Decreased adiponectin levels in familial combined hyperlipidemia patients contribute to the atherogenic lipid profile

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Abstract **Familial combined hyperlipidemia (FCH) is characterized by increased levels of total cholesterol, triglycerides, and/or apolipoprotein B. Other features of FCH are obesity and insulin resistance. Adiponectin is a secretory product of the adipose tissue. Low levels of adiponectin are associated with insulin resistance and accelerated atherosclerosis. The aim of this study was to determine whether decreased adiponectin levels are associated with FCH and its phenotypes. The study population comprised 644 subjects, including 158 patients with FCH. Serum adiponectin levels were determined using a commercially available ELISA. For both males and females, the mean adiponectin level (μg/ml) was significantly lower in FCH patients [2.0 (1.8–2.2) and 2.5 (2.3–2.8), respectively] compared with normolipidemic relatives [2.3 (2.2–2.5) and 3.1 (2.8–3.3), respectively] and spouses [2.4 (2.1–2.7) and 3.2 (2.8–3.6), respectively]. These differences remain significant after adjusting for waist circumference and insulin resistance. Low adiponectin level in FCH patients was a superior independent predictor of the atherogenic lipid profile, including high triglyceride levels, low HDL-cholesterol levels, and the amount of small, dense LDL present, compared with both obesity and insulin resistance. Low adiponectin levels may contribute to the atherogenic lipid profile in FCH, independent of insulin resistance and obesity, as measured by waist circumference. This finding implies a role of adipose tissue metabolism in the pathophysiology of FCH.**—van der Vleuten, G. M., L. J. H. van Tits, M. den Heijer, H. Lemmers, A. F. H. Stalenhoef, and J. de Graaf. **Decreased adiponectin levels in familial combined hyperlipidemia patients contribute to the atherogenic lipid profile.** ***J. Lipid Res.*** **2005.** 46: **2398–2404.**

Supplementary key words obesity • insulin resistance • triglyceride • small, dense low density lipoprotein • high density lipoprotein-cholesterol

In the past, the adipose tissue was seen as an energy depot, storing energy in the form of triglycerides and not having a real function of its own. At present, we know that adipose tissue also secretes several signaling proteins, called adipocytokines (1). Adiponectin is one of the major adipocytokines derived from the adipose tissue and is abundantly present in human plasma, at concentrations ranging from 2 to 10 μg/ml in healthy subjects (2). Adiponectin production is inversely correlated with adipose tissue mass (3).

Low adiponectin levels are found in subjects with obesity (4–6), diabetes mellitus (5, 7), and cardiovascular disease (CVD) (8, 9). These subjects with low adiponectin levels fail some of the protective actions of adiponectin, including the stimulation of fatty acid oxidation and the improvement of glucose metabolism, by increasing lipid oxidation both in pancreas and muscle, thereby increasing insulin sensitivity (3). Furthermore, adiponectin has an insulin-sensitizing effect on hepatocytes, resulting in the suppression of hepatic glucose output (10). In addition, adiponectin inhibits the inflammatory process and possibly atherosclerosis by suppressing tumor necrosis factor-α-induced adhesion molecule expression (9), the adhesion and migration of monocytes/macrophages, and their transformation into foam cells (11). Because of these properties, adiponectin is suggested to be the missing link between obesity, insulin resistance, and atherosclerosis (2).

Besides the effects of adiponectin on whole body glucose metabolism and insulin sensitivity, adiponectin has also been reported to modulate plasma lipid levels, directly or indirectly (12). Several studies have reported a negative correlation of adiponectin levels with serum triglycerides (TGs) and small, dense low density lipoprotein (sdLDL) and a positive correlation with high density lipoprotein-choles-

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Abbreviations: apoB, apolipoprotein B; BMI, body mass index; CVD, cardiovascular disease; FCH, familial combined hyperlipidemia; GEE, generalized estimating equation; HDL-C, high density lipoprotein-cholesterol; HOMA, homeostasis model assessment; LDL-C, low density lipoprotein-cholesterol; sdLDL, small, dense low density lipoprotein; TG, triglycerides; WHR, waist-to-hip ratio.

