EFFECTS OF ATORVASTATIN ON FASTING AND POSTPRANDIAL COMPLEMENT COMPONENT 3 RESPONSE IN FAMILIAL COMBINED HYPERLIPIDEMIA

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ABSTRACT

VLDL overproduction by enhanced hepatic FFA flux, is a major characteristic in familial combined hyperlipidemia (FCHL). The postprandial complement component 3 (C3) response has been associated to impaired postprandial FFA metabolism in FCHL. We investigated the effects of 16 weeks treatment with atorvastatin on postprandial C3 and lipid changes in 12 FCHL patients. Atorvastatin significantly lowered fasting plasma C3 and TG in FCHL. Fasting TG and insulin sensitivity were the best predictors of fasting and postprandial C3. Postprandial triglyceridemia and C3 response, estimated as area under the curve (AUC), were significantly lowered by atorvastatin by 19% and 12%, respectively, albeit still elevated compared to 10 matched controls. Postprandial FFA-AUC and post-heparin plasma lipolytic activities remained unchanged after atorvastatin, suggesting no major effect on lipolysis. After atorvastatin, postprandial hydroxybutyric acid (HBA)-AUC, which was elevated in untreated FCHL, decreased by atorvastatin reaching similar values as in controls. The present data show reduction of postprandial hepatic FFA flux in FCHL by atorvastatin, providing an additional mechanistic explanation for the reduction of VLDL secretion reported earlier for atorvastatin. This was accompanied by a decrease of fasting plasma C3 concentrations and a blunted postprandial C3 response to an acute oral fat load.

Keywords: chylomicrons, postprandial lipemia, FFA, insulin resistance (IR) and acylation stimulating protein (ASP).
INTRODUCTION

Familial combined hyperlipidemia (FCHL) is the most frequent, dominantly inherited disorder of lipid metabolism leading to increased risk for atherosclerosis (1-8). The diagnosis is based on clinical criteria such as the presence of “multiple type hyperlipidemia”, increased plasma apoB, and a positive family history of premature coronary heart disease (CHD) (1-10). Abdominal obesity and increased BMI have been identified as independent factors for the development of hyperlipidemia and CHD in FCHL (4,8,10-12). Associations with the complement system have also been reported (13,14). The genetic basis of FCHL has not been elucidated, although several groups have provided evidence suggesting that different genes are involved in the pathogenesis of this disorder (15-23).

Impaired FFA metabolism, in the postprandial as well as in the post-absorptive period, is closely related to the expression of the FCHL phenotype (24-28). FCHL patients have increased postprandial FFA concentrations compared to healthy controls (24,26,27). Increased postprandial FFA concentrations result in an increased postprandial hepatic FFA flux, which could explain in part the well-known VLDL overproduction in FCHL (26). More recently, an impaired postprandial complement component 3 (C3) response has been associated to the disturbed postprandial FFA handling (27).

In vitro and in vivo experiments have demonstrated that the uptake of FFA by peripheral cells is stimulated by acylation stimulating protein (ASP) (29,30), which is one of the immunologically inactive cleavage products of C3 (30). Different studies, in FCHL and non-FCHL subjects have shown a strong correlation between fasting C3 concentrations and fasting lipid-parameters, especially plasma triglycerides (TG) (13,14,27,31,32). Furthermore, C3 is a powerful indicator of the risk of myocardial infarction in men (32), and recently, it has been shown that C3 depositions are found predominantly in ruptured atherosclerotic plaques in humans (33), suggesting a pathogenetic involvement in the process of atherosclerosis and
acute coronary syndromes. Moreover, both fasting and postprandial C3 concentrations can be decreased by treatment with statins and this has been associated with an improvement in postprandial triglyceridemia (31).

The present study was carried out to evaluate the effects of atorvastatin in FCHL on postprandial lipemia and C3 changes. In addition, postprandial FFA changes and hydroxybutyric acid (HBA), reflecting hepatic FFA delivery, were also evaluated.

