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

Yukiko Matsushima,1,2,3 Yumie Takeshita,1,2,3 Yuki Kita,1,3 Toshiki Otoda,1,3 Ken-ichiro Kato,1,3 Hitomi Toyama-Wakakuri,1,3 Hiroshi Akahori,3 Akiko Shimizu,3 Erika Hamaguchi,3 Yasuyuki Nishimura,3 Takehiro Kanamori,1,3 Shuichi Kaneko,2 Toshinari Takamura1,2,3

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 ±0.69%) compared with those receiving voglibose (−0.30±0.78%). Sitagliptin treatment also lowered serum alkaline phosphatase levels and increased serum creatinine, uric acid, cystatin-C and homeostasis model assessment-β values. Voglibose increased low-density lipoprotein-cholesterol levels and altered serum levels of several fatty acids, and increased Δ-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 patients with type 2 diabetes.

Trial registration number: UMIN 00003503.
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 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.

**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 HbA1c 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 immunoactivity (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 cystatin-C (eGFRCys), and the average estimated glomerular filtration rate (eGFraverage), were calculated using the following formulas: eGFRcreat=194×Cr−1.094×Age−0.287
(males) or \(194\times\text{Cr}^{-1.094}\times \text{Age}^{-0.287}	imes 0.739\) (females); eGFRcys=(104×Cystatin C \(^{−1.019}\times 0.996^{\text{sex}}\)−8 (males) or \(104\times\text{Cystatin C}^{-1.019}\times 0.996^{\text{sex}}\times 0.929\)−8 (females); eGFRaverage=((eGFRcreat+eGFRcys)/2). The homeostasis model assessment of insulin resistance (HOMA-IR) was used as a conventional index for insulin resistance and was calculated as \((\text{IRI (IU/mL)} \times \text{FPG (mmol/L)})/22.5\). \(^{12}\)

To assess basic insulin secretion by \(\beta\) cells, CPR index (CPI), homeostasis model assessment-\(\beta\) (HOMA-\(\beta\)), 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))/FGP (mg/dL)). \(^{13}\)

HOMA-\(\beta\)=(IRI (IU/L)×20)/(FPG (mg/dL)−63)). \(^{14}\)

SUIT index=(1500×CPR (ng/mL)/(FGP (mg/dL)−63))\(^{15}\) and \(\text{QUICKI}=1/(\log \text{IRI(IU/L)}+\log \text{FGP (mg/dL)})\). \(^{16}\)

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-2-110; 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 \(\mu\)L of 0.4 M potassium methoxide methanol/14% boron trifluoride-methanol solution, and the fatty acid concentrations were measured at SRL Inc (Tokyo, Japan). Desaturase activities were estimated as follows: \(\Delta 5\) desaturase, C20:4ω6/C20:3ω6; \(\Delta 6\) 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\% (\(\alpha=0.05\), one-tailed; \(\beta=0.20\)) 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) V.22.0 (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 \(\chi^2\) 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/m\(^2\)) 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±0.9\%, respectively. Baseline demographics and disease characteristics of the two groups did not differ significantly (table 1). The serum TNF-\(\alpha\) 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 \(-0.30±0.78\%, \text{respectively}\)) and FPG concentrations (\(-16.2±26.4\text{ vs }-4.4±38.7\text{ mg/dL}, \text{respectively}\) relative to baseline. There was no significant difference of medication adherence between the groups (table 1). In addition, in the stratified analysis on good (\(\geq0.80\%\)) and poor (\(<0.80\%\)) 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-\(\beta\), 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 296±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


BMJ Open Diab Res Care: first published as 10.1136/bmjdrcc-2015-000190 on 19 April 2016. Downloaded from http://drc.bmj.com/ on December 16, 2023 by guest. Protected by copyright.
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 Δ6 desaturase and increased that of Δ5 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