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terol (HDL-C) (13–19). Furthermore, Chan et al. (15, 20) recently showed that adiponectin regulates triglyceride-rich lipoprotein metabolism. The mechanisms by which adiponectin modulates plasma lipid levels are unknown; however, several possibilities have been proposed. Adiponectin enhances fatty acid oxidation in the circulation and in the skeletal muscle through the activation of AMP kinase (3), so the accumulation of triglycerides occurs with low levels of adiponectin. Recent studies suggest a strong relationship between adiponectin and LPL activity (21). Finally, the effects of adiponectin on lipid levels may be related to the effect of adiponectin on insulin sensitivity.

Familial combined hyperlipidemia (FCH) is the most common genetic hyperlipidemia in humans, affecting 1–3% of the general population. It is strongly associated with premature CVD; of the survivors of a premature myocardial infarction, up to 20% are affected with FCH (22). FCH is characterized by increased levels of plasma total cholesterol, triglycerides, and/or apolipoprotein B (apoB). Other phenotypes of FCH are decreased levels of HDL-C and the presence of sdLDL (23–25). In addition, FCH is associated with obesity and insulin resistance (26).

The pathophysiology of FCH is still unknown, although several metabolic abnormalities have been suggested, including the hypothesis that FCH is caused by disturbances in adipose tissue (26–28). Quantitative and qualitative changes in adipose tissue contribute to fatty acid accumulation in the circulation, which drives apoB secretion in the liver, leading to increased lipid levels and insulin resistance (26, 29). On the other hand, alterations in adipose tissue can result in dysregulation of the secretion of adipocytokines. Because adiponectin is one of the major adipocytokines and, as described above, is associated with obesity, insulin resistance, and dyslipidemia, all features of FCH, adiponectin may play a role in the pathophysiology of FCH or may be a marker for the disturbed adipose tissue metabolism in FCH. Therefore, the inadequate storage and release of fatty acids alone or in combination with dysregulation of the secretion of adipocytokines may contribute to the detrimental metabolic sequelae in FCH.

Here, we address the question of whether in FCH the adiponectin levels are disturbed and whether disturbed adiponectin levels are associated with FCH and its associated phenotypes.

METHODS

Study population

Thirty-seven families comprising 644 subjects (158 subjects diagnosed as FCH patients, 390 normolipidemic relatives, and 89 spouses) were included in the study population, as described previously (30, 31). Seven subjects were not diagnosed because of missing values. The normolipidemic relatives and spouses are regarded as separate reference groups, because of the similar genetic background of the relatives with the FCH patients. The spouses of both the FCH patients and the normolipidemic relatives were included in this study as a separate control group, because they share environment but are not genetically related to FCH patients. All subjects filled out a questionnaire about their previous medical history. After withdrawal of lipid-lowering medication for 4 weeks and an overnight fast, blood was drawn by venipuncture. The ethical committee of the Radboud University Nijmegen Medical Center approved the study protocol, and the procedures followed were in accordance with institutional guidelines. All subjects gave informed consent.

The diagnosis FCH was based on the nomogram, as recently described by our group (31). Plasma triglyceride and total cholesterol levels, adjusted for age and gender, and absolute apoB levels were applied to the nomogram to calculate the probability of being affected by FCH. In short, in the nomogram for each of the three variables, the corresponding number of points is read from a scale and then summed to give a total point score, which is translated into a probability of being affected by FCH. The subject is defined as affected by FCH when the probability is >60%, when the diagnostic phenotype is also present in at least one first-degree relative, and when premature CVD, before the age of 60 years, is also present in at least one individual in the family.

Body mass index (BMI) was calculated as body weight (in kilograms) divided by the square of height (in meters). The maximum hip circumference (centimeters) and waist circumference (centimeters) at the umbilical level were measured in the late exhalation phase while standing. The waist-to-hip ratio (WHR) was calculated.

Biochemical analyses

Plasma total cholesterol and total triglycerides were determined by enzymatic, commercially available reagents [catalog number 237574 (Boehringer Mannheim) and catalog number 6639 (Sera Pak), respectively]. HDL-C was determined by the polyethylene glycol 6000 method (32). Low density lipoprotein-cholesterol (LDL-C) was calculated by subtraction of very low density lipoprotein-cholesterol and HDL-C from plasma total cholesterol according to the method of Friedewald, Levy, and Fredrickson (33). Total plasma apoB concentrations were determined by immunonephelometry (34). LDL subfractions were separated by single-spin density gradient ultracentrifugation. A continuous variable, K, represents the LDL subfraction profile of each individual. A negative K value ($K < -0.1$) reflects a more dense LDL subfraction profile, and a positive K value ($K > -0.1$) reflects a more buoyant profile (35–37). Glucose concentrations were measured in duplicate using the oxidation method (Glucose Analyser2; Beckman Instruments, Inc., Fullerton, CA). Plasma insulin concentrations were determined using a double-antibody method. Insulin resistance was assessed by the homeostasis model assessment (HOMA). The HOMA index was calculated from the fasting concentrations of insulin and glucose using the following formula: HOMA index = fasting plasma insulin (μU/ml) × fasting plasma glucose (mmol/l)/22.5 (38).

