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Metabolic disorders and inflammation are associated with familial combined hyperlipemia

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ABSTRACT

Background: Familial Combined Hyperlipidemia (FCH) is related to different metabolic disorders. The objective of this study was to evaluate the presence of alterations of hydrocarbonated metabolism and lipid profile together with inflammatory and adhesion molecules in subjects with FCH compared to controls.

Methods: 75 HFC patients and 75 healthy individuals were studied. Glucose, insulin, HOMA-IR index and lipid parameters, in addition to anti-oxidized LDL antibodies (Anti ox-LDL), small and dense LDL (sdLDL) and HDL subfractions, proinflammatory cytokines and adhesion molecules were measured.

Results: FCH patients showed higher levels of hydrocarbonated metabolism parameters, total cholesterol, triglycerides, LDLc, Apolipoprotein B and non-HDLc ($p < .001$), and lower levels of HDLc ($p < .001$) and Apolipoprotein AI ($p < .05$) than controls. In addition, the inflammatory markers hsCRP, IL-6, IL-8, P-selectin, *E*-selectin and ICAM were all higher with ($p < .05$) respect to controls. The increase of sdLDL was correlated with the presence of IR and IL-6 levels. Significant differences in diameter and percentage of phenotype B LDL, small HDL subfractions and Anti ox-LDL were also detected between patients and controls.

Conclusions: The lipid characteristics of FCH are confirmed by IR and a low grade inflammatory state in patients, and are associated with the predominance of sdLDL and Anti ox-LDL.

1. Introduction

Familial Combined Hyperlipidemia (FCH; MIM 144250) is the most frequent genetic hyperlipemia [1,2], and is characterized by the appearance of coronary disease before the age of 60 [3]. The prevalence of this disease is 1–2% in the general population [4] and 10–20% among patients with premature coronary disease. FCH presents a complex phenotype that is not completely understood, and which can vary among patients and affected relatives [5], which complicates diagnosis. FCH is associated with insulin resistance (IR), which is in turn related to different metabolic disorders, such as abdominal obesity, metabolic syndrome and type 2 diabetes mellitus (DM2). A common form of dyslipemia associated with FCH is attributed to the atherogenic lipoprotein phenotype, characterized by elevated levels of triglycerides (TG), small LDL particles and reduced HDL cholesterol levels (HDLc) [6–8], a lipid triad frequently seen in patients with premature coronary disease [9]. Small and dense LDL particles (sdLDL) are formed largely as a response to high levels of TG, and increase the risk of coronary

Abbreviations: AIP, Atherogenic Index of Plasma; Anti ox-LDL, Anti oxidized LDL antibodies; Apo AI, Apolipoprotein AI; Apo B, Apolipoprotein B; ASCVD, Atherosclerosis cardiovascular disease; CVD, Cardiovascular disease; DM2, Type 2 Diabetes Mellitus; FCH, Familial Combined Hyperlipidemia; FFA, Free fatty acids; HDLc, High density lipoprotein cholesterol; HOMA, Homeostatic Model Assessment; hsCRP, high sensitivity-C Reactive Protein; ICAM, Intercellular Adhesion Molecule 1; IL-6, interleukin-6; IL-8, interleukin-8; IR, Insulin resistance; LDLc, Low density lipoprotein cholesterol; Non-HDLc, Non High density lipoprotein cholesterol; sdLDL, Small and dense LDL; TC, Total cholesterol; TG, Triglycerides; TNF-α, Tumor necrosis factor alpha; TRLs, Triglyceride-rich lipoproteins; VCAM, Vascular Cell adhesion Protein 1

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heart disease [10]. The peak size of LDL particles displays a bimodal distribution and can be separated into two phenotypes: pattern A, in which larger, more buoyant LDL predominate, and pattern B, in which smaller, more dense LDL predominate. The National Cholesterol Education Program (ATP III) considers small and dense LDL to be a lipid risk factor [11].

In addition to the above mentioned aspects, it is well known that HDLc does not represent a sum of identical particles, but rather a collection of discrete subfractions that differ in their physicochemical properties; namely, size, density, composition and charge [12]. It seems that HDL atherogenity increases as particle size decreases [13,14], and that small HDL are more atherogenic than large HDL, which has a bearing on treatment [15], as such qualitative alterations in lipoprotein metabolism could account for the increased risk of cardiovascular disease in FCH. However, this is a subject that requires clarification, as there have been few studies of lipoprotein subfractions in FCH, and those to have been published offer conflicting results [16,17].

