid profile (including small dense low-density lipoprotein, low-density lipoprotein-cholesterol, adiponectin, tumour necrosis factor α (TNF-α) and leptin); blood pressure; and physical measures (waist circumference, body mass index (BMI)). The estimated glomerular filtration rates based on serum Cre (eGFRcreat) and serum cys-C (eGFRcys), and the average estimated glomerular filtration rate (eGFRaverage), were calculated using the following formulas: 

\[ eGFRcreat = 194 \times (\text{Cre})^{-1.094} \times \text{Age}^{-0.287} \]

\[ eGFRcys = 0.85 \times eGFRcreat \]

\[ eGFRaverage = (eGFRcreat + eGFRcys) / 2 \]
eGFRcys=(104×Cystatin C−wascalculatedas(IRI(μL/mmol/L)/22.5).12

was used as a conventional index for insulin resistance and stasis model assessment of insulin resistance (HOMA-IR).12 To assess basic insulin secretion by β cells, CPR index (CPI), homeostasis model assessment-β (HOMA-β), secretory unit of islet in transplantation index (SUIT index) and quantitative insulin sensitivity check index (QUICKI), were calculated as follows: CPI=(100×fasting CPR (ng/mL))/ FPG (mg/dL))13

HOMA-β=(IRI (IU/L)×20/FPG(mg/dL)−63)).14

SUIT index=(1500×CPR (ng/mL)/ (FPG (mg/dL) −63))15 and QUICKI=(1/[log IRI(IU/L)+log FPG (mg/dL)]).16

Serum fatty acid levels were measured as a secondary outcome. A serum sample (approximately 0.2 mL) and 2 mL of a chloroform-methanol solution (2:1) were placed in a Pyrex centrifuge tube, homogenized with a Polytron homogenizer (PCU-2110; KINEMATICA GmbH, Switzerland) and centrifuged at 3000 rpm for 10 min. An aliquot of the chloroform-methanol extract was transferred to another Pyrex tube and dried under a stream of nitrogen gas. The dried sample was dissolved in 100 µL of 0.4 M potassium methoxide methanol/14% boron trifluoride-methanol solution, and the fatty acid concentrations were measured at SRL Inc (Tokyo, Japan), using a gas chromatograph (Shimizu GC 17A, Kyoto, Japan). Desaturase activities were estimated as follows: Δ5 desaturase, C20:4ω6/C20:3ω6; Δ6 desaturase, 18:3ω6/18:2ω6.17

Medication adherence and adverse events were monitored throughout the study, and were rated by investigators for intensity and relationship to study drug.

**Statistical analysis**
The sample size required to detect a ~0.6% change in HbA1c levels in the sitagliptin group, and a ~0.4% change in the voglibose group, with a power of 80% (α=0.05, one-tailed; β=0.20) and standardized effect size of 0.6, was 112 participants in each group. Taking into account a dropout rate of 15%, we aimed to recruit 260 participants. All analyses used the full analysis set, which included all patients who received at least one dose of study drug and for whom data were available at baseline and from at least one postrandomization time point. Missing data were replaced by the last observed value of each variable in this analysis. Data were expressed as the mean±SD. The Statistical Package for the Social Sciences (SPSS) V22.0 (SPSS Inc, Chicago, Illinois, USA) was used for the statistical analyses. Parameters were analyzed using the Wilcoxon signed-rank test in the internal group comparison, the χ² test or the Mann-Whitney U-test, or the Kruskal-Wallis test, in the intergroup comparison. Associations between variables were assessed using Spearman’s rank correlation coefficient. Multiple regression analysis was carried out to determine independent factors for changes in HbA1c by sitagliptin or voglibose. p Values <0.05 were considered statistically significant.

