C3, Hormone-Sensitive Lipase, and Peroxisome Proliferator-Activated Receptor γ Expression in Adipose Tissue of Familial Combined Hyperlipidemia Patients

Kati Ylitalo, Ilpo Nuotio, Jorma Viikari, Johan Auwerx, Hubert Vidal, and Marja-Riitta Taskinen

This study aimed to assess the role of complement C3, hormone-sensitive lipase (HSL), and peroxisome proliferator-activated receptor γ (PPARγ) gene expression in familial combined hyperlipidemia (FCHL). mRNA expression of these 3 determinants of adipose tissue fatty acid (FA) metabolism was quantified in subcutaneous adipose tissue of 41 Finnish FCHL patients and 14 normolipidemic control subjects. No difference in steady-state mRNA expression level of C3, HSL, or PPARγ mRNA was detected between the FCHL patients and the control subjects. Adipose tissue C3 mRNA expression level correlated with the area under the curve (AUC) for glucose and for insulin in FCHL patients and control subjects. HSL mRNA level was positively correlated with waist-to-hip ratio in patients, whereas the correlation was negative in control subjects. A significant correlation was observed for PPARγ with free FA (FFA)-AUC in the FCHL group, and an inverse correlation with serum triglycerides (TG) in the control subjects. Although no difference in adipose tissue gene expression of C3, HSL, or PPARγ was observed between the FCHL patients and the control subjects, several significant correlations were observed between the mRNA levels and FCHL-related metabolic parameters. Thus, the genes of C3, HSL, and PPARγ may exert a modifying effect on lipid and glucose metabolism in FCHL. However, defects in adipose tissue expression of these genes are not likely to play a primarily role in the pathogenesis of FCHL in Finnish FCHL families.

PATIENTS WITH familial combined hyperlipidemia (FCHL) represent multiple-type hyperlipidemia with elevated serum total cholesterol (TC) and/or triglycerides (TG) together with high serum levels of apolipoprotein B (apo B).[1] High serum levels of free fatty acids (FFA)[2,3] and insulin resistance[3,4] are also inherent features of FCHL. Fat tissue, the body′s major storage of TG and FA, is able to synthesize and secrete several bioactive molecules.[5] Therefore, the role of adipose tissue in the pathogenesis of FCHL has become a target of major interest in recent years.

Complement C3 is an acute-phase protein. Serum concentrations of C3 are associated with serum lipids and insulin,[6-9] as well as with an increased risk of coronary heart disease.[10] The basis for these associations and the origin of elevated serum C3 levels are not known. Enhanced C3 secretion may take place in atherosclerotic plaques, in the liver, or in adipose tissue. Interestingly, C3 is a precursor protein of acylation-stimulating protein (ASP), which is a potent stimulator of TG synthesis in human adipocytes in vitro.[11,12]

Hormone-sensitive lipase (HSL) is the rate-limiting enzyme in hydrolysis of TG in adipocytes. Contrasting results on HSL activity in FCHL have been published: HSL activity was reduced in 2 Swedish FCHL cohorts,[13,14] but not in Finnish FCHL families.[15]

Peroxisome proliferator-activated receptor γ (PPARγ) is a transcription factor that plays a pivotal role in adipogenesis and FA metabolism in adipose tissue. PPARγ target genes include lipoprotein lipase (LPL), fatty acid transport protein 1 (FATP-1), and acyl-coenzyme A synthetase (ACS).[16,17] Induction of these genes potentially enhances FA trapping in adipose tissue.

We examined the mRNA expression levels of 3 important determinants of FA metabolism: C3, HSL, and PPARγ in subcutaneous adipose tissue of Finnish FCHL patients and normolipidemic control subjects. The study aimed specifically to assess (1) whether adipose tissue C3 expression correlates with serum lipids or markers of insulin resistance, as did serum C3 in our previous studies[8,9]; (2) if HSL gene expression is reduced in FCHL as is HSL activity in Swedish FCHL patients,[13,14] but not in Finnish FCHL patients[15]; and (3) whether PPARγ gene expression is reduced in FCHL, resulting in elevated serum levels of TG and free FA in these patients.