Serum adiponectin levels

To measure adiponectin levels, serum samples were assayed in duplicate using a commercially available enzyme-linked immunosorbent assay (catalog number DY1065; R&D Systems, Minneapolis, MN). This assay measures total circulating levels of adiponectin present in the serum. Interassay and intra-assay coefficients of variance were 7.2% and 6.2%, respectively. The detection limit was 0.1 ng/ml.

Statistical analyses

For any given degree of obesity, females have higher adiponectin levels than males. Therefore, all analyses were stratified, standardized, or corrected for gender. Variables with a skewed distribution, including adiponectin levels, triglyceride levels, and the HOMA index, were logarithmically transformed before analysis.

Descriptive statistics, presented separately for FCH patients,

normolipidemic relatives, and spouses, are expressed as means with SD or geometric means with geometric SD for logarithmically transformed variables. Parametric Pearson correlation was used for correlation analysis. Differences in characteristics and adiponectin levels between patients with FCH, normolipidemic relatives, and spouses were tested by means of generalized estimating equations (GEEs) because of possible correlated values within families. GEE analyses were performed to standardize adiponectin levels for waist circumference and HOMA index. Tertiles of adiponectin, standardized for gender, were calculated separately for FCH patients and controls. GEE regression models were used to calculate the prediction of the atherogenic lipid profile in FCH patients and controls by adiponectin levels, HOMA index, and waist circumference, adjusted for age and gender. The standardized β coefficient is calculated by multiplying the β coefficient with the ratio of the standard deviations for the independent and dependent variables. The predicted change in several variables caused by a 25% model-based decrease in adiponectin or a 5% increase in waist circumference was calculated. The choice of a 25% change in adiponectin level and a 5% change in waist circumference was based on the fact that these changes are associated with a 3 to 4 kg change in body weight (39–41). Differences were considered statistically significant at $P < 0.05$. All analyses were computed using STATA 8.0 software.

RESULTS

Subject characteristics

Descriptive statistics of anthropometric and metabolic characteristics of the study population are presented in **Table 1**. FCH patients were older than normolipidemic relatives but younger than the spouses. Evident was the greater incidence of CVD in patients with FCH compared with normolipidemic relatives and spouses. The mean BMI of patients with FCH was significantly higher than that of normolipidemic relatives. Mean WHR and waist circumference were significantly higher in FCH patients compared with normolipidemic relatives and spouses. Compared with normolipidemic relatives and spouses, FCH patients had significantly higher levels of total cholesterol, triglycerides, apoB, and LDL-C and significantly lower levels of HDL-C. Furthermore, FCH patients were characterized by the presence of sdLDL and insulin resistance, as reflected by a significantly lower K value and a significantly higher HOMA index, respectively. Normolipidemic relatives were younger and had lower BMI, WHR, waist circumference, total cholesterol, LDL-C, and HDL-C compared with the spouses (Table 1).

TABLE 1. Characteristics of patients with FCH, normolipidemic relatives, and spouses

