PRECISION MEDICINE

CYP2C8 and *SLCO1B1* Variants and Therapeutic Response to Thiazolidinediones in Patients With Type 2 Diabetes

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OBJECTIVE

Thiazolidinediones (TZDs) are putatively transported into the liver by OATP1B1 (encoded by *SLCO1B1)* and metabolized by CYP450 2C8 enzyme (encoded by *CYP2C8*). While CYP2C83* has been shown to alter TZD pharmacokinetics, it has not been shown to alter efficacy.**

RESEARCH DESIGN AND METHODS

We genotyped 833 Scottish patients with type 2 diabetes treated with pioglitazone or rosiglitazone and jointly investigated association of variants in these two genes with therapeutic outcome.

RESULTS

The CYP2C83* variant was associated with reduced glycemic response to rosiglitazone ($P = 0.01$) and less weight gain ($P = 0.02$). The *SLCO1B1* 521T>C variant was associated with enhanced glycemic response to rosiglitazone ($P = 0.04$). The super responders defined by combined genotypes at *CYP2C8* and *SLCO1B1* had a 0.39% (4 mmol/mol) greater HbA_{1c} reduction ($P = 0.006$) than the poor responders. Neither of the variants had a significant impact on pioglitazone response.**

CONCLUSIONS

These results show that variants in *CYP2C8* and *SLCO1B1* have a large clinical impact on the therapeutic response to rosiglitazone and highlight the importance of studying transporter and metabolizing genes together in pharmacogenetics.

The thiazolidinediones (TZDs), pioglitazone and rosiglitazone, have been widely used in combination with other oral agents for the treatment of type 2 diabetes. They act as peripheral insulin sensitizers by activating the nuclear peroxisome proliferator–activated receptor γ, which regulates the transcription of genes related to glucose metabolism (1). After a meta-analysis of 42 studies that linked rosiglitazone to an increased risk of cardiovascular adverse effects (2), its marketing authorization was withdrawn in Europe and its use restricted in the U.S. However, its restriction has been lifted after the Rosiglitazone Evaluated for Cardiovascular Outcomes in Oral Agent Combination Therapy for Type 2 Diabetes (RECORD) study failed to show cardiac risks associated with rosiglitazone (3). Pioglitazone is still in clinical use in most countries, and its use has been suspended in France, and restricted in Germany, owing to a small absolute increased risk in bladder cancer. However, a recent multipopulation analysis showed no association of pioglitazone or rosiglitazone with the risk of bladder cancer (4).

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TZDs are effective at lowering HbA_{1c} by ~1–1.25% (11–14 mmol/mol) on average (5). Although TZDs show durability in action greater than seen with either metformin or sulfonylureas (6), weight gain induced by TZDs has restrained their clinical utility (7). For every 1% reduction in HbA_{1c}, an estimated 2–3% weight gain is documented (1).

The American Diabetes Association and European Association for the Study of Diabetes guidelines continue to highlight the need to individualize treatment in diabetes (8), and this applies particularly for the TZDs, where substantial interindividual variation exists in glycemic response (9). Epidemiological studies have identified age, sex, baseline weight, and HbA_{1c} as significant predictors of response, which can account for up to 49% of the variation in HbA_{1c} reduction (10,11). Genetic factors are expected to explain at least part of the remaining variation and may be important to better aid targeted treatment in this patient group.

In silico modeling has shown that both pioglitazone and rosiglitazone are putative substrates of transporter OATP1B1, which is encoded by *SLCO1B1* (12). Both agents are extensively metabolized in the liver, mainly by the cytochrome P450 2C8 enzyme encoded by *CYP2C8* (13,14). The main metabolites of rosiglitazone are N-desmethyl-rosiglitazone and rosiglitazone-para-O-sulfate, which are 20- to 55-fold less potent compared with the parent drug (15). The principal metabolites of pioglitazone are M-III and M-IV; in contrast to the metabolites of rosiglitazone, they are shown to be pharmacologically active (16). Gemfibrozil, which inhibits both CYP2C8 and OATP1B1, has been shown to increase the plasma concentration area under the curve (AUC) of pioglitazone and rosiglitazone between 2.4- and 3.0-fold in healthy volunteers (17,18), suggesting a role for both CYP2C8 and OATP1B1 in pharmacokinetics of the agents.