The inflammation that occurs at all stages of atherosclerosis is also common to the different processes associated with FCH, IR, abdominal obesity, metabolic syndrome and DM2. It has been reported that some molecules are related to inflammation and that adhesion molecules are elevated in FCH patients compared with control populations [18,19] although few studies have analysed the relationship between lipids subfractions and inflammation markers in the context of FCH.

The aim of this study was to evaluate the presence of alterations of hydrocarbonated metabolism and lipid profile, including sdLDL and subfractions of HDL, together with inflammatory parameters and adhesion molecules, in subjects with FCH and to compare them with parameters in a control population.

2. Materials and methods

2.1. Patients

Patients diagnosed with FCH (according to the criteria of Bredie et al. [20]) at the outpatient clinic of the Endocrinology Service of University Hospital Dr. Peset in Valencia were enrolled in the study. As a control group, healthy individuals not related to the patients were matched by age and sex.

Exclusion criteria were DM2 according to ADA criteria [21], triglycerides > 400 mg/dl, morbid obesity (BMI ≥ 40 kg/m^2), renal disease (glomerular filtration < 60 ml / min / 1.73m^2), chronic liver disease (transaminase values > 2 SD), acute disease and neoplasms.

Hypertension was diagnosed when systolic blood pressure was above 140 mmHg and/or diastolic blood pressure was above 90 mmHg, or if the subject had previously undergone hypotensive treatment. The following anthropometric parameters were measured: weight (kg), height (m), body mass index (BMI) (Kg/m^2), and waist circumference measurement (cm). IDF criteria [22] (≥94 cm for men, ≥80 cm for women) were employed to confirm high waist circumference. The study was conducted according to the ethical principles stated in the Declaration of Helsinki, and all procedures were approved by the Ethics Committee of the University Hospital Dr. Peset. Written informed consent was obtained from all subjects.

2.2. Biochemical determinations

Blood sampling was performed following 12-h fasting. Samples were immediately centrifuged at 1500*g* at 4 °C for 10 min in a refrigerated centrifuge. Frozen serum aliquots were stored at −80 °C for subsequent determination of inflammatory parameters and lipid subfractions.

Glucose, total cholesterol (TC) and triglycerides (TG) were measured by means of enzymatic assays [23–25], and HDLc concentrations were recorded using a direct method [26] with a Beckman LX-20 autoanalyser (Beckman Coulter, La Brea, CA, USA).

Insulin was evaluated using the immunometricchemiluminescent method in Immulite 1000 from Siemens® and Apolipoprotein AI (Apo AI), Apolipoprotein B (Apo B) and high sensitive C reactive protein (hsCRP) was measured by immunonephelometry assay with Dade Behring's Nephelometer II.

LDLc was determined by the Friedewald formula for triglycerides < 400 mg/dl and non-HDLc by subtracting total cholesterol from HDLc. VLDLc was estimated as TG/5 and the atherogenic index of plasma (AIP) was log TG/HDLc.

Insulin resistance HOMA-IR index (homeostasis model assessment) was calculated by the formula described by Matthews et al. [27] (HOMA = insulin (μU/ml) * [(glucose (mg / dl) / 18) / 22.5]).

The proinflammatory cytokines IL-6 (interleukin-6), IL-8 (interleukin-8) and TNF-α (tumor necrosis factor alpha) were measured by solid-phase sequential enzyme-linked immunoassay analysis by chemiluminescence with Immulite 1000 (Siemens®).

Serum levels of adhesion molecules (ICAM (intercellular adhesion molecule 1), VCAM (vascular cell adhesion protein 1), P-selectin and *E*-selectin were assessed using a Luminex 200 flow analyser system (Austin, TX, USA). Milliplex® MAP human high sensitivity T Cell Magnetic Bead Panel was purchased from Millipore Corporation (Billerica, MA, USA). The intraserial and interserial variation coefficients were < 15 % and < 20%, respectively, for all determinations, except for *E*-selectin, in which case they were < 10% and < 20%.

