

Pioglitazone Decreases Plasma Cholesteryl Ester Transfer Protein Mass, Associated With a Decrease in Hepatic Triglyceride Content, in Patients With Type 2 Diabetes

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OBJECTIVE — Thiazolidinediones reduce hepatic steatosis and increase HDL cholesterol levels. In mice with human-like lipoprotein metabolism (APOE*3-Leiden.CETP transgenic mice), a decrease in hepatic triglyceride content is associated with a decrease in plasma cholesteryl ester transfer protein (CETP) mass and an increase in HDL levels. Therefore, the aim of the present study was to assess the effects of pioglitazone on CETP mass in patients with type 2 diabetes.

RESEARCH DESIGN AND METHODS — We included 78 men with type 2 diabetes (aged 56.5 ± 0.6 years; HbA1c $7.1 \pm 0.1\%$) who were randomly assigned to treatment with pioglitazone (30 mg/day) or metformin (2000 mg/day) and matching placebo, in addition to glimepiride. At baseline and after 24 weeks of treatment plasma HDL cholesterol levels and CETP mass were measured, and hepatic triglyceride content was assessed by proton magnetic resonance spectroscopy.

RESULTS — Pioglitazone decreased hepatic triglyceride content (5.9 [interquartile range 2.6–17.4] versus 4.1 [1.9–12.3]%, $P < 0.05$), decreased plasma CETP mass (2.33 ± 0.10 vs. 2.06 ± 0.10 $\mu\text{g/ml}$, $P < 0.05$), and increased plasma HDL cholesterol level (1.22 ± 0.05 vs. 1.34 ± 0.05 mmol/l, $P < 0.05$). Metformin did not significantly change any of these parameters.

CONCLUSIONS — A decrease in hepatic triglyceride content by pioglitazone is accompanied by a decrease in plasma CETP mass and associated with an increase in HDL cholesterol levels. These results in patients with type 2 diabetes fully confirm recent findings in mice.

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Hepatic steatosis is a prevalent condition in patients with type 2 diabetes and is associated with an increased cardiovascular risk (1,2). Furthermore, many patients with type 2 diabetes display dyslipidemia characterized by high plasma levels of apolipoprotein (apo) B-lipoproteins and triglycerides and low plasma levels of HDL cholesterol. Re-

cently, Toledo et al. (3) showed that hepatic steatosis is associated with more severe hyperlipidemia in type 2 diabetes, which might contribute to the increased risk of cardiovascular disease.

To reduce this increased cardiovascular risk in type 2 diabetes, regular treatment algorithms include lipid-lowering drugs. Our previous studies in

APOE*3-Leiden.CETP transgenic mice, a well-established model for human-like lipoprotein metabolism, showed that treatment with either statins (4), fibrates (5), or niacin (6) resulted in a reduction in plasma apoB-lipoproteins and triglyceride levels and an increase in HDL cholesterol. Moreover, these treatments reduced hepatic lipid content (i.e., both triglycerides and cholesterol) as well as the hepatic expression and plasma levels of cholesteryl ester transfer protein (CETP) (4–6). CETP is a protein that mediates the heteroexchange of cholesteryl esters from HDL to (V)LDL with a simultaneous exchange of triglycerides from (V)LDL to HDL. These studies thus suggest that lowering of hepatic lipid content in APOE*3-Leiden.CETP mice increased HDL cholesterol levels by reduction of plasma CETP mass.

Because the correlation between hepatic triglyceride content and plasma CETP mass has not been studied in humans, the aim of this study was to evaluate whether the relationship between lowering of hepatic triglyceride content and decreased plasma CETP mass also exists in humans. Hepatic triglyceride content can be lowered by thiazolidinediones, including pioglitazone (7). Indeed, in a previous study, we reported that both antidiabetic drugs pioglitazone and metformin improved insulin sensitivity in men with type 2 diabetes whereas only pioglitazone reduced hepatic triglyceride content (8). Therefore, we used pioglitazone treatment as a model to study the effects of a change in hepatic triglyceride content on CETP mass in patients with type 2 diabetes and used metformin treatment as a negative control.