Genetic variants CYP2C8**3* (linked polymorphisms of Arg139Lys and Lys399Arg), and *SLCO1B1* 521T>C (Val174Ala) are commonly seen in populations of European ancestry with allele frequencies at ~12% and 16%, respectively (19). Pharmacokinetic studies of healthy volunteers have established that the gain-of-function CYP2C8**3* variant is associated with modestly enhanced TZD metabolism. Homozygote CYP2C8**3* carriers had 36% lower rosiglitazone plasma concentration and 39% higher weight-adjusted oral clearance rate compared with the wild-type carriers, with clear gene dosage effect seen in the heterozygotes (20,21). A similar trend has been shown with pioglitazone (22). Despite the pharmacokinetic effect of CYP2C8 variant on rosiglitazone, the studies that have assessed its impact on rosiglitazone efficacy have found no associations in a small number of healthy non–insulin resistant volunteers (20,21). For *SLCO1B1*, despite the in silico modeling, a pharmacokinetic study of 32 healthy volunteers found no association between the loss-of-function 521C allele and weight-adjusted plasma drug AUC after single-dose rosiglitazone (4 mg) or pioglitazone administration (23). The lack of consistency of these pharmacokinetic and dynamic studies is potentially due to the limited statistical power in the small samples to detect the moderate genetic effect, and the fact that the variants have previously been considered in isolation.

As TZDs have to be transported into the liver to be metabolized by CYP2C8, we assessed the glycemic response and side effect of weight gain induced by variants in *SLCO1B1* and *CYP2C8* together in a large population of patients with type 2 diabetes treated with rosiglitazone or pioglitazone.

RESEARCH DESIGN AND METHODS

Sample Ascertainment

Patients were ascertained from the Diabetes Audit and Research in Tayside Scotland (DARTS) study, which has previously been described in detail (24). In brief, all the patients can be linked to the Medicine Monitoring Unit/Health Informatics Centre Database to retrieve validated prescribing information and to the clinical information system, the Scottish Care Information–Diabetes Collaboration (SCI-DC), to obtain all biochemistry and clinical phenotypic data back to 1992. Prospective longitudinal data were also collected on these patients. Since October 1997, all patients with diabetes have been invited to give written informed consent to DNA and serum collection as part of the Wellcome Trust United Kingdom Type 2 Diabetes Case Control Collection. As of June 2009, >9,000 patients have participated in this Genetics of DARTS (GoDARTS) study.

From 1,942 incident TZD users in the GoDARTS cohort, we identified a study sample of 833 patients who had TZD as their second-line (added to metformin or sulfonylurea monotherapy) or third-line (added to metformin and sulfonylurea dual therapy) treatment according to guidelines in Scotland. To be included in the study, individuals had to have complete data with respect to age, sex, weight, oral antidiabetes treatment history, TZD treatment dose, adherence, and regular HbA_{1c} measurements. They all had a baseline HbA_{1c} >7%. They were on stable treatment for at least 6 months after TZD was initiated (the index date), which meant they did not start or stop another antidiabetes drug within 6 months on either side of the TZD index date. They were not treated with insulin before or during the studied period. This will help to ascertain TZD-related efficacy outcomes. A detailed sample ascertainment procedure is outlined in Supplementary Fig. 1. The study was approved by the Tayside Regional Ethics Committee, and informed consent was obtained from all subjects.

Drug Response Definitions

Individuals' glycemic response to TZDs was modeled as the maximum HbA_{1c} reduction recorded within 1 to 18 months of the index date while maintained on stable treatment. Similarly, TZD-induced weight gain was measured as the difference between the last measurement within the study period and the baseline weight. The multivariate linear model equation for these two outcomes is as follows: HbA_{1c} reduction (weight gain) ~ baseline HbA_{1c} + adherence + daily dose + study duration + age + sex + genotype. Baseline HbA_{1c} and baseline weight were defined as the nearest measures taken within the 180 days prior to the TZD index date. Adherence was calculated from the population-based drug-dispensing records as the percentage of maximum possible adherence for each participant. Treatment dose was determined as the mean dose of prescriptions encashed during the 3 months prior to the minimum HbA_{1c} within the 1–18 months of TZD index date. When the minimum HbA_{1c} happened in <3 months, the average dose before the treatment HbA_{1c} was recorded.