MATERIALS AND METHODS

Study Subjects

The study subjects were recruited as a part of the European Multicenter Study on Familial Dyslipidaemias (EUFAM) in Helsinki and Turku University Central Hospitals in Finland. The study protocol has been described in detail elsewhere.[9,18] The probands had the diagnosis of coronary heart disease before the age of 60 years. Families with at least 2 affected family members (FCHL patients) presenting different lipid phenotypes were included in the study. Family members were categorized as affected if their serum TC and/or TG was equal to, or exceeded the age and sex-specific 90th Finnish population percentile. The maximum values of TC and TG measured during the project were always used to categorize the study subjects.

Adipose tissue samples were available from 41 FCHL patients (16 men, 25 women) from 22 families, and 14 unrelated, normolipidemic

From the Department of Medicine, Helsinki University Central Hospital, University of Helsinki, Helsinki, Finland; Department of Medicine, Turku University Central Hospital, University of Turku, Turku, Finland; Institut de Génétique et Biologie Moléculaire et Cellulaire (IGBMC), CNRS/INSERM/ULP, Illkirch, C.U. de Strasbourg, France; and INSERM U449 and GENALYS, Faculte de Medecine R.T.H. Laennec, Lyon, France.

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Address reprint requests to Marja-Riitta Taskinen, MD, Department of Medicine, PO Box 340, Floor 11, Haartmaninkatu 4, 00029 HYKS, Finland.

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subjects (5 men, 9 women). None of the subjects had diabetes or was on lipid-lowering medication when examined. The Ethics Committee of the Department of Medicine in Helsinki University Central Hospital and the Joint Ethics Committee of Turku University and Turku University Central Hospital approved the study protocol. All participants gave their informed consent.

Experimental Procedures

Venous blood samples for determination of serum lipid profile and other biochemical parameters were collected in the morning after a 12-hour fast. During the same study visit, a subcutaneous fat biopsy of 300 to 1,000 mg was obtained under local anesthesia from the paraumbilical region using a 14-G needle. The adipose tissue specimen obtained was immediately frozen in liquid nitrogen and stored at -80°C.

Measurements of lipids and other metabolites were performed as described.[9] Briefly, serum TC, TG, and high-density lipoprotein (HDL) cholesterol (after precipitation procedures) were determined by enzymatic methods, and serum total apo B by an immunoturbidimetric method. Commercial standards used for apo B assays had been calibrated against the reference level of the Centers for Disease Control and Prevention.

Serum C3 was measured by nephelometry using antibody against C3c (Behringwerke AG, Marburg, Germany). Plasma ASP was determined by enzyme-linked immunosorbent assay (ELISA; Quidel, San Diego, CA). An oral glucose tolerance test (OGTT) with 75 g of glucose was performed during the initial study visits of the EUFAM project as described.[9] The glucose, insulin, and FFA values presented here are based on this OGTT. Blood glucose concentrations were determined by the glucose dehydrogenase method, serum free insulin concentrations by radioimmunoassay, and concentrations of FFA by the microfluorometric method of Miles.

Total RNA Preparation and Target mRNA Quantification

Total RNA was prepared from adipose tissue by the RNeasy total RNA kit (Qiagen, Courtaboeuf, France). RNA samples were quantified by spectrophotometry, and absorbance ratios at 260/280 nm were between 1.7 and 2.0. The average yield of total RNA from the subcutaneous fat samples was 1.8 ± 0.7 μg total RNA/100 mg adipose tissue. Total RNA samples were stored at -80°C in water dilution until used. The different mRNAs were quantified by using a reverse transcription reaction and competitive polymerase chain reaction (RT-cPCR).[19] The construction of the different competitor molecules, the validation of the RT-cPCR assays, and the sequences of the primers used in the assays have been presented elsewhere.[20-22] The RT-reaction was performed from 0.1 μg of total RNA under previously described conditions that ensure that all of the target mRNA molecules are transformed into single-strand cDNA.[19] The competitive PCR reaction was performed as previously described in detail.[21] The fluorescent-labeled PCR products were separated in 4% polyacrylamide gel with an automated laser fluorescence DNA sequencer (ALFexpress, Pharmacia, Uppsala, Sweden), and analyzed using Fragment Manager software (Pharmacia).[20] The concentration of target mRNA was determined at the competition equivalence point, where the initial concentration of the target corresponds to the initial concentration of the competitor added.[23]

