

Rosiglitazone Increases Indexes of Stearoyl-CoA Desaturase Activity in Humans

Link to Insulin Sensitization and the Role of Dominant-Negative Mutation in Peroxisome Proliferator-Activated Receptor- γ

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Fatty acid desaturases such as stearyl-CoA desaturase (SCD) convert saturated to unsaturated fatty acids and are involved in lipogenesis. Observational and animal data suggest that SCD-1 activity is related to insulin sensitivity. However, the effects of insulin-sensitizing drugs on SCD gene expression and desaturase activities are unknown in humans. In a randomized, placebo-controlled, double-blind, crossover study, 24 subjects with type 2 diabetes and one subject with partial lipodystrophy and diabetes due to dominant-negative mutation in the peroxisome proliferator-activated receptor- γ (PPAR γ) gene (P467L) received placebo and rosiglitazone for 3 months. SCD gene expression in adipose tissue was determined in 23 subjects, and in a representative subgroup ($n = 10$) we assessed fatty acid composition in fasting plasma triglycerides to estimate SCD and $\Delta 6$ - and $\Delta 5$ -desaturase activity, using product-to-precursor indexes. SCD mRNA expression increased by 48% after rosiglitazone ($P < 0.01$). SCD and $\Delta 5$ -desaturase but not $\Delta 6$ -desaturase activity indexes were increased after rosiglitazone versus placebo ($P < 0.01$ and $P < 0.05$, respectively). The change in activity index but not the expression of SCD was associated with improved insulin sensitivity ($r = 0.73$, $P < 0.05$). In the P467L PPAR γ carrier, SCD and $\Delta 5$ -desaturase activity indexes were exceptionally low but were restored (52- and 15-fold increases, respectively) after rosiglitazone treatment. This study

shows for the first time that rosiglitazone increases SCD activity indexes and gene expression in humans. An increased SCD activity index may reflect increased lipogenesis and might contribute to insulin sensitization by rosiglitazone. The restored SCD activity index after rosiglitazone in PPAR γ mutation supports a pivotal role of PPAR γ function in SCD regulation. *Diabetes* 54:1379–1384, 2005

Plasma fatty acid composition has been closely related to insulin resistance in epidemiological studies (1). Recently it was shown that the palmitic acid (16:0) content of plasma triglycerides was independently associated with factors related to insulin resistance (2). These associations can be partly explained by dietary fat intake but also by the endogenous activities of the desaturases involved in fatty acid biosynthesis (3). Desaturase activities are known to be regulated by genetic and hormonal factors that are independent of diet and fat intake (4).

In several (5,6), but not all (7), cross-sectional studies, insulin resistance has been associated with increased indexes of $\Delta 9$ -desaturase (stearyl-CoA desaturase [SCD]) and $\Delta 6$ -desaturase activities and decreased $\Delta 5$ -desaturase activity. This would be in line with the findings from the study of SCD-1-deficient mice (8).

SCD is the key enzyme in the biosynthesis of monounsaturated fatty acids from saturated fatty acids (i.e., the final step in lipogenesis) (4), and the palmitoleic/palmitic acid (16:1/16:0) index (also known as the “desaturation index”) (9) can be used to estimate SCD activity (5,9). However, our knowledge in humans is limited because the link between the regulation of SCD and insulin sensitivity is derived from observational and animal data. Thus, intervention studies in humans are needed to clarify the metabolic function and clinical relevance of SCD. One way to gain useful information is to test the effect of insulin sensitizers, i.e., thiazolidinediones (TZDs) on SCD activity indexes. TZDs are peroxisome proliferator-activated receptor- γ (PPAR γ) agonists that also activate genes encoding lipogenic enzymes including SCD (10). Hitherto, the effect of TZDs on SCD gene expression and activity has

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CLA, conjugated linoleic acid; HOMA%S, homeostasis model assessment of insulin sensitivity; NEFA, nonesterified fatty acid; PPAR γ , peroxisome proliferator-activated receptor- γ ; P/S ratio, polyunsaturated-to-saturated fat ratio; SCD, stearyl-CoA desaturase; TZD, thiazolidinedione.

