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Original Article

Association between triglyceride and high-density lipoprotein cholesterol change following fibrate therapy

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ABSTRACT

Background: Debate surrounding the role of fibrates has followed mixed outcomes from several randomised controlled trials. Subgroup analysis of even the negative trials reveals significant reduction in cardiovascular risk amongst patients with low HDL-C and high TG. We previously described factors associated with HDL-C change following fibrates. As fibrates influence both HDL-C and TG levels via their action on PPAR-α, we now wished to study TG change following fibrate therapy and any associations with baseline and change in HDL-C and TC levels.

Methods: Data was collected from case notes of patients started on fibrates ($n = 248$) between 2002 and 2008 in the lipid clinics at Heart of England NHS Foundation Trust. Regression analyses were carried out to determine factors associated with changes in TG.

Results: Multiple regression analysis revealed that TG change was associated with pre-treatment TG ($p < 0.001$) and TC levels ($p = 0.029$). The association between TG change and pre-treatment TG remained significant when all factors including gender, concurrent statin treatment, diabetes and baseline HDL-C were entered into the regression model. Our previous study demonstrated significant post-fibrate HDL-C change in the group with baseline HDL-C values <1.0 mmol/l. In our present study significant TG reduction was observed regardless of the baseline patient characteristics including HDL-C levels.

Conclusions: The actions of fibrates are considered to be mediated via PPAR-α, but our data suggest that the effects on TG and HDL-C are different. Thus, the mechanisms mediating the changes of these lipids following fibrate treatment may vary.

1. Introduction

Epidemiology studies have established low HDL-C and hypertriglyceridaemia, in addition to raised LDL-C as factors associated with cardiovascular disease [1–6]. Furthermore, an inverse relationship between TG and HDL-C is often seen [7]. TG and HDL-C metabolism is closely linked through CETP and it has been proposed that high TG levels leading to TG enrichment of HDL-C particles could increase the rate of HDL-C catabolism [8,9].

Fibrates bind and activate PPAR-α which alters the regulation of gene transcription of proteins involved in fatty acid and lipoprotein metabolism [10–12]. Fibrate treatment leads to a modest decrease in LDL-C, a variable increase in HDL-C and a greater reduction in TG levels [13]. Following mixed outcomes from randomised controlled studies there is debate on whether fibrates have a clinical role, except in patients with marked hypertriglyceridaemia. However, subgroup analyses of these trials have demonstrated significant benefit in patients with the metabolic syndrome. A meta-analysis of 18 trials (45,058 individuals) with fibrates was carried out by Jun et al. in 2010 and significant decreases were observed in major cardiovascular and coronary events [14]. Subgroup analyses suggested lower coronary events in individuals

Abbreviations: ABCA, ATP-binding cassette transporter; ApoA1, apolipoprotein A1; ApoA2, apolipoprotein A2; ApoB, apolipoprotein B; ApoC3, apolipoprotein C3; BMI, body mass index; c, coefficient (linear regression); CETP, cholesteryl ester transfer protein; CI, 95% confidence intervals; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol; LPL, lipoprotein lipase; PPAR, peroxisome proliferator-activated receptor; RCT, randomised controlled trial; SR-B, scavenger receptor B; TC, total cholesterol; TG, triglycerides; VLDL, very low-density lipoprotein.

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with higher mean baseline TG levels (≥2 mmol/l) compared to the complementary group. Interestingly, despite the well described inverse relationship between baseline TG and HDL-C, no significant difference in outcome was seen in the subgroup of patients with lower baseline HDL-C (<1 mmol/l vs ≥1 mmol/l).

Miller et al. in 2007 investigated the effect that lowering TG levels had on HDL-C following various therapies including treatment with statins, fibrates and niacin [15]. The inverse relationship between TG and HDL-C levels was observed pre-treatment. They revealed that TG reduction was inversely correlated with HDL-C increase, and this pattern remained significant even after the regression analysis was adjusted for several variables such as types of treatment and patient characteristics. Whilst they demonstrated that fibrate therapy led to HDL-C increase in the total cohort, they did not specifically analyse this in relation to TG change in patients on fibrates. The above lipid-regulating drugs not only act through distinct mechanisms but they are also prescribed to patients with different baseline lipid characteristics. It is thus important to study the response to each drug class separately; examining the relation between changes in TG and HDL-C.

There remain unanswered questions in the clinical outcomes amongst subgroups of patients on fibrate therapy, such as why the group with high baseline TG showed greater benefit whilst those with low HDL-C did not [14]. Fibrates, through their action on PPAR-α affect both, TG and HDL-C levels. Despite this, and the well-established inverse relation between baseline TG and HDL-C, a literature search has not identified a study characterising the relation between HDL-C and TG change specifically in patients on fibrate therapy.

Analysis of the data from our metabolic clinics at the Heart of England NHS Foundation Trust in 2012 showed that a greater increase in HDL-C following fibrate treatment was associated with lower HDL-C baseline levels [16]. Interestingly this phenomenon was absent in patients on concurrent statin therapy. We now wished to turn our attention to TG change and its relation to HDL-C in patients on fibrate treatment.