Statistical Analyses

Statistical comparisons of clinical parameters were performed with version 9.0 of the SPSS for Windows software (SPSS Inc, Chicago, IL). Two-way analysis of variance (ANOVA) was used for comparisons of continuous variables. Because the present cohort contained 41 family members from 22 families, all study subjects were not independent (although from 10 families only 1 subject participated). Therefore we used the family number (which indicates belonging to a certain family) as a random variable in the 2-way ANOVA to correct some of the nonindependence of study subjects. We have reported the P values as if the study subjects were independent. We used the χ^2-test or Fisher′s exact test to compare the groups for categorical variables. Correlation analyses were performed using multivariate analysis, into which family number was always entered as an independent variable. To examine partial correlations, gender or age was included in the analysis as an independent variable, in addition to the family number. Logarithmic transformation was applied when appropriate. Area under the curve (AUC) calculations were performed using the trapezoid rule. Multiple tests were performed in the present study. As no formal multiple test procedure was used to control the overall significance level, the probability values must be interpreted cautiously.

When the statistical power of the analyses was determined, we found that 40% differences in C3 and PPARγ1, and 60% differences in HSL and PPARγ2 mRNAs would have been detected with an 80% power at a significance level of .05.

RESULTS

Clinical and biochemical characteristics of the 41 FCHL patients and 14 control subjects are depicted in Table 1. By definition, the TC and TG levels of the FCHL patients were significantly higher than those of the control subjects. Likewise, serum apo B was higher in FCHL patients than in controls ($P = .01$). Though not significantly, the FCHL patients had slightly higher body mass index (BMI) and waist-hip ratio than the controls. Accordingly, their glucose-AUC, insulin-AUC, and FFA-AUC values were higher than those of the control subjects, but the differences were not statistically significant.

mRNA Expression in the Adipose Tissue

The individual subcutaneous adipose tissue mRNA levels of C3, HSL, PPARγ1, and PPARγ2 are presented in Fig 1. There was one FCHL patient whose C3 mRNA level was 86.0 amol/μg of total RNA, much more than the maximum of other subjects (46.3 amol/μg of total RNA). The value obtained in this patient remained identical when the measurement was repeated. This subject was excluded from further analyses but his C3 mRNA value is included in Fig 1. However, all analyses were repeated including also this one outlier, but this did not change the results significantly. There was not enough fat tissue to quantify HSL mRNA in 1 FCHL patient.

C3 mRNA expression was similar in the 2 groups (mean ± SD) (20.0 ± 9.8 *v* 19.7 ± 9.4 amol/μg total RNA, $P = 1.00$). The HSL mRNA level of the FCHL patients (182.6 ± 121.3 amol/μg total RNA) did not differ from that of the control subjects (213.3 ± 162.8 amol/μg total RNA, $P = .86$). Likewise, no statistically significant differences were detected between the FCHL patients and the control subjects with regard to mRNA levels PPARγ1 (17.0 ± 8.2 *v* 16.8 ± 6.4 amol/μg total RNA, $P = .63$), or PPARγ2 (2.0 ± 1.7 *v* 2.1±1.1 amol/μg total RNA, $P = .39$). Adjustment for BMI did not affect the results significantly. No gender difference was observed in C3, HSL, or PPARγ1 gene expression in the whole cohort. Adipose tissue PPARγ2 gene expression was higher in women (2.39 ± 1.57 amol/μg total RNA) than in men (1.36 ± 1.30 amol/μg total RNA) ($P = .001$). Unfortunately, the number of study subjects did not allow further division into subgroups.