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TABLE 1
Baseline characteristics of the subgroup in which plasma measurements were made

Age (years)	50.2 ± 10.0 (31–69)
BMI (kg/m ²)	30.6 ± 4.9 (24.4–41.8)
HbA _{1c} (%)	7.7 ± 1.2 (5.8–9.5)
C-peptide (nmol/l)	0.89 ± 0.28 (0.54–1.45)
HOMA%S	47.4 ± 23.1 (18.6–79.2)

Data are means ± SD (range) ($n = 10$).

only been studied in rats and in vitro, showing divergent results (11–14). We therefore evaluated the effect of rosiglitazone on adipose tissue SCD gene expression, as well as on indexes of SCD and $\Delta 5$ - and $\Delta 6$ -desaturase activity in patients with type 2 diabetes. To further elucidate the role of PPAR γ in the regulation of SCD, we examined the effect of rosiglitazone on desaturase activity indexes in a patient with a dominant-negative P467L PPAR γ mutation (15). This patient represented a lipodystrophic and insulin-resistant phenotype, and the effect of TZD could provide useful information about SCD activity in this phenotype.

RESEARCH DESIGN AND METHODS

This study is a further analysis of a double-blind, placebo-controlled, crossover study of rosiglitazone treatment (8 mg/day) in 24 subjects with diet-treated type 2 diabetes (16). Inclusion criteria were age 30–70, fasting plasma glucose level 7–12 mmol/l, and BMI >24 kg/m². Patients treated with anti-diabetic drugs or agents known to affect glucose or lipid metabolism were excluded. No patient had previously diagnosed heart, liver, or renal disease. All patients were encouraged to maintain their habitual diet and level of physical activity during the study. Generally, this was an overweight group with reasonably well-controlled type 2 diabetes. In subjects with complete metabolic data and available frozen plasma samples ($n = 10$) we assessed fatty acid composition and calculated fatty acid desaturase activity indexes. This group was representative of the whole group and did not differ with regard to metabolic characteristics including insulin sensitivity or metabolic response (i.e., insulin sensitization) to rosiglitazone. Baseline characteristics of the subgroup are shown in Table 1. In addition, a partially lipodystrophic patient with a dominant-negative PPAR γ mutation (P467L) was also assessed to evaluate the effect of rosiglitazone on fatty acid desaturase activity indexes in this patient. The metabolic response to rosiglitazone in this subject has previously been described (15). This study was approved by the Oxfordshire Clinical Research Ethics Committee, and all subjects gave their written informed consent.

Gene expression analysis. Samples for subcutaneous adipose tissue biopsies were taken under local anesthesia using a 12-gauge needle in the late postprandial period after placebo and rosiglitazone treatment, respectively. Samples were immediately frozen in liquid nitrogen and stored at -70°C for later mRNA quantification. cDNAs were generated from 200 ng of RNA reverse transcribed using random Hexamer primers and the SuperScript III First-Strand synthesis system (cat. no. 18080-051; Invitrogen, Paisley, U.K.) following the manufacturer's instructions. After this, 4- μl samples of a 1/10 dilution of the resulting cDNAs were analyzed in duplicate for the expression levels of the SCD gene transcript (refseq accession no. NM_005063), and the four housekeeping gene transcripts: β_2 -microglobulin (*B2M*), cyclophilin (*PPIA*), β -actin (*ACTB*), and acid ribosomal protein PO (*RPLPO*). This analysis was performed in 20- μl TaqMan gene expression assays using the Applied Biosystems Assays-on Demand reagents, Hs00748952_s1, Hs99999907_m1, Hs99999904_m1, Hs99999903_m1, and Hs99999902_m1, for the five genes, respectively, and the TaqMan Universal PCR Master Mix (cat. no. 4304437; Applied Biosystems, Foster City, CA). Assays were run on a Rotor-Gene 2000 real-time PCR machine (Corbett Research, Sydney, Australia) together with a serial dilution of a randomly chosen cDNA sample from the same batch of cDNAs to generate reaction efficiency values ($E = 10^{1/(-1/\text{slope})}$). Cycling conditions were as per Applied Biosystems recommendations. Expression values were calculated by the δ -Ct recommendation method ($Q = E^{(\text{minCt} - \text{sampleCt})}$) (17). The Ct values are as generated by the Rotor-Gene analysis software. It is extremely important that suitable housekeeping genes are chosen for the normalization of expression values as it is becoming increasingly apparent in the literature that many housekeeping genes do in fact vary considerably between experimental conditions (18). In this study we