**MATERIALS AND METHODS**

**Subjects**

The study protocol was approved by the Human Investigations Review Committee of the University Medical Center Utrecht. All participants gave written informed consent. Twelve unrelated FCHL patients were recruited from the Lipid Clinic of the University Medical Center Utrecht. All untreated FCHL subjects met the criteria described previously (24,26,27) and used by different groups (8-23). In addition, all patients fulfilled the following inclusion criteria: absence of xanthomas, absence of secondary factors associated with hyperlipidemia as demonstrated by normal thyroid, renal and liver function tests, absence of diabetes mellitus, BMI < 30 kg/m², absence of apo E2/E2 genotype, no use of drugs affecting lipid metabolism and consumption of less than 3 units of alcohol per day. Ten normolipidemic, healthy controls without a family history of cardiovascular disease or type 2 diabetes, absence of apo E2/E2 genotype and not using drugs known to affect lipid metabolism or the use of more than 2 alcoholic beverages daily, were recruited by advertisement. Controls were matched to FCHL subjects by age, BMI and waist-to-hip ratio.

**Oral fat loading test**
Cream was used as fat source. To the cream 60 g/L dextrose and vitamin A were added (26). After an overnight fast of 12 hours, the subjects ingested the fresh cream, in a dose of 50 g fat/m² body surface and 7.5 g dextrose/m² body surface. After ingestion of the fat load, the participants were allowed to drink only water and sugar-free tea during the following 24 hours. Peripheral blood samples were obtained in sodium EDTA (2 mg/mL) before (t=0 hr) and at hourly intervals up to 10 hours after the fat load and after 12 and 24 hours. For measurement of hydroxybutyric acid (HBA) every 2 hours blood samples were obtained in heparin tubes. Blood was placed on ice and centrifuged immediately for 15 min at 800 g at 4°C. Plasma samples were stored at –20°C immediately after centrifugation.

**Study protocol**

All patients stopped lipid-lowering drugs 4 weeks before the oral fat load but they continued their usual diet. After the oral fat loading test the FCHL patients started with 10 mg atorvastatin once a day. Every four weeks the patients visited our outpatient clinic, where fasting TG and cholesterol were measured. When plasma TG concentrations were above 2.0 mmol/L and/or cholesterol above 6.5 mmol/L the dosage of atorvastatin was doubled, upto 80 mg o.d. after 12 weeks, followed by a second oral fat loading test 4 weeks after the last dose adjustment.

The healthy volunteers received no treatment and underwent an oral fat loading test only once. Those data were used as normal reference. All participants underwent a post-heparin test to measure lipoprotein lipase (LPL) and hepatic lipase (HL) concentrations at the end of the oral fat loading test, e.g. 24 hours after fat intake.

**Analytical methods**
TG and cholesterol were measured in duplicate by commercial colorimetric assay (GPO-PAP and CHOD-PAP, Boehringer Mannheim, respectively). FFA was measured in plasma samples by enzymatic colorimetric method (Wako Chemicals GmbH, Neuss, Germany). HBA was measured spectrophotometrically by the principle of converting NADH to NAD\(^+\) after adding 3-hydroxybutyrate dehydrogenase. For this purpose 0.5 mL heparin blood was denatured by adding 1 mL 0.7 M HClO\(_4\) (26). The detection limit of HBA is 0.02 mmol/L. Complement component 3 (C3) was measured by nephelometry (Dade Behring Nephelometry type II) (27,31). HDL-cholesterol (HDL-C) was determined using the phosphotungstic acid/MgCl\(_2\) method. Plasma apoB was measured by nephelometry (27,31). Glucose was measured by glucose oxidase by dry chemistry (Vitros GLU slides) and colorimetry, and insulin was measured by commercial ELISA (Mercodia, Uppsala, Sweden). ApoB48 and apoB100 concentrations in chylomicron fractions (Sf>400) were determined according to the method used by Karpe et al. (34), and described in detail previously (35). Post-heparin plasma LPL and HL activities were determined by the release of free fatty acids from \[^{14}\text{C}]\)-labeled trioleoyl emulsion. ASP was measured using the ELISA kindly provided by Dr. K Cianflone, as described previously (27). For estimation of insulin sensitivity, the homeostasis model assessment (HOMA = glucose*insulin/22.5) was calculated.