Table 1. Subject Characteristics

Variable	FCHL Patients N	FCHL Patients Mean ± SD	Controls N	Controls Mean ± SD	*P* Value
Age (yr)	41	40.9 ± 11.7	14	42.8 ± 8.9	.98
Males (%, M/F)	41	39 (16/25)	14	36 (5/9)	.83
TC (mmol/L)	41	6.39 ± 0.97	14	5.18 ± 0.57	
TC-max (mmol/L)	41	6.84 ± 1.02	14	5.22 ± 0.58	
HDL-C (mmol/L)	41	1.46 ± 0.58	14	1.41 ± 0.27	.70
TG (mmol/L)	41	1.75 ± 0.88	14	1.11 ± 0.48	
TG-max (mmol/L)	41	2.62 ± 1.84	14	1.31 ± 0.66	
Apo B (mg/dL)	37	111 ± 22	13	89 ± 18	.01
Glucose (mmol/L)	40	4.7 ± 0.6	12	4.5 ± 0.6	.34
Glucose-AUC (mmol/L · h^{-1})	40	793 ± 170	12	677 ± 189	.08
Insulin (mU/L)	39	8.9 ± 4.4	12	6.9 ± 2.5	.09
Insulin-AUC (mU/L · h^{-1})	39	6382 ± 2919	12	4692 ± 2360	.16
FFA-AUC (μmol/L · h^{-1})	36	42433 ± 11158	12	33416 ± 9954	.07
BMI (kg/m^2)	41	27.2 ± 4.3	14	26.2 ± 2.8	.75
Waist-hip ratio	40	0.87 ± 0.10	14	0.85 ± 0.08	.56*

NOTE. For statistical comparisons between the groups, 2-way ANOVA (with family number as a random factor) was used for continuous, and χ^2 test for categorical variables.

*Waist-hip ratio was not significantly different in the 2 groups when male and female subjects were observed separately. There was, by definition, a statistically significant difference in TC and TG values between the 2 groups.

Abbreviations: TC, total cholesterol; HDL-C, HDL-cholesterol; TG, triglycerides. TC-max and TG-max, highest TC and TG values measured for the subject in the EUFAM study; Glucose, fasting blood glucose; insulin, serum fasting insulin; FFA, serum free fatty acids; AUC, area under the curve. BMI, body mass index.

Correlations of mRNA Expression Levels With Other Metabolic and Clinical Variables

Gender-adjusted correlations of the 4 different mRNA expression levels and selected metabolic and clinical variables in FCHL patients and control subjects are shown in Tables 2 and 3. In FCHL patients, C3 mRNA expression level correlated significantly with glucose-AUC ($r = 0.34$), insulin-AUC ($r = 0.36$), and BMI ($r = 0.36$). Age did not have a significant effect on these correlations (data not shown). Significant gender-adjusted correlations between C3 mRNA expression and glucose-AUC ($r = 0.80$) and insulin-AUC ($r = 0.67$) could be observed in the control group (Table 3). Correlations between C3 mRNA and serum C3 ($r = 0.53$) or plasma ASP ($r = 0.59$) did not reach statistical significance in the control subjects.

In FCHL patients, the only significant gender-adjusted correlations of HSL mRNA expression were observed with BMI ($r = 0.41$) and waist-hip ratio ($r = 0.35$) (Table 2). Adjustment for age did not have an effect on these correlations (data not shown). In the control subjects, HSL mRNA expression correlated significantly, but inversely, with waist-hip ratio when adjusted for gender ($r = -0.64$).

In FCHL patients, PPARγ1 (which represents about 85% of total PPARγ) and PPARγ2, correlated significantly with FFA-AUC when adjusted for gender (Table 2 and Fig 2). Age did not affect these correlations (data not shown). In control subjects, no significant correlation with FFA-AUC could be observed for PPARγ1 or PPARγ2 mRNA (Table 3). Instead, PPARγ1 mRNA correlated strongly negatively with TG ($r = -0.86$) (Table 3 and Fig 3), irrespective of age (data not shown). No correlation between PPARγ2 and TG could be found.

No correlations between different PPARγ mRNAs and C3 mRNA or HSL mRNA were observed (data not shown).