Genotyping

CYP2C8**3* (rs10509681) and *SLCO1B1* 521T>C (rs4149056) were genotyped

in the entire GoDARTS cohort with TaqMan-based allelic discrimination assays. As the two CYP2C8**3* variants rs10509681 and rs11572080 are in perfect linkage disequilibrium (r^2 = 1 in the 1,000-genome CEU panel) (25), only rs10509681 was genotyped in the current study. Assays were performed under manufacturer-recommended (Applied Biosystems) standard conditions. Assays were performed on 10 ng genomic DNA in 384-well plates and cycled using a H2OBIT thermal cycler (Thermo Scientific, Surrey, U.K.); fluorescence detection and genotype calling were performed on an ABI 7900FastHT sequence detection system (Applied Biosystems).

Statistical Analysis

One-way ANOVA was used to test for differences in the baseline characteristics by genotype. Allele frequency difference between subgroups and the full sample was compared in a 2 df χ^2 test. The exact test of Hardy-Weinberg equilibrium was carried out with PLINK (26). Multiple linear regression analyses of HbA_{1c} reduction and weight gain were performed with PLINK under an additive genetic model and with all the covariates included.

RESULTS

In the 833 patients studied, the allele frequencies of CYP2C8**3* and *SLCO1B1* 521C were 14.5% and 16%, respectively. The overall genotyping call rate was 94%, and both single nucleotide polymorphisms were in Hardy-Weinberg equilibrium in the sample ($P > 0.05$). In addition, we compared the TaqMan genotypes with the existing genotypes from exome chip array, and the concordance rates for rs10509681 and rs4149056 were 99.8% and 99.7%, respectively. There was no baseline clinical characteristic difference according to *CYP2C8* or *SLCO1B1* variant genotypes (Supplementary Table 1).

The number of patients treated with pioglitazone and rosiglitazone were 273 and 519, respectively, with the other 41 patients switched between the two agents. In the combined analysis, higher baseline HbA_{1c}, higher baseline weight, older age, female sex, higher adherence, and longer treatment duration were independently associated with better glycemic response. Greater weight gain was associated with higher baseline HbA_{1c}, higher baseline weight, higher daily dose, female sex, and treatment with pioglitazone. No significant association with HbA_{1c} reduction was observed when the CYP2C8**3* and *SLCO1B1* 521C variants were included into the clinical model (Supplementary Table 2). However, compared with the wild type, carriers of the **3* allele had less weight gain ($\beta = -0.91$, $P = 0.006$).

Compared with parent drugs, metabolites of rosiglitazone and pioglitazone exert different degrees of glycemic efficacy (16). In addition, differences in baseline characteristics of pioglitazone- and rosiglitazone-treated individuals, as shown in Supplementary Table 3, have been observed. Therefore, we performed multiple linear regression analysis in the two subgroups separately. The same set of clinical covariates was included in the modeling of weight gain and HbA_{1c} reduction. Table 1 shows the full clinical models in the rosiglitazone-treated group. A higher baseline HbA_{1c}, higher baseline weight, older age, female sex, and longer treatment were all independently associated with better glycemic response. A higher daily dose was the only strong predictor of weight gain with patients on 8 mg/day gaining 2 kg more weight than those on 4 kg/day (although dose was not associated with glycemic response to rosiglitazone). For pioglitazone-treated patients, a similar pattern of clinical predictors was observed but with less statistical significance due to the smaller number of patients (Supplementary Table 4). In contrast to rosiglitazone, there was no significant effect of pioglitazone dose on weight gain.

When genetic variants were added to the clinical models, patients carrying the CYP2C8**3* variant achieved less HbA_{1c} reduction (allelic $\beta = -0.21\%$, $P = 0.01$) and experienced less weight gain (allelic $\beta = -0.93$ kg, $P = 0.02$) with rosiglitazone treatment. The *SLCO1B1* 521C variant was associated with greater HbA_{1c} reduction (allelic $\beta = 0.18\%$, $P = 0.04$), but not weight gain, after rosiglitazone treatment. Neither of the two variants was significantly associated with response to pioglitazone (Table 2). This could be due to lack of enough statistical power from a smaller number of patients treated with pioglitazone. Assuming the **3* variant has the same allelic effect size of 0.21% HbA_{1c} reduction on both rosiglitazone and pioglitazone, the current sample size of 273 pioglitazone users will provide only 37% statistical power to detect the association at an α-level of 0.05 (27). More than 800 samples are required to provide sufficient (80%) statistical power to detect such an effect size.

