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# Effects of rosiglitazone on body fat distribution and insulin sensitivity in Korean type 2 diabetes mellitus patients

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**Abstract**

The objective of the study was to investigate the effects of rosiglitazone (RSG), a thiazolidinedione derivative, on body fat distribution and insulin sensitivity in Korean subjects with type 2 diabetes mellitus. This study was a phase IV, multicenter, single-blind, positive-controlled parallel group study. Eighty-nine patients with type 2 diabetes mellitus, aged 30 to 75 years, were enrolled in this study. Their fasting plasma glucose levels ranged from 126 to 270 mg/dL, and subjects had hemoglobin $A_{1c}$ levels of greater than 7.0%. We compared the effect of the treatment with glibenclamide plus RSG 4 mg/d (increased to 8 mg/d after 6 months) with glibenclamide plus placebo on body fat distributions, which were determined by computed tomography scanning and glycemic and insulinemic responses to oral glucose load. During the 12-month treatment period, the difference between the changes in the ratio of the intraabdominal adipose tissue (IAAT) to abdominal subcutaneous adipose tissue areas (SAT) between treatment groups was significant (from 1.13 ± 0.53 to 1.00 ± 0.40 in the RSG group and from 0.92 ± 0.54 to 0.96 ± 0.62 in the placebo group, $P = .0351$). The glycemic responses to oral glucose load (area under the curve, millimoles per liter per hour) were improved in the RSG group with 12 months of treatment (from 4.88 ± 1.10 to 4.38 ± 1.35 in 1 hour and from 13.78 ± 2.83 to 12.16 ± 2.52 in 2 hours), and the difference between the changes of the glycemic response showed statistical significance between groups (RSG group vs placebo group: −0.53 ± 1.42 vs 0.38 ± 1.31, difference in 1 hour; −0.76 ± 2.98 vs 1.43 ± 2.58, difference in 2 hours). However, there was no difference between insulin responses from baseline to follow-up and no differences in the change in insulin response between groups. In Korean subjects with type 2 diabetes mellitus, 12 months of treatment with RSG may increase SAT, but may have a neutral effect on IAAT, resulting in a decrease in the IAAT:SAT ratio. The RSG treatment improved the glucose control in type 2 diabetes mellitus. However, it is important to determine whether the glucose-lowering effect of RSG occurs mainly through direct enhancement of insulin sensitivity.


## 1. Introduction

The pathogenesis of type 2 diabetes mellitus is very complex and is characterized by impaired insulin secretion [1] and diminished insulin action in target tissues, including the liver, skeletal muscle, and adipose tissue [2,3]. It is established that insulin resistance is a common hallmark of both type 2 diabetes mellitus and obesity. Recently, the distribution of body fat has become the focus of major research; and ample data have indicated that intraabdominal (visceral) fat is more strongly associated with insulin resistance, metabolic risk factors, and its major outcomes compared with subcutaneous fat accumulation [4-6].

Thiazolidinedione (TZD) derivatives bind to and activate peroxisome proliferator–activated receptor (PPAR) γ and modulate carbohydrate and lipid metabolism. TZDs are

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frequently used to improve insulin sensitivity in subjects with type 2 diabetes mellitus [7-9], which is often accomplished by the development of excess adipose tissue [10,11]. This paradox may be partly explained by the following mechanisms. First, PPAR-$\gamma$ agonists increase the number of small adipocytes that are more sensitive to insulin and have a less lipolytic nature [12]. Second, TZDs act on adipose tissue to decrease not only the circulating free fatty acids (FFAs) but also adipokines such as tumor necrosis factor $\alpha$, resistin, and leptin [13-16]. Furthermore, TZDs promote the secretion of adiponectin, which has a favorable effect on insulin sensitivity [17,18]. Third, TZDs redistribute the body fat from the intraabdominal region to the subcutaneous region. Moreover, it promotes a mobilization of ectopic fat accumulation of triglycerides in muscle and liver to adipose tissues [19-26].

Therefore, the aim of this study was to evaluate the effect of rosiglitazone (RSG), a TZD derivative, on the body fat distribution pattern, especially the intraabdominal adipose tissue (IAAT) and abdominal subcutaneous adipose tissue areas (SAT), in Korean subjects with type 2 diabetes mellitus.

## 2. Methods

### 2.1. Subjects

We recruited study participants between December 2003 and July 2005 from 4 university hospitals in Seoul, Republic of Korea. Eligible patients were men or women, aged 30 to 75 years, who had type 2 diabetes mellitus (as defined by the American Diabetes Association criteria) with fasting plasma glucose (FPG) levels from 126 to 270 mg/dL at their initial screening and before randomization. Hemoglobin $A_{1c}$ ($HbA_{1c}$) levels were greater than 7.0% at screening in all patients. Patients were excluded if they were pregnant or breastfeeding women, although women of childbearing potential could be included in this study if they were using contraception through the entire study period. Subjects with body mass index (BMI) <23 or >40 kg/m$^2$, severe diabetic neuropathy or retinopathy requiring immediate intervention, a history of congestive heart failure, stage III hypertension, renal disease, hepatic disease, hematologic disorder, concomitant treatment with antiobesity drugs, a planned change in lifestyle, substance abuse, or a major metal implant were excluded from this study. Subjects who have claustrophobia, and therefore were not able to undergo computed tomography (CT) scans, were also excluded from this study.

Written informed consent was obtained from all subjects. The study protocol was approved by the national ethics committee and the institutional review board of each hospital and was conducted under the guiding principles of the Declaration of Helsinki and Good Clinical Practices.