<table>
<thead>
<tr>
<th>Table 1 Characteristic of the study participants</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>All (n=241)</td>
</tr>
<tr>
<td>Sitagliptin (n=120)</td>
</tr>
<tr>
<td>Voglibose (n=121)</td>
</tr>
<tr>
<td>p Value</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Male/Female</td>
</tr>
<tr>
<td>143/98</td>
</tr>
<tr>
<td>72/48</td>
</tr>
<tr>
<td>71/50</td>
</tr>
<tr>
<td>0.603</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>63.2±12.7</td>
</tr>
<tr>
<td>63.2±13.8</td>
</tr>
<tr>
<td>63.2±11.6</td>
</tr>
<tr>
<td>0.699</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Medication adherence rate (≥80%/&lt;80%)</td>
</tr>
<tr>
<td>193/48</td>
</tr>
<tr>
<td>99/21</td>
</tr>
<tr>
<td>94/27</td>
</tr>
<tr>
<td>0.420</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Combination therapy (Diet/SU/BG/TZD)</td>
</tr>
<tr>
<td>116/61/57/7</td>
</tr>
<tr>
<td>59/29/29/3</td>
</tr>
<tr>
<td>57/32/28/4</td>
</tr>
<tr>
<td>0.953</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
</tr>
<tr>
<td>64.8±14.4</td>
</tr>
<tr>
<td>63.8±13.6</td>
</tr>
<tr>
<td>65.8±15.1</td>
</tr>
<tr>
<td>0.515</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
</tr>
<tr>
<td>25.0±4.5</td>
</tr>
<tr>
<td>25.0±4.5</td>
</tr>
<tr>
<td>25.1±4.5</td>
</tr>
<tr>
<td>0.984</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
</tr>
<tr>
<td>89.9±11.1</td>
</tr>
<tr>
<td>88.7±10.5</td>
</tr>
<tr>
<td>91.0±11.7</td>
</tr>
<tr>
<td>0.162</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
</tr>
<tr>
<td>130.8±17.7</td>
</tr>
<tr>
<td>130.0±16.8</td>
</tr>
<tr>
<td>131.6±18.5</td>
</tr>
<tr>
<td>0.413</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>S-Cre (mg/dL)</td>
</tr>
<tr>
<td>154.7±35.1</td>
</tr>
<tr>
<td>156.3±35.1</td>
</tr>
<tr>
<td>153.2±35.2</td>
</tr>
<tr>
<td>0.347</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
</tr>
<tr>
<td>7.9±0.9</td>
</tr>
<tr>
<td>7.9±1.0</td>
</tr>
<tr>
<td>7.8±0.8</td>
</tr>
<tr>
<td>0.935</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>AST (IU/L)</td>
</tr>
<tr>
<td>6.9±4.8</td>
</tr>
<tr>
<td>6.5±4.2</td>
</tr>
<tr>
<td>7.4±5.3</td>
</tr>
<tr>
<td>0.429</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ALT (IU/L)</td>
</tr>
<tr>
<td>15.1±4.5</td>
</tr>
<tr>
<td>14.9±4.1</td>
</tr>
<tr>
<td>15.2±4.9</td>
</tr>
<tr>
<td>0.886</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
</tr>
<tr>
<td>0.72±0.23</td>
</tr>
<tr>
<td>0.70±0.19</td>
</tr>
<tr>
<td>0.74±0.27</td>
</tr>
<tr>
<td>0.870</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>TC (mg/dL)</td>
</tr>
<tr>
<td>188.4±33.0</td>
</tr>
<tr>
<td>185.1±33.4</td>
</tr>
<tr>
<td>191.6±32.4</td>
</tr>
<tr>
<td>0.130</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
</tr>
<tr>
<td>140.1±93.6</td>
</tr>
<tr>
<td>136.0±83.1</td>
</tr>
<tr>
<td>144.2±103.1</td>
</tr>
<tr>
<td>0.899</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
</tr>
<tr>
<td>53.8±16.7</td>
</tr>
<tr>
<td>52.7±15.4</td>
</tr>
<tr>
<td>54.9±18.0</td>
</tr>
<tr>
<td>0.250</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
</tr>
<tr>
<td>106.2±28.1</td>
</tr>
<tr>
<td>105.0±29.6</td>
</tr>
<tr>
<td>107.5±26.5</td>
</tr>
<tr>
<td>0.234</td>
</tr>
</tbody>
</table>

Data are expressed as means±SD. p Value for the intergroup comparison.