LDL phenotype was measured by polyacrylamide gradient gel electrophoresis (2–16%) [28]. LDL subclass phenotype was assigned based on particle diameter: pattern A, mean diameter > 25.5 nm; and pattern B, predominance of small and dense particles with a mean diameter ≤ 25.5 nm [29].

Anti-oxidized LDL antibodies (Anti ox-LDL) were determined by means of a direct quantitative enzyme immunoassay, in which the autoantibodies present in the serum are specifically linked to the antigen (LDL-oxidized, 4-hydroxynonal-modified proteins) that covers the plate (Biomedica Gruppe, Wien). Absorbance at 450 nm was determined by a microplate reader. The antibody titer was calculated by a curve constructed with the standards included in the kit. The coefficients of intra- and interassay variation were 5 and 10%, respectively.

HDL subfractions were separated using the Quantimetrix Lipoprint system (Redondo Beach, CA,USA) [30], and then identified and quantified using a computerized method developed for the Quantimetrix Lipoprint system and NIH image program version 1.62 (Bethesda, MD, USA) for research purposes. The LiposureH (Quantimetrix Corporation, Redondo Beach, CA, USA) was used for quality control. HDL subfractions were classified as large HDL (subfractions 1–3), intermediate HDL (subfractions 4–7) and small HDL (subfractions 8–10).

2.3. Statistical analysis

The sample size was 75 subjects per group in order to provide 80% statistical power; thus, differences between the two groups with respect to the primary efficacy criterion (LDL diameter variation) were > 0.9 nm, assuming a common SD of 0.7 nm.

SPSS 15.0 was used for statistical treatment of results. Arithmetic mean and standard deviation were calculated as measures of descriptive statistics. The Kolmogorov-Smirnov test was applied to the data to determine if the distribution of the variables was normal. We applied the Student's *t*-test to compare the means of parametric variables, and the Mann-Whitney *U* test to compare non-parametric variables. Variables following a parametric distribution were expressed as mean ± standard deviation (SD), and non-parametric as median with 25% and 75% percentiles. To establish correlations between variables the Pearson Correlation coefficient were used for parametric variables and the Spearman Correlation coefficient for non-parametric variables. ANOVA was employed to establish tertiles with quantitative variables. Statistical significance was considered when $p < .05$.

In the multivariable regression models, the relationship between

Table 1
Anthropometric, hydrocarbon and lipid parameters in controls and FCH patients.

	Controls (n = 75)	FCH (n = 75)	P-value
Men/women (n/%)	23/52 (30/70)	30/45 (40/60)	NS
Age (years)	37 ± 13	41 ± 14	NS
BMI (kg/m^2)	23.1 ± 2.8	26.9 ± 4.0	< 0.001
Glycemia (mg/dl)	92.4 ± 9.5	97.8 ± 10.6	< 0.05
Insulinemia (μU/ml)	7.77 ± 4.21	10,81 ± 4.39	< 0.01
HOMA-IR	1.72 ± 0.97	2.65 ± 1.27	< 0.001
TC (mg/dl)	173.8 ± 26.3	230.5 ± 48.4	< 0.001
TG (mg/dl)	56 (39.5, 86.5)	190 (110, 265)	< 0.001
HDLc (mg/dl)	58.3 ± 14.6	44.3 ± 16.0	< 0.001
LDLc (mg/dl)	102.0 ± 25.5	147.8 ± 43.7	< 0.001
VLDLc (mg/dl)	13.4 ± 6.8	43.4 ± 36.1	< 0.001
APO AI (mg/dl)	146.2 ± 18.5	128.7 ± 27.8	< 0.01
APO B (mg/dl)	80.0 ± 19.4	126.7 ± 28.3	< 0.001
Non-HDLc (mg/dl)	107.4 ± 44.5	187.3 ± 35.9	< 0.001
AIP	0.03 ± 0.36	0.05 ± 0.41	< 0.001

Data are expressed as mean ± SD for parametric data and median (interquartile range) for non-parametric data.

two or more explanatory variables (independent variables) and a response variable (dependent variable) was evaluated by fitting a linear equation to the data obtained.