Characteristic	FCH Patients (n = 158)	Normolipidemic Relatives (n = 390)	Spouses (n = 89)
Gender (males)	75 (47.5%)	175 (44.9%)	44 (49.4%)
Age (years)	47.1 (16.3)[a,b]	37.7 (18.0)[c]	52.6 (15.9)
CVD	32 (20.3%)[a,b]	21 (5.4%)	3 (3.4%)
Body mass index (kg/m^2)	27.3 (4.4)[a]	24.2 (5.3)[c]	26.4 (4.2)
Waist-to-hip ratio	0.88 (0.08)[a,b]	0.83 (0.08)[c]	0.85 (0.08)
Waist (cm)	87.4 (14.2)[a,b]	77.6 (12.1)[c]	82.9 (11.3)
Total cholesterol (mmol/l)	6.5 (1.1)[a,b]	4.9 (1.2)[c]	5.2 (1.0)
TG (mmol/l)	2.8 (1.6)[a,b]	1.1 (1.6)	1.1 (1.6)
HDL-C (mmol/l)	0.97 (0.33)[a,b]	1.22 (0.36)[c]	1.29 (0.32)
LDL-C (mmol/l)	4.2 (1.0)[a,b]	3.2 (1.1)[c]	3.5 (1.0)
ApoB (mg/l)	1,371 (236)[a,b]	961 (249)	1,001 (233)
K value	−0.25 (0.24)[a,b]	0.04 (0.27)	0.06 (0.23)
Insulin (mU/ml)	12.7 (1.7)[a,b]	9.1 (1.9)	9.5 (1.7)
Glucose (mmol/l)	5.2 (1.1)[a]	5.0 (1.1)[c]	5.2 (1.1)
HOMA index	2.9 (1.8)[a,b]	2.0 (2.0)	2.2 (1.8)

ApoB, apolipoprotein B; CVD, cardiovascular disease; FCH, familial combined hyperlipidemia; HDL-C, high density lipoprotein-cholesterol; HOMA, homeostasis model assessment; LDL-C, low density lipoprotein-cholesterol; TG, triglyceride. Values shown are means and SD except as indicated. Gender and CVD data are presented as number (%); TG, insulin, glucose, and HOMA index data are presented as geometric means (geometric SD). For K value, K < −0.1 represents the presence of small, dense low density lipoprotein (sdLDL).

[a] $P < 0.05$ compared with normolipidemic relatives.

[b] $P < 0.05$ compared with spouses.

[c] $P < 0.05$ compared with spouses.

Adiponectin levels and FCH

As presented in **Table 2**, both male and female FCH patients had significantly lower mean serum adiponectin levels compared with both normolipidemic relatives and spouses. Mean adiponectin levels were 17% lower in male and 22% lower in female FCH patients compared with male and female spouses (Table 2). Adiponectin levels in normolipidemic relatives and spouses did not differ significantly.

Within the total group, adiponectin levels were associated with BMI (males, $r = -0.285$; females, $r = -0.311$), WHR (males, $r = -0.238$; females, $r = -0.306$), and waist circumference (males, $r = -0.246$; females, $r = -0.339$). The correlations of adiponectin levels with markers of obesity were comparable for FCH patients and non-FCH control subjects. The correlations of adiponectin levels with waist circumference for both FCH patients and controls are shown in **Fig. 1**.

We adjusted the adiponectin levels for waist circumference because of the good correlation and because it is known from the literature that of these three markers of obesity, waist circumference is the best simple anthropometric predictor of abdominal visceral fat mass (42). The adiponectin levels remained significantly lower in both male and female patients with FCH [2.1 (1.9–2.3) and 2.8 (2.5–3.0), respectively] when comparing with male and female spouses [2.5 (2.2–2.8) and 3.2 (2.8–3.6), respectively] and borderline significant when comparing with male and female normolipidemic relatives [2.3 (2.1–2.4) and 3.0 (2.8–3.2), respectively]. When we used BMI or WHR as markers for adiposity, the results remained unchanged (data not shown).

It is known that adiponectin is even more related to whole body insulin sensitivity than to adiposity. Indeed, in our population, we observed a correlation of adiponectin with a HOMA index of −0.34 for males and −0.31 for females; therefore, we adjusted adiponectin levels not only for waist circumference but also for the HOMA index. This did not change the point estimates of adiponectin (data not shown). Adiponectin levels in normolipidemic relatives and spouses did not differ significantly, so they were combined into one group and referred to as controls.

TABLE 2. Mean adiponectin levels in patients with FCH, normolipidemic relatives, and spouses

Subject	Males		Females	
	Adiponectin Level	Difference versus Spouses	Adiponectin Level	Difference versus Spouses
	ng/ml	%	*ng/ml*	%
FCH patients	2.0 (1.8–2.2)[a,b]	−17	2.5 (2.3–2.8)[a,b]	−22
Normolipidemic relatives	2.3 (2.2–2.5)	−4	3.1 (2.8–3.3)	−3
Spouses	2.4 (2.1–2.7)	—	3.2 (2.8–3.6)	—

Values for adiponectin level are geometric means with 95% confidence interval (CI).
[a] $P < 0.05$ between FCH patients and normolipidemic relatives.
[b] $P < 0.05$ between FCH patients and spouses.