**RESULTS**

**Patient characteristics**

A total of 260 patients were screened and randomly assigned to either the sitagliptin or voglibose regimen, and 241 participants (mean age, 63.2±12.7 years; mean BMI, 25.0±4.5 kg/m²) were enrolled in this study (table 1). Nineteen patients were removed after randomisation before the intervention because they withdrew consent (n=17) or did not meet inclusion criteria (n=2; see online supplementary figure S1). No participants took EPA or docosahexaenoic acid (DHA) before or during the study and other subject medications remained unchanged during the study period. One hundred and sixteen patients received diet therapy; 61 patients received SU, 57 patients received BG and seven patients received TZD. FPG and HbA1c levels were 154.7±35.1 mg/dL and 7.9±0.78%, respectively. Baseline demographics and disease characteristics of the two groups did not differ significantly (table 1). The serum TNF-α levels at baseline included two outliers in the sitagliptin group. The median was similar in the two groups (Sitagliptin versus Voglibose, 1.20 vs 1.10 (pg/mL)) and there was no significant difference in the Mann-Whitney U test (p=0.166).

**Clinical outcomes**

Compared to baseline, FPG and HbA1c levels decreased significantly in both groups at the end of the study (table 2). Sitagliptin was superior to voglibose in lowering HbA1c levels (~0.78±0.69 vs ~0.30±0.78%, respectively) and FPG concentrations (~16.2±26.4 vs ~4.4 ±38.7 mg/dL, respectively) relative to baseline. There was no significant difference of medication adherence between the groups (table 1). In addition, in the stratified analysis on good (>80%) and poor (≤80%) adherence, adherence rate did not affect these results (see online supplementary table S1).

Both agents significantly increased 1,5-AG concentrations, but voglibose was superior to sitagliptin in this regard. Sitagliptin, but not voglibose, increased indices for insulin secretion such as HOMA-β, SUIT and CPI. Both agents lowered proinsulin levels and both agents exerted marked effects on the insulin sensitivity index, QUICKI.

Sitagliptin significantly reduced the counts of lymphocytes (p=0.007) and significantly increased the counts of neutrophils (p=0.008) at week 12, whereas voglibose had no effect on them (table 2). Sitagliptin significantly lowered ALP levels from 290±71 IU/L at baseline to 226 ±76 IU/L at week 12 (p=0.000) without changing bone alkaline phosphatase (BAP), whereas voglibose had no effect on ALP levels. Both agents were almost neutral in their effects on liver enzymes, except that voglibose
Changes in fatty acid composition in serum lipids

Sitagliptin, but not voglibose, significantly decreased serum levels of total polyunsaturated fatty acids, including linoleic acid and total ω6 fatty acids. Voglibose, but not sitagliptin, significantly decreased total saturated fatty acids (including palmitic acid and stearic acid), total monounsaturated fatty acids (including palmitoleic acid and oleic acid) and some polyunsaturated fatty acids (such as γ-linolenic acid, 5,8,11-eicosatrienoic acid, dihomo-γ-linolenic acid, docosatetraenoic acid and docosapentaenoic acid). Voglibose significantly decreased the activity of Δ-6 desaturase and increased that of Δ-5 desaturase (table 4). No correlation was observed between ΔHbA1c and eicosapentaenoic acid (EPA) levels at baseline in the sitagliptin group (table 3).

Adverse events

The incidence of AEs was significantly lower in the sitagliptin group. This difference was attributable to the decreased incidence of gastrointestinal AEs, such as heartburn, abdominal pain, constipation, loose stool, diarrhea, meteorism and flatulence. Most AEs were mild or moderate but one patient in the voglibose group discontinued the treatment due to diarrhea. The incidence of hypoglycemia was low and similar in both groups. All incidences of hypoglycemia in this study were mild or moderate in severity, but one patient in the sitagliptin group discontinued the treatment due to hypoglycemia. Four serious adverse events (SAEs)—inguinal hernia, heart failure, pancreatitis and urinary tract infection—occurred in the voglibose group, but were considered not related to the study. Due to these SAEs, three patients discontinued the agents (see online supplementary table S2).