**Statistics**

All values are expressed as mean ± standard error of the mean (SEM). Comparisons are made between FCHL patients and controls (unpaired t-test) and with FCHL patients, before and after therapy (paired t-test). In addition, a subgroup analysis was performed between subjects on the highest dose of atorvastatin (80 mg. o.d.) and the lowest doses. The area under the curve (AUC) and incremental area under the curve (dAUC) were calculated by the trapezoidal rule and after correction for fasting values, respectively. The first 8 hours after
ingestion of the fat load were used as representing the postprandial period (26,27). Mean fasting differences between controls and FCHL subjects were calculated by unpaired t-test, fasting difference before and after treatment in FCHL patients were calculated by paired t-test. Mean differences in apoB48-AUC and apoB100-AUC were calculated by non-parametric test due to the skewed distribution of these variables. Mean differences of fasting plasma TG were calculated by parametric tests after log transformation. For statistical analysis of changes in C3, TG, FFA and HBA concentrations, repeated measures ANOVA was used, with the LSD test as post-hoc test. For the calculation of correlations, in untreated patients and controls, Spearman’s correlation coefficient was determined. All significantly correlated variables were used as independent variables in stepwise multiple regression analysis with fasting C3 levels and postprandial C3-AUC as dependent variables. Calculations were performed using SPSS/PC 10.0 (SPSS Inc. Chicago, IL, USA). Calculations of AUC’s were performed with GraphPad Prism version 3.0 (GraphPad Software Inc. San Diego, CA, USA). Statistical significance was reached when P<0.05 (two-tailed).

RESULTS

General characteristics of untreated FCHL patients and controls (Tables 1 & 2)

FCHL patients and controls did not differ in anthropometric characteristics (Table 1). Fasting plasma TG, cholesterol, apoB, C3 and insulin were significantly higher in untreated FCHL compared to controls. Fasting ASP concentrations were not different in untreated FCHL compared to controls. FCHL patients were more insulin resistant than controls, according to the elevated HOMA index (Table 2).

Treatment effects of atorvastatin (Table 2)
After 16 weeks, 2 patients were using atorvastatin at a dose of 10 mg, 4 patients 20 mg, 1 patient 40 mg and 5 patients 80 mg atorvastatin. Except for age (36±4 and 52±2 years, respectively; P=0.01) the anthropometric characteristics were not different between the group using the lower doses up to 40 mg and the five subjects on 80 mg. There were no significant differences in baseline (off-treatment) characteristics in the seven subjects at low doses compared to the five at high doses.

After the final dose-adjustment, the patients at 80 mg had significantly higher fasting plasma TG concentrations (2.92±0.80 mmol/L) compared to the group at lower doses (1.90±0.22 mmol/L, P=0.01), but similar fasting plasma cholesterol (4.01±0.17 and 4.27±0.36 mmol/L, respectively) and apoB concentrations (0.82±0.07 and 0.80±0.07 g/L). Similar reductions of postprandial plasma TG concentrations were observed in the patients at low doses compared to those using 80 mg of atorvastatin.

In the total FCHL group, atorvastatin significantly lowered plasma TG, cholesterol, apoB and C3 concentrations (Table 2). Plasma apoB concentrations reached normal levels as compared to controls and plasma cholesterol concentrations were reduced below the mean levels in these control subjects. These effects were mainly due to a reduction of LDL-apoB (data not shown). LPL and HL concentrations were not different in FCHL patients and controls and were not affected by atorvastatin. HDL-C, apoAI, ASP and anthropometric characteristics did not change after treatment.

Postprandial C3 changes (Table 2 and Figure 1)

Fasting plasma C3 concentrations decreased after atorvastatin, but were still elevated compared to controls (Table 2). Before treatment, the first significant increase in C3 concentration was seen 6 hours after fat intake in FCHL (upto 1.49±0.16 g/L). In controls, however, C3 increased significantly already after two hours (upto 1.02±0.04 g/L). After
treatment, no significant increase was seen over time by repeated measures ANOVA, but there was a tendency to increase 4 hours after fat intake (1.27±0.06 g/L; P=0.09).