DISCUSSION

We have quantified the mRNA expression of C3, HSL, and the nuclear receptors PPARγ1 and PPARγ2 in subcutaneous abdominal adipose tissue of 41 Finnish FCHL patients and 14 healthy, normolipidemic control subjects. Adipose tissue mRNA level of C3, HSL, PPARγ1, or PPARγ2 did not differ between the FCHL patients and the normolipidemic control subjects.

In the present study we expressed the mRNA level per the amount of total RNA, but it is still possible that variation in obesity and, consequently, adipocyte size could have affected the results. However, there was no significant difference in BMI between the FCHL patients and the control subjects. It is of note that only gene expression was assessed in this study. Differences in protein expression of C3, HSL, and PPARγ, and in a number of other factors that regulate the function of the adipocyte or these proteins, may still play a role in the pathogenesis of FCHL. Especially, as regards HSL it is known that HSL gene expression affects HSL activity, but it seems to have a less important role in the control of lipolysis than post-translational mechanisms.[14,24,25] However, in obese subjects, low HSL activity was associated with a reduction in HSL gene expression.[25] Therefore, we wanted to study also the adipose tissue HSL gene expression to further verify our previous negative results as regards HSL as a major gene in FCHL.[18] Finally, the lack of differences in gene expression may be due to a limited number of control subjects. On the other hand, there was not even a trend toward differences in mRNA levels between the groups.

Although no differences in mRNA levels were found between the study groups, several interesting correlations were observed between mRNA levels and different metabolic pa-