AG, anhydroglucitol; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BG, biguanide; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c; HDL-c, low-density lipoprotein cholesterol; LDL-c, low-density lipoprotein-cholesterol; s-Cre, serum creatinine; SU, sulfonilurea; TC, total cholesterol; TG, triglyceride; TZD, thiazolidinedione; γ-GTP, γ-glutamyl transpeptidase.

Copyright © 2016 BMJ Publishing Group Ltd. All rights reserved. For permission to reuse any portion of this article, please contact the copyright holder.
Table 2 Changes in the characteristics of patients between baseline and 12 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sitagliptin</th>
<th>Voglibose</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12-week</td>
<td>p Value*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>118</td>
<td>24.9±4.5</td>
<td>0.777</td>
<td>119</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>116</td>
<td>88.7±10.5</td>
<td>0.195</td>
<td>120</td>
</tr>
<tr>
<td>SBP (mm Hg)</td>
<td>120</td>
<td>130.0±16.8</td>
<td>0.998</td>
<td>121</td>
</tr>
<tr>
<td>DBP (mm Hg)</td>
<td>120</td>
<td>76.0±12.1</td>
<td>0.576</td>
<td>121</td>
</tr>
<tr>
<td>WBC (/mm$^3$)</td>
<td>120</td>
<td>5815±1362</td>
<td>0.040</td>
<td>119</td>
</tr>
<tr>
<td>Neutrophils (/mm$^3$)</td>
<td>108</td>
<td>3279±1015</td>
<td>0.008</td>
<td>107</td>
</tr>
<tr>
<td>Eosinophils (/mm$^3$)</td>
<td>105</td>
<td>156±120</td>
<td>0.000</td>
<td>105</td>
</tr>
<tr>
<td>Basophils (/mm$^3$)</td>
<td>105</td>
<td>30±23</td>
<td>0.359</td>
<td>105</td>
</tr>
<tr>
<td>Lymphocytes (/mm$^3$)</td>
<td>105</td>
<td>195±160</td>
<td>0.007</td>
<td>105</td>
</tr>
<tr>
<td>Monocytes (/mm$^3$)</td>
<td>105</td>
<td>323±113</td>
<td>0.004</td>
<td>105</td>
</tr>
<tr>
<td>PLT (10$^4$/mm$^3$)</td>
<td>120</td>
<td>21.0±5.5</td>
<td>0.281</td>
<td>119</td>
</tr>
<tr>
<td>RBC (10$^3$/mm$^3$)</td>
<td>120</td>
<td>458.4±43.7</td>
<td>0.723</td>
<td>119</td>
</tr>
<tr>
<td>Hb (g/mL)</td>
<td>120</td>
<td>13.9±1.6</td>
<td>0.943</td>
<td>119</td>
</tr>
<tr>
<td>AST (IU/L)</td>
<td>120</td>
<td>26±13</td>
<td>0.000</td>
<td>118</td>
</tr>
<tr>
<td>ALT (IU/L)</td>
<td>120</td>
<td>32±25</td>
<td>0.459</td>
<td>119</td>
</tr>
<tr>
<td>ALP (IU/L)</td>
<td>120</td>
<td>236±71</td>
<td>0.000</td>
<td>118</td>
</tr>
<tr>
<td>BAP (μg/L)</td>
<td>116</td>
<td>12.6±5.6</td>
<td>0.140</td>
<td>116</td>
</tr>
<tr>
<td>γ-GTP (IU/L)</td>
<td>120</td>
<td>44±50</td>
<td>0.000</td>
<td>119</td>
</tr>
<tr>
<td>CK (IU/L)</td>
<td>117</td>
<td>105.5±71.6</td>
<td>0.920</td>
<td>117</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>120</td>
<td>14.9±4.1</td>
<td>0.000</td>
<td>118</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>119</td>
<td>0.71±0.19</td>
<td>0.000</td>
<td>120</td>
</tr>
<tr>
<td>UA (mg/dL)</td>
<td>119</td>
<td>5.08±1.14</td>
<td>0.001</td>
<td>120</td>
</tr>
<tr>
<td>Cystatin C (mg/L)</td>
<td>114</td>
<td>0.82±0.18</td>
<td>0.001</td>
<td>112</td>
</tr>
<tr>
<td>eGFR creat (ml/min/1.73 m$^2$)</td>
<td>120</td>
<td>85.0±28.4</td>
<td>0.000</td>
<td>120</td>
</tr>
<tr>
<td>eGFRcys (ml/min/1.73 m$^2$)</td>
<td>114</td>
<td>91.1±23.2</td>
<td>0.000</td>
<td>112</td>
</tr>
<tr>
<td>eGFRaverage (ml/min/1.73 m$^2$)</td>
<td>114</td>
<td>88.0±23.3</td>
<td>0.000</td>
<td>111</td>
</tr>
<tr>
<td>TC (mg/dL)</td>
<td>120</td>
<td>185.1±33.4</td>
<td>0.910</td>
<td>118</td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>118</td>
<td>52.7±15.4</td>
<td>0.873</td>
<td>118</td>
</tr>
<tr>
<td>Triglyceride (mg/dL)</td>
<td>118</td>
<td>136.0±83.1</td>
<td>0.098</td>
<td>118</td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>118</td>
<td>104.9±29.6</td>
<td>0.499</td>
<td>117</td>
</tr>
<tr>
<td>sdLDL (mg/dL)</td>
<td>118</td>
<td>36.8±15.4</td>
<td>0.134</td>
<td>120</td>
</tr>
<tr>
<td>IRI (IU/L)</td>
<td>116</td>
<td>8.46±8.20</td>
<td>0.342</td>
<td>118</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>118</td>
<td>2.10±0.88</td>
<td>0.421</td>
<td>120</td>
</tr>
<tr>
<td>HMW adiponectin (μg/dL)</td>
<td>118</td>
<td>3.17±2.30</td>
<td>0.000</td>
<td>120</td>
</tr>
<tr>
<td>Hypersensitive TNF-α (pg/mL)</td>
<td>118</td>
<td>3.11±12.47</td>
<td>0.079</td>
<td>120</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>118</td>
<td>8.26±6.90</td>
<td>0.561</td>
<td>117</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>115</td>
<td>3.30±3.44</td>
<td>0.056</td>
<td>117</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>115</td>
<td>36.0±32.8</td>
<td>0.000</td>
<td>117</td>
</tr>
<tr>
<td>SUIT index</td>
<td>117</td>
<td>39.5±30.4</td>
<td>0.000</td>
<td>117</td>
</tr>
</tbody>
</table>
Table 2 Continued