To better assess the impact of these variants in rosiglitazone response, we considered a composite model consisting of a group of super responders (reduced transport at OATP1B1 [*SLCO1B1* 521C] and "normal" metabolizers at CYP2C8 [wild type]), intermediate responders (wild type at *CYP2C8* and *SLCO1B1*), and poor responders ("normal" transport of rosiglitazone into the liver across OATP1B1 [*SLCO1B1* 521T] and increased metabolism by CYP2C8 [CYP2C8**3*]). When the two variants were considered together, as shown in Fig. 1, the super responders had a 0.39% (4 mmol/mol) ($P = 0.006$) greater HbA_{1c} reduction than the poor responders. A similar, but nonsignificant, effect was seen on weight gain.

Table 1—Multiple linear models for HbA_{1c} reduction and weight gain in rosiglitazone

	Weight gain			HbA_{1c} reduction		
	β	95% CI	*P*	β	95% CI	*P*
Baseline HbA_{1c}	0.33	0.15, 0.65	0.04	0.65	0.59, 0.72	<0.001
Baseline weight	0.23	−0.01, 0.47	0.06	0.07	0.02, 0.13	0.004
Age	0.19	−0.19, 0.58	0.33	0.23	0.15, 0.31	<0.001
Sex	0.82	−0.12, 1.66	0.06	0.28	0.09, 0.46	0.003
Dose	0.41	0.25, 0.59	< 0.001	0.03	−0.01, 0.06	0.19
Adherence	0.23	−0.06, 0.51	0.11	0.05	−0.01, 0.11	0.09
Study duration	−0.08	−0.20, 0.04	0.18	0.06	0.03, 0.08	<0.001

Sex was coded 1 and 2 for male and female, respectively. Age was coded in the unit of 10 years. Baseline HbA_{1c} was measured as percentage. Dose was measured as 10% of the recommended maximum daily dose. Adherence was measured in 10%. Baseline weight was measured in 10 kg. The study duration was measured in month as the time from TZD index date to the treatment outcome measurement date.

Table 2—Genetic effect of *CYP2C8* and *SLCO1B1* variants on HbA_{1c} reduction and weight gain (additive genetic model)

		Weight gain			HbA_{1c} reduction		
Treatment	Gene	β	95% CI	*P*	β	95% CI	*P*
Rosiglitazone (*n* = 444)	CYP2C8**3*	−0.93	−1.73, −0.13	0.02	−0.21	−0.38, −0.04	0.01
	SLCO1B1	−0.13	−0.92, 0.67	0.75	0.18	0.01, 0.34	0.04
Pioglitazone (*n* = 239)	CYP2C8**3*	−0.46	−1.45, 0.51	0.34	0.14	−0.10, 0.38	0.26
	SLCO1B1	−0.02	−0.92, 0.87	0.96	−0.10	−0.32, 0.12	0.37

Since dosing is a strong predictor of rosiglitazone-induced weight gain, we performed a stratified genetic analysis of the rosiglitazone-treated patients by daily dose. As shown in Supplementary Table 5, the CYP2C8**3* variant had a similar impact on weight gain and HbA_{1c} reduction in those treated with 4 mg/day and 8 mg/day. The *SLCO1B1* variant had a stronger impact on glycemic response in those treated with 8 mg/day than those treated with 4 mg/day. Owing to the limited sample size, this observed pharmacogenetic difference is not statistically significant in a formal gene-by-dose interaction test ($P = 0.73$).