Adiponectin and the atherogenic lipid profile

FCH patients were stratified by gender-specific tertiles of adiponectin levels, as presented in **Table 3**. FCH patients with low adiponectin levels were more obese, as reflected by a higher waist circumference, and more insulin resistant, as reflected by an increased HOMA index, compared with FCH patients with intermediate or high adiponectin levels. Furthermore, low adiponectin levels in FCH patients were associated with an atherogenic lipid profile characterized by higher triglyceride levels, low HDL-C levels, and the presence of sdLDL. No relationships between adiponectin and total cholesterol, LDL-C, and apoB levels were found. Similar associations of adiponectin levels with obesity, insulin resistance, and the atherogenic lipid profile were found in controls (data not shown).

Multivariate regression analyses showed that, in the total study population, gender, waist circumference, and HOMA index could explain only 20% of the variation in adiponectin levels. Expanding the model with age and smoking led to a further 4% of variation that was explained. A maximum of 30% of the variation in adiponectin levels could be explained when HDL-C and K value were also added to the model.

In **Table 4**, the results of regression models are presented, including adiponectin, HOMA index, and waist circumference, as predictors of the atherogenic lipid profile, independent of each other and adjusted for age and gender. Among FCH patients, a reduction in serum adiponectin level was associated with a significant increase in triglyceride level, a decrease in HDL-C level, and a decrease in the K value (Table 4). A model-based reduction of 25% in serum adiponectin level resulted in a 6.2% increase in triglyceride level, a 3.7% decrease in HDL-C level, and a 0.06 decrease in the absolute value of parameter K, reflecting the presence of more sdLDL. An increase in waist circumference was also associated with a significant increase in triglyceride level, a decrease in HDL-C level, and a decreased K value, indicating the presence of sdLDL. A model-based increase of 5% in waist circumference was associated with an increase in triglyceride level of 3.2%, a decrease of 1.7% in HDL-C level, and a 0.02 decrease in the absolute value of parameter K. A change in HOMA index was not associated with an independent change in any of these lipid parameters (Table 4). The results found in the control group were comparable to those found in patients with FCH (Table 4). A significant effect for the HOMA index on triglyceride level and K value was found only in the controls.

DISCUSSION

In this study, we show that patients with FCH have low serum levels of adiponectin, even after adjusting for their

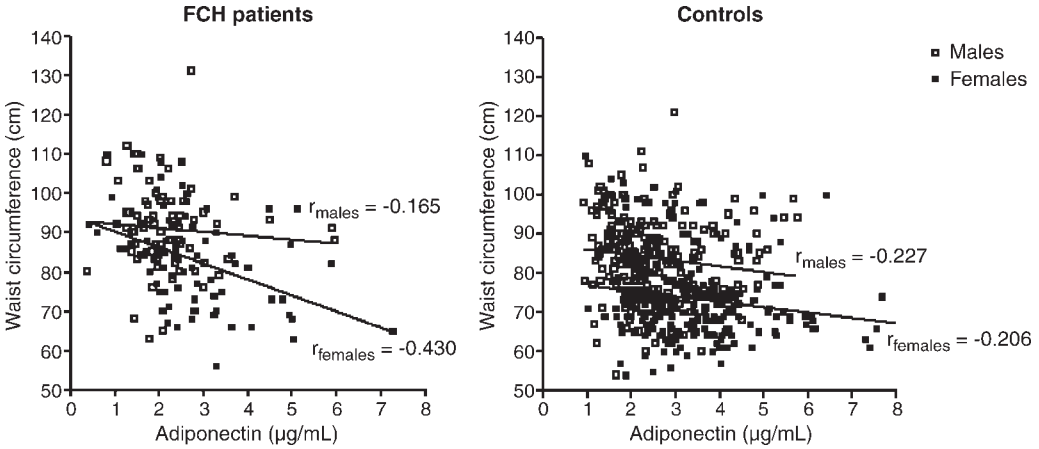

Fig. 1. Correlation between waist circumference and serum adiponectin levels in patients with familial combined hyperlipidemia (FCH) and controls. Open squares represent males and closed squares represent females.