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Sitagliptin n Baseline</th>
<th>12-week</th>
<th>p Value*</th>
<th>Voglibose n Baseline</th>
<th>12-week</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>CPI</td>
<td>117</td>
<td>1.41±0.67</td>
<td>1.52±0.71</td>
<td>0.001</td>
<td>118</td>
<td>1.38±0.68</td>
</tr>
<tr>
<td>QUICKI</td>
<td>112</td>
<td>0.34±0.04</td>
<td>0.34±0.04</td>
<td>0.093</td>
<td>116</td>
<td>0.34±0.05</td>
</tr>
<tr>
<td>Proinsulin (pM)</td>
<td>112</td>
<td>26.9±17.2</td>
<td>22.5±14.3</td>
<td>0.000</td>
<td>104</td>
<td>26.5±17.9</td>
</tr>
<tr>
<td>Proinsulin/Insulin Ratio</td>
<td>101</td>
<td>0.70±0.67</td>
<td>0.54±0.33</td>
<td>0.000</td>
<td>91</td>
<td>0.63±0.39</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>120</td>
<td>7.94±1.03</td>
<td>7.15±0.88</td>
<td>0.000</td>
<td>121</td>
<td>7.86±0.78</td>
</tr>
<tr>
<td>1.5AG (μg/mL)</td>
<td>109</td>
<td>6.45±4.16</td>
<td>10.55±5.96</td>
<td>0.000</td>
<td>105</td>
<td>7.43±5.29</td>
</tr>
<tr>
<td>FPG (mg/dL)</td>
<td>119</td>
<td>156.3±35.1</td>
<td>140.0±31.7</td>
<td>0.000</td>
<td>119</td>
<td>153.2±35.2</td>
</tr>
</tbody>
</table>

* p Value for the intragroup comparison (baseline vs 12 weeks).
† p Value for the intergroup comparison (difference in changes from baseline between groups).