found that two genes, *B2M* and *ACTB*, were both stable between sample groups, and a single normalization factor for each sample was calculated as the mean expression value of the two chosen housekeeper genes. (The other two genes, *ACTB* and *RPLPO*, were also analyzed but were found to be too variable between groups to be included in the analysis.) The relative expression levels for SCD were generated by dividing the SCD expression value by the normalization factor for that sample.

Fatty acid composition and desaturase activity indexes. Frozen (-80°C) fasting arterialized plasma was analyzed for triglyceride fatty acid composition. After lipid extraction according to Folch et al. (19), the lipid classes were separated by solid-phase extraction (20). Triglycerides and nonesterified fatty acids (NEFAs) were isolated and fatty acids were methylated in methanolic sulfuric acid. Fatty acid composition was analyzed by gas chromatography as previously described (21). The proportions of the fatty acids were calculated and expressed as mole percent of the sum of the total fatty acids analyzed. Desaturase activity indexes were calculated from plasma product-to-precursor ratios as follows: 16:1n-7/16:0 (SCD), 18:3n-6/18:2n-6 ($\Delta 6$ -desaturase), and 20:4n-6/20:3n-6 ($\Delta 5$ -desaturase) (5).

Metabolic parameters. Whole-body insulin sensitivity was evaluated in the fasting state using the homeostasis model assessment of insulin sensitivity (HOMA%S) (22). Plasma glucose, insulin, and C-peptide were measured as previously described (23).

Statistics. Results are presented as means ± SD with ranges where appropriate. Normality of variables was tested using Shapiro-Wilk tests. Non-normally distributed variables were logarithmically transformed. Parametric or nonparametric statistical analysis (paired t test or Wilcoxon signed-rank, respectively) was performed in which each subject served as his or her own control. The patient with PPAR γ mutation was not included in statistical analyses. Correlations between desaturase activities and insulin sensitivity were determined using Spearman rank correlation. $P < 0.05$ was regarded as statistically significant. For statistics the JMP software package was used (SAS Institute, Cary, NC).

RESULTS

As expected, whole-body insulin sensitivity (HOMA%S) was improved after rosiglitazone treatment in the subgroup (from 40.5 ± 18.0 after placebo to 50.5 ± 15.7 after rosiglitazone, $P = 0.037$, $n = 10$). Fasting glucose concentrations decreased after rosiglitazone (from 8.2 ± 1.6 mmol/l after placebo to 6.8 ± 1.1 mmol/l after rosiglitazone, $P < 0.001$, $n = 10$). These effects accord well with the effect observed from the original study ($n = 24$) (16). The subject with PPAR γ P467L mutation displayed a drastic improvement in glycemic control (HbA_{1c} from 8.7 to 5.6%) (15).

SCD gene expression. Complete adipose tissue expression data were available for 23 subjects. SCD mRNA relative expression levels increased after rosiglitazone versus placebo (from 3.1 ± 1.9 after placebo to 4.6 ± 2.3 after rosiglitazone [+48%], $n = 23$, $P = 0.007$). SCD expression also increased in the subgroup, but the change did not reach significance (from 3.6 ± 2.7 to 6.1 ± 4.0 [+69%], $n = 10$, $P = 0.076$). There was no significant correlation between change of SCD expression and change of insulin sensitivity.