3. Results

3.1. Anthropometric, hydrocarbonated and lipid parameters

A total of 75 patients with FCH with a mean age of 41 ± 14 years and a BMI of 26.9 ± 4.0 kg/m^2–30 men (40%) and 45 women (60%) - were matched by age and sex with 75 controls. FCH patients showed higher percentages of excess weight (49% vs 12%), obesity (20% vs 4%), hypertension (28% vs 1%), women's waist ≥80 cm (50% vs 18%) and men's waist ≥94 cm (27% vs 6%) than controls ($p < .001$ for all). As expected, differences between the FCH and control groups were significant for all lipid and hydrocarbonated metabolism parameters (Table 1). LDL diameter was lower in FCH (25.3 ± 0.8 nm) than in controls (26.2 ± 0.57 nm), % phenotype B of LDL particles was higher in patients (52%) than in controls (5%) and small HDL subfractions were higher in patients (24%) than controls (17%).

Significant differences in diameter and percentage of phenotype B of LDL were also detected between FCH patients and controls (Fig. 1A and B, respectively). The percentage of small HDL subfractions was significantly higher and the percentage of large HDL subfractions significantly lower in patients vs. controls (Fig. 1C). In addition, levels of Anti ox-LDL were higher in FCH patients than in control subjects (Fig. 1D).

3.2. Inflammatory markers and adhesion molecules

The FCH group showed a significant increase in virtually all inflammatory parameters (IL-6, IL-8, TNF-α and hsCRP) and adhesion molecules (P-selectin, *E*-selectin, ICAM) with respect to the control group, with the exception of VCAM (Table 2).

3.3. Study of correlation between hydrocarbons, lipids and inflammatory parameters

Glucose was positively correlated with TG (r = 0.463, p = .001), non-HDLc (r = 0.305, p = .009) and AIP (r = 0.375, p = .01), and negatively correlated with LDL diameter (r = −0.518, p = .009). Insulin was positively correlated with AIP (r = 0.351, p = .033) and negatively correlated with HDLc (r = −0.333, p = .044) and LDL diameter (r = −0.435, p = .038). HOMA-IR correlated positively with TG (r = 0.401, p = .014), non-HDLc (r = 0.305, p = .042) and AIP (r = 0.422, p = .009) (r = −0.357, p = .030) and negatively with LDL diameter (r = −0.486, p = .019).

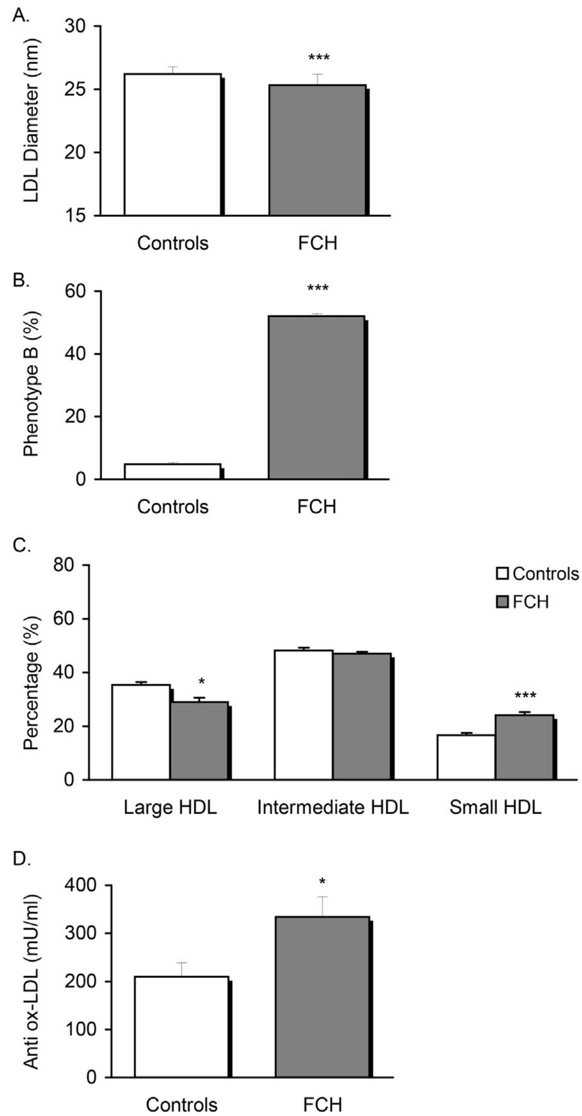

Fig. 1. LDL diameter (A), LDL Phenotype B (B), HDL subfractions (C), Anti-oxidized LDL antibodies (D) in controls and FCH patients. *$p < .05$, ***$p < .0001$.

