Effects of metformin and alogliptin on body composition in people with type 2 diabetes

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ABSTRACT

Aims/Introduction: The aim of the present study was to investigate the effects of metformin and a dipeptidyl peptidase-4 inhibitor, alogliptin, on body composition in a 12-week randomized add-on trial in Japanese participants with type 2 diabetes.

Materials and Methods: A total of 84 participants with poorly controlled type 2 diabetes undergoing antidiabetic therapy were randomly assigned to receive alogliptin (25 mg, once daily) or metformin (1,000 mg, twice daily) for 12 weeks. The primary efficacy end-point was body composition. The secondary end-points included factors associated with decreased bodyweight.

Results: Compared with the baseline values, alogliptin significantly increased body-weight (66.5 ± 19.2 to 67.6 ± 19.3 kg), body mass index (BMI; 25.4 ± 6.1 to 25.8 ± 6.3 kg/m²) and fat mass (20.3 ± 12.8 to 21.8 ± 14.5 kg), whereas metformin had no significant effect on body composition. Alogliptin was inferior to metformin in reducing bodyweight (0.84 ± 1.57 vs −0.35 ± 1.53 kg, P = 0.002), BMI (0.34 ± 0.69 to −0.15 ± 0.56 kg/m², P = 0.002) and fat mass (1.49 ± 5.06 vs −0.04 ± 1.81 kg, P = 0.042). BMI at baseline was associated with changes in bodyweight negatively in the metformin group and positively in the alogliptin group.

Conclusions: Metformin and alogliptin exert opposite effects on bodyweight in type 2 diabetes patients who are overweight. The higher the BMI, the more metformin reduces bodyweight and alogliptin increases weight.

INTRODUCTION

A recent large-scale clinical trial found that intensive antidiabetic therapies that cause hyperinsulinemia are associated with poor cardiovascular outcomes in people with type 2 diabetes, and might cause hypoglycemia and weight gain1. Treatment with metformin and incretin-based agents could prevent unnecessary hyperinsulinemia. Metformin is a first-line treatment for type 2 diabetes because of its efficacy, long history of use and well-known safety profile in Western countries2. However, its use is limited by gastrointestinal intolerance and the risk of lactacidosis. Thus, dipeptidyl peptidase-4 (DPP-IV) inhibitors, which are generally accepted as a second-/third-line therapy3, might be an alternative to metformin monotherapy for participants with type 2 diabetes under a variety of clinical conditions3,4. Several recent clinical trials have shown that DPP-IV inhibitors and metformin are well tolerated and produce sustained glycemic control5-12. However, the pleiotropic effects of DPP-IV inhibitors and metformin have not been examined sufficiently. We compared the pleiotropic effects of alogliptin, a DPP-IV inhibitor, and metformin on various parameters, including body composition, β-cell insulin secretion, cardiovascular parameters, serum fatty acid levels and treatment satisfaction, in a 12-week add-on trial in Japanese participants with poorly controlled type 2 diabetes.

METHODS

Overview

We carried out a randomized, parallel trial of alogliptin and metformin in Japanese participants with type 2 diabetes at Kanazawa University Hospital (Kanazawa, Japan) in accordance with the Declaration of Helsinki. All participants provided written informed consent. The trial was registered with the University Hospital Medical Information Network Clinical Trials
Registry (number UMIN000010385). A total of 84 participants with type 2 diabetes and poor glycemic control (glycated hemoglobin [HbA1c] >6.5%) were recruited from Kanazawa University Hospital between April and December 2013.

**Patient eligibility**

The eligibility criteria were as follows: aged ≥20 years, diagnosed with type 2 diabetes mellitus, HbA1c ≥6.5% within 12 weeks of screening, and undergoing any combination of diet therapy, oral hypoglycemic therapy and insulin therapy for ≥12 weeks. The exclusion criteria included: (i) hypersensitivity or contraindication for alogliptin or metformin; (ii) history of type 1 diabetes; (iii) history of ketoacidosis; (iv) experienced symptoms of hypoglycemia; (v) treatment with alogliptin or metformin within 4 weeks of screening; (vi) concomitant corticosteroid therapy; (vii) poorly controlled unstable diabetes (the state with ketoacidosis or with an increase in HbA1c >3% in the 12 weeks before screening); (viii) alanine aminotransferase and/or aspartate aminotransferase >2.5-fold the upper limit of normal; (ix) poorly controlled hypertension or systolic blood pressure >160 mmHg or diastolic blood pressure >100 mmHg; (x) presence of a severe health problem and not suitable for the study; (xi) pregnant or breast-feeding; and (xii) inability to participate in the study (including psychiatric and psychosocial conditions), as assessed by the investigators.