Data are expressed as means±SD.

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; 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.
Both sitagliptin and voglibose significantly increased plasma adiponectin levels, as stated in previous reports.32 33 There was a negative correlation between ΔHbA1c and Δadiponectin (table 3), suggesting that glyceremic control at least partly contributes to the increase in adiponectin levels. The increased adiponectin levels might improve endothelial function and likely yield antiatherosclerotic effects.34 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.35 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 ω6 fatty acids, whereas voglibose altered serum levels of many kinds of fatty acids, unlike in a previous study with acarbose.36 Notably, voglibose, but not sitagliptin, increased Δ-5 desaturase activity. Several cross-sectional studies showed that the Δ-5 desaturase activity index, which refers to the ratio of arachidonic acids to dihomo-γ-linolenic acids, is positively associated with insulin sensitivity37 38 and the onset of newly diagnosed type 2 diabetes,39 and is negatively associated with several metabolic risk factors in patients with metabolic syndrome.40 High Δ-5 desaturase activity was associated with reduced coronary heart disease risk.41 Conversely, voglibose decreased Δ-6 desaturase activity. Δ-6 desaturase activity was associated with an increased probability of metabolic syndrome.40 These findings suggest the possibility that voglibose, rather than sitagliptin, might reduce coronary heart disease risk by altering fatty acids profiling. However, as a limitation, because the present 3-month, open-label study was designed to compare the antihyperglycemic effects of sitagliptin and voglibose, clinical benefits beyond glycemic control might not be observed.