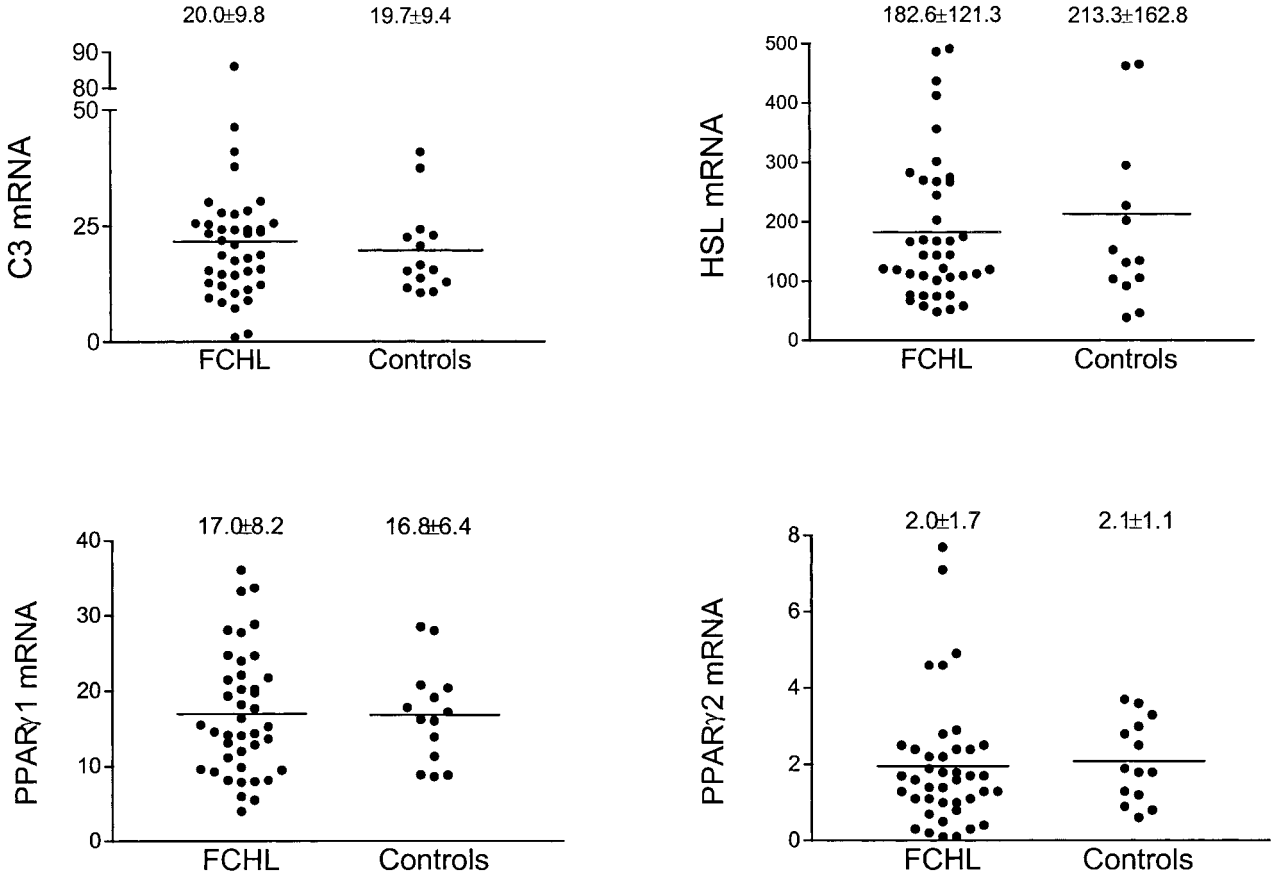

Fig 1. Individual adipose tissue mRNA expression levels (amol/μg of total RNA) of C3, HSL, PPARγ1, and PPARγ2 in FCHL patients and control subjects. Solid lines correspond to the mean values of the group. No significant differences were observed between the 2 groups for any of the mRNAs studied. The 1 subject with a C3 mRNA expression level of 86.0 amol/μg of total RNA is shown in the figure but was excluded from the analyses.

rameters. Adipose tissue C3 mRNA expression level correlated significantly with glucose-AUC and insulin-AUC in both the FCHL and the control subjects. This is in line with recent results that showed a negative correlation between adipose tissue C3 mRNA expression and insulin sensitivity in nondiabetic individuals.[26] Substantial evidence exists to support the role of serum C3 in various disease states linked to dyslipidemias. In this cohort significant correlations between C3

Table 2. Gender Adjusted Correlations Between Adipose Tissue C3, HSL, PPARγ1, and PPARγ2 mRNAs and Selected FCHL Related Variables in FCHL Patients.

	C3		HSL		PPARγ1		PPARγ2	
Variable	*N*	*r*	*N*	*r*	*N*	*r*	*N*	*r*
Age (yr)	40	0.24	40	0.01	41	−0.26	41	−0.07
TC (mmol/L)	40	0.31	40	0.00	41	−0.06	41	0.08
HDL-C (mmol/L)	40	−0.07	40	−0.05	41	0.04	41	−0.12
TG (mmol/L)	40	0.25	40	0.03	41	−0.02	41	0.31
Apo B (mg/dL)	36	0.41	36	0.08	37	−0.16	37	−0.02
Glucose-AUC (mmol/L · h^{-1})	39	0.34*	39	0.07	40	−0.10	40	−0.09
Insulin-AUC (mU/L · h^{-1})	38	0.36*	38	0.17	39	0.08	39	0.01
FFA-AUC (μmol/L · h^{-1})	35	0.22	35	0.07	36	0.37*	36	0.46†
BMI (kg/m^2)	40	0.36*	40	0.41*	41	0.08	41	0.16
Waist-hip ratio	39	0.31	39	0.35*	40	−0.11	40	0.11
C3 (g/L)	39	0.20						
ASP (ng/mL)	34	−0.02						

NOTE. Correlation coefficients (*r*) were obtained using multivariate analysis with family number and gender as independent variables.
Abbreviations: C3, serum complement component C3; ASP, plasma acylation-stimulating protein. Other abbreviations as in Table 1.
*$P < .05$.
†$P < .01$.

Table 3. Gender-Adjusted Correlations Between Adipose Tissue C3, HSL, PPARγ1, and PPARγ2 mRNAs and Selected FCHL-Related Variables in Control Subjects

