gram analysis were performed as needed using the SPSS Statistics 20 software package (IBM, Armonk, NY, USA). In all comparisons, the significance level was set at $P < .05$.

Results

The clinical profiles of the controls and the patients with diabetes are shown in Table 1. As a group, the patients with diabetes were about 5 years younger than the controls. By definition, the patients with diabetes had a significantly higher maximum HbA1c than the controls (median; 8.8% vs 5.7%, $P < .01$). Those in the diabetes group had a significantly lower eGFR than the controls ($P = .03$). Other continuous variables showed no significant differences between the two groups. The prevalence of CHD was significantly higher in the patients with diabetes than in the controls, whereas the prevalence of cerebral vascular disease and malignancy, including malignancy diagnosed at autopsy, showed no significant intergroup difference. The mean(±SD) duration of diabetes was 19(±10) years in affected individuals. Thirty-nine (83%) patients with diabetes had a history of treatment with HA: 57% with oral agents only, 15% with insulin only, and 11% with both oral agents and insulin.

Representative FISH images of control and diabetes specimens are shown in Figure 1. Multiple small signals for the telomere (red) and centromere (green) were clearly observed in the nuclei of the islet, the exocrine, and the endothelial cells. Staining with anti-insulin and antiglucagon antibodies demonstrated strong positivity in the cytoplasm of the respective islet cells.

The NTCRβ value was significantly lower in the patients with diabetes than in the controls (Figure 2, $P < .01$), despite the slightly younger age of the former patients. NTCRα was also significantly lower in the patients with diabetes (Figure 2, $P = .01$). Importantly, fractional shortening in the patients with diabetes relative to the controls was 27 ± 25% for β cells and 15 ± 27% for α cells, and the difference between the two cell types was statistically significant ($P < .01$). In the entire group, NTCRβ and NTCRα were positively correlated ($P < .01$). The HbA1c level was significantly and inversely correlated with NTCRβ and NTCRα (Figure 3).

The value of eGFR was positively correlated with

Table 1. Clinical profiles of the control subjects and patients with diabetes.

	Control (n = 51)	Diabetes (n = 47)	P value
Age (yr)	84 (78–90)	79 (75–85)	0.01
Male (%)	45.1	63.8	0.07
BMI (kg/m^2)	17.6 (15.0–20.0)	18.4 (15.2–20.2)	0.44
HbA1c (%)	5.7 (5.4–6.0)	8.8 (7.5–10.4)	<0.01
TC (mg/100 ml)	160 (138–201)	149 (123–183)	0.22
TG (mg/100 ml)	79 (56–106)	90 (59–116)	0.45
HDL-cholesterol (mg/100 ml)	45 (34–59)	39 (30–48)	0.14
eGFR (mL/min/1.73 m^2)	52 (35–82)	42 (17–64)	0.03
CHD history (%)	21.3	47.7	<0.01
CVD history (%)	30.4	35.6	0.66
Malignancy (%)	25.5	42.6	0.09

Data for continuous variables are medians (25^{th}-75^{th} percentiles). TC, total cholesterol; TG, triglyceride; eGFR, estimated glomerular filtration rate; CHD, coronary heart disease; CVD, cerebral vascular disease. BMI values were calculated from height and weight at autopsy. For HbA1c, the maximum value ever recorded was adopted, and for other chemical data, the first data obtained during the last hospitalization or the most recent data obtained before admission were used. CHD and malignancy included cases in which diagnoses were made after autopsy. Mann-Whitney U tests were performed to compare continuous variables. Sex, IHD, CVD, and malignancy were evaluated using Fisher's exact test.