**Study participants**

Participants were randomly assigned to the alogliptin or metformin treatment group at a 1:1 ratio using a computer-generated randomization sequence. In the present parallel-group trial, eligible participants received alogliptin or metformin added to their current treatment for 12 weeks. Alogliptin (Takeda Pharmaceutical Co. Ltd., Osaka, Japan) was started at 1,000 mg (500-mg tablets, twice daily) and adjusted at the discretion of the physician-investigators; metformin dose was reduced when necessary for better glycemic control.

The participants were then crossed over without washout to the other treatment for an additional 12 weeks, as originally planned. We used a multilevel model as recommended by Mills et al. for cross-over study analysis. This model was used specifically to assess the effects of time or carryover effects from one treatment phase to another. In the present study, we mainly presented the first half of our dataset. Further detail of the study participants is provided in the Appendix S1.

**Efficacy end-points**

The primary efficacy end-point was a change in body composition from baseline.

The secondary end-points recorded at baseline and week 12 were: glucose metabolism (fasting plasma glucose; HbA1c; C-peptide immunoreactivity, 1,5-anhydroglucitol blood); fasting lipid profile; and laboratory tests, including hematology, serum chemistry, bone alkaline phosphatase, tumor necrosis factor-α and leptin; blood pressure and physical measurements (waist circumference and body mass index [BMI]). Further detail of the efficacy end-points including bioelectrical impedance analysis measurements and treatment satisfaction is provided in Appendix S1.

**Statistical analysis**

The sample size required to detect a −1.1-kg change in body-weight in the metformin group, and a 0.2-kg change in the alogliptin group, with a power of 95% (α = 0.05, one-tailed; β = 0.05), was 32 participants in each group. Taking into account a dropout rate of 20%, we aimed to recruit 80 participants.

The results are expressed as mean ± standard deviation. The Statistical Package for the Social Sciences version 22.0 (SPSS Inc., Chicago, IL, USA) was used to carry out the statistical tests. P-values <0.05 were deemed to show statistical significance. We carried out a completed case analysis (through week 12), because there were few dropouts. We excluded patients with serious adverse events, such as esophageal cancer and pneumonitis, from the per-protocol analysis. The Wilcoxon signed-rank test was used for intergroup comparisons, and the Mann–Whitney U-test was used for intragroup comparisons. Associations between variables were assessed using Spearman’s rank correlation coefficient.

**RESULTS**

**Baseline metabolic parameters**

The 84 eligible participants were screened and randomly assigned to the metformin or alogliptin treatment group. The baseline clinical characteristics were the same for the alogliptin and metformin groups (Table S1). All participants were naive to metformin and alogliptin at baseline in the present study. Of the 84 participants enrolled in the study, four dropped out after randomization and before initiation of the intervention (Figure S1); 87.8% of the participants in the alogliptin group and 89.7% in the metformin group achieved 100% compliance. The average final dose in the metformin group was 1075.8 ± 430.4 mg by the physician’s discretion.

**Primary clinical outcomes**

Compared with the baseline values, alogliptin significantly increased body weight (66.5 ± 19.2 to 67.6 ± 19.3 kg, P = 0.001), BMI (25.4 ± 6.1 to 25.8 ± 6.3 kg/m², P = 0.002) and fat mass (20.3 ± 12.8 to 21.8 ± 14.5 kg, P = 0.003), whereas metformin had no significant effect on body composition. Alogliptin was inferior to metformin in reducing body weight (0.84 ± 1.57 vs −0.35 ± 1.53 kg, P = 0.002), BMI (0.34 ± 0.69 to −0.15 ± 0.56 kg/m², P = 0.002) and fat mass (1.49 ± 5.06 vs −0.04 ± 1.81 kg, P = 0.042; Table 1).
Table 1 | Treatment effects of metformin or alogliptin on body composition and metabolic parameters