The postprandial C3-AUC was reduced by atorvastatin in FCHL from 11.25±0.69 g.h.L^{-1} to 9.70±0.35 g.h.L^{-1} (in controls: 8.02±0.29 g.h.L^{-1}) (Figure 1, right panel), with a maximal relative postprandial increase of 9.8±8.6% before and 6.2±3.0% after atorvastatin compared to a 21.8±3.8% increase in controls. C3-AUC was still higher after treatment than in controls.

When the group using upto 40 mg atorvastatin was compared to the group using 80 mg, fasting C3 (1.27±0.07 and 1.21±0.08 g/L, respectively) and postprandial C3-AUC (9.49±0.50 and 9.36±0.49 g/L, respectively) were not different.

**Plasma TG, FFA and hydroxybutyric acid changes (Figures 2A, B and C)**

In FCHL before and after treatment as well as in controls, postprandial plasma TG increased significantly to maximal concentrations at 5 hours from 3.19±0.43 to 5.31±0.64 mmol/L in untreated FCHL (P<0.01), from 2.27±0.23 to 3.88±0.88 mmol/L in treated FCHL (P<0.01) and from 1.15±0.13 to 2.36±0.50 mmol/L in controls (P<0.01). The maximal TG increase was not changed by treatment (160 and 173%, respectively). The postprandial TG-AUC in FCHL decreased after atorvastatin by 23% (from 33.77±4.38 to 25.85±2.81 mmol.h.L^{-1}), which was still elevated compared to controls (14.30±1.97 mmol.h.L^{-1}) (Figure 2A). The group using upto 40 mg and the group on 80 mg atorvastatin had a similar reduction in fasting TG (19% and 21% reduction, respectively) and in postprandial (0-8 hrs) TG-AUC (16% and 23% reduction, respectively).

Postprandial FFA increased in untreated FCHL from 0.39±0.03 mmol/L to a maximum of 0.80±0.05 mmol/L at t=5 hrs (P<0.01), in treated FCHL from 0.35±0.03 mmol/L to a maximum of 0.89±0.07 mmol/L at t=6 hrs (P<0.01) and in controls from 0.31±0.03 mmol/L to 0.68±0.06 mmol/L (P<0.01) reaching a peak at t=7 hrs (P<0.01). The postprandial FFA-
AUC was significantly higher in FCHL before and after atorvastatin (4.96±0.23 and 5.30±0.29 mmol.h.L⁻¹, respectively) compared to controls (4.07±0.18 mmol.h.L⁻¹). The postprandial FFA-AUC was not statistically different between the untreated and treated patients (Figure 2B, right panel).

HBA concentrations increased in untreated FCHL from fasting 0.02±0.001 mmol/L to a maximum of 0.30±0.04 mmol/L at t=6 hr (P<0.01) and in treated FCHL patients from 0.02±0.001 mmol/L to a maximum of 0.18±0.03 mmol/L at t=8 hr (P<0.01). In controls, a similar postprandial HBA response as in treated FCHL was seen up to 10 hours. The postprandial (0-8 hrs) HBA-AUC was higher in untreated (1.39±0.16 mmol.h.L⁻¹) than in treated patients (0.81±0.11 mmol.h.L⁻¹) and in controls (0.95±0.16 mmol.h.L⁻¹) (Figure 2C, right panel).

**ApoB48, apoB100 and TG changes in the Sf>400 fraction (Figure 3A, B and C)**

Fasting concentrations of apoB48, in the chylomicron fraction (Sf>400), were similar in untreated (0.31±0.14 mg/L) and treated FCHL patients (0.21±0.09 mg/L), but significantly higher compared to controls (0.02±0.01 mg/L; P=0.05). Fasting chylo-B48 increased postprandially reaching maximal concentrations after 4 hours (0.91±0.27 mg/L; P<0.05 compared to fasting concentrations) in untreated FCHL patients. In treated patients and in controls a delayed peak was found at t=6 hrs, reaching lower concentrations (0.70±0.26 and 0.16±0.02 mg/L, respectively; P<0.05 for each), than in FCHL before treatment. The postprandial apoB48-AUC did not improve significantly by atorvastatin (5.07±1.35 before versus 4.31±1.31 mg.h.L⁻¹ after atorvastatin, P=0.52). Control subjects had a significantly lower apoB48-AUC (0.92±0.20 mg.h.L⁻¹; P<0.05).

