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Serum ferritin is a major determinant of lipid phenotype in familial combined hyperlipidemia and familial hypertriglyceridemia

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Abstract

Familial combined hyperlipidemia (FCH) and familial hypertriglyceridemia (FHTG) share pathogenic mechanisms and a high interaction with components of the metabolic syndrome. The metabolic syndrome associates increased serum ferritin concentration and high cardiovascular risk. The objective was to describe the frequency of iron overload and the relationship between serum ferritin and the phenotype in patients with FCH and FHTG. The study was composed of 211 consecutive unrelated patients aged at least 18 years with primary hypertriglyceridemia, 149 with FCH, and 62 with FHTG. The prevalence of the metabolic syndrome and hyperferritinemia was very high in both hypertriglyceridemic groups (51.7% and 20.1% in FCH and 62.9% and 16.1% in FHTG, respectively), without significant statistical differences between them. Serum ferritin concentration did not show any significant association with the number of metabolic syndrome criteria. Subjects in the highest tertile of ferritin concentration (ferritin >200 μg/L) presented higher concentrations of triglycerides and liver enzymes than subjects in the first tertile of ferritin concentration (ferritin <90 μg/L). The highest positive correlation coefficient for triglycerides was found with ferritin in FCH and in FHTG subjects ($R = 0.317$ [$P < .001$] when combined). Ferritin was also the covariate that showed the highest independent association with triglycerides in FCH and FHTG. In contrast, ferritin was not associated with carotid intima-media thickness. In summary, serum ferritin is commonly increased in FCH and in FHTG, it is not related with the presence of metabolic syndrome, and it is highly correlated with liver enzymes.

1. Introduction

Familial combined hyperlipidemia (FCH) and familial hypertriglyceridemia (FHTG) are the most common primary lipid abnormalities associated with high triglycerides in plasma and increased risk of coronary disease [1]. Both diseases are of unknown etiology, and some of their clinical features overlap between them [1]. Although primary hypertriglyceridemias (HTGs) are genetically heterogeneous, family and cohort studies have demonstrated that, in most cases, they are complex diseases produced by the interaction of unknown polygenes [2] with environmental factors, especially adiposity and the metabolic syndrome [3-5].

Several cross-sectional studies have reported a strong association between increased serum ferritin concentration, as a marker of iron deposits, and a variety of metabolic cardiovascular risk factors including the metabolic syndrome [6,7], diabetes [7], obesity [8], and insulin resistance [9,10], although the mechanisms by which they are associated are not fully established. Furthermore, Wolff et al [11] have described in the Study of Health in Pomerania an independent association between serum ferritin levels and carotid atherosclerosis. This association became stronger with increasing low-density lipoprotein cholesterol levels.

Because of the association between primary HTG and all the components of the metabolic syndrome, which are also associated with iron overload, we hypothesized that iron deposits could be an important modulating factor of the phenotypic expression in FCH and FHTG.

The objective of the present study was to describe the frequency of iron overload in subjects with FCH and FHTG and to study the relationship between iron deposits and the concentration of lipids, lipoproteins, and carotid intima-

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media thickness (IMT), a well-established surrogate marker of atherosclerosis [12].

2. Subjects and methods

2.1. Study subjects

From January 2006 to October 2008, consecutive unrelated patients aged at least 18 years with HTG attending our lipid clinic were recruited into a protocol for the genetic and metabolic study of hyperlipidemia. This protocol has been approved by the local review boards, and all subjects provided written informed consent. The diagnosis of FCH was based on the presence of primary combined hyperlipidemia in untreated patients whose serum cholesterol and triglyceride concentrations were greater than the sex- and age-adjusted 90th percentile for the Spanish population, whose serum total apolipoprotein (apo) B levels were at least 120 mg/dL, and who had at least 1 first-degree relative with hyperlipidemia (total cholesterol and/or triglycerides >90th percentile). The diagnosis of FHTG was based on the presence of primary HTG in untreated patients whose triglyceride concentration was greater than the sex- and age-adjusted 90th percentile, who had at least 1 first-degree relative with triglycerides greater than the 90th percentile, and whose serum total apo B levels were less than 120 mg/dL. Secondary hyperlipidemia, including hypothyroidism, renal disease, uncontrolled diabetes mellitus (blood glucose >200 mg/dL), cholestasis, and the use of drugs affecting lipid metabolism were ruled out in all subjects. Subjects with alcohol consumption greater than 30 g/d were also excluded.