	C3		HSL		PPARγ1		PPARγ2	
Variable	*N*	*r*	*N*	*r*	*N*	*r*	*N*	*r*
Age (yrs)	14	0.48	14	0.03	14	0.09	14	−0.03
TC (mmol/L)	14	0.08	14	0.22	14	0.002	14	−0.24
HDL-C (mmol/L)	14	0.04	14	0.44	14	0.29	14	−0.11
TG (mmol/L)	14	−0.06	14	−0.20	14	−0.86†	14	−0.24
Apo B (mg/dL)	13	0.42	13	−0.45	13	−0.31	13	−0.11
Glucose-AUC (mmol/L · h^{-1})	12	0.80†	12	−0.28	12	0.38	12	0.24
Insulin-AUC (mU/L · h^{-1})	12	0.67*	12	−0.53	12	−0.29	12	0.04
FFA-AUC (μmol/L · h^{-1})	12	0.42	12	−0.29	12	0.02	12	0.06
BMI (kg/m^2)	14	0.44	14	−0.28	14	−0.31	14	0.26
Waist-hip ratio	14	0.32	14	−0.64*	14	−0.44	14	−0.19
C3 (g/L)	13	0.53						
ASP-(ng/mL)	12	0.59						

NOTE. Correlation coefficients (*r*) were obtained using multivariate analysis with gender as an independent variable. Abbreviations as in Tables 1 and 2.

*$P < .05$.

†$P < .01$.

mRNA level and serum apo B ($r = 0.41$) and TG ($r = 0.34$) were observed in FCHL patients only without gender adjustment. It is controversial whether elevated serum C3 levels observed in dyslipidemia reflect the potential metabolic defect of the C3/ASP pathway in the adipose tissue, are due to complement activation in atherosclerotic lesions, or result from the effect of a common factor that stimulates overall protein synthesis in the liver.[27] Our recent results imply that serum C3 may share common genetic determinants with TG, HDL-cholesterol, FFA, and insulin.[8] Our results fit the hypothesis proposed recently by Muscari et al, that there may be common mechanisms mediated by, eg, cytokines, that enhance secretion of C3 and induce insulin resistance, which in turn is associated with several risk factors of coronary heart disease.[28] The observed associations do not allow us to completely rule out the contribution of adipose tissue C3 production to elevated serum C3 levels in hyperlipidemia, although no strong evidence for the hypothesis could be found. With regard to the relationship between adipocyte C3 gene expression (and possibly C3 production) and plasma ASP levels, no such correlation was detected in the present study. This is not surprising considering that C3 is a direct gene product, whereas ASP is generated through a complex cascade involving several proteins. Furthermore, in our recent study we have shown that measurement of plasma ASP concentrations in peripheral plasma may not have any clinical significance.[8]

Previously, a marked defect in the subcutaneous adipose tissue lipolytic capacity and HSL activity was observed in 2 Swedish FCHL cohorts,[13,14] but there was no correlation between HSL activity and serum lipids.[13] In this study, no cor-

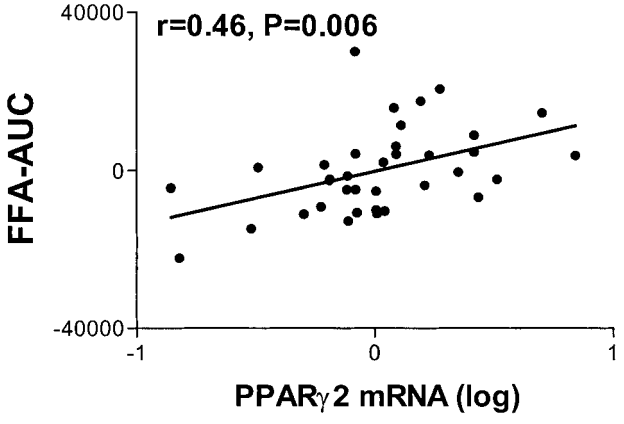

Fig 2. Scatter plot of adipose tissue PPARγ2 mRNA expression (log) *v* FFA-AUC in FCHL patients. Both variables were adjusted for gender and family number. Adjusted numbers were obtained by calculating residuals using multivariate analysis. Therefore, the scales of the axes do not have clinical significance