TABLE 3. Obesity, insulin resistance, and lipid parameters in patients with FCH stratified by gender-specific tertiles of adiponectin levels

Characteristic	First Tertile (0–1.9 ng/ml)	Second Tertile (1.9–2.6 ng/ml)	Third Tertile (2.6–∞ ng/ml)
Waist (cm)	91.4 (88.0–94.9)[a,b]	86.5 (83.0–89.9)	84.2 (80.8–87.6)
HOMA index	3.9 (3.3–4.5)[a,b]	2.9 (2.5–3.4)[c]	2.3 (2.0–2.7)
TG (mmol/l)	3.2 (2.9–3.6)[a,b]	2.7 (2.5–3.1)	2.4 (2.2–2.7)
HDL-C (mmol/l)	0.93 (0.86–1.00)[b]	0.96 (0.89–1.03)	1.03 (0.95–1.10)
K value	−0.33 (−0.41–−0.26)[b]	−0.24 (−0.31–−0.16)	−0.19 (−0.26–−0.12)
Total cholesterol (mmol/l)	6.5 (6.2–6.8)	6.4 (6.1–6.8)	6.5 (6.2–6.8)
LDL-C (mmol/l)	4.07 (3.73–4.41)	4.18 (3.82–4.53)	4.31 (3.96–4.66)
ApoB (mg/l)	1,378 (1,304–1,452)	1,383 (1,307–1,459)	1,358 (1,284–1,432)

Values shown are means and (95% CI) except as indicated. HOMA index and TG data are presented as geometric means (95% CI). For K value, $K < -0.1$ represents the presence of sdLDL.

[a] $P < 0.05$ compared with second tertile.

[b] $P < 0.05$ compared with third tertile.

[c] $P < 0.05$ compared with third tertile.

body adiposity and degree of insulin resistance. Furthermore, we show that the adiponectin level in patients with FCH is the strongest independent predictor of the atherogenic lipid profile, including high triglyceride level, low HDL-C level, and the presence of sdLDL.

Several metabolic pathways have been proposed to explain the dyslipidemia in FCH, including increased production of VLDL, with or without impaired clearance of triglyceride-rich lipoproteins (43). The increased production of VLDL may be attributable to increased hepatic lipid supply and availability, associated with obesity (44), and to the intrinsic effects of insulin resistance on the hepatic output of VLDL and the catabolism of VLDL in peripheral tissue (43). Therefore, both obesity and insulin resistance are suggested to be involved in the cause of dyslipidemia of FCH. Recently, a defect in adipose tissue metabolism was proposed as the primary cause of this increased production of VLDL in FCH (43). Our finding that low adiponectin levels contribute to the atherogenic lipid profile in FCH, independent of insulin resistance and obesity, as measured by waist circumference, supports the hypothesis of a role for a disturbed adipose tissue metabolism in the pathophysiology of FCH.

Adiponectin is one of the major adipocytokines produced by adipose tissue. There is a growing body of evidence that adiponectin is involved in the regulation of both lipid and carbohydrate metabolism. Chan et al. (15) showed that adiponectin exerts an independent role in regulating triglyceride-rich lipoproteins in healthy men. In fact, the mechanism that may underlie the association between serum adiponectin levels and dyslipidemia was recently investigated, and adiponectin was shown to be an independent predictor of VLDL-apoB catabolism (20). We now show for the first time that adiponectin level is decreased in patients with FCH and that low adiponectin levels in FCH, as in non-FCH populations (13–19), are associated with the atherogenic lipid profile, including high levels of triglycerides, low levels of HDL-C, and the presence of sdLDL. Obesity and insulin resistance, both characteristic independent features of FCH (29), are also known to be associated with the atherogenic lipid profile. Most importantly, we now demonstrate that in FCH, adiponectin is a superior independent predictor of the atherogenic lipid profile compared with obesity and insulin resistance. Assuming a 3 to 4 kg increase in body weight, adiponectin levels will decrease by ~25% (39) and waist circumference will increase by ~5% (40, 41). This model-based 25% decrease in adiponectin levels resulted in a 2-fold higher increase in triglyceride levels, a 2-fold higher decrease in HDL-C levels, and a 3-fold higher decrease in K value compared with a 5% increase in waist circumference. In contrast, insulin resistance was not associated with a significant change in these lipid parameters. Therefore, adiponectin has a greater impact on the expression of the atherogenic lipid profile than obesity and insulin resistance. Recently, the increase in adiponectin after weight loss was found to be correlated with serum lipid improvement, independent of insulin sensitivity changes (19). These results support the role of adiponectin in the lipid phenotype expression of FCH.