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

<table>
<thead>
<tr>
<th></th>
<th>Sitagliptin</th>
<th>p Value</th>
<th>Voglibose</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>−0.051</td>
<td>0.577</td>
<td>−0.082</td>
<td>0.374</td>
</tr>
<tr>
<td>Body mass index</td>
<td>−0.142</td>
<td>0.126</td>
<td>−0.08</td>
<td>0.390</td>
</tr>
<tr>
<td>Fasting plasma glucose (mg/dL)</td>
<td>−0.113</td>
<td>0.222</td>
<td>0.107</td>
<td>0.246</td>
</tr>
<tr>
<td>1,5 AG (%)</td>
<td>0.338</td>
<td>0.000</td>
<td>−0.034</td>
<td>0.714</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>−0.589</td>
<td>0.000</td>
<td>−0.121</td>
<td>0.185</td>
</tr>
<tr>
<td>Total cholesterol (mg/dL)</td>
<td>0.050</td>
<td>0.588</td>
<td>0.009</td>
<td>0.948</td>
</tr>
<tr>
<td>Fasting serum insulin (IU/L)</td>
<td>−0.092</td>
<td>0.328</td>
<td>−0.079</td>
<td>0.392</td>
</tr>
<tr>
<td>CPR (ng/mL)</td>
<td>−0.101</td>
<td>0.275</td>
<td>−0.004</td>
<td>0.965</td>
</tr>
<tr>
<td>HMW adiponectin (µg/mL)</td>
<td>0.223</td>
<td>0.015</td>
<td>0.137</td>
<td>0.137</td>
</tr>
<tr>
<td>CPI</td>
<td>−0.048</td>
<td>0.609</td>
<td>−0.038</td>
<td>0.684</td>
</tr>
<tr>
<td>HOMAIR</td>
<td>−0.128</td>
<td>0.171</td>
<td>0.114</td>
<td>0.222</td>
</tr>
<tr>
<td>HOMA-β</td>
<td>−0.016</td>
<td>0.861</td>
<td>0.033</td>
<td>0.722</td>
</tr>
<tr>
<td>EPA (ng/mL)</td>
<td>−0.064</td>
<td>0.490</td>
<td>0.062</td>
<td>0.502</td>
</tr>
<tr>
<td>DHA (ng/mL)</td>
<td>−0.077</td>
<td>0.118</td>
<td>−0.078</td>
<td>0.396</td>
</tr>
<tr>
<td>Change from baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ΔFPG</td>
<td>0.386</td>
<td>0.000</td>
<td>0.421</td>
<td>0.000</td>
</tr>
<tr>
<td>ΔBW</td>
<td>0.212</td>
<td>0.020</td>
<td>0.047</td>
<td>0.609</td>
</tr>
<tr>
<td>ΔBMI</td>
<td>0.206</td>
<td>0.025</td>
<td>0.058</td>
<td>0.533</td>
</tr>
<tr>
<td>ΔALP</td>
<td>0.269</td>
<td>0.003</td>
<td>0.187</td>
<td>0.042</td>
</tr>
<tr>
<td>ΔTC</td>
<td>0.231</td>
<td>0.011</td>
<td>−0.062</td>
<td>0.502</td>
</tr>
<tr>
<td>ΔLDLC</td>
<td>0.266</td>
<td>0.004</td>
<td>0.151</td>
<td>0.103</td>
</tr>
<tr>
<td>ΔTG</td>
<td>0.084</td>
<td>0.362</td>
<td>−0.152</td>
<td>0.098</td>
</tr>
<tr>
<td>ΔHMW adiponectin</td>
<td>−0.310</td>
<td>0.001</td>
<td>−0.346</td>
<td>0.000</td>
</tr>
<tr>
<td>ΔHOMA-IR</td>
<td>0.233</td>
<td>0.012</td>
<td>0.105</td>
<td>0.262</td>
</tr>
<tr>
<td>ΔHOMA-β</td>
<td>−0.304</td>
<td>0.001</td>
<td>−0.222</td>
<td>0.016</td>
</tr>
<tr>
<td>ΔSUIT index</td>
<td>−0.377</td>
<td>0.000</td>
<td>−0.261</td>
<td>0.004</td>
</tr>
<tr>
<td>ΔQUICKI</td>
<td>−0.185</td>
<td>0.047</td>
<td>−0.175</td>
<td>0.060</td>
</tr>
<tr>
<td>ΔCPI</td>
<td>−0.235</td>
<td>0.011</td>
<td>−0.156</td>
<td>0.091</td>
</tr>
<tr>
<td>ΔProinsulin insulin ratio</td>
<td>0.199</td>
<td>0.046</td>
<td>0.177</td>
<td>0.094</td>
</tr>
<tr>
<td>ΔEPA</td>
<td>−0.010</td>
<td>0.914</td>
<td>−0.062</td>
<td>0.502</td>
</tr>
<tr>
<td>ΔDHA</td>
<td>0.073</td>
<td>0.430</td>
<td>−0.065</td>
<td>0.482</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Siteglitin C12.0 (ng/mL)</th>
<th>Voglibose C16.0 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n Baseline 12-week p Value*</td>
<td>n Baseline 12-week p Value*</td>
</tr>
<tr>
<td>Lauric acid C12:0</td>
<td>118 2.3±2.2 0.555</td>
<td>120 2.5±2.1 0.139</td>
</tr>
<tr>
<td>Myristic acid C14:0</td>
<td>118 29.5±18.9 0.147</td>