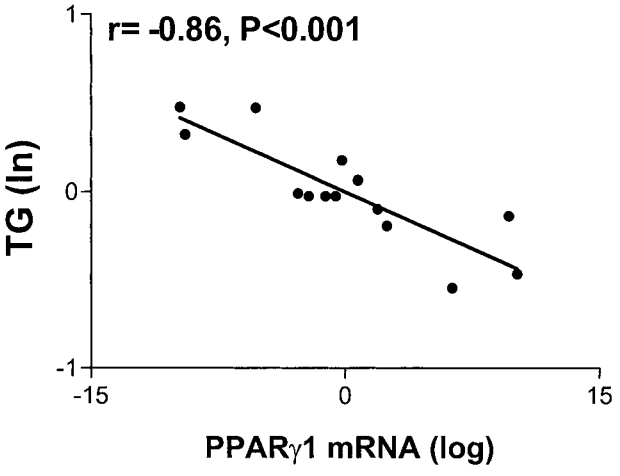

Fig 3. Scatter plot of adipose tissue PPARγ1 mRNA expression *v* serum TG (ln) in control subjects. All variables were adjusted for gender. Adjusted numbers were obtained by calculating residuals using multivariate analysis. Therefore, the scales of the axes do not have clinical significance.

relation was found between adipose tissue HSL gene expression and serum lipids. We observed negative correlations between HSL gene expression and BMI and waist-hip ratio in the control subjects. A relatively high, though statistically insignificant, negative correlation between HSL gene expression and insulin-AUC was also observed in control subjects ($r = -0.53$, $P = .10$), but not in FCHL patients when adjusted for gender. This might imply more effective HSL function in lean and thus more insulin sensitive subjects as compared with more obese subjects. Surprisingly, the correlations between HSL mRNA and BMI and waist-hip ratio were positive in FCHL patients. It is known that a number of hormones, such as catecholamines and insulin, affect HSL activity at the post-translational level and, consequently, the rate of lipolysis probably more than gene expression.

To summarize, in addition to present results, we have not been able to detect a reduction in HSL activity in Finnish FCHL patients as compared with healthy controls, and HSL activity has not been linked to any FCHL-related lipid variable studied, even though it seemed to be familial.[15] Furthermore, no linkage between FCHL and HSL has been found.[18]

PPARγ affects plasma levels of TG-rich lipoproteins mainly by enhancing TG clearance[29] and FA trapping in adipose tissue. Antidiabetic drugs of the thiazolidinedione group, which are synthetic PPARγ ligands, act as hypolipidemic agents by reducing plasma TG levels, possibly through PPARγ.[29,30] Positive correlations between PPARγ mRNA expression and HDL-cholesterol and apo A-I have been reported, whereas the association has been negative with LDL-cholesterol and apo B.[31-33] Some, but not all, studies have shown inverse correlations between PPARγ gene expression and insulin resistance or fasting insulin.[20,31,33] In the present study, no obvious correlations between PPARγ mRNAs and serum lipid levels were observed in FCHL patients. However, a positive gender-adjusted correlation with FFA-AUC was found with both PPARγ1 and PPARγ2 mRNAs. The lack of a correlation between PPARγ mRNA expression and FFA-AUC in control subjects may in part be due to the well-known wide variation of FFA values. Considering the effect of thiazolidinediones, an inverse correlation between PPARγ gene expression and FFA-AUC would be expected. The positive correlation seen in FCHL patients may indicate a disturbance of this metabolic pathway. There was a strong inverse correlation between PPARγ1 mRNA and serum TG in control subjects, suggesting that effective trapping of FA by adipose tissue takes place in the healthy subjects. That PPARγ mRNA expression was not strongly associated with serum lipids in FCHL patients may have several explanations. Knowledge on regulation of PPAR activity has grown enormously recently, and it has become evident that post-transcriptional mechanisms play an important role, though this has been mostly investigated in vitro or in animal models.

In summary, no differences in subcutaneous adipose tissue mRNA levels of C3, HSL, or PPARγ were observed between the Finnish FCHL patients and healthy, normolipidemic control subjects. However, several significant correlations were observed between the mRNA levels studied and selected FCHL-related metabolic parameters. We conclude that the genes of C3, HSL, and PPARγ may exert a modifying effect on lipid and glucose metabolism in FCHL, but defects in adipose tissue expression of these genes are not likely to play a primarily role in the pathogenesis of FCHL in Finnish FCHL families.

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