|                      | Metformin      | Alogliptin     |                      |                      |
|----------------------|----------------|----------------|----------------------|----------------------|
|                      | Week 0         | Week 12        | P*                   | Change from baseline |
| Bodyweight (kg)      | 663 ± 14.1     | 662 ± 14.1     | 0.875                | -0.35 ± 1.53         |
| BMI (kg/m²)          | 244 ± 40       | 244 ± 40       | 0.130                | -0.15 ± 0.56         |
| Waist circumference (cm) | 886.1 ± 11.8   | 886.9 ± 9.6    | 0.721                | 0.08 ± 2.34          |
| Lean body mass (kg)  | 25.9 ± 5.6     | 25.8 ± 5.9     | 0.638                | -0.02 ± 0.82         |
| Fat mass (kg)        | 18.7 ± 7.3     | 18.4 ± 6.5     | 0.511                | -0.04 ± 1.81         |
| Waist-to-hip ratio   | 0.88 ± 0.06    | 0.87 ± 0.06    | 0.633                | -0.01 ± 0.03         |
| FPG (mg/dL)          | 156.6 ± 47.5   | 134.6 ± 33.9   | 0.007                | -22.0 ± 41.6         |
| HbA1c (%)            | 7.4 ± 12       | 6.8 ± 9.0      | 0.000                | -0.56 ± 102          |
| 1,5-AG (µg/mL)       | 95 ± 6.3       | 130 ± 75       | 0.000                | 3.50 ± 3.74          |
| CPR (mg/mL)          | 21.2 ± 12      | 22.2 ± 12      | 0.700                | 0.09 ± 0.78          |
| CPI                  | 15.1 ± 11      | 18 ± 12        | 0.000                | 0.26 ± 0.64          |
| Systolic BP (mmHg)   | 130.9 ± 14.4   | 134.3 ± 13.5   | 0.281                | 3.33 ± 17.05         |
| HR (rate/min)        | 661.7 ± 10.8   | 672 ± 12.6     | 0.402                | 1.42 ± 6.62          |
| WBC (µL)             | 5964 ± 1657    | 5962 ± 1605    | 0.527                | 1629 ± 15705         |
| BUN (mg/dL)          | 16.5 ± 6.2     | 16.5 ± 5.1     | 0.973                | 0.12 ± 3.38          |
| Cr (mg/dL)           | 0.82 ± 0.26    | 0.78 ± 0.23    | 0.013                | -0.04 ± 0.09         |
| AST (I/U)            | 243.1 ± 11.6   | 228 ± 9.9      | 0.446                | -1.38 ± 8.29         |
| ALT (I/U)            | 29.4 ± 24.7    | 27.2 ± 19.2    | 0.488                | -2.68 ± 16.36        |
| γGTP (I/U)           | 340.1 ± 22.0   | 322 ± 21.5     | 0.505                | -2.1 ± 12.3          |
| ALP (I/U)            | 233.2 ± 85.1   | 214.1 ± 68.4   | 0.225                | -190 ± 40.9          |
| Ca (mg/dL)           | 9.5 ± 0.4      | 9.6 ± 0.3      | 0.609                | 0.04 ± 0.36          |
| iP (mg/dL)           | 3.4 ± 0.6      | 3.4 ± 0.5      | 0.714                | 0.01 ± 0.36          |
| BAP (µg/L)           | 14.4 ± 6.2     | 12.3 ± 4.6     | 0.001                | -1.98 ± 3.18         |
| TC (mg/dL)           | 1838 ± 37.0    | 1810 ± 37.6    | 0.153                | -49 ± 22.6           |
| HDL-C (mg/dL)        | 1238 ± 73.4    | 1182 ± 86.0    | 0.276                | -70 ± 51.7           |
| sLDL-C (mg/dL)       | 497.1 ± 15.8   | 494.3 ± 13.6   | 0.851                | 10 ± 13.7            |
| U-Alb (mg/gCr)       | 398.2 ± 16.2   | 357.6 ± 16.6   | 0.006                | -43 ± 8.3            |
| U-80HdG (ng/mgCr)    | 410.1 ± 47.4   | 330.7 ± 123.3  | 0.339                | 1615 ± 706.2         |
| Adiponectin (µg/dL)  | 21.9 ± 3.8     | 3.9 ± 37       | 0.773                | -0.03 ± 0.75         |
| TNF-α (pg/mL)        | 4.0 ± 38       | 3.7 ± 39       | 0.080                | -0.14 ± 2.86         |
| Leptin (ng/mL)       | 8.4 ± 10.7     | 8.5 ± 87       | 0.955                | -0.15 ± 3.85         |