DISCUSSION

This study directly compared HbA1c and the pleiotropic effects of sitagliptin with voglibose added to concurrent treatment decreased γ-GTP levels from 49±57 IU/L at baseline to 47±51 IU/L at week 12 (p=0.011). Sitagliptin, but not voglibose, increased serum Cre, uric acid and cys-C. Both agents lowered serum triglyceride levels, whereas voglibose, but not sitagliptin, significantly increased LDL-C. Voglibose significantly increased TNF-α levels, whereas sitagliptin, rather, tended to decrease TNF-α levels. Both agents significantly increased adiponectin levels. In stratified analyses on each concomitant therapy, there was no significant difference in glycemic parameters (see online supplementary figure S2). SU significantly increased neutrophils and decreased diastolic blood pressure compared to BG in the sitagliptin group (data not shown).

Factors predicting the effects of sitagliptin and voglibose are shown in table 3. In the sitagliptin group, there was a significant correlation between ΔHbA1c and baseline levels of 1,5-AG (rs=0.338, p=0.000), HbA1c (rs=0.589, p=0.000) and adiponectin (rs=0.223, p=0.015; supplementary table S2). There was no predicting factor in the voglibose group. In a multiple regression analysis, only baseline HbA1c was the independent factor of ΔHbA1c in the sitagliptin group (β=−0.0525, p=0.000, adjusted R²=0.268).