Table 2
Inflammatory parameters and adhesion molecules in controls and FCH patients.

	Controls	FCH	P-value
IL-6 (pg/ml)	0.81 ± 0.72	2.69 ± 2.62	< 0.01
IL-8 (pg/ml)	5.8 (4.9; 9.8)	12.2 (7.9; 24.6)	< 0.05
TNF-α (pg/ml)	2.22 ± 2.59	8.99 ± 4.04	< 0.001
hsCRP (mg/l)	1.23 ± 1.51	2.58 ± 2.95	< 0.05
P-selectin (ng/ml)	61.3 ± 18.6	78.8 ± 22.8	< 0.05
E-selectin (ng/ml)	31.1 ± 12.1	44.8 ± 16.9	< 0.05
VCAM (ng/ml)	574.1 ± 131.5	674.4 ± 401.3	NS
ICAM (ng/ml)	126.7 ± 44.4	167.9 ± 21.8	< 0.05

Data are expressed as mean ± SD for parametric data and median (interquartile range) for non-parametric data.

Regarding inflammatory markers, hsCRP was positively correlated with glucose (r = 0.286, p = .012), ins (r = 0.367, p = .006), HOMA-IR (r = 0.404, p = .002), IAP (r = 0.481, $p < .001$), non-HDLc (r = 0.367, p < .001) ApoB (r = 0.467, p < .001), LDLc (r = 0.225, p = .023), TG (r = 0.490, p < .001), TC (r = 0.264, p = .005), BMI

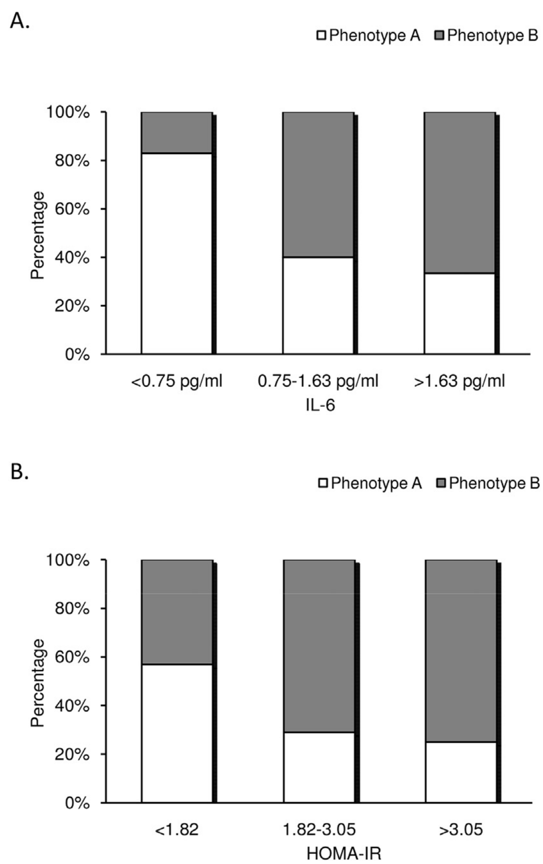

Fig. 2. Percentage of LDL Phenotype according to tertiles of IL-6 (A) and tertiles of HOMA (B) in FCH patients. $p < .05$ in both.

($r = 0.388$, $p = .004$) and waist ($r = 0.338$, $p = .025$), and was negatively correlated with LDL diameter ($r = -0.242$, $p = .034$), HDLc ($r = -0.217$, $p = .023$). IL-6 was positively correlated with IAP ($r = 0{,}329$, $p = 0{,}014$), non-HDLc ($r = 0.440$, $p = .001$), ApoB ($r = 0.404$, $p = .01$), LDLc ($r = 0.438$, $p = .001$), TG ($r = 0.322$, $p = .016$), TC ($r = 0.367$, $p = .006$) and BMI ($r = 0.617$, $p = .025$), and negatively correlated with HDLc ($r = -0.305$, $p = .024$).

3.4. Study of LDL phenotype and its relation to HOMA-IR and inflammation

When the percentages of LDL phenotypes A and B were distributed according to IL-6 tertile, it was observed that the increased inflammation (IL-6) the predominance of phenotype B were greater (Fig. 2A). Phenotypes A and B were distributed according to HOMA tertiles in a similar pattern; when IR-HOMA increased, the predominance of phenotype B was greater (Fig. 2B).