### 2.2. Study design

This study was a phase IV, multicenter, single-blind, positive-controlled parallel group study. After 2 months of run-in treatment with glibenclamide (5 mg/d), subjects were randomly assigned to receive 12 months of treatment with glibenclamide plus RSG or glibenclamide plus placebo. During the treatment period, subjects were followed-up at regular intervals (after 2, 4, 6, 8, 10, and 12 months of

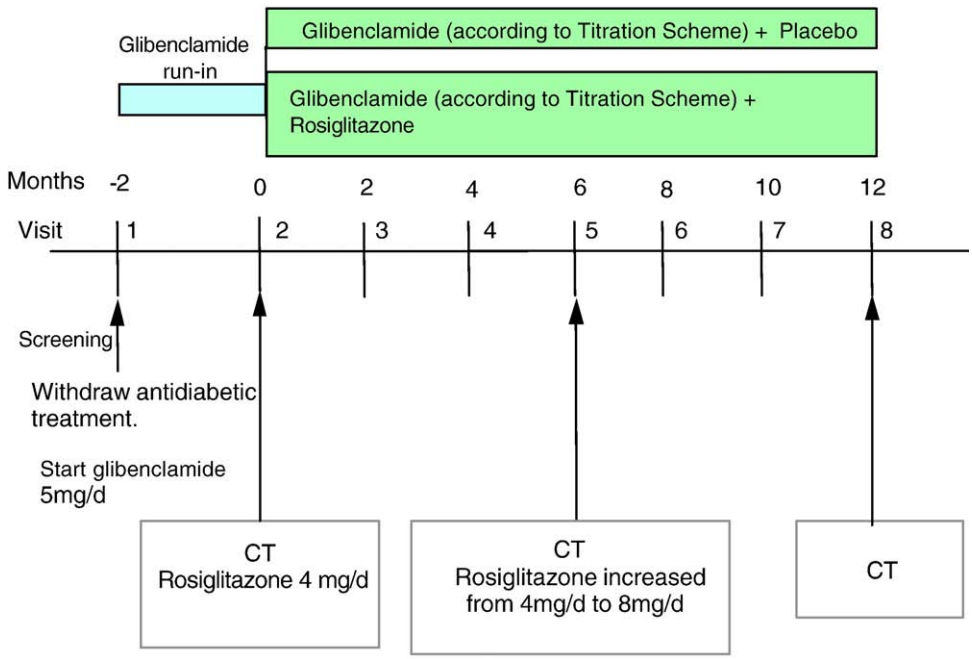


Fig. 1. Schematic diagram of the study design.

therapy) to assess the safety, tolerability, and efficacy of treatment. A diagram of the study design is shown in Fig. 1.

All relevant demographic and medical histories, including information about their status of diabetes, smoking history, and menopausal status for women, were assessed at screening. Height, weight, waist circumference, and vital signs were measured at all visits. Standard 12-lead electrocardiograms (ECGs) were obtained at the beginning of the study, at visit 5, and at the final visit. The study subjects took concomitant medications such as aspirin, antihypertensive drugs, and lipid-lowering agents; and no statistical differences were observed between the RSG group and the placebo group during the study. All laboratory tests were carried out after overnight fasting. We took blood samples at baseline to assess the efficacies of concentrations of FPG, fasting plasma insulin (FPI), $HbA_{1c}$, triglycerides, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and FFA. Thereafter, FPG and $HbA_{1c}$ levels were measured at all visits; and FPI, triglycerides, HDL cholesterol, LDL cholesterol, and FFA were measured at 6 months and at the final visit. A 75-g oral glucose tolerance test (OGTT) was performed at baseline, 6 months, and the final visit; and a homeostasis model assessment (HOMA) value was calculated to estimate the insulin sensitivity and $\beta$-cell function. Insulin resistance was estimated by the HOMA–insulin resistance (HOMA-IR), [FPI (in microunits per milliliter) × FPG (in millimoles per liter)]/22.5, and the HOMA-%B, calculated by (20 × FPI)/(FPG − 3.5), and was representative of $\beta$-cell function. In addition, the insulinogenic index, as defined by the ratio of the increment of insulin to that of plasma glucose 30 minutes after a 75-g oral glucose load ($\Delta$ insulin, 0 to 30 minutes/$\Delta$ glucose, 0 to 30 minutes) [27], was measured to assess $\beta$-cell function. Urinary microalbumin concentrations and complete blood cell counts were measured at regular intervals; and liver function tests, including alanine aminotransferase, aspartate aminotransferase, total bilirubin, $\gamma$-glutamyl aminotransferase ($\gamma$-GT), and alkaline phosphatase, and creatinine levels were monitored at all visits.

In this study, our main goal was to determine the effect of RSG on body fat composition; and thus, we thoroughly evaluated the changes of the fat tissue area at multiple levels. A detailed method of the CT scan has been described previously [28]. In brief, IAAT and SAT were measured at the lumbar IV level by fitting a spline curve to points on the border of the subcutaneous and visceral regions selected by the operator; and nonfat regions within the visceral region were also outlined with a spline fit and subtracted from the total visceral region. In addition, CT images at the levels of the right thigh, cervical spine IV, and liver-spleen were also obtained. The CT scans were performed within 1 week before visit 2 (baseline) and within ±1 week of visit 5 (month 6) and visit 8 (month 12). If a subject withdrew from the study prematurely, then every effort was made to conduct "early withdrawal" CT scan assessments, if appropriate.

Our primary end point was a comparison of the effect of 12 months of treatment with glibenclamide (dose to be titrated from a starting dose of 5 mg/d) plus RSG 4 mg/d (increased to 8 mg/d after 6 months) with that of glibenclamide (dose to be titrated from a starting dose of 5 mg/d) plus placebo on body fat distribution, as measured by the change in the ratio between IAAT and SAT, in Korean patients with type 2 diabetes mellitus.