A significant increase of apoB100, from fasting to a peak at 6 hours postprandially was found in untreated FCHL patients before (from 4.27±1.46 to 9.13±2.62 mg/L; P<0.05) as well as
after atorvastatin (from 2.71±0.99 to 6.34±2.90 mg/L; P<0.05) and in controls (from 0.07±0.04 to 0.55±0.25 mg/L; P<0.05). The postprandial apoB100-AUC was not significantly decreased by atorvastatin (55.5±14.9 and 38.3±14.5 mg.h.L⁻¹, respectively; P=0.26). Controls showed a significantly lower apoB100 response (3.2±1.0 mg.h.L⁻¹; P<0.01).

Fasting TG in the Sf>400 fraction tended to decrease after atorvastatin (0.25±0.07 to 0.13±0.03 mmol/L; P=0.11), but the TG concentrations in this fraction were still elevated compared to controls (0.03±0.01 mmol/L; P<0.01). All subjects reached their peak value 4 hours after fat-intake. The percentage increase of plasma TG concentration was not different in untreated and treated FCHL patients (595% and 634%, respectively). The postprandial TG-AUC of the Sf>400 fraction was not significantly different in untreated or treated patients (5.00±1.38 and 3.70±1.38 mg.h.L⁻¹) compared to controls (2.34±0.43 mg.h.L⁻¹).

**Determinants of fasting and postprandial C3 levels (Table 3)**

All significant correlations between fasting C3 and postprandial C3, represented as C3-AUC, apoB, postprandial plasma TG, FFA, apoB48, apoB100 and (Sf>400)-TG and general characteristics are listed in Table 3. Multiple regression analysis showed that the best determinant of fasting C3 in all subjects was the fasting plasma TG (adjusted R² = 0.55, β = 0.75, P<0.001). Addition of HOMA and plasma apoB further improved the model significantly (adjusted R² = 0.68 and 0.72, respectively). Postprandial C3-AUC was best predicted by the HOMA (adjusted R² = 0.60, β = 0.78, P<0.001). Addition of fasting plasma TG also improved this model (adjusted R² = 0.73; P<0.01).

**DISCUSSION**

The present study shows an improvement of postprandial triglyceridemia, a blunted postprandial C3 response and a suppressed hepatic FFA flux in FCHL subjects by
monotherapy with atorvastatin. Atorvastatin, a 3-hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, reduces VLDL secretion \textit{in vitro} by impairing the translocation of apoB in the lumen of the endoplasmatic reticulum (36). This is supported by \textit{in vivo} stable isotope studies in patients with combined hyperlipidemia (37). Atorvastatin improves the clearance of chylomicron remnants, but it does not have an effect on the production of intestinal lipoproteins, e.g. chylomicrons (38-40). In our FCHL patients, atorvastatin lowered fasting plasma TG, cholesterol and apoB. Neither HDL-cholesterol nor apoAI improved after treatment.

Fasting C3 levels were correlated with the different lipid parameters, like fasting plasma TG, cholesterol, and apoB concentrations and also to insulin and HOMA, as a marker for insulin resistance, in accordance with different previous studies (13,14,27,31,32). C3 is the precursor of ASP and plays an important role in FFA uptake by adipocytes, following lipolysis of chylomicrons (29). In a previous study we found that untreated FCHL had higher fasting C3 and an exaggerated and delayed postprandial C3 response (27). We concluded that this could be a consequence of C3-resistance at the level of adipocytes. The latter could result in decreased uptake of FFA by peripheral cells and consequently lead to VLDL overproduction (26,41). In this study evidence is provided suggesting that atorvastatin improves peripheral FFA trapping which potentially may reduce VLDL overproduction in FCHL. Studies directly investigating the effects of statins on FFA fluxes and VLDL secretion in FCHL are needed.