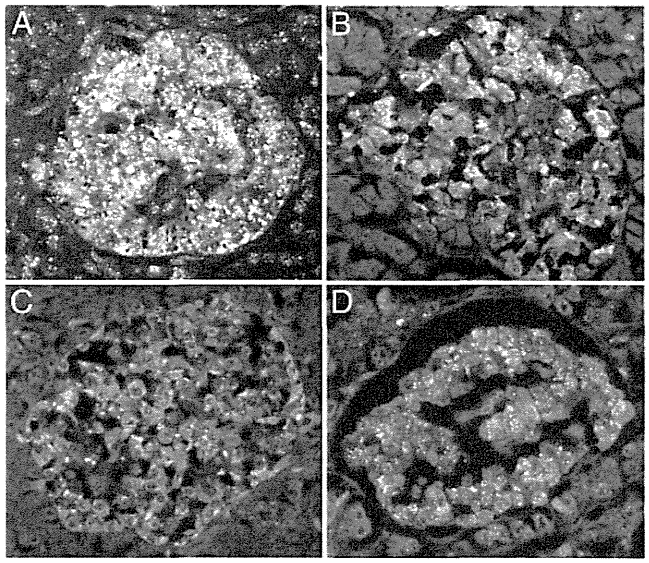

Figure 1. Representative FISH images with immunofluorescence for insulin and glucagon in specimens from a control patient and a patient with type 2 diabetes mellitus. Original magnification, ×40. In A and B: cytoplasmic green, insulin-Cy-5 signals; nuclear red, telomere-Cy3 signals; nuclear green, centromere-FITC signals, nuclear blue, DAPI counterstaining for DNA; stromal yellow signals, nonspecific fluorescence. Multiple small signals of telomeres and centromeres are evident within the nuclei. Image of a normal control specimen from a 65-year-old woman (A): the NTCR of insulin signal-positive cells was 1.98 in this example. Images of a specimen from a 78-year-old woman with type 2 diabetes (B): the NTCR of the insulin signal-positive cells was 0.49 in this example. In C and D: cytoplasmic pink, glucagon-Cy-5 signals; nuclear red, telomere-Cy3 signals; nuclear green, centromere-FITC signals; nuclear blue, DAPI counterstaining for DNA: stromal brownish yellow signals, nonspecific fluorescence. Multiple small signals of telomeres and centromeres are evident within the nuclei. Image of a normal control specimen from a 74-year-old man (C): the NTCR of glucagon-signal positive cells was 1.53 in this exsample. Image of a specimen from an 81-year-old man with type 2 diabetes (D): the NTCR of glucagon signal-positive cells was 0.50 in this example.

NTCRβ ($P = .04$) but not with NTCRα ($P = .32$). On the other hand, there was no significant correlation between age and NTCRβ or NTCRα in this population (data not shown). Multivariate analysis showed that HbA1c was independently correlated with NTCRβ ($P < .01$) after adjustment for eGFR. Addition of age and sex as covariates did not affect the result.

On the basis of a history of treatment with HA including insulin, the patients were categorized as HA+ and HA-. As shown in Figure 4, the values for NTCRβ in HA+ patients were significantly lower than those in HA- patients. In contrast, NTCRα did not differ significantly between the HA+ and HA- groups.

Finally, the pattern of distribution of NTCRβ and NTCRα was compared between the patients with diabetes and the controls. As shown in Figure 5, the pattern differed significantly between the two groups, the mode in the patients with diabetes showing a clear shift to the left relative to the controls. Also, the distribution in the controls was non-normal and positively skewed, whereas in the patients with diabetes the distribution of NTCRβ and

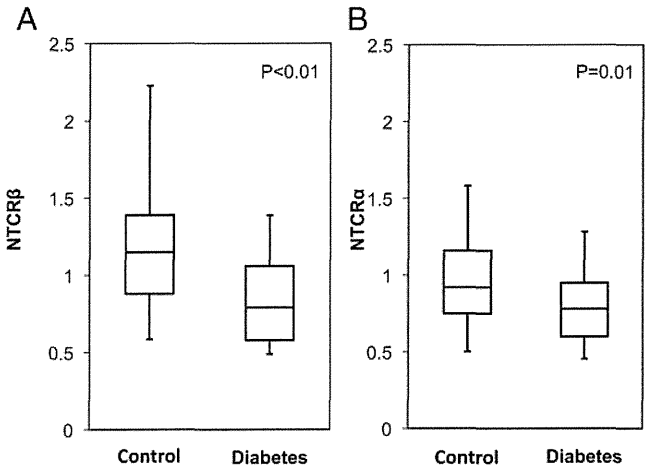

Figure 2. Box plots of NTCRβ (A) and NTCRα (B) in the controls and the patients with diabetes. Boxes represent the 25th and 75th percentiles, the bands inside the boxes are medians, and the whiskers are the fifth and 95th percentiles. NTCRα, NTCRs for α cells; NTCRβ, NTCR for β cells.

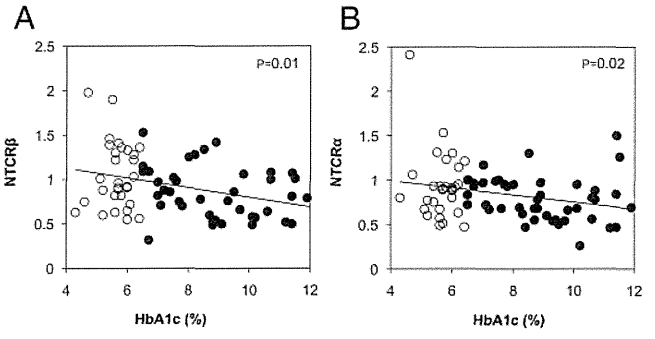

Figure 3. Correlation between maximum recorded HbA1c level and NTCRβ and NTCRα. Solid circles, the patients with diabetes; clear circles, the controls. The slope (95%CI) and the y-intercept (95%CI) for NTCRβ were −0.05 (-0.09 - −0.02) and 1.34 (1.06–1.62), respectively, and the corresponding values for NTCRα were −0.04 (-0.07 - −0.01) and 1.15 (0.88–1.42), respectively.