CONCLUSIONS

In this large population pharmacogenetic study of patients with type 2 diabetes, we have jointly investigated whether variants in the putative drug transporter gene *SLCO1B1* and the metabolizing enzyme gene *CYP2C8* contribute to variation in glycemic response and weight gain in response to treatment with TZDs. We confirm previous reports that TZDs work better in women and with increasing obesity (28,29). The combined genotypes at *CYP2C8* and *SLCO1B1* can be used to define super response and poor response groups to rosiglitazone, who differ in HbA_{1c} reduction by ~0.39% (4 mmol/mol). This effect size is approximately one-third of the average HbA_{1c} reduction achieved by 8 mg daily rosiglitazone (5) or approximately one-half of the HbA_{1c} reduction related to dipeptidyl peptidase 4 inhibitor monotherapy (30). Therefore, the effect size observed in this study could be clinically relevant in stratified medicine. On the other hand, these variants do not alter pioglitazone response.

We showed that rosiglitazone-treated individuals carrying the CYP2C8**3* variant had poorer glycemic response but less weight gain in a gene-dosage–dependent manner compared with the wild-type carriers. These results are consistent with previous pharmacokinetic studies that showed that the CYP2C8**3* variant was associated with higher rosiglitazone oral clearance and lower plasma concentration AUC (20,21). Other previous investigations into the pharmacodynamic impact of CYP2C8 variations on rosiglitazone response have found no evidence in small samples of subjects with normal insulin sensitivity (20,21). However, association of the CYP2C8**3* variant with impaired HbA_{1c} lowering has been reported in individuals with type 2 diabetes (31). The current study has demonstrated that the mild pharmacokinetic difference between CYP2C8**3* genotype can be translated into pharmacodynamic difference in rosiglitazone-treated individuals with type 2 diabetes, with the lower drug exposure among the CYP2C8**3* variant carriers

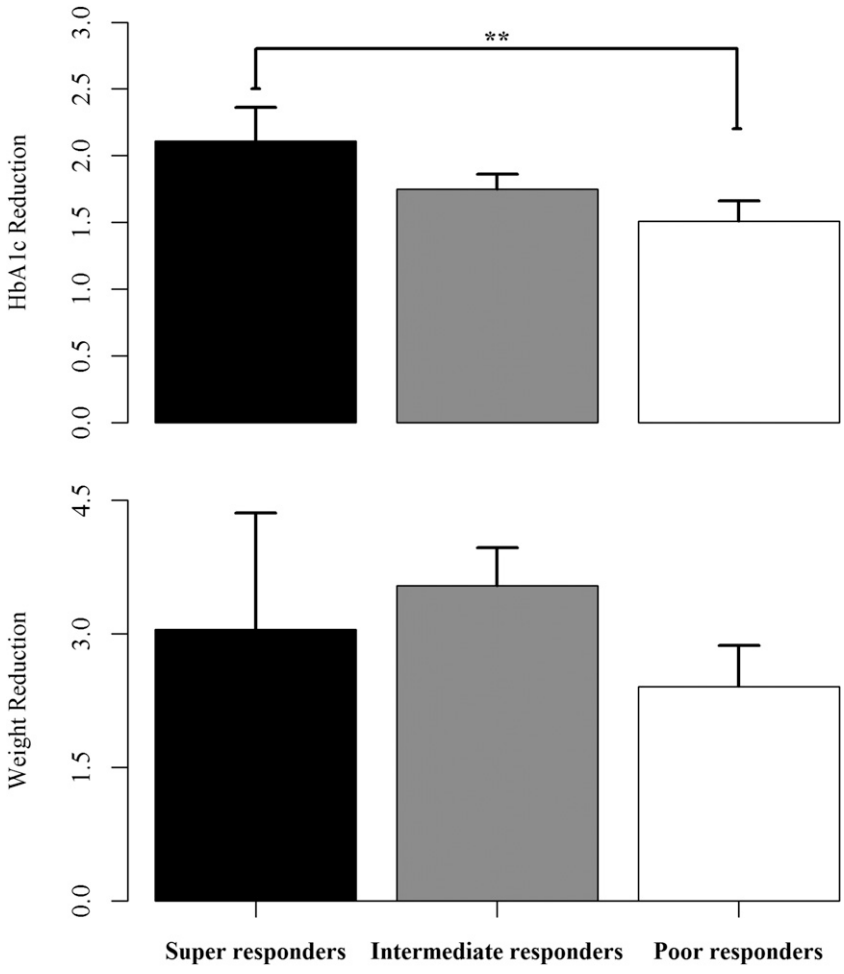

Figure 1—Rosiglitazone response by *SLCO1B1* and *CYP2C8* genotypes. Super responders (wild type at *CYP2C8* and one or more variant C allele at *SLCO1B1*), intermediate responders (wild type at both *CYP2C8* and *SLCO1B1*), and poor responders (one or more **3* allele at *CYP2C8* and wild type at *SLCO1B1*). The error bars represent the SEM. $^{**}P < 0.01$.

resulting in less HbA_{1c} reduction and weight gain.