Changes in fatty acid composition in serum lipids

Sitagliptin, but not voglibose, significantly decreased serum levels of total polyunsaturated fatty acids, including linoleic acid and total ω6 fatty acids. Voglibose, but not sitagliptin, significantly decreased total saturated fatty acids (including palmitic acid and stearic acid), total monounsaturated fatty acids (including palmitoleic acid and oleic acid) and some polyunsaturated fatty acids (such as γ-linolenic acid, 5,8,11-eicosatrienoic acid, dihomo-γ-linolenic acid, docosatetraenoic acid and docosapentaenoic acid). Voglibose significantly decreased the activity of Δ-6 desaturase and increased that of Δ-5 desaturase (table 4). No correlation was observed between ΔHbA1c and eicosapentaenoic acid (EPA) levels at baseline in the sitagliptin group (table 3).
| Parameter                  | Sitagliptin | Voglibose | p Value* | p Value† |
|---------------------------|-------------|-----------|----------|----------|
|                          | Baseline    | 12-week   |          |          |
| Body weight (kg)          | 63.8±13.6   | 63.7±13.3 | 0.842    |          |
| BMI                       | 24.9±4.5    | 24.9±4.4  | 0.777    |          |
| Waist (cm)                | 88.7±10.5   | 88.2±10.0 | 0.195    |          |
| SBP (mm Hg)               | 130.0±16.8  | 129.5±17.1| 0.998    |          |
| DBP (mm Hg)               | 76.0±12.1   | 75.4±12.1 | 0.576    |          |
| WBC (10^3/mm^3)           | 5815±1362   | 6057±1590 | 0.050    |          |
| Neutrophils (/mm^3)       | 3279±1015   | 3570±1096 | 0.008    |          |
| Eosinophils (/mm^3)       | 156±120     | 151±120   | 0.359    |          |
| Basophils (/mm^3)         | 30±23       | 31±23     | 0.395    |          |
| Lymphocytes (/mm^3)       | 1951±607    | 1866±586  | 0.007    |          |
| Monocytes (/mm^3)         | 323±113     | 345±122   | 0.004    |          |
| PLT (10^4/mm^3)           | 21.0±5.5    | 20.8±5.6  | 0.281    |          |
| RBC (10^5/mm^3)           | 458.4±43.7  | 459.2±45.4| 0.723    |          |
| Hb (g/mL)                 | 13.9±1.6    | 14.0±1.8  | 0.943    |          |
| AST (IU/L)                | 26±13       | 26±13     | 0.554    |          |
| ALT (IU/L)                | 32±25       | 30±21     | 0.459    |          |
| ALP (IU/L)                | 236±71      | 226±76    | 0.000    |          |
| BAP (μg/L)                | 12.6±5.6    | 12.3±5.6  | 0.140    |          |
| γ-GTP (IU/L)              | 44±50       | 49.2±87.6 | 0.836    |          |
| CK (IUL)                  | 105.5±71.6  | 105.2±68.0| 0.920    |          |
| BUN (mg/dL)               | 14.9±4.1    | 15.0±4.6  | 0.838    |          |
| Cr (mg/dl)                | 0.7±0.19    | 0.74±0.19 | 0.000    |          |
| UA (mg/dL)                | 5.08±1.4    | 5.30±1.24 | 0.001    |          |
| Cystatin C (mg/L)         | 0.82±0.18   | 0.85±0.19 | 0.001    |          |
| eGFRcreat (ml/min/1.73 m^2) | 85.0±28.4   | 80.6±26.5 | 0.000    |          |
| eGFRcys (ml/min/1.73 m^2) | 91.1±23.2   | 91.1±29.3 | 0.969    |          |
| eGFRaverage (ml/min/1.73 m^2) | 88.0±23.3   | 85.6±24.6 | 0.006    |          |
| TC (mg/dL)                | 185.1±33.4  | 184.9±39.0| 0.910    |          |
| HDL-C (mg/dL)             | 52.7±15.4   | 52.3±14.8 | 0.873    |          |
| Triglyceride (mg/dL)      | 130.0±83.1  | 129.8±85.5| 0.098    |          |
| LDL-C (mg/dL)             | 104.9±29.6  | 106.5±34.1| 0.499    |          |
| sdLDL (mg/dL)             | 36.8±15.4   | 34.9±15.1 | 0.134    |          |
| IRI (μI/L)                | 8.46±8.20   | 8.69±9.37 | 0.342    |          |
| CPR (ng/mL)               | 2.10±0.88   | 2.04±0.84 | 0.421    |          |
| HMW adiponectin (μg/dL)   | 3.17±2.30   | 3.50±2.57 | 0.000    |          |
| Leptin (ng/mL)            | 8.26±6.90   | 8.27±7.17 | 0.561    |          |
| Hypersensitive TNF-α (pg/mL) | 3.11±12.47   | 2.23±5.21 | 0.079    |          |
| Leptinogenic index        | 3.30±3.44   | 2.98±3.02 | 0.056    |          |
| HOMA-IR                   | 36.0±32.8   | 47.2±57.6 | 0.000    |          |
| HOMA-β                    | 39.5±30.4   | 45.9±28.3 | 0.000    |          |

Continued
Table 2  Continued

| Parameter                     | Sitagliptin |          | p Value* | Voglibose |          | p Value* | p Value† |
|-------------------------------|-------------|----------|----------|-----------|----------|----------|----------|
|                               | n Baseline  | 12-week  |          | n Baseline | 12-week  |          |          |
| CPI                           | 117         | 1.41±0.67 | 1.52±0.71| 0.001     | 118      | 1.38±0.68| 1.43±0.78| 0.207    |
| QUICKI                        | 112         | 0.34±0.04 | 0.34±0.04| 0.003     | 116      | 0.34±0.05| 0.34±0.05| 0.080    |
| Proinsulin (pM)               | 112         | 26.9±17.2 | 22.5±14.3| 0.010     | 104      | 26.5±17.9| 25.3±17.4| 0.036    |
| Proinsulin/Insulin Ratio      | 101         | 0.70±0.67 | 0.54±0.33| 0.000     | 91       | 0.63±0.39| 0.65±0.49| 0.698    | 0.015    |
| HbA1c (%)                     | 120         | 7.94±1.03 | 7.15±0.88| 0.000     | 121      | 7.86±0.78| 7.56±1.02| 0.000    | 0.000    |
| 1.5AG (μg/mL)                 | 109         | 6.45±4.16 | 10.55±5.96| 0.000     | 105      | 7.43±5.29| 12.6±8.12| 0.000    | 0.047    |
| FPG (mg/dL)                   | 119         | 156.3±35.1| 140.0±31.7| 0.000     | 119      | 153.2±35.2| 148.0±43.0| 0.000    | 0.006    |