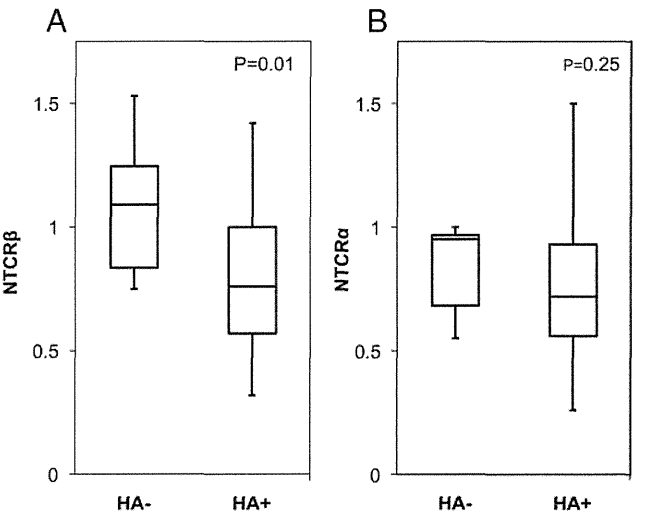

Figure 4. Box plots of NTCRβ (A) and NTCRα (B) in the patients with diabetes with (HA+) and without (HA-) a history of treatment with hypoglycemic agents. Boxes represent the 25th and 75th percentiles, the bands inside the boxes are medians, and the whiskers display the full ranges of variation (from min to max).

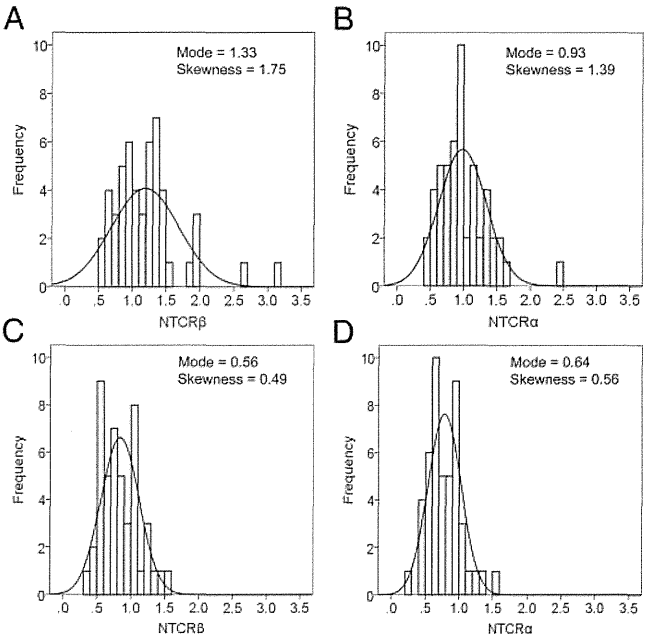

Figure 5. Histogram of the distribution of NTCRβ and NTCRα in the controls (upper panels, A, β cells; B, α cells) and the patients with diabetes (lower panels, C, β cells; D, α cells). In the patients with diabetes, the mode was shifted to the left in both β and α cells. In the controls, the pattern of distribution was significantly different from normal: $P = <0.01$ by Kolmogorov-Smirnov test for A (β cells) and $P = .01$ for B (α cells). In diabetes, it was not significantly different from normal: $P > .20$ by K-S test for C (β cells) and $P > .20$ for D (α cells). Solid lines indicate a normal distribution. The difference between the controls and the patients with diabetes was more pronounced for β cells than for α cells. Skewness was calculated as $\Sigma((x - \mu)/\sigma)^3/N$. For details see text.

NTCRα was not significantly different from a normal distribution. This phenomenon was qualitatively similar for both NTCRβ and NTCRα. However, the difference between the controls and the patients with diabetes appeared qualitatively more pronounced for β cells than for α cells, as indicated by larger differences in the modal and skewness values. Namely, the modal values of NTCRα were 0.93 in the patients with diabetes and 0.64 in the controls, and those of NTCRβ were 1.33 in the patients with diabetes and 0.56 in the controls; the skewness values of NTCRα were 1.39 in the patients with diabetes and 0.56 in the controls, and those of NTCRβ were 1.75 in the patients with diabetes and 0.49 in the controls.

Discussion

In this study, we examined for the first time the telomere length of β cells in patients with diabetes, and found that it was significantly shorter than in the control subjects. The findings obtained in experimental animals have suggested that β cell dysfunction in diabetes may be at least partly induced by telomere shortening in these cells (19, 20). However, telomere length in β cells has never been evaluated in patients with diabetes.