Maslowska et al. demonstrated \textit{in vitro}, that the main stimulators of C3 and ASP production in human adipocytes are insulin and large TRL (Sf>400), which the authors defined as “chylomicrons” (42). However, this Sf>400 fraction also contains large apoB100 particles besides the apoB48-containing lipoproteins, as clearly shown here and by different groups (35,43,44). The positive correlations between fasting C3 and postprandial C3 with the postprandial apoB100 (and not with apoB48) suggest that chylomicrons may not be the main
stimulators of C3 production \textit{in vivo}, but rather large VLDL. A reduction in VLDL secretion may be responsible for the decrease in C3 production as seen after atorvastatin treatment. Previous work from our department has shown that postprandial C3 responses decreased in non-FCHL/coronary artery disease (CAD) patients by expanded dose simvastatin (31), providing support for the view that C3 reduction may be one of the consequences of statin therapy.

Untreated FCHL had a delayed C3 peak, in accordance with previous work (27). Atorvastatin lowered fasting and postprandial C3 concentrations, but also changed the shape of the postprandial C3 curve. Although no normalization of the fasting C3 and the postprandial curve was reached, HBA concentrations returned to control values after atorvastatin. HBA was measured as a marker of hepatic FFA flux, since the largest amount of ketone bodies are formed in the liver from acetyl-CoA (45), derived from fatty acid oxidation. This could be interpreted in different ways. One explanation could be that the conversion of acetyl-CoA into ketone bodies in the liver is inhibited by atorvastatin, in a similar way as atorvastatin inhibits the HMG-CoA reductase. However, to our knowledge, there is no evidence supporting such a theory. Another explanation is that there is a decreased postprandial hepatic FFA flux after atorvastatin treatment. It is not likely that net production of FFA released by hydrolysis of TRL decreased by atorvastatin, since the lipolytic activities were not changed after atorvastatin and the amount of TG hydrolyzed by LPL was not affected substantially as indicated by the unchanged postprandial TG in plasma and Sf>400 fractions. Also, the postprandial FFA concentrations (from 0-8 hrs after fat intake) were not changed by atorvastatin. In our view, the data indicate improved peripheral fatty acid uptake by extrahepatic tissues. Since the FCHL patients did not gain weight after treatment, improved peripheral FFA trapping by adipocytes can not be the only explanation for the observed postprandial decrease of ketone bodies. It remains to be determined which other tissues
extract FFA at a higher rate and thereby decrease the hepatic FFA flux in FCHL by atorvastatin.

It has been suggested that chylomicrons compete efficiently with VLDL for the same lipolytic pathway (46), which leads to accumulation of postprandial VLDL (47). In the present study we found a significant reduction of postprandial plasma triglycerides without improvement of large TRL-apoB48 or apoB100 clearance. This may have been due to the relatively small sample size of FCHL patients and to the fact that fasting plasma TG (the best determinants of postprandial lipemia) were not normalized. However, in other postprandial studies investigating the effects of atorvastatin, including similar numbers of non-FCHL participants, statistical significant improvements have been reported (39,40). This underlines once again how difficult it is to reduce postprandial lipemia in FCHL subjects (48,49). The small non-significant changes obtained by atorvastatin of postprandial apoB100 and apoB48 clearance suggest that a more effective reduction of fasting plasma TG could improve postprandial lipemia in this disorder.

It should be noted that total plasma apoB was normalized in FCHL by atorvastatin, in contrast to the less efficient reduction of fasting plasma TG. This may be explained by the fact that atorvastatin reduced dramatically LDL with less significant effects on large TRL’s. In a recent paper by Parhofer and co-workers, atorvastatin significantly reduced the postprandial concentrations of large TRL’s with less effect on small TRL’s in 10 hypertriglyceridemic patients (50). Detailed data on the effects of atorvastatin on lipoprotein composition in FCHL will be published separately.