The secondary end points were the comparisons of efficacies of the 2 treatment arms on changes between baseline and 6 and 12 months with respect to the following parameters: other CT scan variables of SAT and IAAT at the lumbar IV level; total subcutaneous adipose tissue area (TSAT) of the right leg at the thigh level (1 cm below the gluteal fold); the SAT:TSAT ratio; the IAAT:TSAT ratio; 1- and 2-hour glycemic and insulinemic response, expressed as the area under the curve (millimoles per liter per hour in glycemic response and picomoles per liter per hour in insulinemic response), to OGTT with or without adjustment of their respective time 0 level; and insulinogenic index.

Other efficacy end points included (1) total tissue area (TTA), total abdominal adipose tissue area, intraperitoneal adipose tissue area (IPAT), retroperitoneal adipose tissue area (RPAT), intermuscular adipose tissue area (adipose tissue between muscle bundles) (IMAT), sagittal diameter, and circumference of CT scan at the lumbar IV level; (2) TTA, peripheral subcutaneous adipose tissue area, IMAT, and mean attenuation of the quadriceps muscle (MAQM) of a CT scan of the right leg at the thigh level; (3) CT image at the liver-spleen level for the assessment of hepatic fat infiltration; (4) TTA, total adipose tissue area (TAT), peripheral subcutaneous adipose tissue area, and IMAT of CT image at the cervical spine IV level; (5) body weight, waist circumference, and BMI; and (6) FPI, HOMA-IR, and HOMA-B%.

Any severe adverse events were reported to the study monitor within 24 hours. This was to be followed by a written report containing relevant hospital case records and autopsy reports when applicable. We defined *severe adverse events* as resulting in death, life-threatening conditions, a need for or prolongation of hospitalization, resulting in disability or inactivity, congenital anomaly or birth defect, or a need for intervention to prevent any of the above.

### 2.3. Statistical analysis

The analysis was performed using SAS version 8.1 (SAS Institute, Cary, NC). We used the unpaired *t* test, analysis of covariance test, and Wilcoxon signed rank test to compare the difference in continuous variables between treatment groups. Paired *t* test and Wilcoxon rank sum test were applied to detect any significant difference between pre- and posttreatment conditions. By using the $\chi^2$ test and Fisher exact test, categorical variables between treatment groups were compared. Pearson correlation coefficients were used to determine the correlations between variables. All data are

Table 1
Baseline characteristics of the 2 treatment groups

| | RSG/GLIB (n = 43) | PBO/GLIB (n = 46) | Total (n = 89) | P |
|---|---|---|---|---|
| Age (y) | 55.1 ± 10.0 | 53.4 ± 9.7 | 54.2 ± 9.8 | .41 |
| No. of women (%) | 20 (46.5) | 25 (54.3) | 45 (50.5) | .46 |
| Height (cm) | 161.8 ± 8.0 | 161.0 ± 8.3 | 161.4 ± 8.1 | .62 |
| Weight (kg) | 69.4 ± 8.9 | 69.2 ± 9.1 | 69.3 ± 9.0 | .83 |
| BMI (kg/m$^2$) | 26.5 ± 2.8 | 26.6 ± 2.5 | 26.6 ± 2.6 | .59 |
| Waist circumference (cm) | 89.5 ± 6.3 | 88.7 ± 6.7 | 89.1 ± 6.5 | .57 |
| Current smoking (%) | 11 (25.5) | 5 (10.8) | 16 (17.9) | .52 |
| Postmenopausal women (%) | 9 (44.4) | 11 (44.0) | 20 (44.4) | .75 |

Data are expressed as mean ± SD. GLIB indicates glibenclamide; PBO, placebo.

expressed as means ± SD. A $P$ value less than .05 was considered statistically significant.

## 3. Results

A total of 129 subjects were screened for eligibility, of which 90 subjects were randomized to receive RSG (n = 43) or placebo (n = 47). One subject, randomized at baseline (visit 2), was excluded from the study because she did not adhere to the study medication schedule. The baseline characteristics of the 2 treatment groups are listed in Table 1, and no statistical differences were observed.

After treatment with RSG for 6 months, the difference in the changes in the IAAT:SAT ratio between the RSG group and the placebo group was significant (−0.11 ± 0.21 in the RSG group and 0.08 ± 0.32 in the placebo group, $P$ = .0020); and this difference was also significant after 12 months of treatment with RSG (−0.13 ± 0.36 in the RSG group and 0.04 ± 0.29 in the placebo group, $P$ = .0351) (Table 2 and Fig. 2). More specifically, IAAT did not change throughout the treatment periods; and SAT increased almost immediately from baseline to month 6 (from 149.60 ± 66.30 to 173.94 ± 77.08, $P$ = .0001), and this was maintained to month 12 (from 146.58 ± 61.85 to 171.01 ± 71.62, $P$ = .0001) in the RSG treatment arm. Furthermore, the difference between the changes of the SAT between the 2 groups was statistically significant from baseline to month 6. Multiple linear regression was performed to reveal the variables that affected the results for the IAAT:SAT ratios at 6 and 12 months. However, there were no variables—such as age, sex, BMI, waist circumference, or the degree of glucose control—that significantly affected the results (data not shown).

In accordance with the result of the SAT, TSAT, which was measured at the thigh level, gradually increased in the RSG group; and the difference between the 2 groups reached statistical significance at month 12 (from 120.75 ± 69.60 to 135.06 ± 70.80, $P$ = .0437). The difference between the changes in the IAAT:TSAT ratios of the RSG group and the placebo group was statistically significant at month 12 (−0.15 ± 0.65 in RSG group and 0.18 ± 0.79 in placebo group, $P$ = .0481) (Table 2).