RESEARCH DESIGN AND METHODS

Methods — This study used the data from the Pioglitazone Influence on tRiglyceride Accumulation in the Myocardium in Diabetes (PIRAMID) study. This was a prospective, randomized, double-blind, intervention study, which compared the effects of pioglitazone and

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Table 1—Hepatic triglyceride content, plasma CETP mass, cholesterol, triglycerides, and apoB100 at baseline and after 24 weeks of treatment

	Pioglitazone		Metformin		P value between groups
	Baseline	24 weeks	Baseline	24 weeks	
Hepatic triglyceride content (%)*	5.9 (2.6–17.4)	4.1 (1.9–12.3)†	7.7 (3.7–23.9)	10.7 (5.1–22.0)	< 0.01
CETP mass ($\mu\text{g/ml}$)	2.33 \pm 0.10	2.06 \pm 0.10†	2.44 \pm 0.08	2.24 \pm 0.12	NS
HDL cholesterol (mmol/l)	1.22 \pm 0.05	1.34 \pm 0.05†	1.22 \pm 0.06	1.23 \pm 0.06	0.02
Total cholesterol (mmol/l)	4.90 \pm 0.16	5.19 \pm 0.22†	5.15 \pm 0.18	4.99 \pm 0.18	< 0.01
Triglycerides (mmol/l)	1.74 (0.97–3.09)	1.37 (0.88–1.80)†	2.08 (1.08–2.74)	1.23 (0.68–1.92)†	NS
ApoB100 (mg/dl)	84.88 \pm 5.08	75.41 \pm 4.03†	89.72 \pm 5.01	74.58 \pm 4.22†	NS

Data are means \pm SEM or median (interquartile range). *Data from van der Meer et al. (8). †Within group $P < 0.05$.

metformin on cardiac function and metabolism. The results were reported previously (8), and the study design will be summarized here. The study included male patients with type 2 diabetes without cardiovascular disease or diabetes-related complications. Inclusion criteria were BMI 25–32 kg/m², age between 45 and 65 years, and diabetes well controlled with metformin, a sulfonylurea, or both (HbA1c 6.5–8.5%). Patients were excluded on the following criteria: uncontrolled hypertension (blood pressure > 150/85 mmHg), medical history of diabetes-related complications, liver disease, cardiovascular disease, or use of thiazolidinediones or insulin before the study. This study was executed at two hospitals in the Netherlands (Leiden University Medical Center, Leiden, and VU University Medical Center, Amsterdam), and both local ethics committees gave their approval. All participants signed informed consent.

If patients met the inclusion criteria, their glucose-lowering medication was switched to glimepiride monotherapy, until a stable dose was reached 2 weeks before the start of the intervention. At baseline, patients were randomly assigned to metformin (500 mg twice daily, titrated to 1,000 mg twice daily) or pioglitazone (15 mg once daily, titrated to 30 mg once daily after 2 weeks) in addition to glimepiride. In both the metformin and pioglitazone groups, 39 patients were included. In the pioglitazone group 34 patients and in the metformin group 37 patients completed the study.

Patients were studied at baseline and after 24 weeks of treatment. Blood sampling and magnetic resonance spectroscopy were performed after an overnight fast.

Hepatic triglyceride content

Hepatic triglyceride content was measured by proton (¹H) magnetic resonance spectroscopy on a 1.5-T whole-body

magnetic resonance scanner (Gyrosan ACS/NT15; Philips, Best, the Netherlands). The technical details were described previously (8). The voxel was placed in the hepatic parenchyma, carefully preventing placement in vascular structures. Java Magnetic Resonance User interface software (jMRUI version 2.2; developed by A. van den Boogart, Katholieke Universiteit Leuven, Leuven, Belgium) was used for fitting of the spectra. Technical details of spectra acquisition and spectra quantification were described previously (8,9). Spectra with and without water suppression were acquired to calculate hepatic triglyceride content relative to water (signal amplitude of triglyceride/signal amplitude of water \times 100%).

Plasma cholesterol, triglyceride, apoB100, and CETP mass analyses

All plasma samples were obtained in the postabsorptive state on the day of randomization and at 24 weeks and analyzed in one laboratory (Leiden, the Netherlands). To ascertain that we could make adequate correlations, these measurements were performed in the same blood samples. Plasma triglyceride and cholesterol concentrations were determined using commercially available enzymatic kits (1488872 and 236691; Roche Molecular Biochemicals, Indianapolis, IN). This cholesterol assay was also used for determination of plasma HDL cholesterol after precipitation of apoB-lipoproteins from 20 μl of plasma by adding 10 μl of heparin (500 units/ml; LEO Pharma, The Netherlands) and 10 μl of 0.2 mol/l MnCl₂ (6). Plasma apoB100 was determined with a Human ApoB ELISA kit (3715–1H; Mabtech, Nacka Strand, Sweden). The plasma CETP mass was quantified using a CETP ELISA Daiichi kit (Daiichi Pure Chemicals, Tokyo, Japan).