Effect of rosiglitazone on desaturase activity indexes. The SCD activity index (16:1n-7/16:0 in the plasma triglyceride fraction) increased after rosiglitazone by 15% (from 0.159 ± 0.03 after placebo to 0.184 ± 0.03 after rosiglitazone, $P = 0.005$). In 9 of 10 subjects the SCD activity index was numerically increased, and in 1 subject it was decreased after rosiglitazone (Fig. 1A). The $\Delta 5$ -desaturase activity index increased by 20% (from 3.71 ± 0.95 after placebo to 4.45 ± 1.82 after rosiglitazone, $P = 0.049$) (Fig. 1A and B, respectively). The $\Delta 6$ -desaturase activity index did not change significantly (Fig. 1C). However, if one potential outlier was excluded (Fig. 1C), there

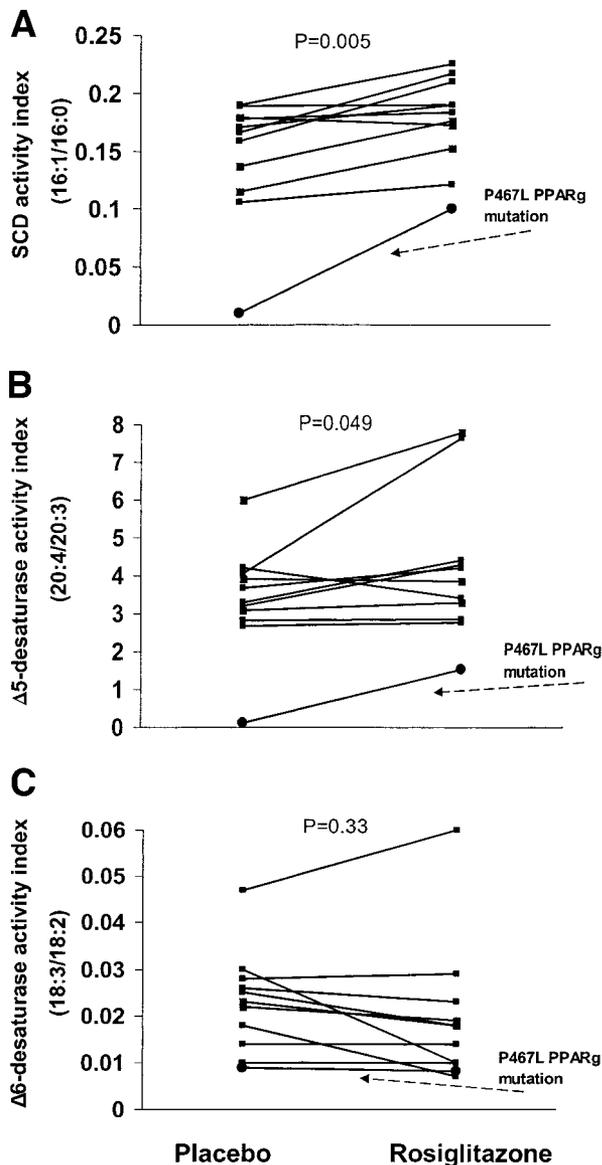


FIG. 1. Changes in desaturase activity indexes after placebo and rosiglitazone treatment for 12 weeks ($n = 10$). P values are calculated from 10 subjects and derived from paired t test (A) and Wilcoxon's signed-rank test (B and C). The subject with the P467L PPAR γ mutation is not included in statistical analyses.

was a borderline significant decrease in $\Delta 6$ -desaturase activity index (-23% , $P = 0.055$, $n = 9$).

With regard to sex, only one woman was included in the group from which desaturase activity indexes were calculated, but the significant effect of rosiglitazone on the SCD activity index remained if this woman was excluded from analyses (paired t test, $P < 0.01$, $n = 9$).

Considering the significant rise in SCD activity index as determined in triglycerides, we also calculated the activity index from the NEFA fraction although the individual fatty acid concentrations were much lower in the NEFA fraction, resulting in higher analytical variability. However, there was a similar relative increase ($+14\%$) in SCD activity index from the NEFA fraction as observed from the triglyceride fraction, but it did not reach significance after rosiglitazone ($P = 0.10$). The change in SCD activity index determined in triglycerides was positively correlated

with the change in SCD activity index determined in NEFA (Spearman; $r = 0.62$, $P = 0.05$). Because of very low concentrations in several of the polyunsaturated fatty acids, we did not estimate $\Delta 5$ - or $\Delta 6$ -desaturase activity indexes in the NEFA fraction.