All values are mean ± standard deviation. *P-value for the intragroup comparison (baseline vs 16 weeks); **P-value for the intergroup comparison (change from baseline between groups); ***P-value for the intergroup comparison (12 weeks). γGTP, serum γ-glutamyltransferase; 1,5-Ag, 1,5-anhydroglucot; ALP, alkaline phosphatase; ALT, alanine aminotransferase; BAP, bone alkaline phosphatase; BMI, body mass index; BP, blood pressure; BUN, blood urea nitrogen; Ca, calcium; CPR, C-peptide immunoreactivity; CPI, C-peptide immunoreactivity index; Cre, creatinine; FPG, fasting plasma glucose; HbA1c, glycated hemoglobin; HDL-C, high-density lipoprotein cholesterol; HR, heart rate; iP, phosphorus; sLDL, small dense low-density lipoprotein; TC, total cholesterol; TG, triglyceride; U-Alb, urinary albumin (measured by immunoturbidimetry and adjusted using urinary creatinine); U-80HdG, urinary 8-hydroxy-deoxyguanosine; TNF, tumor necrosis factor; WBC, white blood cells.
Secondary clinical outcomes

Blood chemistry

Both treatments significantly decreased fasting plasma glucose (FPG) levels, HbA1c and bone alkaline phosphatase, and significantly increased 1,5-anhydroglucitol and C-peptide immunoreactivity, with no significant differences between groups. Metformin was superior to alogliptin in reducing creatinine (–0.04 ± 0.09 vs 0.02 ± 0.07 mg/dL, \( P = 0.003 \)). Metformin, but not alogliptin, significantly decreased alkaline phosphatase (233.2 ± 85.1 to 214.1 ± 68.4 mg/dL, \( P = 0.025 \)) and small dense low-density lipoprotein (39.8 ± 16.2 to 35.7 ± 16.6 mg/dL, \( P = 0.006 \)), with no significant differences between groups. Alogliptin, but not metformin, significantly increased leptin levels (11.2 ± 12.8 to 12.9 ± 15.0 ng/mL; \( P = 0.009 \)), with no significant differences between groups (Table 1). Metformin significantly decreased eicosapentaenoic acid levels, with no significant differences between groups (Table S2). Almost similar results were obtained regarding the changes in body composition and glucose metabolism in the cross-over trial (Table S3).

Factors associated with decreased bodyweight and glucose levels

We carried out univariable analyses to extract the clinical characteristics associated with the effects of metformin and alogliptin on changes in bodyweight, FPG and HbA1c. BMI at baseline was associated with changes in bodyweight negatively in the metformin group and positively in the alogliptin group (Table 2). The FPG level at baseline was a significant predictor of the change of FPG in both treatment groups (Table S4a). The HbA1c level at baseline was a significant predictor of the change of HbA1c in both treatment groups (Table S4b). The concomitantly used drug, diabetes duration and fatty acid composition, such as eicosapentaenoic acid and docosahexaenoic acid were not associated with changes in bodyweight, FPG and HbA1c in either group.

Treatment satisfaction

The overall Diabetes Treatment Satisfaction Questionnaire score increased significantly in the alogliptin group (21.6 ± 0.9 to 25.5 ± 5.8, \( P = 0.002 \)). Alogliptin was superior to metformin in increasing the sum of treatment satisfaction score (\( P = 0.005 \)). Furthermore, the scores for items related to the perception of hyperglycemia (items 2) were significantly lower after treatment in both groups. The score for satisfaction with the treatment (items 1) was significantly decreased from baseline in the metformin group and was not changed in the alogliptin group. The scores for convenience of the treatment (item 4), understanding of your diabetes (item 6), recommend to others (item 7) and wish to continue treatment (item 8) were significantly increased from baseline in the alogliptin group, and were not changed in the metformin group (Table 3).

Adverse events

The most common adverse events were gastrointestinal symptoms, such as diarrhea, loose stools, flatulence, abdomen distension, stomach heaviness, nausea and appetite loss, which occurred primarily in the metformin group (Table S5). Metformin doses were reduced to minimum of 500 mg among five patients because of gastrointestinal symptoms under the physician’s discretion. Two participants in each treatment group experienced mild hypoglycemic symptoms. In the alogliptin group, one participant was treated with insulin, and another patient was treated with diet only. In the metformin group, two participants were treated with insulin. One patient in the metformin group wanted to withdraw consent and discontinue metformin because of severe gastrointestinal symptoms, such as severe nausea and vomiting. Metformin was discontinued and replaced with intensive insulin therapy by the investigator for two patients with serious adverse effects (esophageal cancer and pneumonitis).

DISCUSSION

We carried out the present open-label randomized, parallel trial comparing the DPP-IV inhibitor, alogliptin, and metformin as add-on to current hypoglycemic agents in Japanese participants with type 2 diabetes. Our study was the first to investigate the pleiotropic effects of these drugs, and identify clinical factors associated with reduced bodyweight and glucose levels after add-on therapy.