The RSG group demonstrated improved 1- and 2-hour glycemic responses to OGTT after 12 months of treatment,

Table 2
Change in body fat composition from baseline to months 6 and 12

| | RSG/GLIB | | | | | | PBO/GLIB | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 mo | | | 12 mo | | | 6 mo | | | 12 mo | | |
| | n | Baseline | Δ | n | Baseline | Δ | n | Baseline | Δ | n | Baseline | Δ |
| IAAT: SAT | 32 | 1.12 ± 0.53 | −0.11 ± 0.21 * | 31 | 1.13 ± 0.53 | −0.13 ± 0.36 | 38 | 0.94 ± 0.52 | 0.08 ± 0.32 † | 35 | 0.92 ± 0.54 | 0.04 ± 0.29 † |
| SAT (cm$^2$) | 32 | 149.60 ± 66.30 | 24.33 ± 24.00 * | 31 | 146.58 ± 61.85 | 24.44 ± 30.25 * | 38 | 165.29 ± 66.32 | 1.28 ± 25.63 † | 35 | 165.79 ± 65.23 | 6.31 ± 47.37 |
| IAAT (cm$^2$) | 32 | 147.19 ± 48.29 | 6.38 ± 28.76 | 31 | 146.72 ± 49.74 | 6.49 ± 26.25 | 38 | 136.25 ± 43.58 | 9.01 ± 25.26 * | 35 | 132.94 ± 43.36 | 4.99 ± 38.08 |
| TSAT (cm$^2$) | 33 | 116.87 ± 67.32 | 8.65 ± 35.14 | 32 | 120.75 ± 69.60 | 14.31 ± 38.50 * | 37 | 137.65 ± 62.72 | −2.77 ± 35.61 | 34 | 141.95 ± 64.32 | −0.81 ± 47.52 |
| SAT: TSAT | 32 | 1.48 ± 0.62 | 0.09 ± 0.53 | 31 | 1.45 ± 0.66 | 0.02 ± 0.36 | 37 | 1.32 ± 0.52 | 0.06 ± 0.64 | 34 | 1.28 ± 0.50 | 0.09 ± 0.55 |
| IAAT: TSAT | 32 | 1.73 ± 1.09 | −0.06 ± 0.64 | 31 | 1.71 ± 1.13 | −0.15 ± 0.65 | 37 | 1.18 ± 0.70 | 0.18 ± 0.65 | 34 | 1.13 ± 0.72 | 0.18 ± 0.79 † |
| IPAT (cm$^2$) | | ND | ND | 31 | 106.10 ± 41.26 | −1.69 ± 24.42 | | ND | ND | 35 | 96.84 ± 33.91 | 1.20 ± 29.84 |
| RPAT (cm$^2$) | | ND | ND | 31 | 40.29 ± 15.82 | 7.74 ± 12.00 * | | ND | ND | 35 | 36.09 ± 14.46 | 3.79 ± 13.09 |
| IPAT: RPAT | | ND | ND | 31 | 3.03 ± 2.01 | −0.77 ± 1.76 * | | ND | ND | 35 | 2.90 ± 1.13 | −0.34 ± 0.88 * |

Data are expressed as mean ± SD. RSG, rosiglitazone; GLIB, glibenclamide; PBO, placebo; IAAT, intra-abdominal adipose tissue area; SAT, abdominal subcutaneous tissue area; TSAT, total subcutaneous adipose tissue area; ND, not determined.

* $P$ <.05 from baseline.

† $P$ <.05 for difference between treatments.

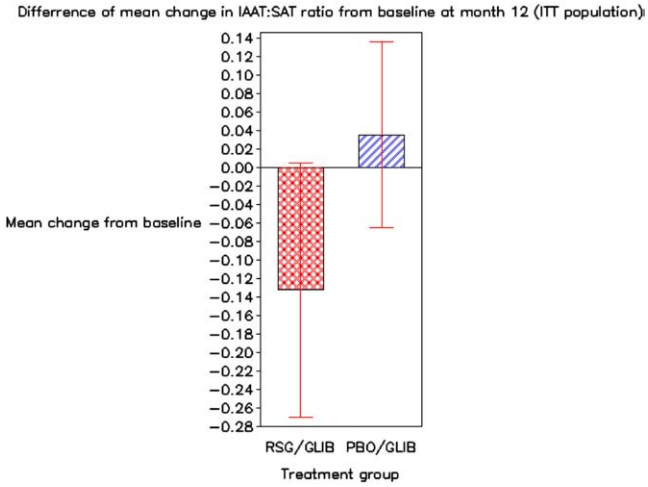


Fig. 2. Difference of mean change in the IAAT:SAT ratio from baseline to month 12. GLIB indicates glibenclamide; PBO, placebo.

and the difference between the changes of the responses showed statistical significance between groups at month 6 and month 12. In contrast to the results for the glycemic response, there were no differences in insulin response between the groups and no changes from baseline to follow-up in any of the groups (Table 3). Although the difference between the changes in the insulinogenic index in both groups showed slight incremental changes from baseline to 6 months (from 1.87 ± 1.95 to 1.97 ± 2.13 in the RSG group and from 2.02 ± 1.50 to 2.06 ± 1.60 in the placebo group, respectively) and 12 months (from 1.75 ± 1.71 to 2.22 ± 1.98 in the RSG group and from 2.15 ± 1.48 to 2.67 ± 1.94 in the placebo group, respectively), no significant changes were observed (data not shown).

Among parameters for the CT image in the right leg, TTA showed significant changes between groups from baseline to 12 months (from 421.00 ± 81.34 to 448.68 ± 79.76 in the RSG group and from 435.87 ± 71.79 to 435.85 ± 62.99 in the placebo group, respectively; $P = .0372$). However, IMAT and MAQM, which represent intramuscular adipose tissues, showed no differences in changes between groups. In the case of the CT image at the lumbar IV level, only the IMAT showed statistical significance between groups (from 15.62 ± 12.93 to 17.74 ± 10.46 in the RSG group and from 13.18 ± 5.86 to 13.19 ± 5.85 in the placebo group, respectively; $P = .0020$); at the cervical IV level, only the TAT area showed significance (from 36.37 ± 13.54 to 43.08 ± 17.78 in the RSG group and from 35.77 ± 12.23 to 36.81 ± 12.87 in the placebo group, respectively; $P = .0270$). The hepatic fat infiltration (Hounsfield units) did not show any significantly different changes between the 2 groups (from 1.11 ± 0.20 to 1.09 ± 0.18 in the RSG group and from 1.01 ± 0.24 to 1.03 ± 0.21 in the placebo group, respectively) (data not shown). Anthropometric measurements, including body weight, waist circumference, and BMI, increased significantly after 12 months of treatment with RSG; in particular, body weight and BMI showed significantly different changes between groups.