Statistics

Data are expressed as means \pm SEM or as median (interquartile range) because hepatic triglyceride content and plasma triglycerides were not normal distributed. Paired *t* tests or Wilcoxon signed-rank tests were used for within-group differences. We used ANOVA to assess between-group differences. For correlation analysis, Spearman correlation analyses were used. We used SPSS software (version 16.0; SPSS, Chicago, IL) for statistical analyses. $P < 0.05$ was considered statistically significant.

RESULTS— At baseline, patients in both treatment groups were well-matched for age (pioglitazone 56.8 \pm 1.0 years and metformin 56.4 \pm 0.9 years, between-group $P > 0.05$), duration of diabetes (pioglitazone 4 [3–6] years and metformin 3 [1–5] years, $P > 0.05$), and BMI (pioglitazone 28.2 \pm 0.5 kg/m² and metformin 29.3 \pm 0.6 kg/m², between-group $P > 0.05$) (8).

Treatment effect

The effects of treatment on hepatic triglyceride content and plasma lipid profiles are presented in Table 1. As we showed before (8), treatment with pioglitazone for 24 weeks decreased hepatic triglyceride content (5.9 [2.6–17.4] vs. 4.1 [1.9–12.3]%, $P < 0.05$). This was accompanied by a decrease in plasma CETP mass (2.33 \pm 0.10 vs. 2.06 \pm 0.10 $\mu\text{g/ml}$, $P < 0.05$) and an increase in plasma total cholesterol (4.90 \pm 0.16 vs. 5.19 \pm 0.22 mmol/l, $P < 0.05$), which was explained in part by an increase in HDL cholesterol levels (1.22 \pm 0.05 vs. 1.34 \pm 0.05 mmol/l, $P < 0.05$). Treatment with metformin did not significantly affect either of these parameters. Treatment with pioglitazone and metformin both decreased plasma triglycerides and apoB100 significantly; however, there was no difference

Table 2—Hepatic triglyceride content, plasma CETP mass, cholesterol, triglycerides, and apoB100 in patients treated with pioglitazone, selected on the use of statins at baseline

	No statin use		Statin use		P value between groups
	Baseline	24 weeks	Baseline	24 weeks	
Hepatic triglyceride content (%)	6.4 (2.5–18.9)	4.9 (1.9–14.7)*	8.0 (2.8–16.5)	3.7 (1.9–10.9)*	NS
CETP mass ($\mu\text{g/ml}$)	2.64 \pm 0.14	2.16 \pm 0.12*	1.98 \pm 0.09	1.96 \pm 0.15	0.03
HDL cholesterol (mmol/l)	1.14 \pm 0.06	1.32 \pm 0.06*	1.30 \pm 0.06	1.36 \pm 0.08	NS
Total cholesterol (mmol/l)	5.32 \pm 0.22	5.87 \pm 0.35	4.44 \pm 0.19	4.55 \pm 0.19	NS
Triglycerides (mmol/l)	1.74 (0.82–3.11)	1.32 (0.80–3.02)	1.61 (1.02–2.41)	1.46 (0.99–1.69)	NS
ApoB100 (mg/dl)	86.59 \pm 6.22	82.06 \pm 5.77	83.07 \pm 8.29	68.77 \pm 5.34*	NS

Data are means \pm SEM or median (interquartile range). *Within group $P < 0.05$.

in the reduction between the groups (Table 1).

Correlations

Changes in plasma CETP mass after 24 weeks in the pioglitazone-treated patients correlated with changes in hepatic triglyceride content ($r = 0.34$, $P < 0.05$), although this association was not present in the metformin group.

Effect of statin use in the pioglitazone-treated group

In the pioglitazone group, 19 of the 39 patients used a statin at the start of the study. Table 2 compares the changes in lipid levels and hepatic triglyceride content between statin users versus nonstatin users in the patients treated with pioglitazone. In nonstatin users, pioglitazone decreased liver triglyceride content (6.4 [2.5–18.9] vs. 4.9 [1.9–14.7]%, $P < 0.05$), increased HDL cholesterol levels (1.14 \pm 0.06 vs. 1.32 \pm 0.06 mmol/l, $P < 0.05$), and decreased CETP mass (2.64 \pm 0.14 vs. 2.16 \pm 0.12 $\mu\text{g/ml}$, $P < 0.05$). However, remarkably, in statin users, pioglitazone also reduced liver triglyceride content (8.0 [2.8–16.5] versus 3.7 [1.9–10.9]%, $P < 0.05$), but did not affect either HDL cholesterol or CETP mass. ApoB100 decreased significantly only in the statin users (83.07 \pm 8.29 vs. 68.77 \pm 5.34 mg/dl, $P < 0.05$).