The change in SCD activity index determined as 16:1n-7/16:0 was related to the change of 18:1n-9/18:0 (another marker of SCD activity) in triglycerides (Spearman; $r = 0.77$, $P = 0.009$, data not shown). Similarly, when we calculated the SCD activity index in the NEFA fraction, there was a significant correlation between the changes in these two different SCD activity indexes (Spearman; $r = 0.83$, $P = 0.003$).

Fatty acid composition. There were few significant changes of proportions of individual fatty acids after rosiglitazone. The proportions of the SCD precursor and product, 16:0 and 16:1, respectively, did not change significantly (Table 2). However, there was a significant increase in the proportion of triglyceride 20:4n-6 (arachidonic acid) ($P = 0.002$). Furthermore, the polyunsaturated-to-saturated fat ratio (P/S ratio) in triglyceride increased after rosiglitazone (0.65 ± 0.20 vs. 0.90 ± 0.20 , $P = 0.03$).

Desaturase activity indexes in PPAR γ P467L mutation. The SCD activity index calculated in triglycerides was severely blunted at baseline in this subject, but rosiglitazone treatment dramatically increased (52-fold) the SCD activity index (Fig. 1A). This increase in the SCD activity index was mainly due to a marked increase in the proportion of 16:1. Rosiglitazone also increased (15-fold) the very low $\Delta 5$ -desaturase activity index (Fig. 1B). However, the $\Delta 6$ -desaturase activity index only decreased modestly (10%) after rosiglitazone (Fig. 1C). Also the SCD activity index measured in the free fatty acid fraction was threefold lower than in the other subjects, but increased (approximately twofold) after rosiglitazone treatment (data not shown).

Desaturase activity indexes and insulin sensitivity. The change in the SCD activity index determined from triglycerides was significantly correlated to the change of insulin sensitivity (Fig. 2) but not to glucose concentrations ($r = 0.01$, $P = 0.99$). Although there was no significant change in 18:1/18:0 after rosiglitazone (data not shown), the change in this ratio was also related to a change in HOMA $\%S$ ($r = 0.88$, $P < 0.001$). There was no significant association between the change in $\Delta 5$ - or $\Delta 6$ -desaturase activity indexes and the change in insulin sensitivity. There was no significant correlation between age and changes in SCD activity indexes in response to rosiglitazone ($r = 0.35$, $P > 0.3$, data not shown).

DISCUSSION

This study is the first to investigate the effects of rosiglitazone on fatty acid desaturase activity indexes in humans. The SCD activity index increased after rosiglitazone, and the change was associated with the improvement in insulin sensitivity. In addition, SCD gene expression was significantly increased in response to rosiglitazone. There was also an increase in the $\Delta 5$ -desaturase activity index, which was not related to insulin sensitization. Notably, the increase in the SCD activity index after rosiglitazone treatment was particularly marked in the patient with the

TABLE 2
Effect of rosiglitazone on plasma fatty acid composition

	Triglycerides			NEFAs		
	Placebo	Rosiglitazone	P	Placebo	Rosiglitazone	P
14:0	2.22 ± 1.0	1.71 ± 0.4	0.18	1.49 ± 0.7	1.64 ± 0.5	0.46
16:0	29.1 ± 4.9	26.3 ± 1.8	0.10	24.6 ± 2.6	24.2 ± 1.7	0.59
16:1n-7	4.68 ± 1.3	4.87 ± 1.1	0.23	3.61 ± 1.0	4.0 ± 1.0	0.19
18:0	3.5 ± 0.8	3.0 ± 0.4	0.14	13.8 ± 1.8	13.6 ± 2.1	0.74
18:1n-9	37.8 ± 8.4	36.5 ± 6.1	0.54	40.6 ± 3.2	42.0 ± 4.1	0.18
18:2n-6	17.1 ± 5.5	21.5 ± 6.7	0.10	13.0 ± 2.8	11.8 ± 4.1	0.48
18:3n-6	0.42 ± 0.3	0.43 ± 0.3	0.70	0.35 ± 0.2	0.41 ± 0.4	0.24
18:3n-3	1.29 ± 0.5	1.19 ± 0.4	0.53	1.25 ± 0.4	1.14 ± 0.6	0.46
20:3n-6	0.33 ± 0.10	0.39 ± 0.09	0.07	0.27 ± 0.2	0.20 ± 0.15	0.28
20:4n-6	1.16 ± 0.3	1.71 ± 0.7	0.002	0.94 ± 0.2	1.00 ± 0.2	0.61
20:5n-3	0.46 ± 0.2	0.65 ± 0.4	0.08	ND	ND	
22:5n-3	0.39 ± 0.2	0.5 ± 0.4	0.21	ND	ND	
22:6n-3	0.83 ± 0.5	1.2 ± 1.1	0.19	ND	ND	
PS-ratio	0.65 ± 0.2	0.90 ± 0.2	0.03	ND*	ND*	