<td>120 33.1±23.0 0.012</td>
</tr>
<tr>
<td>Palmitic acid C16:0</td>
<td>118 746.7±259.6 0.019</td>
<td>120 796.9±268.7 0.001</td>
</tr>
<tr>
<td>Palmitoleic acid C16:1ω7</td>
<td>118 80.4±46.2 0.130</td>
<td>120 89.7±51.6 0.000</td>
</tr>
<tr>
<td>Stearic acid C18:0</td>
<td>118 214.7±53.6 0.532</td>
<td>120 224.2±57.7 0.033</td>
</tr>
<tr>
<td>Oleic acid C18:1ω9</td>
<td>118 656.2±236.6 0.799</td>
<td>120 714.9±295.4 0.049</td>
</tr>
<tr>
<td>Linoleic acid C18:2ω6</td>
<td>118 744.8±182.1 0.021</td>
<td>120 798.6±208.2 0.902</td>
</tr>
<tr>
<td>γ-linolenic acid C18:3ω6</td>
<td>118 11.4±6.5 0.291</td>
<td>120 12.4±6.6 0.036</td>
</tr>
<tr>
<td>α-Linolenic acid C18:3ω3</td>
<td>118 26.7±11.2 0.010</td>
<td>120 27.3±11.1 0.007</td>
</tr>
<tr>
<td>Arachidonic acid C20:0</td>
<td>118 7.2±1.3 0.087</td>
<td>120 7.2±1.3 0.033</td>
</tr>
<tr>
<td>Eicosanoic acid C20:1ω9</td>
<td>118 5.5±2.0 0.052</td>
<td>120 6.1±2.1 0.368</td>
</tr>
<tr>
<td>Eicosadinoic acid C20:2ω6</td>
<td>118 5.9±2.1 0.059</td>
<td>120 6.3±2.0 0.764</td>
</tr>
<tr>
<td>5-8-11-Eicosatrienoic acid C20:3ω3</td>
<td>118 2.2±1.4 0.049</td>
<td>120 2.8±2.6 0.008</td>
</tr>
<tr>
<td>Dihomo-γ-linolenic acid C20:3ω6</td>
<td>118 38.6±13.2 0.260</td>
<td>120 42.4±15.5 0.005</td>
</tr>
<tr>
<td>Arachidonic acid C20:4ω6</td>
<td>118 173.2±46.7 0.706</td>
<td>120 184.5±46.5 0.891</td>
</tr>
<tr>
<td>Eicosapentaenoic acid C20:5ω3</td>
<td>118 80.6±48.3 0.884</td>
<td>120 81.2±70.0 0.659</td>
</tr>
<tr>
<td>Behenic acid C22:0</td>
<td>118 7.2±1.3 0.087</td>
<td>120 7.2±1.3 0.033</td>
</tr>
<tr>
<td>Erucic acid C22:1ω9</td>
<td>118 1.6±0.8 0.613</td>
<td>120 1.8±0.9 0.768</td>
</tr>
<tr>
<td>Docosatetraenoic acid C22:4ω6</td>
<td>118 5.2±2.2 0.248</td>
<td>120 5.1±2.1 0.011</td>
</tr>
<tr>
<td>Docosapentaenoic acid C22:5ω3</td>
<td>118 25.2±10.0 0.399</td>
<td>120 25.8±13.1 0.004</td>
</tr>
<tr>
<td>Lignoceric acid C24:0</td>
<td>118 16.3±2.8 0.775</td>
<td>120 17.5±3.4 0.423</td>
</tr>
<tr>
<td>Docosahexaenoic acid C22:6ω3</td>
<td>118 175.2±65.3 0.305</td>
<td>120 175.2±94.5 0.095</td>
</tr>
<tr>
<td>Nervonic acid C24:1ω9</td>
<td>118 34.8±7.5 0.357</td>
<td>120 37.0±8.2 0.028</td>
</tr>
<tr>
<td>EPA+DHA (ng/mL)</td>
<td>118 255.9±107.5 0.036</td>
<td>120 256.3±160.3 0.436</td>
</tr>
<tr>
<td>EPA/AA ratio</td>
<td>118 0.49±0.31 0.050</td>
<td>120 0.44±0.32 0.435</td>
</tr>
<tr>
<td>Total ω3 fatty acids (ng/mL)</td>
<td>118 308.7±121.9 0.370</td>
<td>120 309.4±181.0 0.308</td>
</tr>
<tr>
<td>Total ω6 fatty acids (ng/mL)</td>
<td>118 1008.7±224.8 0.024</td>
<td>120 1049.2±238.2 0.684</td>
</tr>
<tr>
<td>Total ω9 fatty acids (ng/mL)</td>
<td>118 700.2±239.2 0.794</td>
<td>120 762.6±300.8 0.053</td>
</tr>
<tr>
<td>ω3/ω6 ratio</td>
<td>118 0.32±0.13 0.236</td>
<td>120 0.30±0.14 0.409</td>
</tr>
<tr>
<td>Total saturated fatty acids (ng/mL)</td>
<td>118 1034.9±330.7 0.050</td>
<td>120 1101.1±346.5 0.002</td>
</tr>
<tr>
<td>Monounsaturated fatty acids (ng/mL)</td>
<td>118 778.5±276.8 0.762</td>
<td>120 854.3±346.8 0.020</td>
</tr>
<tr>
<td>Polyunsaturated fatty acids (ng/mL)</td>
<td>118 1319.5±277.3 0.014</td>
<td>120 1361.4±336.2 0.562</td>
</tr>
<tr>
<td>δ-5desaturase (20:4ω6/20:3ω6)</td>
<td>118 4.7±3.42 0.595</td>
<td>120 4.7±1.77 0.014</td>
</tr>
<tr>
<td>δ-6desaturase (18:3ω6/18:2ω6)</td>
<td>118 0.015±0.008 0.321</td>
<td>120 0.016±0.009 0.009</td>
</tr>
</tbody>
</table>