More specifically, the aims of this study were to determine the following after fibrate treatment:

(1) TG change in the total cohort as well as patient subgroups.
(2) The baseline predictors of TG change.
(3) The association between changes in TG and other lipids (HDL-C and TC).
(4) Pattern of TG change; whether the change in TG follows the same pattern as the change in HDL-C that we reported in a previous study [16], particularly in patients on concurrent statin therapy.

2. Subjects, materials and methods

Patients commencing on fibrates between 2002 and 2008 in the lipid clinics run by the Heart of England NHS Foundation Trust were identified from the electronic patient record databases by using appropriate search keywords. Data were collected from 248 case notes (Good Hope Hospital 150 patients, Birmingham Heartlands Hospital: 98 patients). Demographic data included the following: males 181/248 (73.0%), type 2 diabetes 84/247 (34.0%), hypertension 128/239 (53.6%).

Lifestyle advice was provided to all patients at the initial appointment, preceding fibrate treatment. The pre-fibrate treatment lipid values (TC, TG, HDL-C and calculated LDL-C concentrations) were obtained from the pathology database just before the fibrate therapy commenced. The post-treatment levels were either the most recent results available (up to 30.03.2009) or those prior to the addition of another lipid lowering agent. In a previous publication we have described the patient group in detail [16].

TC, TG and HDL-C levels were measured on the Roche Modular platform P800 analyser using Roche reagents. The LDL-C was calculated using the Friedewald equation when TC, HDL-C and TG (when levels were lower than 4.5 mmol/l) values were available. The data were entered on an excel spreadsheet and then transferred to the statistics programme STATA (version 8.0 for Windows) for analysis. Paired *t*-tests were performed to determine significant change in TG following fibrate treatment. Simple and multiple regression analyses were carried out to study factors that were associated with changes in TG (outcome). When the independent variable was not continuous, one characteristic of the variable was chosen as the reference category and the other characteristics of that variable were factorised and compared to the reference category with regard to the selected outcome (dependent variable). Thus the ability to factorise variables permitted multiple comparisons to be made on a single model.

3. Results

The baseline lipid data suggested that fibrates were principally used on both hospital sites to treat patients with hypertriglyceridaemia; pre-treatment TG (mean/SD): 7.82/0.68 mmol/l (Good Hope Hospital), 8.54/0.75 mmol/l (Birmingham Heartlands Hospital), no significant difference between these TG distributions, p (t test) = 0.49. The distribution of pre-treatment TG levels in the total cohort were as follows; median = 5.9 mmol/l, range = 0.7–58.1 mmol/l, 10th/25th/75th/90th percentiles = 2.5/4.0/9.1/15.9 mmol/l. The mean decrease in TG following fibrate treatment was 4.27 mmol/l (pre/post treatment TG values: 8.05/3.78 mmol/l, n = 241 patients, p (paired t-test) <0.0001). The mean pre/post TC values were 6.8/5.5 mmol/l whilst the mean pre/post HDL-C consisted of 1.1/1.2 mmol/l. It can be clearly seen from Fig. 1 that TG decreases were seen in all subgroups (gender, age, diabetes, smoking status, concurrent statins and alcohol intake) we examined, unlike our previous observations regarding the change in HDL-C following fibrate treatment.

We then studied associations between TG change following fibrate treatment and baseline characteristics. Separate linear regression analyses were carried out with TG change as the outcome (dependent variable) and patient characteristics, pre-treatment lipid levels and treatment duration as independent variables; this is presented in Table 1: model 1. Age, pre-treatment TG, TC and HDL-C levels were significantly associated with change in TG. All the above significant factors were entered simultaneously in a multiple regression model and only pre-treatment TG and TC levels remained significant; Table 1: model 2. The association between the change in TG (dependent variable) and pre-treatment TG concentration (independent variable) remained significant regardless of the fibrate used, HDL-C level (stratified into <1.0 mmol/l and ≥1.0 mmol/l), gender, concurrent statin treatment or diabetes (p values <0.001 in all subgroup analyses). Fig. 2 characterises this relationship demonstrating the change in TG for stratified baseline TG values (<2.5, 2.5–4.99, 5–7.49, 7.5–9.99 and >10 mmol/l). The percentage TG decrease (dependent variable) following fibrate therapy increased significantly (linear regression) with higher baseline TG concentrations (independent variable); c: −1.5, 95% CI: −2.1/−0.10, $p < 0.001$, n = 241.

We then carried out separate linear regression analyses with TG change as outcome and TC and HDL-C change following fibrate treatment as the independent variables. TG change was significantly associated with TC change (c: 2.27, 95% CI: 2.04/2.50, $p < 0.001$, n = 241), however not with change in HDL-C (c: −0.33, 95% CI: −2.39/1.73, p = 0.75, n = 203) in the total group. We have previously reported that HDL-C significantly increased with fibrate