Data are means of molar proportions (%) ± SD. P values are differences within groups using a paired t test or Wilcoxon signed-rank test (n = 10). *Because several long-chain polyunsaturated fatty acids were nondetectable, the P/S ratio was not calculated for NEFAs.

PPARγ P467L mutation, supporting a direct role of PPARγ in the regulation of SCD-1. The basal SCD activity index was clearly suppressed in this patient compared with patients without the mutation. This is of interest because this patient represents a lipodystrophic phenotype including insulin resistance and fatty liver, all of which improved after rosiglitazone treatment (15).

However, results from animal models have indicated that SCD is upregulated in corresponding conditions (4), which is in apparent contrast to the situation in humans. Indeed, the current results are somewhat unexpected considering the fact that several (5,6), but not all (7), observational studies have suggested an inverse association between SCD activity indexes and insulin sensitivity.

SCD-1-deficient mice have signs of improved insulin sensitivity (8), and in vitro data in mouse adipocytes showed that troglitazone decreased SCD activity (14). It has been speculated from the results in SCD-null mice (8) that inhibition of SCD expression could be of benefit in the treatment of type 2 diabetes, but our results do not appear to be consistent with such a hypothesis. Notably, the observed effect of rosiglitazone on the SCD activity index was moderate and within a physiological range in contrast to the situation in SCD-null mice. Furthermore, mice and humans differ with regard to SCD isoforms, expression,

and gene homology (24), which could also explain the apparently contradictory relationship of SCD activity indexes and insulin sensitivity between rodents and humans.

The effect of TZDs on SCD activity or gene expression has only been explored in rodents so far. There was no change in SCD activity after troglitazone (12), whereas a study using rosiglitazone showed increased SCD gene expression in skeletal muscle and fat of ZDF rats (11). The latter accord with an apparently increased SCD expression in our study. In contrast, another study in ZDF rats using troglitazone reported a modest decrease in SCD-1 whereas SCD-2 (another SCD isoform in mice) increased 13-fold (13). These inconsistencies may be due to differences in the TZD used or in the tissue or animal model under investigation.

Furthermore, studies using *trans10cis12* conjugated linoleic acid (CLA) indirectly support a link between SCD, insulin sensitization, and PPARγ. CLA, which is the most potent fatty acid known to impair insulin action in humans (25), inhibits apparent SCD activity in humans (26) as well as in adipose tissue (27) and liver (28,29) in animals. Interestingly, CLA induces lipodystrophic diabetes in mice (30) and inhibits PPARγ expression in adipocytes (30,31) and thus acts as a PPARγ-antagonist. Those data accord with our finding that the PPARγ agonist rosiglitazone increased the SCD activity index and thus suggest that an increased SCD index may not necessarily be a sign of insulin resistance as previously suggested (4–6). Thus, the current literature together with our results suggest a complex role for SCD in insulin sensitivity and its regulation by PPARγ.

The conversion of 16:0 to 16:1 by SCD, thereby reducing the availability of palmitic acid in cell membranes and tissues, could be an important regulatory role of SCD that ensures optimal insulin signaling (4,5). High proportions of 16:0 in various plasma lipid fractions have been consistently related to type 2 diabetes (32) and insulin resistance (5). Notably, 16:0 but not 16:1 is a precursor to ceramide, an intracellular signal substance believed to be involved in the development of insulin resistance (33).