3.5. Study multivariable regression models

The association of LDL diameter with HDLc, LDLc, triglycerides, glucose, insulin and hsCRP was evaluated in multivariable regression models using the stepwise method, in each case as a potential independent predictor. Our results showed that triglycerides were inversely and independently associated with LDL diameter, and that non-HDLc was independently associated with hsCRP ($p < .05$ in both, Table 3).

4. Discussion

As expected, our results show that FCH patients exhibit a worse lipid profile, which is reflected by IR, increased inflammation parameters and adhesion molecules, and alterations of the subfractions of LDL and HDL. In accordance with previous reports, in our patients FCH was associated with a more pronounced atherogenic lipoprotein profile, evident in reduced HDLc and Apo AI levels and increased LDLc, non-HDLc, Apo B and triglyceride levels [31–33].

FCH exacerbates the deleterious effects of IR on lipoprotein profile, leading to impairment of trygliceride-rich lipoprotein metabolism, manifested by higher levels of non-HDLc, triglycerides, AIP and Apo B and by the predominance of sdLDL [34–36]. Indeed, in the Spanish Atherosclerosis Society (SEA)'s Registry of Hypertriglyceridemias the majority of severe hypertriglyceridemias correspond to FCH [37]. The hipertrygliceridemia common to IR and FCH is a result of adipocyte lipolysis, which in turn leads to FFA flux to the liver and increased VLDL secretion. Higher VLDL triglyceride output activates the cholesterol ester transfer protein, which results in triglyceride enrichment of LDL and HDL. The TG content within these particles is hydrolyzed by hepatic triglyceride lipase, which results in sdLDL particles and small HDL particles.

Regarding the sdLDL particles, we have not found references in the literature to variations of sdLDL in populations with FCH in southern Europe. Some experimental studies suggest that hypertriglyceridemic HDL is dysfunctional [38,39], and that sdLDL is more susceptible to oxidative modifications [40,41], which is in line with the present results. This increase in the number of atherogenic particles may have an adverse influence on CVD risk [42]. However, there are no clinical outcome trials to determine whether or not normalization of particle composition or reduction of particle number reduces CVD risk. LDL can be trapped in the arterial intima or attached to proteoglycans or other components of the arterial intima. TRLs present in the plasma in mild-to-moderate hypertriglyceridemia can actually enter the intima, becoming phagocytosed by macrophages in the subendothelial space and contributing to the formation of foam cells, which gives rise to the formation and progression of the atheromatous plaque. TLRs are even more atherogenic than LDLs; unlike the former, the remaining particles of TLRs can be directly absorbed by macrophages without oxidative modification via the VLDL receptor, without downregulation by intracellular lipoproteins, and with the help of lipoprotein lipase [44]. In addition, due to their larger size, TLRs transport more cholesterol per particle than LDLs [43]. It has also been shown that the remnants of

Table 3
Stepwise multivariate regression model for biochemical variables and LDL diameter or hsCRP as dependent variables.

Dependent variable	Independent variable	Unstandardized coefficients		Standardized coefficients	*P* value
		B	SE	B	
LDL diameter[a]	Triglycerides	−2.599	0.521	−0.870	0.001
	Multiple R square-adjusted	0.727			
	R	0.870			
	p	0.001			
hsCRP[b]	Non-HDLc	0.050	0.013	0.811	0.004
	Multiple R square-adjusted	0.615			
	R	0.811			
	p	0.004			

Triglyceride levels were a log-transformed variable.
[a] Glucose, HDLc, LDLc, Non-HDLc, IL6, hsCRP, insulin and Anti ox-LDL antibodies were excluded from the model since they were not significant predictors ($p > .05$).
[b] Glucose, HDLc, LDLc, Triglyceride, LDL diameter, IL6, insulin and Anti ox-LDL antibodies were excluded from the model since they were not significant predictors ($p > .05$).

TLRs promote endothelial dysfunction, which enhances atherogenesis [45]. New insight provided by epidemiological, genetic and biological research regarding the underlying mechanisms of these processes indicate that elevated TRL levels represent a causal risk factor for inflammation. [46,47]. However, further evidence from randomized intervention trials is needed to confirm whether or not lowering TRLs and remnant cholesterol can reduce inflammation, ASCVD and all-cause mortality. The first of such studies is underway [48], but as yet no data are available.