2.2. Clinical and laboratory determinations

All subjects were assessed for family history of early-onset coronary heart disease, clinical history, medication use, demographic characteristics, adiposity measurements, and cardiovascular risk factors. Alcohol consumption was determined by a validated food frequency questionnaire [13]. *Diabetes mellitus* was defined as fasting glucose level of at least 126 mg/dL or treatment with antidiabetic agents.

In asymptomatic subjects, fasting blood for baseline biochemical profiles was drawn after at least 4 weeks without hypolipidemic drug treatment. In patients with prior coronary heart disease, baseline lipid values were obtained from clinical records. Cholesterol and triglyceride concentrations were determined by using timed end point enzymatic methods on the Synchron LX20 System (Beckman Coulter, Fullerton, CA). High-density lipoprotein (HDL) cholesterol was measured without sample pretreatment also by a timed end point method. Non–high-density lipoprotein cholesterol was calculated as total cholesterol minus HDL cholesterol. Apolipoprotein B and lipoprotein (a) (Lp[a]) were determined using a rate nephelometric immunochemistry assay by Immage System (Beckman Coulter). Plasma insulin concentration was measured with the immunoassay Access Ultrasensitive Insulin (Beckman Coulter). Homeostatic model assessment (HOMA) index was calculated as the product of the fasting plasma insulin level (in microunits per milliliter) and the fasting plasma glucose level (in millimoles per liter) divided by 22.5. Serum iron and unsaturated iron binding capacity was measured by spectrophotometry, serum ferritin was measured by turbidimetric immunoassay (Beckmann Coulter), and transferrin saturation was calculated. *Iron overload* was defined as presence of high serum ferritin concentration ($\geq$300 μg/L in men and $\geq$200 μg/L in women) and/or transferrin saturation of at least 45% [14]. *Metabolic syndrome* was defined according to the updated Adult Treatment Panel III criteria [15] but without considering triglycerides. Therefore, subjects could only be scored from a maximum of 4 criteria.

2.3. Carotid IMT

An Acuson Sequoia sonograph (Siemens Medical Solutions, Erlangen, Germany) equipped with a linear array ultrasound probe (L7, 5- to 12-MHz small parts broadband transducer) was used for carotid IMT measurement as previously described [16]. Scans were performed imaging the carotid segments from a fixed lateral angle. The far walls of 6 carotid segments were visualized: the right and left common carotid arteries, carotid bifurcations, and internal carotid arteries. The variables of interest were mean and maximum values at both common carotid artery and at all 6 carotid segments.

2.4. Statistical analyses

Data are presented as mean (±SD) for continuous variables (median and interquartile range for variables with a skewed distribution) and as frequencies or percentages for categorical variables. Differences in mean values were assessed using t tests or the Mann-Whitney U test, as appropriate. Categorical variables were compared using χ^2 tests. Spearman correlations between ferritin and triglycerides, and the other variables were performed. The Kruskal-Wallis 1-way analysis of variance by ranks was used for testing equality of clinical and biochemical characteristics among ferritin tertile groups. Multivariable linear regression was used to determine independent associations of carotid IMT and triglycerides with ferritin concentration. Because of their skewed distribution, triglycerides were transformed into their natural logarithm for analysis. The independent variables used in these models were age, sex, glucose, waist circumference, alcohol consumption, and alanine transaminase (ALT). All statistical analyses were performed with SPSS (Chicago, IL) software (version 15.0), with significance set at $P < .05$.