Importantly, although telomere attrition was also found in the α cells of the patients with diabetes, the attrition was significantly more pronounced in β cells. In addition, the telomeres of β, but not α, cells were significantly shorter in patients with a history of HA use than in those without. Several mechanisms can be considered to account for the differences. First, it has been shown that hyperglycemia induces replication of existing β cells to match the increased demand for insulin secretion, whereas this is not the case for α cells (25). This β-cell burden resulting from sustained hyperglycemia would lead to excessive telomere attrition in this cell type. Second, Sakuraba et al reported that β cell mass in patients with type 2 diabetes was reduced and associated with positive staining for oxidative stress-related substances (26). Oxidative stress induced by high-glucose conditions may have caused telomerase dysfunction selectively in the β cells (27). The data for markers of oxidative stress might have been helpful for interpretation of the data because telomeres are highly susceptible to oxidative stress. Unfortunately, however, we were unable to obtain or measure such data. Third, it was possible that drugs such as sulfonylurea (SU) might have selectively accelerated telomere attrition in the β cells. SU has been commonly employed as HA in Japan (28) and it reportedly induces apoptotic β cell death (29, 30). Alternatively, the fact that subjects using HA have shorter telomeres suggested they may have had a longer duration of disease and higher glucose levels, which had accelerated the attrition of β cell telomeres. In contrast, α cell telomere attrition might be a reflection of generalized telomere attrition in diabetes.

It was noteworthy that patients with higher HbA1c had significantly shorter β and α cell telomeres. Such an inverse correlation between HbA1c and telomere length in peripheral blood cells has been reported in one study (17) but not in others (13, 15, 31).

The patients in the diabetes group had lower eGFR levels than the controls, and the eGFR value was significantly correlated with telomere length in β cells, although the data should be interpreted with some caution because eGFR is not a strictly valid estimation method in terminally ill patients. From these results and previous reports that have suggested a deleterious effect of renal dysfunction on leukocyte telomere length (32, 33), one may argue that the telomeres of patients with diabetes have shortened as a result of renal dysfunction, and not as a result of diabetes itself. However, our multivariate analysis showed that HbA1c was independently and inversely correlated with β cell telomere length after adjustment for renal function, suggesting that hyperglycemia itself was a key factor for telomere attrition in this population.

The prevalence of malignancy was slightly higher in patients with diabetes than in the controls. However, the difference was not statistically significant and, as far as we are aware, no previous study has shown differences in β cell telomere attrition in individuals with malignancy.

We previously found that in normal cells telomere length distribution was positively skewed, ie, tailing off to the right (34). This distribution pattern was preserved even in aged cells. Namely, in TIG-1 cells, the right-skewed distribution pattern of telomere length was preserved even at population doubling levels (PDLs) representing the stage of extreme cell senescence (13, 32, 60, and 62). This right-skewed distribution was also the case for NTCRβ and NTCRα in the controls. The fact that the telomere length distribution in patients with diabetes did not differ significantly from a normal distribution, showing little positive skewness, suggested that the cells with longer telomeres might have preferentially perished in diabetes. It is known that somatic stem cells in humans have low telomerase activity, unlike somatic cells in which telomerase activity is absent (35). The presence of cells with telomerase activity would account for the skewed distribution of telomere length to the right in normal individuals. In fact, upon analysis of the NTCR distribution of individual β and αcells in each nondiabetic subject, almost all of them held substantial numbers of cells with a skewed long telomere length, and skewness was significantly smaller in the patients with diabetes than in the controls, for both β and

α cells (data not shown). Together, these facts indicate that the cells in the right-hand tail of distribution in the controls might represent a cluster of progenitor cells. If this hypothesis holds true, such progenitor cells would be more susceptible to damage in diabetes, further leading to impaired differentiation and proliferation of β cells, which in turn might lead to deterioration of insulin secretion capacity in patients with diabetes. Also, the preferential disappearance of β cells with longer telomere could strongly account for the high incident rate of diabetes caused by telomere shortening.

Probably as a result of the narrow age distribution of the patients analyzed in this study, no significant effects of age on telomere length were observed in either α or β cells. This accords with the previous findings from our group that telomere length in the cerebral gray matter and adenohypophyseal cells was not inversely correlated with age among subjects > 60 years of age, although they were significantly shorter in elderly (>60 years) than in younger (<1 year) subjects when a group-wise comparison was made (36, 37).

We., mean: 2.4 years) and an olde and background used autopsy specimens for determining telomere length because of the difficulty in obtaining specimens of the pancreas from biopsy or surgically resected materials. It has been demonstrated that there is no significant postmortem shortening of telomeric DNA if autolysis is absent (38), and that this is also the case in pancreatic specimens (39).

There were some limitations to this study. First, since it was cross-sectional in design, we were unable to elucidate with certainty the causality of telomere shortening for the onset and progression of diabetes. As described above, telomerase deficiency in mice resulted in reduction of β cell mass and impaired insulin release in response to a glucose challenge (19). In a recent prospective cohort study of native Americans, it has been reported that short leukocyte telomere length are related to the incidence of diabetes (40). On the other hand, as also described above, high-glucose conditions induce oxidative stress and may cause selective telomerase dysfunction in β cells (27). Thus, causality in both directions, ie, an effect of diabetes on telomere length and an effect of telomere length on diabetes, is most likely. Second, because no data for serum insulin or C-peptide were obtained, we were unable to evaluate the relationship between β cell telomere length and insulin secretion.