CONCLUSIONS— In this study, we assessed the associations among changes in hepatic triglyceride content, plasma CETP mass, and lipid profiles in patients with type 2 diabetes. The results show that pioglitazone decreased hepatic triglyceride content, associated with decreased plasma CETP mass, and increased HDL cholesterol levels. These findings are in full concordance with our recent studies in APOE*3-Leiden.CETP mice, which showed that classic lipid-lowering drugs

concurrently lowered hepatic lipid content and decreased hepatic CETP mRNA expression, resulting in decreased plasma CETP mass (4–6).

In this study, plasma triglycerides and plasma apoB100 decreased equivalently in both the pioglitazone and metformin group. Accordingly, other studies have shown that pioglitazone and metformin both decrease plasma triglycerides (10–13). Given the generally observed inverse relationship between plasma triglycerides and HDL cholesterol found in epidemiological studies, a decrease in plasma triglycerides may induce an increase in HDL cholesterol only. However, in the present study the decrease in plasma triglycerides was not different between the groups and plasma HDL cholesterol only increased in the pioglitazone group, indicating that another mechanism may be responsible for eliciting this difference, i.e., the reduction in CETP.

It is intriguing to speculate on the mechanism underlying the correlation between hepatic lipid content and plasma CETP mass. It is known that cholesterol derivatives are agonists for the nuclear receptor liver X receptor α (LXR α). Activation of LXR α results in increased transcription of CETP and sterol regulatory element-binding proteins-1c (14). Thus, our studies in APOE*3-Leiden.CETP mice suggest that a decrease in hepatic cholesterol content, associated with a decrease in cholesterol derivatives, such as oxysterols, reduces LXR α activation, thereby further downregulating CETP mRNA transcription. It is therefore likely that in our study pioglitazone decreased hepatic cholesterol content in addition to triglyceride content, thereby downregulating LXR α -activity. Although it is not possible at this time to noninvasively measure hepatic cholesterol content in humans, studies in APOE*3-Leiden.CETP mice with a human-like protein

profile generally demonstrate a strong relation between hepatic cholesterol and hepatic triglyceride content.

Notably, thiazolidinediones such as pioglitazone, can also upregulate LXR α expression via activation of peroxisome proliferator-activated receptor- γ , which is most dominantly expressed in adipose tissue (15). Moreover, CETP expression is prominent in adipose tissue. Radeau et al. (16) have shown that CETP mRNA expression in adipose tissue correlates with plasma CETP concentrations. The increased subcutaneous fat mass as induced by pioglitazone treatment may contribute to increased plasma CETP levels, thereby potentially counteracting the decrease in plasma CETP levels due to the decrease in hepatic lipid content by pioglitazone. Therefore, the observed decrease in plasma CETP mass due to the decrease in hepatic triglyceride content may, in fact, be larger.

To our knowledge, only one other study evaluated the effect of thiazolidinediones on CETP expression, but the hepatic triglyceride content was not studied. Chappuis et al. (17) performed a crossover study comparing pioglitazone versus rosiglitazone in 17 patients with type 2 diabetes. They found that rosiglitazone increased total cholesterol levels and decreased plasma CETP activity in accordance with our study. However, pioglitazone did not have any effect on these parameters. The differences in their results on the effects of pioglitazone compared to our study may be due to the shorter treatment duration of 12 weeks and/or to the smaller sample size in the previous study.

Finally, we found that pioglitazone did not further decrease CETP mass in patients who already used a statin. Experimental studies in APOE*3-Leiden.CETP mice have demonstrated that statins decrease plasma CETP mass by decreasing

hepatic mRNA expression, again related to decreased hepatic cholesterol content (4). Apparently the effect of statins is dominant over the effect of pioglitazone. We hypothesize that statins specifically decrease hepatic cholesterol content and downregulate CETP mRNA expression. Therefore, additional lowering of hepatic triglyceride content will not result in an additional decrease in CETP expression. However, the current study was not designed to assess the effects of statins on these parameters.

A limitation of this study is that only men were included. Kinoshita et al. (18) showed that men have lower CETP activity than women; thus, these data may not be readily extrapolated to women with type 2 diabetes.

In summary, this study shows that in male patients with type 2 diabetes a decrease in hepatic triglyceride content by pioglitazone is associated with a decrease in CETP mass and an increase in HDL cholesterol levels. Furthermore, we confirmed that use of statins is associated with a decreased plasma CETP mass. Both findings are in full agreement with our recent findings in APOE*3-Leiden.CETP mice and support the validity of these mice as a model for human-like lipoprotein metabolism.

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