Although the differences in the changes of FPG and the level of $HbA_{1c}$ between groups were statistically significant, the levels of the FPI, HOMA-IR, and HOMA-%B did not show any differences in changes between groups. In the assessment of lipid profiles, the total and LDL cholesterol differed from baseline to month 12 between the 2 groups. Other parameters such as HDL cholesterol, triglycerides, ratio of total cholesterol to HDL cholesterol, and FFA did not show any differences in changes between groups. The microalbuminuria in the RSG group decreased, but no

Table 3
Changes in time 0 adjusted response to OGTT from baseline to months 6 and 12

| | RSG/GLIB | | | | | PBO/GLIB | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | n | 1 h | | 2 h | | n | 1 h | | 2 h | |
| | | Baseline | Δ | Baseline | Δ | | Baseline | Δ | Baseline | Δ |
| 6 mo | | | | | | | | | | |
| Glycemic response (mmol/L × h) | 37 | 4.87 ± 1.04 | −0.30 ± 1.35 | 13.70 ± 2.74 | −1.00 ± 3.04 | 40 | 4.92 ± 1.28 | 0.40 ± 1.31† | 12.86 ± 3.25 | 0.75 ± 2.84† |
| Insulinemic response (pmol/L × h) | 33 | 66.55 ± 48.16 | 1.71 ± 42.83 | 198.09 ± 138.90 | 5.07 ± 109.76 | 33 | 85.57 ± 72.53 | −4.02 ± 52.92 | 277.95 ± 243.32 | −48.26 ± 181.59 |
| 12 mo | | | | | | | | | | |
| Glycaemic response (mmol/L × h) | 32 | 4.88 ± 1.10 | −0.53 ± 1.42* | 13.78 ± 2.83 | −0.76 ± 2.98* | 34 | 4.96 ± 1.21 | 0.38 ± 1.31† | 12.84 ± 3.31 | 1.43 ± 2.58*,† |
| Insulinemic response (pmol/L × h) | 29 | 64.09 ± 38.29 | 3.23 ± 38.03 | 194.35 ± 135.30 | 8.83 ± 103.50 | 27 | 90.21 ± 72.95 | 15.05 ± 89.48 | 290.66 ± 247.24 | −7.74 ± 229.86 |

Data are expressed as mean ± SD.
* $P < .05$ from baseline.
† $P < .05$ for difference between treatments.

Table 4
Changes in other variables from baseline to month 12

| | RSG/GLIB | | | PBO/GLIB | | |
|---|---|---|---|---|---|---|
| | n | Baseline | Δ | n | Baseline | Δ |
| Body weight (kg) | 33 | 68.93 ± 7.54 | 2.87 ± 2.29 * | 35 | 68.02 ± 8.83 | 0.62 ± 2.47 † |
| Waist circumference (cm) | 33 | 88.92 ± 5.31 | 1.80 ± 2.69 * | 35 | 86.88 ± 5.43 | 1.52 ± 2.86 |
| BMI (kg/m$^2$) | 34 | 26.04 ± 2.25 | 1.01 ± 0.89 * | 35 | 26.16 ± 2.21 | 0.20 ± 1.02 † |
| Systolic BP (mm Hg) | 33 | 125.42 ± 17.00 | 1.81 ± 19.76 | 35 | 122.71 ± 12.46 | 8.74 ± 12.54 * |
| Diastolic BP (mm Hg) | 33 | 78.57 ± 10.38 | −2.66 ± 9.93 | 35 | 78.85 ± 8.11 | 2.20 ± 9.73 † |
| Pulse rate (beats/min) | 33 | 76.18 ± 10.64 | −3.54 ± 9.06 * | 35 | 75.94 ± 12.78 | 1.20 ± 9.78 † |
| FPG (mmol/L) | 33 | 9.41 ± 1.78 | −2.03 ± 2.07 * | 33 | 9.66 ± 1.80 | −0.52 ± 2.41 † |
| FPI (pmol/L) | 33 | 63.92 ± 28.52 | −4.28 ± 26.43 | 34 | 81.38 ± 48.37 | 1.55 ± 28.35 |
| HOMA-IR | 33 | 3.79 ± 1.69 | −0.98 ± 1.64 * | 32 | 4.74 ± 2.43 | −0.31 ± 1.91 |
| HOMA-%B | 33 | 34.04 ± 17.47 | 21.10 ± 33.30 * | 32 | 42.34 ± 37.13 | 10.65 ± 37.54 |
| $HbA_{1c}$ (%) | 33 | 7.81 ± 0.73 | −0.73 ± 0.59 * | 33 | 7.90 ± 1.12 | 0.26 ± 1.27 † |
| Total cholesterol (mmol/L) | 33 | 4.81 ± 0.64 | 0.30 ± 0.91 | 35 | 5.11 ± 0.87 | −0.09 ± 0.69 † |
| LDL cholesterol (mmol/L) | 33 | 2.98 ± 0.54 | 0.29 ± 0.88 | 33 | 3.09 ± 0.72 | −0.11 ± 0.63 † |
| HDL cholesterol (mmol/L) | 33 | 1.20 ± 0.27 | 0.08 ± 0.27 | 33 | 1.27 ± 0.30 | −0.03 ± 0.19 |
| Triglyceride (mmol/L) | 33 | 2.24 ± 1.11 | 0.01 ± 1.00 | 35 | 2.62 ± 1.58 | −0.08 ± 1.41 |
| Total cholesterol to HDL cholesterol | 33 | 4.16 ± 0.94 | 0.04 ± 1.27 | 35 | 4.16 ± 0.89 | −0.02 ± 0.64 |
| Free fatty acid (μEq/L) | 33 | 644.03 ± 256.42 | −75.09 ± 327.05 | 33 | 729.06 ± 300.20 | −115.06 ± 349.21 |
| Microalbuminuria (g/L) | 33 | 0.24 ± 0.33 | −0.08 ± 0.23 * | 35 | 0.20 ± 0.37 | −0.03 ± 0.25 |

Data are expressed as mean ± SD. BP indicates blood pressure.
* $P < .05$ from baseline.
† $P < .05$ for difference between treatments.

difference in changes between groups was observed from baseline to month 12 (Table 4).