3. Results

3.1. Clinical characteristics

The primary HTG group was composed of 211 subjects, of which 149 were diagnosed with FCH and 62 with FHTG. Table 1 shows the main clinical characteristics of both

Table 1
Clinical characteristics of the FCH and FHTG studied groups

	FCH (n = 149)	FHTG (n = 62)	*P*
Age, y	49.6 ± 12.6	45.6 ± 10.6	.029
Sex, men/women	91/58	54/8	.000
Coronary heart disease, n (%)	22 (14.8)	1 (1.7)	.006
Diabetes, n (%)	25 (16.8)	9 (14.5)	.753
Hypertension, n (%)	54 (36.2)	18 (29.0)	.510
Tobacco consumption			.245
Nonsmoker, n (%)	48 (32.2)	23 (37.1)	
Current smoker, n (%)	43 (28.9)	22 (35.5)	
Former smoker, n (%)	58 (38.9)	17 (27.4)	
Packs/d × y	28.0 (15.0-36.0)	24.5 (17.2-48.5)	.533
Waist circumference, cm	97.8 ± 10.3	99.5 ± 9.94	.269
Alcohol, g/d	4.08 (0-14.1)	2.39 (0-10.2)	.392
Systolic blood pressure, mm Hg	137 ± 18.9	136 ± 18.7	.705
Diastolic blood pressure, mm Hg	82.5 ± 10.2	84.8 ± 10.9	.158
Total cholesterol, mg/dL	296 ± 49.0	232 ± 58.6	.000
Triglycerides, mg/dL	294 (221-463)	420 (295-1056)	.000
HDL cholesterol, mg/dL	42.1 ± 12.1	31.4 ± 8.0	.000
Non-HDL cholesterol, mg/dL	254 ± 47.7	203 ± 59.4	.000
Apo A1, mg/dL	139 ± 29.5	124 ± 26.7	.002
Apo B, mg/dL	164 ± 28.0	108 ± 14.4	.000
Lp(a), mg/dL	22.0 (5.60-51.5)	11.9 (3.62-30.2)	.018
Glucose, mg/dL	99.0 (92.0-114)	101 (92.7-119)	.770
HOMA index	2.09 ± 1.23	2.10 ± 1.28	.996
ALT, IU/L	26 (21-36.7)	27.5 (22-36)	.679
GGT, IU/L	32.0 (21.0-52.0)	29.0 (25.5-46.2)	.487
CRP, mg/L	2.80 (1.35-5.30)	1.70 (0.92-3.50)	.028
Iron, μg/dL	95.0 ± 33.0	87.5 ± 29.8	.122
Ferritin, μg/L	123 (62.9-222)	170 (98.0-244)	.080
Transferrin saturation, %	28.8 ± 10.8	27.6 ± 11.4	.474
Mean carotid IMT of 2 common segments, mm	0.784 ± 0.170	0.721 ± 0.152	.037
Mean carotid IMT for each of the 6 artery segments, mm	0.854 ± 0.232	0.780 ± 0.183	.068
Metabolic syndrome, n (%)	77 (51.7)	39 (62.9)	.135
Iron overload, n (%)	30 (20.1)	10 (16.1)	.499

Values are mean ± standard deviation or median (interquartile range). *Packs per day × years* refers to the number of packs of cigarettes per day × the number of years smoking among current and former smokers. *Iron overload* is defined as serum ferritin of at least 300 μg/L in men or at least 200 μg/L in women and/or transferrin saturation of at least 45%. CRP indicates C-reactive protein.

groups. The FCH subjects were older and had higher prevalence of coronary heart disease and higher concentrations of total cholesterol, non-HDL cholesterol, HDL cholesterol, apo B, Lp(a), and C-reactive protein than subjects with FHTG. The sex distribution showed striking differences between groups because 54 of 62 subjects (87.1%) in the FHTG group were men vs 91 of 149 (61.1%) in the FCH group ($P < .001$). Other cardiovascular risk factors, including blood pressure, blood glucose, prevalence of diabetes, smoking, or waist circumference, did not show differences between groups. Iron parameters were also similar in FCH and FHTG groups. The FCH subjects had significantly higher mean common carotid IMT than the subjects with FHTG (Table 1).