In this study we showed association of CYP2C8**3* with response to rosiglitazone but not pioglitazone despite an established role of CYP2C8 in pioglitazone pharmacokinetics. This is entirely consistent with the contrast between the pharmacological properties of the two agents (Fig. 2). As the main rosiglitazone metabolites are less potent, pharmacokinetic difference of the parent drug was translated into efficacy difference. For pioglitazone, the principal biotransformation products, M-III and M-IV, are reported to exert sustained hypoglycemic action and therefore ameliorate the pharmacokinetic difference in the parent drug on overall efficacy (32).

In this study, we have for the first time showed that the *SLCO1B1* 521C allele is associated with better glycemic response in patients treated with rosiglitazone. Our results also indicated that the pharmacogenetic effect of the *SLCO1B1* 521T>C variant on rosiglitazone response was more pronounced in the 8 mg/day group than in the 4 mg/day group. This might explain why previous rosiglitazone pharmacokinetic studies reported no significant association between *SLCO1B1* 521T>C genotypes and drug exposure after 4 mg/day treatment and suggests that the variant becomes rate limiting only at high doses (19,20).

Joint investigation of variants in genes encoding for proteins involved in pharmacokinetics and pharmacodynamics of a given drug is believed to give better understanding of the role of genetics in drug response than individual variants per se. For example, studies investigating joint effect of variants in metformin transporters have previously been published (33–35). With this in mind, we have investigated joint effect of variants in genes encoding TZD transporter (*SLCO1B1*) and metabolizer (*CYP2C8*). In a composite model that consists of super responders and poor responders, the glycemic effect of the *SLCO1B1* variant is much greater when considered on a *CYP2C8* wild-type background (allelic effect 0.22) compared with on a *CYP2C8* variant background (allelic effect 0.1). This finding highlights the importance, when considering drug transporters and drug metabolizing enzymes, of assessing variants that alter drug availability for metabolism and variants that alter the rate of metabolism together; otherwise clinically important variants may be overlooked. Moreover, other functional variants such as those regulatory variants in these two genes could also affect the pharmacokinetics of TZDs and therefore contribute to the variation in treatment outcome. Locus-wise genetic screening would be useful to identify other functional variants in these two genes. In addition, further functional studies investigating the joint role of these variants in HbA_{1c} reduction and weight gain are also warranted.

There were some limitations of our study. The main limitation is the observational nature of our data set, which may introduce bias. Response modeling has shown that baseline HbA_{1c} and weight, the dose given, treatment duration, age, and sex all added variation to TZD response among the patients. Despite adjustment for these clinical characteristics in the model, the association between genetic variants and drug response could still be confounded. However, there was no phenotypic difference by genotype in our study sample, as shown in Supplementary Table 1, and the clinicians and participants were clearly blind to genotype, so these extrinsic factors will not introduce bias to the pharmacogenetic effect. A further limitation is our measure of weight gain. It is not possible to differentiate whether measured weight gain reflects fluid retention or increase in fat mass or both. Finally, our sample size, despite being much larger than any published study, is still small. This in particular limits the phenotypes