Rosiglitazone was generally well tolerated and had a good safety profile; and no between-group differences in adverse events in terms of degrees of recovery, intensity, and relationship to study medication and no difference in the incidence of on-therapy hypoglycemia events by last on-therapy $HbA_{1c}$ were found. The most common adverse event was hypoglycemia in both groups, and 2 subjects withdrew from the study because of the occurrence of adverse events. One subject in the RSG group experienced 5 adverse events during this study; and among this subject's adverse events, only one adverse event was related with the study medication. In the case of the placebo group, one subject had severe hypoglycemia that was associated with the study medication. All subjects recovered from their adverse events. Laboratory examinations did not reveal any liver or renal toxicity. Liver enzymes, γ-GT, and total bilirubin levels were all within reference ranges; and no liver function–related adverse events were reported. The ECG results were comparable between the 2 groups. At the end of study, no clinically significant abnormal ECG results were revealed. Altogether, the results suggest that there were no specific safety concerns related to the use of RSG.

## 4. Discussion

In rodents, TZDs differentiate adipocytes to decrease the cell size; and these smaller cells are more sensitive to insulin. Moreover, the adipogenic effect of TZDs was prominent in subcutaneous fat and induced the differentiation of pre-adipocytes into mature fat cells in subcutaneous fat, but not in omental fat in humans [17], whereas sulfonylurea-associated weight gain includes increases in intraabdominal fat depots [19,20].

It is well documented that subjects with central (intraabdominal) obesity are more prone to insulin resistance than those with peripheral (subcutaneous) fat accumulation. In addition, intraabdominal fat accumulation was associated with a significant increase in overall morbidity and mortality [4-6]. The reason for this is uncertain, but the most plausible explanation is that intraabdominal fats are richly innervated by β-adrenergic receptors. Thus, this type of storage is more lipolytic and rapidly mobilizes FFA; and the increased intraportal FFA flux might inhibit insulin clearance and promote insulin resistance. Another possibility is that the intraabdominal fat releases a different nature of adipokines compared with the subcutaneous fats; and these factors are more likely to impair insulin action systemically [29].

In this study, 12 months of treatment with RSG, a TZD derivative, decreased the IAAT:SAT ratio (from 1.13 ± 0.53 to 1.00 ± 0.40) and the difference in the change in the IAAT:SAT ratio compared with the placebo group; these changes were already evident at month 6 and continued to month 12. More specifically, the first component, SAT, was significantly higher in the RSG group than in the placebo group at month 6 and showed a similar tendency at month 12. No statistical differences were found in IAAT, the second component, in month 6 or month 12. Therefore, although the changes in IAAT and SAT did not show statistically significant differences between groups at month 12, the observed changes were magnified after being processed as a ratio; and it was noticeable that the subcutaneous fat

distribution was dominant in the RSG group. Our results were partially in agreement with previous reports that documented the effects of TZDs on body fat composition [19-26]. Carey et al [23] reported that 16 weeks of treatment with RSG caused a significant increase (8%) of SAT compared with baseline, and this change was accompanied by a significant reduction in the IAAT:SAT ratio and no increase in IAAT. Furthermore, according to a study in Japanese patients, who are genetically more similar to our study subjects than are white persons, 12 months of troglitazone treatment resulted in increased accumulation of subcutaneous fat without a change in the visceral fat area. Consequently, the visceral fat to subcutaneous fat ratio was decreased significantly [26].

It has not yet been addressed whether TZD treatment increases subcutaneous adiposity in all body regions equally, which is very important because adverse metabolic events occur more frequently in those with upper-body (abdominal) subcutaneous fat distribution (SAT) than those with lower-body (including femorogluteal) distribution (TSAT) [30]. In our study, RSG treatment did not show any preferential changes in subcutaneous adiposity (SAT:TSAT ratio). These results suggested that TZD treatment might increase subcutaneous adiposity in all body regions equally, and it seems that the effect of TZDs on subcutaneous fat deposition does not preferentially act on the lower-body subcutaneous fat region.

In general, among the intraabdominal fat (IAAT) types, IPAT provides an additional contribution to insulin resistance due to its unique venous drainage; it directly drains into the liver through the portal vein compared with the RPAT, which drains into the systemic circulation and increases lipolytic activity. Therefore, it may be more detrimental to hepatic insulin sensitivity [30]. To date, most studies have not addressed the effects of the TZDs on the redistribution of the subdivision in intraabdominal adipose tissue. In this study, we divided total IAAT and quantified IPAT or RPAT separately. As mentioned above, despite the fact that RSG treatment has a neutral effect on IAAT, its effect on intraabdominal fat was somewhat different between IPAT and RPAT. Although it did not show statistical significance, RSG treatment decreased IPAT and increased RPAT; and these results are in accordance with another report by Carey et al [23]. As a result, it has been suggested that RSG treatment may exert a favorable effect on the subdivision of the intraabdominal adipose tissue, although the net fat mass was not changed.