All patients were treated with their own minimal dose of atorvastatin to reach a normolipidemic state, resembling the situation in clinical practice where titration to optimal doses is prescribed to patients. However, 5 of the 12 patients were treated with the maximal dose, 80 mg, and had still increased fasting and postprandial plasma TG levels. Although they
had a higher triglyceridemia, the percentage decrease in fasting plasma TG, postprandial triglyceridemia, fasting and postprandial C3 as well as HBA-AUC was not different between both groups, indicating a similar response of hepatic FFA flux after treatment. Why some patients need higher doses of atorvastatin than others to reach the fasting treatment targets is not clear at present and may depend on different genetic and environmental factors.

In conclusion, atorvastatin decreased the postprandial hepatic FFA flux in FCHL patients and the total postprandial plasma triglyceridemia. This effect was accompanied by reduced fasting and postprandial C3 concentrations. Further studies investigating FFA metabolism in vivo in different tissues will be necessary to estimate the FFA handling by different cells and to better delineate the role of C3 after lipid-lowering intervention.
ACKNOWLEDGEMENT

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REFERENCES


protein is elevated in Finnish patients with familial combined hyperlipidemia. 


LEGENDS

Figure 1
Mean changes of plasma complement component 3 (C3) concentrations (left panel) and postprandial (0-8 hr) C3 area under the curve (AUC) (right panel), Note: The Y-axis starts at 0.6 g/L. * P<0.05, † P<0.01.

Figure 2
A: Mean changes of TG concentrations (left panel) and postprandial TG-AUC (right panel) in 12 untreated FCHL patients (#), 12 treated FCHL patients ($) compared to 10 matched controls (+). B: Mean changes of FFA concentrations (left panel) and postprandial (0-8 hr) FFA area under the curve (AUC) (right panel). C: Mean changes of HBA concentrations (left panel) and postprandial HBA-AUC (right panel) in 12 untreated FCHL patients (#), 12 treated FCHL patients ($) compared to 10 matched controls (+). Data are mean ± SEM. * P<0.05, † P<0.01.

Figure 3
A: Mean changes of apoB48 concentrations (left panel) and postprandial apoB48-AUC (right panel) in 12 untreated FCHL patients (#), 12 treated FCHL patients ($) compared to 10 matched controls (+). B: Mean changes of apoB100 concentrations (left panel) and postprandial (0-8 hr) apoB100 area under the curve (AUC) (right panel). C: Mean changes of TG (in Sf>400 fraction) concentrations (left panel) and postprandial TG-AUC (right panel) in 12 untreated FCHL patients (#), 12 treated FCHL patients ($) compared to 10 matched controls (+). Data are mean ± SEM. * P<0.05.
Table 1

Anthropometric characteristics of 12 FCHL patients and 10 matched control subjects. Data are mean ± SEM.

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<td>Gender</td>
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<td>6 F / 4 M</td>
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<tr>
<td>Age (yr.)</td>
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<td>44.8 ± 3.1</td>
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<tr>
<td>BMI (kg/m²)</td>
<td>26.1 ± 0.5</td>
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<td>BP diast (mmHg)</td>
<td>85 ± 3</td>
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<td>BP syst (mmHg)</td>
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Table 2

Fasting laboratory values at the time of the oral fat loading test of 12 FCHL patients before and after atorvastatin treatment and 10 matched control subjects. Data are mean ± SEM.