Adiponectin levels are linked to triglyceride, HDL-C, and sdLDL levels, but they do not relate to plasma apoB levels, a characteristic feature of FCH. We propose that the lack of association of adiponectin with apoB supports the concept of a separate, but additive, genetic origin of high apoB levels in patients with FCH (29). FCH is a mul-

TABLE 4. Adiponectin levels, HOMA index, and waist circumference as predictors of the atherogenic lipid profile in patients with FCH and controls

Variable	Predictor	FCH Patients β	Controls β
TG (mmol/l)	Adiponectin	−0.219[a]	−0.114[a]
	Waist	0.222[a]	0.185[a]
	HOMA	−0.066	0.167[a]
HDL-C (mmol/l)	Adiponectin	0.222[a]	0.273[a]
	Waist	−0.197[a]	−0.260[a]
	HOMA	0.081	−0.050
K value	Adiponectin	0.329[a]	0.129[a]
	Waist	−0.173[a]	−0.129[a]
	HOMA	0.124	−0.098[a]

Values shown are standardized β coefficients of 1 SD change in adiponectin levels (ng/ml) (log-transformed), waist circumference (cm), and HOMA (log-transformed) independent of age and gender. For K values, $K < -0.1$ represents the presence of sdLDL.

[a] $P < 0.05$.

tifactorial disease in which the phenotype develops over a lifetime. The most common expression of FCH in children involves high apoB levels (45–47). Therefore, a primary (genetic) defect in FCH results in the hyper-apoB phenotype, supported by segregation and linkage analyses providing evidence of a major gene influencing apoB levels (23). The fact that the lipid phenotype of FCH is not fully expressed until the third decade of life is possibly associated with the accumulation of central abdominal fat, resulting from changes in adipocyte size and function with aging. Alternatively, as hypothesized by Cnop et al. (16), low adiponectin levels result in hepatic insulin resistance, and this, together with increased plasma nonesterified fatty acid concentrations, will shift the fate of apoB away from degradation toward secretion by the liver, resulting in increased triglyceride levels.

FCH patients are obese, and with this increased body adiposity, large triglyceride-filled visceral adipocytes produce less adiponectin (48), yet the low adiponectin levels in patients with FCH are not completely attributable to the degree of insulin resistance or the degree of obesity, as measured by waist circumference. Even though waist circumference is the best simple anthropometric predictor of abdominal visceral fat mass, we cannot exclude the possibility that the apparent independence of adiponectin levels may be attributable to the fact that intra-abdominal fat was not measured with a more sophisticated technique. However, an intrinsic defect in the adipocytes may also contribute to this hypoadiponectinemia in patients with FCH. To further explore the decreased adiponectin levels in patients with FCH, expression studies of adiponectin in adipose tissue should be performed in patients with FCH. Lihn et al. (49) showed that adiponectin mRNA expression in both visceral and subcutaneous adipose tissue is 6-fold higher in lean individuals than in obese individuals. Studies of the expression levels of adiponectin in adipose tissue of patients with FCH can help unravel the cause of the decreased adiponectin levels in these patients that are unexplained by their adiposity and state of insulin resistance.

Furthermore, we demonstrate in our FCH population that body adiposity, insulin sensitivity, HDL-C, the presence of sdLDL, smoking, and age explained only 30% of the variation in adiponectin levels. Therefore, other factors must contribute to the variation in adiponectin levels. Recent analyses in a predominantly northern European population suggested that variation in serum adiponectin levels had a strong genetic component (heritability estimate = 46%), and adiponectin concentrations were significantly linked (logarithm of the odds = 4.1) to a quantitative trait locus on chromosome 5p (50). Possibly, a large part of the remaining 70% of the variation in adiponectin levels in FCH could also be explained by a genetic component, which requires further research.

In summary, adiponectin levels are decreased in patients with FCH, independent of their insulin resistance and body adiposity, as measured by waist circumference. Furthermore, low adiponectin level in FCH predicts the presence of the atherogenic lipid profile. Our results support the concept of a disturbed adipose tissue metabolism in the pathophysiology of FCH.

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