In conclusion, we have demonstrated telomere attrition in β cells of patients with type 2 diabetes. A sustained high plasma glucose level and administration of hypoglycemic agents may be the key factors causing telomere shortening in β cells. Nevertheless, β cell telomere attrition, and reduction of β cell mass/impaired insulin secretion/β cell overload, sustained hyperglycemia, and use of hypoglycemic agents may constitute a vicious cycle, so that β cell telomere attrition may well be self-perpetuating. A comprehensive understanding of age-related telomere shortening and its relationship to hyperglycemia would be important for clarifying the pathophysiology of type 2 diabetes. Our present findings will be of help for clarifying the mechanisms of β cell senescence and dysfunction in humans, and for developing new therapeutic approaches for diabetes focusing on maintenance of telomere length in pancreatic β cells.

Acknowledgments

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research letter

Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin compared with α-glucosidase inhibitor in Japanese patients with type 2 diabetes inadequately controlled on sulfonylurea alone (SUCCESS-2): a multicenter, randomized, open-label, non-inferiority trial

We assessed the efficacy and safety of sitagliptin compared with α-glucosidase inhibitor (αGI) in 120 of Japanese patients with type 2 diabetes mellitus (T2DM) inadequately controlled on stable ≤2 mg/day glimepiride alone [mean hemoglobin A1c (HbA1c) 7.7%] by the randomized, active-controlled, non-inferiority trial. Patients were randomly assigned to receive additional sitagliptin or αGI for 24 weeks. The primary endpoint was change in HbA1c from baseline to week 12. After 12 weeks, sitagliptin reduced HbA1c by −0.44% ($p < 0.001$) relative to αGI. At 24 weeks, the reduction was almost identical between the groups (−0.091%, $p = 0.47$). Gastrointestinal disorders were more common with αGI than with sitagliptin, but only minor hypoglycaemia occurred in both groups at similar frequency. These data suggested that sitagliptin was not inferior to αGI for reduction of HbA1c in Japanese T2DM patients receiving glimepiride alone, and well tolerated with minimum risk of gastrointestinal symptoms and hypoglycaemia.

Keywords: α-glucosidase inhibitor, DPP-IV inhibitor, randomized trial, sulphonylureas, type 2 diabetes

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Introduction

To prevent vascular complications in type 2 diabetes mellitus (T2DM), blood glucose levels should be maintained to as close to normal levels as possible, while preventing hypoglycaemia and weight gain [1]. Sulfonylureas, potent oral insulin secretagogues, are commonly used for T2DM patients [1,2], but most of them usually requires multiple drugs to attain or maintain glycaemic control [3]. The recent oral antidiabetic drug dipeptidyl peptidase-4 (DPP-4) inhibitor, including sitagliptin, lowers blood glucose levels by inhibiting the degradation of incretin hormones such as glucagon-like peptide-1 (GLP-1) [4] with the reportedly low risk of hypoglycaemia and weight gain [5,6]. On the other hand, α-glucosidase inhibitor (αGI) has been widely used in Japan for delaying the absorption of glucose and decreasing the postprandial glucose excursion with low risk of hypoglycaemia as well as gaining body weight [7]. Therefore, in the present SUCCESS-2 (Study for an Ultimate Combination therapy to Control diabetES with Sitagliptin) trial, we aimed to assess the efficacy and safety of sitagliptin compared with αGI in Japanese patients with T2DM inadequately controlled on sulfonylurea alone.

Subjects and Methods

This multicenter, comparative, parallel-group, active-controlled, randomized, open-label and non-inferiority trial was undertaken at 37 sites in Chiba prefecture, Japan. The study was approved by each center's ethics committee and registered (UMIN-ID: UMIN 000004674; http://www.umin.ac.jp/ctr/). Eligible study participants were aged 20–79 years, had T2DM, had been receiving ≤2 mg/day glimepiride alone for ≥2 months, and had an hemoglobin A1c (HbA1c) of 6.9–8.8%. All patients provided written informed consent before participation, and were randomly assigned to either 24 weeks of treatment with sitagliptin (50 mg once a day) or αGI (0.2 mg voglibose or 50 mg miglitol three times a day) in addition to glimepiride (dose unchanged throughout the study). The primary efficacy endpoint was a change in HbA1c from baseline to week 12. Safety and tolerability were also assessed throughout the study. The details about secondary endpoints, data management and statistical analysis were described in Detailed Subjects and Methods (Appendix S1, Supporting Information).

Results

Details of demographics throughout this study is showed as flow chart in Figure S1. Patient characteristics were well balanced between treatment groups (Table S1).