Data are expressed as means±SD.
* p Value for the intragroup comparison (baseline vs 12 weeks).
† p Value for the intergroup comparison (difference in changes from baseline between groups).

ALT, alanine aminotransferase; ALP, alkaline phosphatase; AST, aspartate aminotransferase; BAP, bone alkaline phosphatase; BMI, body mass index; BUN, blood urea nitrogen; CK, creatinine kinase; CPI, CPR index; CPR, C-peptide immunoreactivity; Cr, creatinine; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; Hb, hemoglobin; HDL-c, low-density lipoprotein cholesterol; HMW, high molecular weight; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment-β; IRI, fasting serum insulin; LDL-C, low-density lipoprotein-cholesterol; PLT, platelet; QUICKI, quantitative insulin sensitivity check index; RBC, red blood cell; SBP, systolic blood pressure; sdLDL, small dense low-density lipoprotein; SUIT, secretory unit of islet in transplantation index; TC, total cholesterol; TNF-α, tumour necrosis factor α; UA, uric acid; WBC, white blood cell count.

T2D therapy is as follows: First, dynamic randomization is performed. If, after institution of diet therapy or a single OHA, patients could not achieve adequate glycemic control, we compared sitagliptin with voglibose, not only as a parallel-group study but also as an add-on therapy to SU-26 or TZD. Second, pleiotropic effects of sitagliptin and voglibose include previously yet-recognized actions related to severe renal insufficiency status over the course of the study.30 31

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Both sitagliptin and voglibose significantly increased plasma adiponectin levels, as stated in previous reports. There was a negative correlation between ΔHbA1c and Δadiponectin (table 3), suggesting that glycemic control at least partly contributes to the increase in adiponectin levels. The increased adiponectin levels might improve endothelial function and likely yield antiatherosclerotic effects. In addition, baseline levels of adiponectin were negatively correlated with ΔHbA1c only in the sitagliptin group, suggesting that adiponectin level might be a predictive maker for the effect of sitagliptin in glycemic control. Serum EPA concentrations are reported to be associated with the glucose-lowering effect of DPP-IV inhibitors in Japanese patients with type 2 diabetes. However, in our study, baseline EPA levels were not correlated with the change in HbA1c in the sitagliptin group (table 3). On the other hand, sitagliptin significantly decreased polyunsaturated fatty acids, especially ω-6 fatty acids, whereas voglibose altered serum levels of many kinds of fatty acids, unlike in a previous study with acarbose. Notably, voglibose, but not sitagliptin, increased Δ-5 desaturase activity.