The prevalence of the metabolic syndrome and iron overload was very high in both HTG groups (51.7% and 20.1% in FCH and 62.9% and 16.1% in FHTG, respectively), without statistical differences between them (Table 1). Serum ferritin concentration did not show any significant association with the number of metabolic syndrome criteria present in the subjects (Fig. 1). A total of 73 subjects (54 in the FCH group and 19 in the FHTG group) presented elevation of liver enzymes (ALT >40 IU/L and/or γ-glutamyl transpeptidase [GGT] >50 IU/L). The prevalence of the metabolic syndrome and iron overload in this subgroup was 58.9% and 26.0%, respectively, not significantly different than in the whole cohort.

To describe the clinical characteristics of FCH and FHTG according to serum ferritin, both groups were divided by ferritin tertiles. Subjects in the highest tertile of ferritin (ferritin >200 μg/L) were more often men, consumed more tobacco and alcohol, and presented higher concentrations of triglycerides and liver enzymes than subjects in the first tertile of ferritin (ferritin <90 μg/L). The HOMA index or the prevalence of metabolic syndrome was very similar across ferritin tertiles (57.7%, 51.4%, and 51.4%; $P = .744$). All carotid IMT measurements were not different among ferritin tertiles.

The highest positive correlation coefficient for triglycerides was found with ferritin in FCH and also in FHTG subjects, and when both groups were combined ($R = 0.317$, $P < .001$). Triglycerides also correlated positively with waist circumference, non-HDL cholesterol, apo B, and liver enzymes (ALT and GGT), and negatively with HDL cholesterol and apo AI (Table 2). Iron parameters did not significantly correlate with carotid IMT measurements in FCH and FHTG subjects (data not shown).

Table 3 shows the results of multivariable linear regression analysis using triglycerides as the independent variable. Nonlipid covariates that were independently associated with triglycerides were ferritin concentration, blood glucose, and sex, in this order, together explaining 16% of its variability. Ferritin was also the covariate that showed the highest independent association when the regression analysis was done in the FCH and FHTG groups separately (Table 3). The results of the multivariable analysis did not substantially differ when age, alcohol consumption, and waist circumference were forced to enter in the model. The same type of analysis was performed with the subgroup of subjects who consumed less than 5 g/d of alcohol. Again, ferritin was the first variable to enter in the model followed by glucose and GGT (data not shown).

4. Discussion

In this study, we observed a clear relationship between ferritin concentration and triglycerides in patients with FCH and FHTG. This association is independent of other known factors traditionally affecting triglycerides such as waist circumference, blood glucose, sex, age, and alcohol consumption [17]. Furthermore, ferritin explains approximately