HbA1c was significantly reduced with sitagliptin when compared with αGI at 12 weeks after treatment. However, at 24 weeks, the reduction in HbA1c from baseline was similar between the groups (Figure 1A, B). At 12 weeks, adjusted mean reductions in HbA1c from baseline were −0.72% (95% confidence interval (CI): −0.86 to −0.57) with sitagliptin and −0.28% (−0.43 to −0.12) with αGI in the full analysis set (Figure 1B). The least squares mean of the treatment difference

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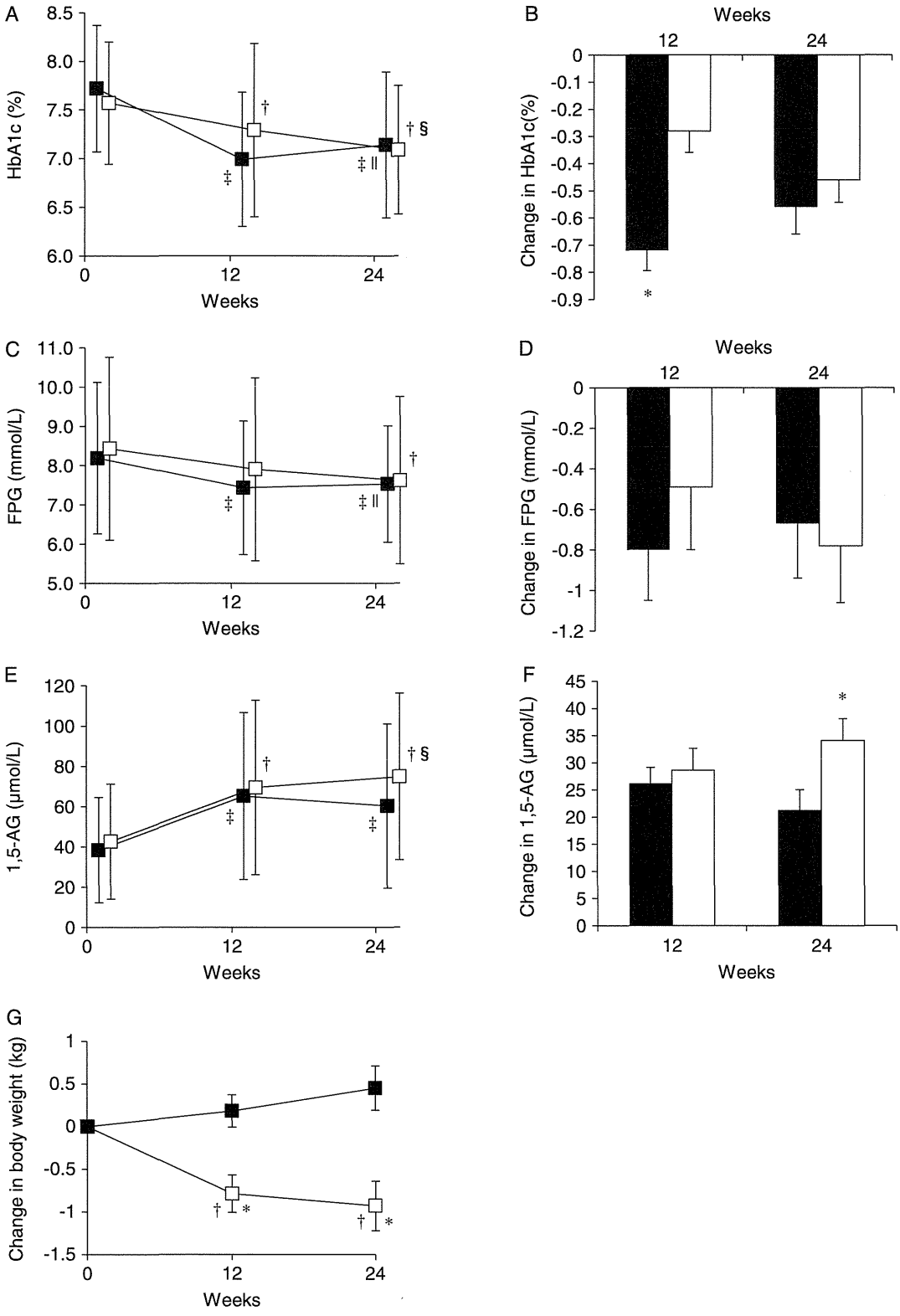

Figure 1. Changes in representative endpoints. (A) Mean ± standard deviation (s.d.) hemoglobin A1c (HbA1c) during the study period. (B) Change ± standard error (s.e.) from baseline in HbA1c values. (C) Mean ± s.d. fasting plasma glucose (FPG) during the study period. (D) Change ± s.e. from baseline in FPG values. (E) Mean ± s.d. 1,5-anhydroglucitol (AG) during the study period. (F) Change ± s.e. from baseline in 1,5-AG values. (G) Change ± s.e. from baseline in body weight. Black squares and bars represent sitagliptin, white squares and bars represent α-glucosidase inhibitor (αGI). *$P < 0.05$ between sitagliptin and αGI with same week. †, §$P < 0.05$ compared with week 0 or week 12 in αGI, respectively. ‡, ||$P < 0.05$ compared with week 0 or week 12 in sitagliptin, respectively.

Table 1. Changes in secondary endpoints from baseline to week 12 and 24*.