### Table 3 Factors associated with a change in HbA1c

|                                      | Sitagliptin | p Value | Voglibose | p Value |
|--------------------------------------|------------|---------|-----------|---------|
| Baseline Body weight (kg)            | 0.051      | 0.577   | 0.082     | 0.374   |
| Baseline Body mass index             | 0.142      | 0.126   | 0.08      | 0.390   |
| Baseline Fasting plasma glucose (mg/dL) | 0.113    | 0.222   | 0.107     | 0.246   |
| Baseline 1.5 AG (%)                  | 0.338      | 0.000   | 0.034     | 0.714   |
| Baseline HbA1c (%)                   | 0.589      | 0.000   | 0.121     | 0.185   |
| Baseline Total cholesterol (mg/dL)   | 0.050      | 0.588   | 0.009     | 0.948   |
| Baseline Fasting serum insulin (IU/L) | 0.092   | 0.328   | 0.079     | 0.392   |
| Baseline CPR (ng/mL)                 | 0.101      | 0.275   | 0.004     | 0.965   |
| Baseline HMW adiponectin (µg/mL)     | 0.223      | 0.015   | 0.137     | 0.137   |
| Baseline CPI                         | 0.048      | 0.609   | 0.038     | 0.684   |
| Baseline HOMAIR                      | 0.128      | 0.171   | 0.114     | 0.222   |
| Baseline HOMA-β                      | 0.016      | 0.861   | 0.033     | 0.722   |
| Baseline EPA (ng/mL)                 | 0.064      | 0.490   | 0.062     | 0.502   |
| Baseline DHA (ng/mL)                 | 0.077      | 0.118   | 0.078     | 0.396   |

Change from baseline

|                                      | rs         | p Value | rs         | p Value |
|--------------------------------------|------------|---------|------------|---------|
| ΔFPG                                 | 0.386      | 0.000   | 0.421      | 0.000   |
| ΔBW                                  | 0.212      | 0.020   | 0.047      | 0.609   |
| ΔBMI                                 | 0.206      | 0.025   | 0.058      | 0.533   |
| ΔALP                                 | 0.269      | 0.003   | 0.187      | 0.042   |
| ΔTC                                  | 0.231      | 0.011   | 0.062      | 0.502   |
| ΔLDLC                                | 0.266      | 0.004   | 0.151      | 0.103   |
| ΔTG                                  | 0.084      | 0.362   | 0.152      | 0.098   |
| ΔHMW adiponectin                     | 0.310      | 0.001   | 0.346      | 0.000   |
| ΔHOMA-IR                             | 0.233      | 0.012   | 0.105      | 0.262   |
| ΔHOMA-β                              | 0.304      | 0.001   | 0.222      | 0.016   |
| ΔSUIT index                          | 0.377      | 0.000   | 0.261      | 0.004   |
| ΔQUICKI                              | 0.185      | 0.047   | 0.175      | 0.060   |
| ΔCPI                                 | 0.235      | 0.011   | 0.156      | 0.091   |
| ΔProinsulin insulin ratio            | 0.199      | 0.046   | 0.177      | 0.094   |
| ΔEPA                                 | 0.010      | 0.914   | 0.062      | 0.502   |
| ΔDHA                                 | 0.073      | 0.430   | 0.065      | 0.482   |