In the present study, alogliptin significantly increased bodyweight, BMI and fat mass, whereas metformin had no effect on
body composition. In addition, BMI at baseline was associated with changes in bodyweight negatively in the metformin group and positively in the alogliptin group. These findings suggest that metformin and alogliptin exert opposite effects on bodyweight in diabetes patients who were overweight. In mice, alogliptin is neutral in body composition, but decreases the weight in diabetes patients who were overweight. In humans, a recent meta-analysis found that DPP-IV inhibitors increase bodyweight in Asian and Caucasian patients with type 2 diabetes, the finding is in agreement with our present study. In contrast, metformin is well known to reduce appetite, caloric food intake and bodyweight in diabetes patients with obesity. In the meta-analysis of metformin versus placebo/sulfonylureas studies, metformin was superior in reducing bodyweight against sulfonylureas, whereas it had no advantage in bodyweight against a placebo. In another meta-analysis of metformin versus DPP-IV inhibitors, metformin was associated with more weight loss compared with DPP-IV inhibitors. However, metformin doses in these studies were as high as 2,000–3,000 mg/day, whereas mean doses of metformin in the present study were as small as 1,076 ± 430 mg/day. Therefore, evidence is still lacking on the effects of a relatively small dose of metformin on the body composition of relatively lean Asian people with type 2 diabetes. In this regard, we conclude that moderate doses of metformin ameliorate hyperglycemia at least without affecting bodyweight in relatively lean (BMI 24.6 ± 5.1 kg/m²) Japanese patients with type 2 diabetes.

Metformin and alogliptin significantly decreased FPG and HbA1c, and increased 1,5-anhydroglucitol. The β-cell function index, C-peptide immunoreactivity index, increased significantly in both treatment groups. Previous clinical studies have shown that DPP-IV inhibitors significantly improved indices of β-cell function, including homeostasis model assessment of β-cell function, the proinsulin-to-insulin ratio and the insulinogenic index, with no effect on insulin resistance. Furthermore, metformin is thought to induce glucagon-like peptide-1 (GLP-1) secretion through the bile acid-TGR5 pathway. Alogliptin and metformin significantly decreased bone alkaline phosphatase in the present study. Metformin has been shown to have a direct inhibitory effect on osteoclast differentiation in vitro and prevent bone loss in ovariectomized rats. A recent meta-analysis found that the risk of bone fracture was significantly reduced in participants treated with DPP-IV inhibitors. It might be that DPP-IV inhibitors increase bone mineral density by increasing active gastric inhibitory polypeptide. Furthermore, GLP-1 might be a useful therapeutic agent for improving the deficient bone formation and structure associated with glucose intolerance. We found that alogliptin, but not metformin, significantly increased leptin levels. Interestingly, changes in leptin concentration were not correlated with changes in body composition variables, such as bodyweight (r = 0.275, P = 0.109), BMI (r = 0.184, P = 0.124), waist circumference (r = 0.023, P = 0.852) and fat mass (r = 0.126, P = 0.293) in the alogliptin group. These findings suggest that alogliptin induces leptin resistance through as yet unknown mechanisms.

In agreement with the previous findings that high baseline HbA1c levels have been shown to be a strong predictor of the hypoglycemic effect of antidiabetic drugs, we found that a higher baseline level of HbA1c was significantly associated with a reduction in HbA1c in both the metformin and alogliptin groups. In contrast, our finding that body composition variables, such as body weight, BMI and fat mass, were not associated with the glucose-lowering effect of alogliptin is inconsistent with previous reports. Our finding was unexpected, because DPP-4 activity is positively associated with BMI and waist-to-hip ratio, and because DPP-IV inhibitors have been shown to significantly lower blood glucose in participants who were overweight.