	Mean change from baseline (week 12)			Mean change from baseline (week 24)		
	Sitagliptin	α-Glucosidase inhibitor	P value†	Sitagliptin	α-Glucosidase inhibitor	P value†
Glycaemic control						
Glycoalbumin (%)	−2.6 (−3.1 to −2.1)	−1.0 (−1.6 to −0.47)	<0.0001	−1.9 (−2.6 to −1.2)	−1.5 (−2.1 to −1.0)	0.35
β-cell function						
Fasting insulin (pmol/l)	7.3 (−5.4 to 19.9)	0.69 (−14.7 to 16.1)	0.50	−2.39 (−12.1 to 7.4)	−6.7 (−19.7 to 6.4)	0.59
Fasting C-peptide (nmol/l)	0.04 (−0.04 to 0.13)	0.026 (−0.083 to 0.14)	0.80	0.0007 (−0.063 to 0.063)	−0.03 (−0.13 to 0.059)	0.53
Fasting proinsulin-to-insulin molar ratio	−0.22 (−0.49 to 0.041)	−0.0010 (−0.081 to 0.079)	0.12	−0.19 (−0.47 to 0.081)	−0.034 (−0.10 to 0.036)	0.28
HOMA-β	20.1 (10.1 to 30.1)	11.4 (−1.3 to 24.2)	0.28	9.9 (2.5 to 17.3)	6.0 (−6.3 to 18.2)	0.58
HOMA-IR	−0.19 (−1.2 to 0.83)	−0.22 (−1.5 to 1.1)	0.98	−0.62 (−1.6 to 0.35)	−0.73 (−1.9 to 0.47)	0.88
Vital signs						
Systolic blood pressure (mmHg)	0.93 (−2.0 to 3.9)	−4.9 (−9.6 to −0.19)	0.033	0.80 (−3.1 to 4.7)	−2.9 (−7.0 to 1.2)	0.19
Diastolic blood pressure (mmHg)	−1.00 (−2.7 to 0.76)	−3.3 (−6.1 to 0.50)	0.15	−1.3 (−4.1 to 1.4)	−2.4 (−5.3 to 0.41)	0.59
Heart rate (beats per min)	−1.3 (−3.9 to 1.3)	−0.79 (−3.5 to 2.0)	0.79	0.21 (−2.5 to 2.9)	−0.33 (−2.7 to 2.0)	0.77
Fasting lipid profiles						
Total cholesterol (mmol/l)	0.1 (−0.09 to 0.24)	−0.001 (−0.15 to 0.15)	0.50	−0.05 (−0.22 to 0.12)	0.08 (−0.11 to 0.27)	0.31
LDL cholesterol (mmol/l)	0.1 (−0.05 to 0.21)	0.1 (−0.07 to 0.19)	0.83	0.01 (−0.13 to 0.16)	0.09 (−0.07 to 0.26)	0.46
HDL cholesterol (mmol/l)	0.01 (−0.04 to 0.06)	−0.02 (−0.1 to 0.02)	0.33	0.001 (−0.04 to 0.048)	0.02 (−0.02 to 0.06)	0.48
Triglycerides (mmol/l)	0.1 (−0.14 to 0.30)	−0.1 (−0.28 to 0.065)	0.19	−0.03 (−0.22 to 0.16)	−0.15 (−0.33 to 0.014)	0.31
Non-HDL cholesterol (mmol/l)	0.1 (−0.09 to 0.21)	0.02 (−0.1 to 0.1)	0.68	−0.05 (−0.20 to 0.11)	0.06 (−0.11 to 0.23)	0.36

LDL, low density lipoprotein; HDL, high density lipoprotein; HOMA-β, homoeostasis model assessment of β-cell function; HOMA-IR, homoeostasis model assessment of insulin resistance.
*Changes from baseline to week 12 or 24 are expressed as least squares mean change (95% confidence interval).
†P value was calculated by comparing the difference from baseline between sitagliptin and α-glucosidase inhibitor.

was −0.44% (−0.65 to −0.23) ($p < 0.001$). This result met the predefined non-inferiority criterion of 0.25% and after that confirmed the superiority of sitagliptin over αGI at 12 weeks as the primary endpoint. On the other hand, at 24 weeks, adjusted mean reductions in HbA1c from baseline were −0.56% (95% CI −0.75 to −0.36) with sitagliptin and −0.46% (−0.62 to −0.30) with αGI (difference −0.091%, 95% CI −0.34 to 0.16) ($p = 0.47$) (Figure 1B).

Treatment with both sitagliptin and αGI reduced fasting plasma glucose (FPG) at 12 and 24 weeks compared to baseline (Figure 1C, D). The least squares mean of the treatment difference in FPG was −0.32 mmol/l (95% CI −1.1 to −0.44, $p = 0.40$) and 0.11 mmol/l (95% CI −0.64 to 0.87, $p = 0.77$) at 12 and 24 weeks, respectively. Conversely, αGI equally elevated 1,5-anhydroglucitol (1,5-AG) as the same level as sitagliptin at 12 weeks, then continuously increased the value until 24 weeks with significant difference than sitagliptin (Figure 1E, F). The least squares mean of the treatment difference in 1,5-AG was −2.62 μmol/l (95% CI −12.2 to 6.7, $p = 0.58$) and −12.8 μmol/l (95% CI −23.2 to −2.4, $p = 0.016$) at 12 and 24 weeks, respectively.