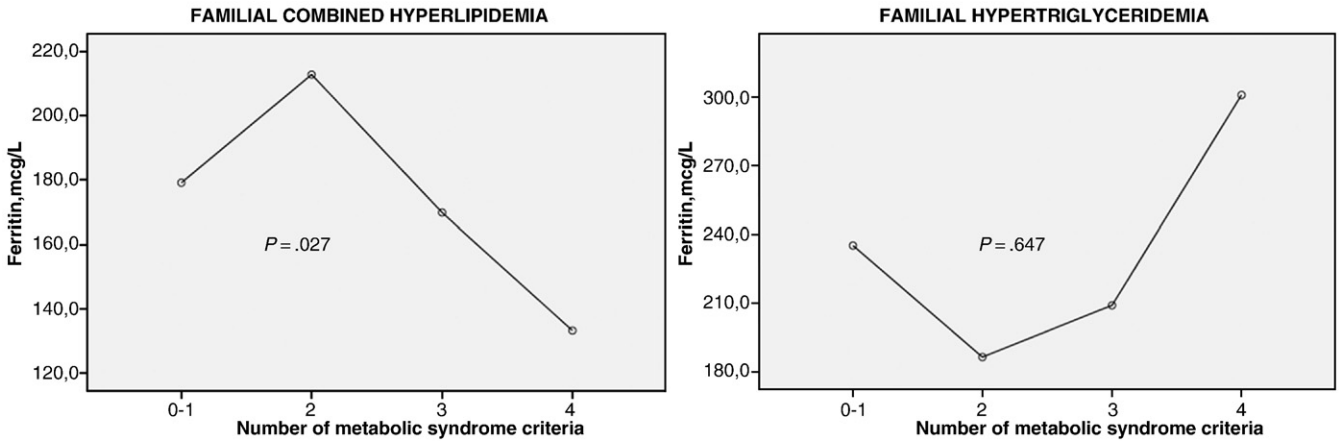

Fig. 1. Predicted mean values of triglycerides and ferritin adjusted by age and sex in FCH and FHTG according to the number of metabolic syndrome criteria.

10% of the variations in triglyceride concentration in these 2 diseases, becoming the factor with the highest independent prediction power for triglyceride concentration in our study. In contrast, carotid IMT is not associated with iron parameters in our study.

Several important conclusions can be derived from our work. Firstly, iron overload is common in FCH and FHTG, even in the absence of elevated liver enzymes or alcohol consumption. This association is especially frequent in men. This would suggest that iron accumulation and HTG share common pathogenic mechanisms or that HTG per se is contributing to iron deposits in primary HTG. Iron accumulation in nonalcoholic fatty liver disease seems to result from down-regulation of the iron-export protein ferroportin-1 that is due, at least in part, to increased levels of cytokines such as tumor necrosis factor–α [18]. Elevated levels of tumor necrosis factor–α have recently been found in FCH and are independently associated with this phenotype [19], so it is conceivable that this inflammatory cytokine could also be involved in the observed hyperferritinemia and that this high ferritin concentration could be an inflammatory manifestation.

Secondly, ferritin in primary HTG is not associated with the presence of the metabolic syndrome, any particular combination of its components except for HTG, or the HOMA index. This observation is consistent with the fact that, in FCH and FHTG, some factors that are independent of insulin resistance and the metabolic syndrome contribute to their pathogenesis [1]; and one of those mechanisms would be a predisposition to iron accumulation. This lack of association probably also explains the absence of relationship between ferritin and carotid atherosclerosis in our study. Serum ferritin has shown to be an independent risk factor for the prevalence [11] and progression [20] of carotid

Table 2
Clinical and biochemical Spearman rank correlation coefficients (*R*) in the study groups