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<th>2: FCHL treated</th>
<th>3: Controls</th>
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<th>P value 1 vs. 2</th>
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<td>Cholesterol (mmol/L)</td>
<td>6.54±0.36</td>
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<td>TG (mmol/L)</td>
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<td>2.27±0.23</td>
<td>1.15±0.13</td>
<td>&lt; 0.01</td>
<td>0.03</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>HDL-C (mmol/L)</td>
<td>0.93±0.07</td>
<td>0.99±0.08</td>
<td>1.12±0.09</td>
<td>0.11</td>
<td>0.22</td>
<td>0.31</td>
</tr>
<tr>
<td>ApoB (g/L)</td>
<td>1.27±0.09</td>
<td>0.85±0.05</td>
<td>0.83±0.06</td>
<td>&lt; 0.01</td>
<td>&lt; 0.01</td>
<td>0.77</td>
</tr>
<tr>
<td>ApoAI (g/L)</td>
<td>1.22±0.08</td>
<td>1.23±0.06</td>
<td>1.40±0.05</td>
<td>0.08</td>
<td>0.98</td>
<td>0.04</td>
</tr>
<tr>
<td>LPL (mU/mL)</td>
<td>108±14</td>
<td>101±11</td>
<td>123±9</td>
<td>0.39</td>
<td>0.63</td>
<td>0.15</td>
</tr>
<tr>
<td>HL (mU/mL)</td>
<td>328±56</td>
<td>299±39</td>
<td>382±48</td>
<td>0.47</td>
<td>0.35</td>
<td>0.21</td>
</tr>
<tr>
<td>FFA (mmol/L)</td>
<td>0.39±0.03</td>
<td>0.35±0.03</td>
<td>0.31±0.03</td>
<td>0.08</td>
<td>0.38</td>
<td>0.32</td>
</tr>
<tr>
<td>Complement 3 (g/L)</td>
<td>1.41±0.04</td>
<td>1.24±0.05</td>
<td>0.91±0.03</td>
<td>&lt; 0.01</td>
<td>0.02</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>ASP (nmol/L)</td>
<td>46.71±6.08</td>
<td>36.04±4.27</td>
<td>42.90±10.74</td>
<td>0.38</td>
<td>0.15</td>
<td>0.13</td>
</tr>
<tr>
<td>Insulin (IU/L)</td>
<td>14.8±1.9</td>
<td>14.2±2.3</td>
<td>9.4±1.1</td>
<td>0.02</td>
<td>0.80</td>
<td>0.08</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>5.2±0.4</td>
<td>5.2±0.1</td>
<td>4.9±0.1</td>
<td>0.14</td>
<td>0.42</td>
<td>0.12</td>
</tr>
<tr>
<td>HOMA</td>
<td>3.26±0.37</td>
<td>3.24±0.61</td>
<td>2.04±0.22</td>
<td>&lt; 0.01</td>
<td>0.82</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Table 3
Spearman’s correlation coefficients between fasting and postprandial C3-AUC and biochemical variables in untreated FCHL patients and controls. Only significant correlations are given. * P<0.05 and † P<0.01.

<table>
<thead>
<tr>
<th></th>
<th>Fasting C3</th>
<th>C3-AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting plasma TG</td>
<td>0.72†</td>
<td>0.76†</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>0.56†</td>
<td>0.56†</td>
</tr>
<tr>
<td>Fasting apoB</td>
<td>0.63†</td>
<td>0.66†</td>
</tr>
<tr>
<td>Fasting apoB48</td>
<td>0.46*</td>
<td>0.59†</td>
</tr>
<tr>
<td>Fasting apoB100</td>
<td>0.65†</td>
<td>0.72†</td>
</tr>
<tr>
<td>Fasting (Sf&gt;400)-TG</td>
<td>0.65†</td>
<td>0.73†</td>
</tr>
<tr>
<td>ApoB100-AUC</td>
<td>0.49*</td>
<td>0.53*</td>
</tr>
<tr>
<td>Insulin</td>
<td>0.63†</td>
<td>0.59†</td>
</tr>
<tr>
<td>HOMA</td>
<td>0.69†</td>
<td>0.66†</td>
</tr>
<tr>
<td>TG-AUC</td>
<td>0.66†</td>
<td>0.72†</td>
</tr>
<tr>
<td>Fasting C3</td>
<td>-</td>
<td>0.97†</td>
</tr>
</tbody>
</table>
Figure 1

Graph showing the change in C3 (g/L) over time (hr) with error bars indicating variability. The graph compares untreated FCHL, Ator, and controls.

Bar chart showing postprandial (6h) C3-AUC (g h/L) with asterisks indicating statistical significance.*