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 glycemic parameters.

In summary, we showed that sitagliptin is superior to voglibose in terms of improving glycemic control as a first/second-line therapy in Japanese people with type 2 diabetes. However, both agents exert unique pleiotropic effects on surrogate cardiovascular risks, which suggests a theoretical basis for potential benefits through combined therapy. A large-scale clinical trial on cardiovascular events is required to test this hypothesis.

Author affiliations
1 Department of Endocrinology and Metabolism, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Ishikawa, Japan
2 Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Sciences, Kanazawa, Ishikawa, Japan
3 ERA-DM Chapter 1 Study Group, Kanazawa, Ishikawa, Japan

Collaborators Clinical Centres for the ERA-DM study Chapter 1 group: Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Science (Kanazawa, Ishikawa), Municipal Tsuruga Hospital (Tsuruga, Fukui), Koshino Hospital (Kanazawa, Ishikawa), Ishida Hospital (Kanazawa, Ishikawa), Handa Medical Clinic (Kanazawa, Ishikawa), Yumie Takeshita, MD PhD, Toshinari Takamura, MD PhD, Toshiki Otoda, MD PhD; Ken-ichiro Kato MD, Hitomi Wakahuki, MD, Masayuki Yamada, MD, Hirofumi Mitsu, MD PhD, Shuichi Kaneko, MD PhD, Tsuguhito Ota, MD PhD, Takehiro Kanamori, MD, Yukiko Matsushima (coordinator), Shima Kitakata (coordinator); Public Hakui Hospital (Hakui, Ishikawa), Toshiki Otoda, MD PhD; Japanese Red Cross Kanazawa Hospital (Kanazawa, Ishikawa), Yuki Hataguchi, MD PhD, Yasuyuki Nishimura, MD PhD; Toyama City Hospital (Toyama, Toyama), Akiko Shimizu, MD PhD; Public Central Hospital of Matto Ishikawa (Matto, Ishikawa), Yuki Kita, MD PhD, Kozi Kawai, MD PhD; Kahoku Central Hospital (Kahoku, Ishikawa), Kensi Kuri, MD, Fukui Saiseikai Hospital (Fukui, Fukui), Kosuke R Shima, MD, Yuukihiro Iida, MD PhD; Kanazawa Municipal Hospital (Kanazawa, Ishikawa), Nobuhiko Koike, MD PhD.

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, 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. YK, TO, KK, HT-W, HA, AS, EH, YN and TK 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.

Funding This work was supported by Grants-in-Aid from the Ministry of Education, Culture, Sports, Science, and Technology of Japan, and Research grants from ONO Pharmaceutical Co, Ltd (to TT and SK).

Competing interests None declared.

Patient consent Obtained.

Ethics approval Kanazawa University Hospital Institutional Review Board.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

REFERENCES
25. Pratley RE, Schweizer A, Rosenstock J, et al. Robust improvements in fasting and prandial measures of beta-cell function with