	FCH (n = 149)		FHTG (n = 62)		All (N = 211)	
	Ferritin	Triglycerides	Ferritin	Triglycerides	Ferritin	Triglycerides
Alcohol	0.333 (0.001)	0.042 (0.690)	0.319 (0.045)	−0.042 (0.796)	0.314 (0.000)	−0.007 (0.933)
Age	−0.033 (0.106)	0.117 (0.055)	0.172 (0.188)	−0.026 (0.841)	−0.082 (0.240)	0.010 (0.880)
Waist circumference	0.068 (0.421)	0.120 (0.157)	0.113 (0.407)	0.206 (0.124)	0.084 (0.239)	0.159 (0.025)
Body mass index	−0.134 (0.686)	0.129 (0.120)	−0.082 (0.545)	0.128 (0.337)	−0.040 (0.574)	0.123 (0.079)
Total cholesterol	−0.009 (0.915)	0.179 (0.029)	0.259 (0.044)	0.614 (0.000)	−0.008 (0.904)	0.043 (0.536)
Triglycerides	0.284 (0.000)	1.000	0.328 (0.010)	1.000	0.317 (0.000)	1.000
Non-HDL cholesterol	0.051 (0.535)	0.313 (0.000)	0.263 (0.048)	0.679 (0.000)	0.031 (0.661)	0.157 (0.024)
HDL cholesterol	−0.056 (0.499)	−0.354 (0.000)	0.017 (0.897)	−0.073 (0.571)	−0.095 (0.172)	−0.374 (0.000)
Apo A1	−0.075 (0.377)	−0.062 (0.002)	−0.023 (0.871)	0.029 (0.844)	−0.052 (0.478)	0.250 (0.001)
Apo B	−0.152 (0.076)	0.084 (0.332)	0.144 (0.310)	−0.165 (0.242)	−0.131 (0.072)	0.187 (0.010)
Glucose	0.060 (0.469)	0.185 (0.024)	0.146 (0.270)	0.157 (0.231)	0.086 (0.215)	0.170 (0.014)
HOMA index	0.180 (0.183)	0.288 (0.032)	0.130 (0.575)	0.152 (0.511)	0.148 (0.200)	0.259 (0.023)
HbA_{1c}	−0.058 (0.495)	0.122 (0.149)	0.051 (0.703)	0.169 (0.201)	−0.032 (0.651)	0.080 (0.263)
CRP	−0.120 (0.170)	0.075 (0.392)	−0.250 (0.071)	−0.042 (0.763)	−0.157 (0.032)	−0.006 (0.938)
ALT	0.348 (0.000)	0.257 (0.002)	0.402 (0.002)	0.224 (0.085)	0.362 (0.000)	0.242 (0.000)
GGT	0.393 (0.000)	0.203 (0.014)	0.283 (0.030)	0.179 (0.171)	0.350 (0.000)	0.162 (0.020)
Ferritin	1.000	0.284 (0.000)	1.000	0.328 (0.010)	1.000	0.317 (0.000)

Values refer to *R* (*P* value). HbA_{1c} indicates hemoglobin A_{1c}.

Table 3
Variables independently associated with triglycerides (natural logarithm of triglycerides) by multivariate lineal regression analysis in subjects with a primary HTG

Variable	Standardized coefficient (β)	P	Adjusted R^2
All subjects			
Ferritin	0.275	.000	0.101
Glucose	0.215	.001	0.146
Sex (male)	0.145	.034	0.160
FCH subjects			
Ferritin	0.268	.001	0.091
GGT	0.215	.004	0.126
Systolic blood pressure	0.145	.032	0.148
FHTG subjects			
Glucose	0.309	.012	0.089
Ferritin	0.278	.023	0.153

Variables allowed to enter the model were those with P values < .20 in the bivariate analysis: sex, blood glucose, ferritin, GGT, and creatinine in all subjects; ferritin, systolic blood pressure, GGT, and alanine aminotransferase in FCH subjects; and glucose, ferritin, creatinine, and sex in FHTG subjects.

atherosclerosis. However, ferritin concentration in the general population is highly related with the presence of the metabolic syndrome [6,7] and nonalcoholic fatty liver disease [21]; and both abnormalities predispose to carotid atherosclerosis [22].

Thirdly, liver enzymes ALT and GGT correlate much better with serum ferritin than with triglycerides in FCH and FHTG. Liver disease in primary HTG, mainly studied in FCH, is heterogeneous, with only some forms secondary to body fat excess driven to liver steatosis [23]. Our results would indicate that, in some cases, iron overload could be an important associated mechanism to elevated liver enzymes in primary HTG independently of liver steatosis.

Lastly, iron depletion by phlebotomy was found to improve insulin resistance and liver enzymes in patients with nonalcoholic fatty liver disease [24]. Because of the association between ferritin and phenotype in FCH and FHTG, our results should stimulate further research into the effect of iron depletion in these abnormalities.

In summary, serum ferritin is commonly increased in primary HTG, it is not related to the presence of the metabolic syndrome or carotid atherosclerosis, and it is associated with triglycerides and liver enzymes.

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