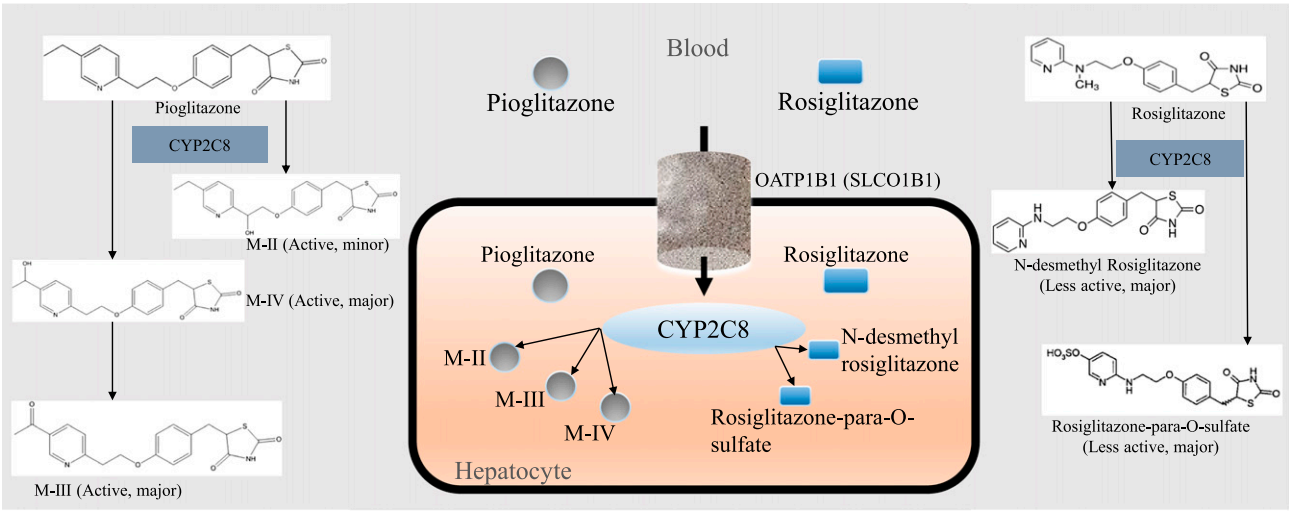

Figure 2—Pharmacogenetic effect of *CYP2C8* and *SLCO1B1* on TZDs pharmacokinetics and pharmacodynamics. Pharmacogenetic influence by *CYP2C8* and *SLCO1B1* variants is expected to affect rosiglitazone pharmacodynamics because both its main metabolites (N-desmethyl-rosiglitazone and rosiglitazone-para-O-sulfate) are less potent than its parent drug and pharmacokinetic differences will alter the drug exposure of active components (the parent drug, rosiglitazone) and therefore therapeutic response. Patients carrying the wild-type *SLCO1B1* allele and gain-of-function *CYP2C8* variants are expected to eliminate rosiglitazone much faster (poor responders) than carriers of the loss-of-function *SLCO1B1* variants on a wild-type *CYP2C8* background (super responders). In comparison, no pharmacogenetic effect is expected on pioglitazone response, as its main metabolites (M-II, M-III, and M-IV) remain active and the exposure of total active drug components is not altered by pharmacokinetic difference.

we are able to study. For example, it is not possible to assess the impact of these variants on other side effects such as incident heart failure owing to a major lack of power.

Finally, we acknowledge that we have undertaken a number of statistical tests in this study. We performed a total number of eight independent genetic association tests (two variants against two outcomes in two treatment groups), which carry a threshold of $P = 0.006$ (0.05/8) for any individual signal to be study-wide significant under a stringent Bonferroni correction. As shown in Table 2, three independent signals did reach the conventional threshold of $P < 0.05$ with the current sample size. In addition, when the genotypes of the two variants were combined together based on known biological mechanisms, a study-wide significant ($P = 0.006$) result was observed between super responders and poor responders to rosiglitazone. Further replication of these variants in larger independent samples is required to establish the role of these two variants in rosiglitazone response unequivocally.

This study established that glycemic response and weight gain in rosiglitazone-treated individuals with type 2 diabetes were associated with genetic variants in the drug transporter gene *SLCO1B1* and the metabolizing enzyme gene *CYP2C8* and highlighted the importance of studying pharmacokinetic genes together. The genetically defined super responders had an extra 0.39% (4 mmol/mol) HbA_{1c} reduction compared with those nonresponders. While our results establish key pharmacogenetic variants that alter response to rosiglitazone, there could be factors that hinder its direct clinical applicability. The variants that increase glycemic efficacy to rosiglitazone also increase weight gain; i.e., the "benefit" and "harm" are both increased. With the increasing awareness of risk associated with TZDs there is a need to optimize the benefit and reduce the risk for an individual. We believe that this is a key opportunity for pharmacogenetics to potentially identify individuals who can benefit from the considerable therapeutic advantages of TZDs and who are least at risk for the side effects. Rather than letting TZDs slide into disuse, we should concentrate efforts on identifying predictors of response or harm to TZDs.

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