AG, anhydroglucitol; ALP, alkaline phosphatase; BMI, body mass index; BW, body weight; CPR, C-peptide immunoreactivity; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; HOMA-β, homeostasis model assessment-β; HMW, high molecular weight; LDLC, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglyceride.
| Parameter                        | Sitagliptin | Voglibose |
|---------------------------------|-------------|-----------|
| Lauric acid C12:0 (ng/mL)       | 2.3±1.2     | 2.3±1.2   |
| Myristic acid C14:0 (ng/mL)     | 29.3±18.9   | 28.5±19.3 |
| Palmitic acid C16:0 (ng/mL)     | 74.6±259.6  | 709.8±254.1 |
| Palmitoleic acid C16:1ω7 (ng/mL)| 80.3±46.2   | 77.0±51.6 |
| Stearic acid C18:0 (ng/mL)      | 214.7±53.6  | 212.0±28.7 |
| Oleic acid C18:1ω9 (ng/mL)      | 565.2±236.6 | 653.2±260.1 |
| Linoleic acid C18:2ω6 (ng/mL)   | 774.4±182.1 | 736.3±188.6 |
| γ-linolenic acid C18:3ω6 (ng/mL)| 11.4±6.5    | 10.8±6.0  |
| α-Linolenic acid C18:3ω3 (ng/mL)| 27.6±12.5   | 25.9±11.1 |
| Arachidic acid C20:0 (ng/mL)    | 7.2±1.3     | 7.3±1.6   |
| Eicosanoic acid C20:1ω9 (ng/mL) | 5.5±2.0     | 5.3±2.2   |
| Eicosadienoic acid C20:2ω6 (ng/mL)| 5.9±1.8    | 5.9±2.0   |
| 5-8-11Eicosatrienoic acid C20:3ω9 (ng/mL) | 2.2±1.4 | 2.2±1.6 |
| Dihomo-γ-linolenic acid C20:3ω6 (ng/mL) | 38.8±13.2 | 39.7±16.4 |
| Arachidonic acid C20:4ω6 (ng/mL)| 173.2±46.7  | 172.0±51.3 |
| Eicosapentaenoic acid C20:5ω3 (ng/mL) | 80.6±48.3 | 79.7±43.5 |
| Behenic acid C22:0 (ng/mL)      | 17.6±3.3    | 17.9±3.6  |
| Erucic acid C22:1ω9 (ng/mL)     | 1.6±0.8     | 1.6±0.7   |
| Docosatetraenoic acid C22:4ω6 (ng/mL) | 5.2±2.2   | 5.1±2.6   |
| Docosapentaenoic acid C22:5ω3 (ng/mL) | 25.2±10.0  | 24.3±9.4  |
| Lignoceric acid C24:0 (ng/mL)   | 16.3±2.8    | 16.3±3.3  |
| Docosahexaenoic acid C22:6ω3 (ng/mL) | 175.2±65.3 | 164.5±58.7 |
| Nervonic acid C24:1ω9 (ng/mL)   | 34.8±7.5    | 34.5±7.5  |
| EPA+DHA (ng/mL)                 | 255.9±107.5 | 249.2±92.6 |
| EPA/AA ratio                    | 0.49±0.31   | 0.49±0.30 |
| Total ω3 fatty acids (ng/mL)    | 308.7±121.9 | 299.0±105.3 |
| Total ω6 fatty acids (ng/mL)    | 1008.7±224.8| 968.9±237.7 |
| Total ω9 fatty acids (ng/mL)    | 700.2±39.2  | 696.8±263.6 |
| ω3/ω6 ratio                    | 0.32±0.13   | 0.32±0.11 |
| Total saturated fatty acids (ng/mL) | 1034.9±330.7 | 994.1±330.3 |
| Monounsaturated fatty acids (ng/mL) | 778.3±276.8 | 771.7±305.2 |
| Polyunsaturated fatty acids (ng/mL) | 1319.5±277.3 | 1270.9±289.2 |
| δ-5desaturase (20:4ω6/20:3ω6)   | 4.73±1.42   | 4.72±1.62 |
| δ-6desaturase (18:3ω6/18:2ω6)   | 0.015±0.008 | 0.015±0.007 |

Data are expressed as means±SD.

*p Value for the intragroup comparison (baseline vs 12 weeks).

†p Value for the intergroup comparison (difference in changes from baseline between groups).

AA, arachidonic acid; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid.
the study duration may be insufficient to evaluate some of the pleiotropic effects. In the subgroup analysis, concomitant antidiabetic agents did not affect the results in glycomic parameters.

In summary, we showed that sitagliptin is superior to voglibose in terms of improving glycomic control as a glycemic parameter.

**Contributors** TT is the guarantor of this study and, as such, had full access to all of the data, and takes responsibility for the integrity and accuracy of the data and the analysis. YM designed the study, analysed and interpreted the data. The manuscript was written, analysed and interpreted the data, and wrote the manuscript. YT designed the study, recruited the patients, collected clinical information, analysed and interpreted the data, and wrote the manuscript. YK, TO, KK, HT-W, HA, AS, EH, YN and TK collected clinical information, analysed and interpreted the data and wrote the manuscript. YM designed the study, analysed and interpreted the data and wrote the manuscript.

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**Patient consent** Obtained.

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