In this study, we evaluated whether there was any correlation between the changes in HOMA values, that is, HOMA-IR and HOMA-%B, and the changes in body fat stores such as IAAT, SAT, IAAT:SAT, IPAT, RPAT, and IPAT:RPAT. We found that there were no correlations between HOMA values and body fat stores irrespective of their groups, that is, total study subjects, men, women, RSG group, and placebo group (data not shown).

In terms of glycemic control, consistent with other studies [31-35], the RSG group exhibited better FPG and $HbA_{1c}$ levels; and the glycemic response to OGTT was also improved. However, the insulinemic response to OGTT and the level of HOMA-IR did not differ between groups. Although this inconsistency may be due to the small sample size of this study, other possibilities should be considered. First, because the baseline HOMA-IR levels showed some differences between groups (RSG group vs placebo group: 3.79 ± 1.70 vs 4.75 ± 2.43, $P = .0717$), we compared the percentage of the change between groups to adjust the baseline difference. Thereafter, marginal statistical difference of the change in HOMA-IR between groups was shown (RSG group vs placebo group: −17.9% ± 41.6% vs 2.6% ± 47.4%, $P = .0665$). Thus, RSG may improve the whole-body insulin sensitivity in Korean type 2 diabetes mellitus patients. Second, although systemic insulin sensitivity, which was expressed as HOMA-IR and FPI, was not changed significantly, it was possible that RSG treatment improved the hepatic insulin sensitivity in this study population. It was recently suggested that the elevated γ-GT level was associated with insulin resistance and obesity [36]. Furthermore, it was also shown to be an independent predictor of type 2 diabetes mellitus [37]. In this study, the serum γ-GT level was significantly decreased in the RSG group compared with the placebo group after 12 months of treatment (from 33.06 ± 22.57 to 25.79 ± 22.36 in the RSG group and from 26.94 ± 12.91 to 27.40 ± 12.30 in the placebo group, respectively; $P = .0007$). Thamer et al [38] reported that the elevated serum γ-GT level was associated with glucose intolerance caused by insulin resistance, and this may be primarily related to hepatic insulin resistance. Therefore, it was possible that this striking reduction of the serum γ-GT level in the RSG group resulted from the improvement of hepatic insulin resistance. Additional evidence indicated that improved hepatic insulin sensitivity with RSG treatment could be found along with a significant improvement in the FPG level. In our study, although the decrement of the $HbA_{1c}$ level was relatively modest in the RSG group, the FPG level was decreased notably (−2.03 ± 2.07 mmol/L) compared with their matched $HbA_{1c}$ reductions (−0.73% ± 0.59%). Therefore, it can be speculated that RSG exerts a favorable effect on insulin sensitivity, particularly in the liver, in our study subjects. Third, it was suggested that the insulin secretory capacity is reduced by the intrauterine environment and/or genetically determined defects in Asian people [39]; and it has also been reported that an insulin secretory defect is the main abnormality in the development of type 2 diabetes mellitus in Koreans [40]. Therefore, it may be possible that compensatory β-cell expansion and insulin secretion in response to insulin resistance is limited in Korean subjects and that they are more vulnerable to the development of type 2 diabetes mellitus when they are challenged with only a subtle aggravation of insulin sensitivity. As a result, insulin resistance can be more critical in Koreans compared with white populations, who have relatively greater β-cell mass than Asians. Conversely, although

insulin sensitivity, as measured by HOMA-IR and FPI, did not change significantly after treatment with RSG, glucose control may have been improved by only a small improvement of insulin sensitivity; but this difference did not reach statistical significance.

Although these results are somewhat similar to those of previous reports, our present study has been powered by the following concepts: (1) This study was carried out with a relatively large number of patients for a long-term follow-up period in a Korean type 2 diabetes mellitus population. (2) We thoroughly evaluated the effects of RSG at multi-compartment body fat depots using a highly valid and reproducible technique. (3) Although the reason is not yet clear, this study raises a question as to the principal mechanism of the glucose-lowering properties of TZDs in relatively less insulin-resistant type 2 diabetes mellitus.

In conclusion, these results indicate that RSG treatment may redistribute the body fats toward a metabolically healthier status that is accompanied by a reduction in the visceral fat to subcutaneous fat ratio. Although RSG improves glucose control in type 2 diabetes mellitus, it is necessary to clarify the principal mechanism by which RSG lowers the glucose levels in Koreans.