It is unclear whether increase in SCD activity index by

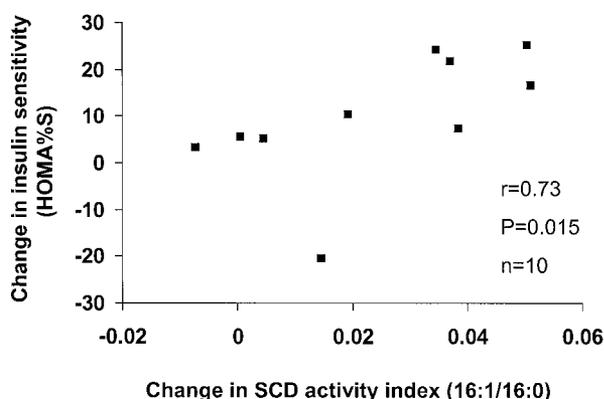


FIG. 2. Relationship between the change in insulin sensitivity and the change in SCD activity index (n = 10).

rosiglitazone is clinically important, and it is unknown whether the rosiglitazone-induced change in the SCD activity index was mediated by a change in insulin sensitization or as a direct effect of the drug as a PPAR γ agonist. However, the latter is a distinct possibility because a functional PPAR response element has been found in the promoter region of the SCD gene (34). This notion would be supported by the drastic enhancement of SCD activity index in the PPAR γ P467L carrier. Although the mutant PPAR γ allele clearly acts as a dominant-negative repressor of coexpressed wild-type receptor in transfected cells, it should be noted that the transcriptional activity of the mutant can be partially rescued by exposure to rosiglitazone (15). Thus, the profoundly increased SCD activity index in this patient after rosiglitazone is not as paradoxical as it might seem at first glance. However, the unliganded mutant is a strong constitutive repressor of PPAR γ target genes, and the finding that the basal SCD activity index was blunted in this patient accords with an important role for PPAR γ in the control of SCD expression.

There were few significant changes in individual fatty acids, but the plasma P/S ratio and the proportion of arachidonic acid (20:4n-6) increased in triglycerides after rosiglitazone. This accords with data showing that the P/S ratio is low in serum and skeletal muscle lipids in insulin-resistant subjects (35,36). Also, an increased serum 20:4 proportion has been associated with insulin sensitivity in both healthy and diabetic subjects (35,37).

There are some limitations of this study. First, we do not have direct measurements of desaturase activities. As should be the case for previous observational human data, the present results for SCD activity (as well as for Δ 5- or Δ 6-desaturase activity) should therefore be interpreted with caution until they can be confirmed using direct measurements. However, the change in SCD determined as 16:1n-7/16:0 was related to the change of 18:1n-9/18:0 in both plasma triglyceride and NEFA fractions. Although the latter index was not increased significantly after rosiglitazone, the correlation between these different SCD activity indexes strengthens the results. It is also unlikely that changes in plasma triglyceride concentrations explained differences in the 16:1/16:0 ratio because there was no significant change in triglyceride concentrations after rosiglitazone versus placebo (16), nor was any subject receiving triglyceride-lowering drugs (i.e., fibrates). Second, although both indexes reflect apparent SCD activity, we used 16:1/16:0 rather than 18:1/18:0 as the primary index to estimate SCD activity because the former may be more closely related to insulin resistance (5), and 16:1/16:0 is probably a more sensitive index to detect any change in SCD activity because of the lower dietary proportion of 16:1 compared with 18:1. The increased SCD expression in adipose tissue after rosiglitazone may indicate that plasma 16:1/16:0 reflects SCD activity in adipose tissue, but since we have not measured the activities directly in tissues it still remains to be elucidated whether the ratio mainly reflects SCD activity in adipose tissue, liver, or both. Lastly, we did not assess dietary intake during the study. Thus, because factors such as polyunsaturated fatty acids regulate the activities of desaturases, it cannot be completely excluded that changes in dietary intakes affected desaturase activity indexes, although the randomized de-

sign should have minimized the risk for such a bias, and subjects were instructed to maintain their habitual diet. The latter is relevant since in this study we used intra-subject comparisons.

In summary, this study supports the role of PPAR γ in the physiological regulation of SCD and points to a potential link with insulin sensitivity. Because this is the first human study to explore the effect of TZD on desaturase activity indexes, the unexpected link between insulin sensitization and estimated SCD activity requires further investigation.

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