The relationship between triglycerides and CV risk has long been controversial [49]. Evidence from prospective studies supports a higher CV risk in subjects with lower levels of HDLc and LDLc [50] and with DM2 [51]. Other more recent studies with non-fasting triglycerides suggest they are a more accurate predictor of CVD incidence than fasting levels [52]. In case-control and angiographic studies, triglycerides have routinely been identified as a risk factor, even after adjustment for total cholesterol or LDLc and HDLc.

In summary, the independence of triglyceride levels as a causal factor in promoting CVD remains debatable, though it does appear to provide unique information as a biomarker of risk, especially when combined with low HDLc and elevated LDLc, as occurs in FCH.

Due to this association of hypertriglyceridaemia with CVD risk and pancreatitis, and the coexistence with other metabolic disturbances, a simplification in the definition hypertriglyceridaemia has been recommended; namely, normal (< 2 mmol/l), mild-to-moderate (2–10 mmol/l) and severe (> 10 mmol/l) [53]. In summary, the presence of highly atherogenic lipoprotein remnants would appear to play an important role in the pathogenesis of cardiovascular diseases in FCH.

With respect to HDL particles, low HDLc levels in FCH subjects are consistently reported in the literature, although little is known about the composition of HDL particles in the disease. We have observed modifications of HDL subfractions in our FCH patients; specifically, the percentage of small HDL subfractions was higher and that of large HDL subfractions was lower. As already mentioned [54], the decrease in HDLc in FHC is independently correlated with an increase in cardiovascular risk [55], even in the presence of optimal LDLc levels [56]. It seems that the functionality of these particles is what confers cardiovascular risk, with smaller size being correlated with said risk. In accordance with our results, a recent report showed that small HDL subfractions predicted cardiovascular events in patients with metabolic dyslipemia [57].

Only a few studies about FCH have evaluated inflammatory markers such as interleukins, adhesion molecules and selectins, and their results concerning the increase or decrease of their levels in relation to control populations are inconclusive [18,19]. Some studies suggest that low-grade inflammatory state is the basis of CV disease and may be related with other metabolic disturbances observed in patients. In this context, the Physicians Heart Study (PHS) and Heart Outcomes Prevention and Evaluation (HOPE) showed that ICAM, but not VCAM, is related with CV disease. Conversely, the AtheroGene Study and British Regional Heart Study concluded that VCAM is a marker of future cardiovascular events.

Our study demonstrates a relation among disturbances in TRL metabolism, inflammatory state and IR [58]. We have seen a significant increase in all inflammatory markers except for VCAM in our patients. This is in line with the fact that ICAM has been described as a potential predictor of cardiovascular risk in subjects without cardiovascular disease, while VCAM may be related with the extent and progression of lesions in subjects diagnosed with cardiovascular disease.

There are data suggesting that chronic low-grade inflammation itself lowers insulin sensitization in organs that are targets of this hormone [59]. Insulin regulates inflammatory molecule levels, interrupting the inflammation cascade. Therefore, a state of IR favours chronic inflammation; when chronic inflammation decreases, IR improves.

The present research confirms a chronic inflammatory state in FCH patients that may lead to the atherosclerosis that often develops in these subjects. In fact, although we did not detect a direct relationship between hsCRP and TG, we did find one between non-HDLc and hsCRP. TRLs can be quantified by non-HDL cholesterol, which illustrates the relationship between hypertriglyceridemia and inflammation. Indeed, the literature suggests that the inflammation which occurs during FCH is the basis of the cardiovascular disease that often develops in patients, thus endorsing an association with metabolic alterations [60].

The current data show that, as sdLDL increases, the proinflammatory state and IR also increase. In addition, they suggest that LDL and HDL subfractions provide additional information to conventional lipoprotein parameters. In conclusion, the findings of this study confirm the expected lipid profile of FCH, characterized by the presence of atherogenic dyslipidemia, as well as sdLDLs, small HDLs and anti ox-LDLs. In addition, IR and a low-grade inflammatory state increase in parallel with the presence of metabolic disturbances, highlighting the importance of metabolic control in FCH.

Conflict of interest

The authors declare that they have no competing interests.

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