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## References

[1] Kahn SE. Clinical review 135: the importance of β-cell failure in the development and progression of type 2 diabetes. J Clin Endocrinol Metab 2001;86:4047-58.
[2] Lazar MA. How obesity causes diabetes: not a tall tale. Science 2005; 307:373-5.
[3] Porte Jr D. Clinical importance of insulin secretion and its interaction with insulin resistance in the treatment of type 2 diabetes mellitus and its complications. Diabetes Metab Res Rev 2001;17:181-8.
[4] Bjorntorp P. Metabolic implications of body fat distribution. Diabetes Car 1991;14:1132-43.
[5] Emery EM, Schmid TL, Kahn HS, et al. A review of the association between abdominal fat distribution, health outcome measures, and modifiable risk factors. Am J Health Promot 1993;7:342-53.
[6] Kissebah AH, Krakower GR. Regional adiposity and morbidity. Physiol Rev 1994;74:761-811.
[7] Olefsky JM. Treatment of insulin resistance with peroxisome proliferator–activated receptor γ agonists. J Clin Invest 2000;106: 467-72.
[8] Semple RK, Chatterjee VK, O'Rahilly S. PPARγ and human metabolic disease. J Clin Invest 2006;116:581-9.
[9] Lebovitz HE, Banerji MA. Insulin resistance and its treatment by thiazolidinediones. Recent Prog Horm Res 2001;56:265-94.
[10] Rosen ED, Walkey CJ, Puigserver P, et al. Transcriptional regulation of adipogenesis. Genes Dev 2000;14:1293-307.
[11] Rosen ED, Spiegelman BM. PPARγ: a nuclear regulator of metabolism, differentiation, and cell growth. J Biol Chem 2001;276: 37731-4.
[12] Okuno A, Tamemoto H, Tobe K, et al. Troglitazone increases the number of small adipocytes without the change of white adipose tissue mass in obese Zucker rats. J Clin Invest 1998;101:1354-61.
[13] Katsuki A, Sumida Y, Murata K, et al. Troglitazone reduces plasma levels of tumour necrosis factor–α in obese patients with type 2 diabetes. Diabetes Obes Metab 2000;2:189-91.
[14] Guan HP, Li Y, Jensen MV, et al. A futile metabolic cycle activated in adipocytes by antidiabetic agents. Nat Med 2002;8:1122-8.
[15] Steppan CM, Bailey ST, Bhat S, et al. The hormone resistin links obesity to diabetes. Nature 2001;409:307-12.
[16] Adams M, Montague CT, Prins JB, et al. Activators of peroxisome proliferator–activated receptor γ have depot-specific effects on human preadipocyte differentiation. J Clin Invest 1997;100:3149-53.
[17] Yu JG, Javorschi S, Hevener AL, et al. The effect of thiazolidinediones on plasma adiponectin levels in normal, obese, and type 2 diabetic subjects. Diabetes 2002;51:2968-74.
[18] Yang WS, Jeng CY, Wu TJ, et al. Synthetic peroxisome proliferator–activated receptor–γ agonist, rosiglitazone, increases plasma levels of adiponectin in type 2 diabetic patients. Diabetes Care 2000;25: 376-80.
[19] Katoh S, Hata S, Matsushima M, et al. Troglitazone prevents the rise in visceral adiposity and improves fatty liver associated with sulfonylurea therapy—a randomized controlled trial. Metabolism 2001;50:414-7.
[20] Akazawa S, Sun F, Ito M, et al. Efficacy of troglitazone on body fat distribution in type 2 diabetes. Diabetes Care 2000;23:1067-71.
[21] Virtanen KA, Hällsten K, Parkkola R, et al. Differential effects of rosiglitazone and metformin on adipose tissue distribution and glucose uptake in type 2 diabetic subjects. Diabetes 2003;52:283-90.
[22] Tiikkainen M, Hakkinen AM, Korsheninnikova E, et al. Effects of rosiglitazone and metformin on liver fat content, hepatic insulin resistance, insulin clearance, and gene expression in adipose tissue in patients with type 2 diabetes. Diabetes 2004;53:2169-76.
[23] Carey DG, Cowin GJ, Galloway GJ, et al. Effect of rosiglitazone on insulin sensitivity and body composition in type 2 diabetic patients [corrected]. Obes Res 2002;10:1008-15.
[24] Miyazaki Y, Mahankali A, Matsuda M, et al. Effect of pioglitazone on abdominal fat distribution and insulin sensitivity in type 2 diabetic patients. J Clin Endocrinol Metab 2002;87:2784-91.
[25] Kelly IE, Han TS, Walsh K, et al. Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. Diabetes Care 1999;22:288-93.
[26] Mori Y, Murakawa Y, Okada K, et al. Effect of troglitazone on body fat distribution in type 2 diabetic patients. Diabetes Care 1999;22:908-12.
[27] Matthews DR, Hosker JP, Rudenski AS, et al. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28:412-9.
[28] Chowdhury B, Sjöström L, Alpsten M, et al. A multicompartment body composition technique based on computerized tomography. Int J Obes Relat Metab Disord 1994;18:219-34.
[29] Kahn CR, Weir GC, King GL, et al. Joslin's diabetes mellitus. 14th ed. Boston: LWW; 2005. p. 207-26.
[30] Garg A. Regional adiposity and insulin resistance. J Clin Endocrinol Metab 2004;89:4206-10.
[31] Fonseca V, Rosenstock J, Patwardhan R, et al. Effect of metformin and rosiglitazone combination therapy in patients with type 2 diabetes mellitus: a randomized controlled trial. JAMA 2000;283: 1695-702.
[32] Wolffenbuttel BH, Gomis R, Squatrito S, et al. Addition of low-dose rosiglitazone to sulphonylurea therapy improves glycaemic control in type 2 diabetic patients. Diabet Med 2000;17:40-7.
[33] St John Sutton M, Rendell M, Dandona P, et al. A comparison of the effects of rosiglitazone and glyburide on cardiovascular function and glycemic control in patients with type 2 diabetes. Diabetes Care 2002; 25:2058-64.

[34] Raskin P, Rappaport EB, Cole ST, et al. Rosiglitazone short-term monotherapy lowers fasting and post-prandial glucose in patients with type II diabetes. Diabetologia 2000;43:278-84.
[35] Nolan JJ, Jones NP, Patwardhan R, et al. Rosiglitazone taken once daily provides effective glycaemic control in patients with type 2 diabetes mellitus. Diabet Med 2000;17:287-94.
[36] Clark JM, Brancati FL, Diehl AM. The prevalence and etiology of elevated aminotransferase levels in the United States. Am J Gastroenterol 2003;98:960-7.
[37] Lee DH, Silventoinen K, Jacobs Jr DR, et al. γ-Glutamyltransferase, obesity, and the risk of type 2 diabetes: observational cohort study among 20,158 middle-aged men and women. J Clin Endocrinol Metab 2004;89:5410-4.
[38] Thamer C, Tschritter O, Haap M, et al. Elevated serum GGT concentrations predict reduced insulin sensitivity and increased intrahepatic lipids. Horm Metab Res 2005;37:246-51.
[39] Yoon KH, Lee JH, Kim JW, et al. Epidemic obesity and type 2 diabetes in Asia. Lancet 2006;368:1681-8.
[40] Kim DJ, Lee MS, Kim KW, et al. Insulin secretory dysfunction and insulin resistance in the pathogenesis of Korean type 2 diabetes mellitus. Metabolism 2001;50:590-3.