Table 3 | Changes in treatment satisfaction

|                | Metformin |         | Alogliptin |         |        |        |
|----------------|-----------|---------|------------|---------|--------|--------|
|                | Week 0    | Week 12 |            | Week 0  | Week 12|        |
| Item 1         | 4.5 ± 1.2 | 3.7 ± 1.4| 0.029      | 4.0 ± 1.5| 4.1 ± 1.3| 0.054  | 0.029  |
| Item 2         | 4.2 ± 1.2 | 3.4 ± 1.2| 0.030      | 3.9 ± 1.3| 2.9 ± 1.7| 0.002  | 0.743  |
| Item 3         | 1.1 ± 1.5 | 1.7 ± 1.6| 0.114      | 1.4 ± 1.4| 2.1 ± 1.4| 0.034  | 0.710  |
| Item 4         | 4.6 ± 1.2 | 4.3 ± 1.0| 0.392      | 3.5 ± 1.6| 4.6 ± 1.2| 0.003  | 0.005  |
| Item 5         | 4.6 ± 1.3 | 4.2 ± 1.0| 0.189      | 3.8 ± 1.7| 4.2 ± 1.2| 0.146  | 0.049  |
| Item 6         | 4.2 ± 1.4 | 4.3 ± 1.0| 0.644      | 3.6 ± 1.4| 4.0 ± 1.1| 0.030  | 0.321  |
| Item 7         | 4.3 ± 1.6 | 4.1 ± 1.2| 0.455      | 3.5 ± 1.3| 4.1 ± 1.4| 0.006  | 0.030  |
| Item 8         | 4.7 ± 1.0 | 4.5 ± 1.2| 0.581      | 4.0 ± 1.7| 4.7 ± 1.2| 0.041  | 0.051  |
| SUM            | 26.6 ± 6.3| 25.1 ± 6.0| 0.316      | 21.6 ± 7.9| 25.5 ± 5.8| 0.002  | 0.005  |

Data are mean ± standard deviation. *P-value for the intragroup comparison (baseline vs 12 weeks); **P-value for the intergroup comparison (change from baseline between groups). “Satisfaction with the treatment” for item 1, “Perceived hyperglycemia frequency” for item 2, “Perceived hypoglycemia frequency” for item 3, “Convenience of the treatment” for item 4, “Flexibility of the treatment” for item 5, “Understanding of your diabetes” for item 6, “Recommend to others” for item 7 and “Wish to continue treatment” for item 8. Treatment satisfaction score (SUM): sum of items 1, 4, 5, 6, 7 and 8.
with a low baseline BMI. C-peptide immunoreactivity was not associated with a reduction in FPG and HbA1c in both the metformin and alogliptin groups in the present study. This finding is in contrast to that of a recent clinical trial in which low baseline β-cell function was an independent predictor of a good response in participants undergoing combination therapy with sitagliptin and metformin. The administration of ω-3 polyunsaturated fatty acids has been reported to induce GLP-1 secretion in mice. Docosahexaenoic acid stimulation of G protein-coupled receptor 120, a receptor for unstructured long-chain fatty acids, has been shown to promote GLP-1 secretion in vitro. However, in contrast to previous reports, we did not find an association between docosahexaenoic acid or eicosapentaenoic acid baseline levels and the alogliptin-mediated hypoglycemic effect. The concomitantly used drug, such as sulphonylurea and insulin, did not predict the changes in bodyweight and glucose levels in either group.

Three of four participants who experienced mild hypoglycemic symptoms in the present study were treated with insulin. The Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results trial suggested that the insulin-treated participants experienced hypoglycemia more often compared with those treated with other oral hypoglycemic agents. Fewer than 30% of the participants in the metformin group experienced gastrointestinal symptoms. Alogliptin was well tolerated, and the rate of adverse events was lower than that for metformin. A previous meta-analysis found that the risk of adverse gastrointestinal effects was lower for DPP-IV inhibitor monotherapy than for metformin monotherapy. In terms of quality of life, the Diabetes Treatment Satisfaction Questionnaire scores for convenience, understanding of your diabetes, and Treatment Satisfaction Questionnaire scores for convenience, understanding of your diabetes, were carried over after cross-over. Therefore, we mainly present the results from the first half of the dataset in the present study, and add the cross-over data in Table S3.

In summary, alogliptin, but not metformin, was associated with an increase in bodyweight. Metformin and alogliptin exert opposite effects on bodyweight in type 2 diabetes patients who are overweight. The higher the BMI, the more metformin reduces bodyweight and alogliptin increases weight.

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All authors have read and approved the manuscript, and all agree with submission to your journal. All authors contributed significantly to this work.

DISCLOSURE
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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1 | Characteristics of the study participants.
Table S2 | Changes in plasma fatty acid composition.
Table S3 | Treatment effects of metformin or alogliptin on body composition and metabolic parameters in the cross-over trial.
Table S4 | (a) Factors associated with changes in fasting plasma glucose. (b) Factors associated with changes in glycated hemoglobin.
Table S5 | Adverse events.
Figure S1 | Flow diagram of the study.