Body weight did not change markedly from baseline in the sitagliptin group. However, αGI resulted in a significant decrease of body weight from baseline (Figure 1G). The adjusted mean differences were 0.97 kg (95% CI 0.38 to 1.5; $p = 0.0014$) and 1.3 kg (0.62 to 2.1; $p = 0.0005$) at 12 and 24 weeks, respectively, between the two groups.

Changes in other secondary endpoints are summarized in Table 1 and Table S3. Contrary to expectations, the parameters of insulin secretion did not show notable differences between the groups.

The treatment-emergent adverse events are summarized in Table S2. In summary, the frequency of overall adverse events as well as minor hypoglycaemia were similar in both groups. Additionally, the assigned medication compliance was lower with αGI than sitagliptin (94.4 vs. 97.6%; $p = 0.019$), but the small difference was not considered to influence the result of comparison of glucose lowering effect between those drugs.

Discussion

Our study revealed that sitagliptin reduced HbA1c levels as effectively as the αGI in combination with sulfonylurea, although there were some differences in the patterns of glucose-lowering effects. Sitagliptin rapidly reduced HbA1c and FPG levels at 12 weeks, although this effect was slightly blunted at 24 weeks. In contrast, the αGI showed gradual and continuous decrease of HbA1c and FPG throughout 24 weeks.

A chronological change of glycaemic lowering effect with sitagliptin was more or less similar to the inverted pattern of change in homoeostasis model assessment of β-cell function (HOMA-β), which significantly increased at 12 weeks followed by a slight, but significant, decrease at 24 weeks (data not shown). The result would suggest that the rapid reduction of HbA1c in sitagliptin group was because of the additive effect of two insulin secretagogues, sitagliptin and glimepiride, with different mechanism for stimulation of insulin secretion [4].

On the other hand, all the indicators of insulin secretion did not change significantly in the αGI group despite the gradual and continuous decrease in HbA1c and FPG levels (data not shown). In addition, the αGI also improved 1,5-AG, an indicator of postprandial plasma glucose levels [8], gradually and continuously with significance at each time periods as observed in HbA1c levels. Therefore, it was proposed that the reduction of HbA1c by the αGI relatively reflected the improvement in postprandial plasma glucose levels rather than in FPG, which was brought without a significant enhancement of insulin secretion [9,10] even in combination with sulfonylurea, in contrast to sitagliptin.

α-Glucosidase inhibitor significantly and continuously decreased body weight up to 24 weeks compared with sitagliptin. The result suggested that the effect of αGI in reducing body weight was elicited even in the combination therapy with low dose of sulfonylurea as well as showed with the administration of αGI alone in previous studies [9,11]. In fact, it was also reported in some clinical studies performed abroad that αGI had no effect on body weight [10,12]. However, those studies used much higher doses of sulfonylurea with αGI this study.

In conclusion, this study showed that the glucose-lowering efficacy of sitagliptin was similar to that of αGI and was safe when used in combination with $\leq$2 mg/day of glimepiride in Japanese type 2 diabetic patients. The results may open the way for choosing optimal combination of drugs to achieve good glycaemic control.

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All the authors participated in the design of the study and the planning of the analyses. The first author wrote the first draft of the manuscript, and all the authors participated in subsequent revisions and approved the final version of the manuscript. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication. K. K., H. Y., K. I., M. T., K. S., S. O., D. U., A. K., N. K., N. H., T. T. and K. Y. contributed to the study conduct, discussion and patient enrolment. H. H. had final responsibility for data collection and source data validation. Y. S. undertook statistical analyses and had final responsibility for the statistical analyses.

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Conflict of Interest

The SUCCESS-2 study was funded by the Waksman Foundation of Japan Inc., Tokyo, the Grant-in-Aid from the Japanese Ministry of Health, Labour and Welfare, and the Ministry of Education, Culture, Sports, Science and Technology. K. Y. has received a research endowment for his department from MSD (Merck). No other potential competing interest relevant to this article were reported.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Detailed subjects and methods.

Figure S1. Flow chart of study participants throughout the trial. One hundred and twenty patients were initially screened and randomly assigned to receive either sitagliptin (n = 60) or αGI (n = 60) in addition to $\leq$2 mg/day glimepiride. Overall, 114 (95.0%) received at least one dose of treatment, and 106 (88.3%) completed the study. Four individuals (6.7%) receiving sitagliptin and 10 (16.7%) receiving αGI withdrew from treatment during the trial.

Table S1. Baseline demographic and clinical characteristics.

Table S2. Adverse events observed. The frequency of overall adverse events as well as minor hypoglycaemia were similar in both group. The most common adverse events were gastrointestinal symptoms, the incidence of which was significantly greater with αGI [21 (38.2%)] than sitagliptin [5 (8.5%)].

Table S3. Changes in other secondary endpoints from baseline to week 12 and 24.

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Appendix

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