Familial Combined Hyperlipidemia, Metabolic Syndrome and Cardiovascular Disease

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Our aim was to investigate the relationship between metabolic syndrome and cardiovascular disease (i.e., survivors of myocardial infarction) in patients with familial combined hyperlipidemia (FCH). We compared a group of 20 male patients with FCH who had survived a myocardial infarction with two other groups matched for age and body mass index, comprising 20 individuals with FCH who had not had a myocardial infraction and 20 control subjects. Plasma lipid, glucose, and insulin levels were determined. Metabolic syndrome was judged to present on the basis of World Health Organization (WHO) and National Cholesterol Education Program-Adult treatment panel (NCEP-ATPIII) criteria. Differences between the groups were evaluated using non-parametric tests and the association between ischemic coronary disease and other parameters was assessed by logistic regression analysis. According to WHO criteria, the metabolic syndrome was present in 19 FCH patients who had survived a myocardial infarction, in 11 individuals with FCH who had not had a myocardial infraction, and in six control subject (*P*<.001); the difference between FCH patients with and without myocardial infarction was significant (*P*<.01). Presence of the metabolic syndrome, as defined by WHO criteria, is a marker of cardiovascular risk in individuals with FCH.

Key words: *Familial combined hyperlipidemia. Metabolic syndrome. Insulin resistance. Acute myocardial infarction.*

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Hiperlipidemia familiar combinada, síndrome metabólico y enfermedad cardiovascular

Se estudia la relación entre síndrome metabólico (SM) e infarto agudo de miocardio (IAM) en la hiperlipidemia familiar combinada (HFC). Se comparan 20 sujetos varones con HFC supervivientes a IAM con otras 2 series de sujetos emparejados por edad e índice de masa corporal (IMC): 20 individuos con HFC que no han presentado IAM y 20 controles sanos. Se determinaron los lípidos, la glucosa y la insulina en plasma y la presencia de SM definido por criterios de la Organización Mundial de la Salud (OMS) y National Cholesterol Education Program-Adults Treatment Panel (NCEP-ATP-III). El SM definido por criterios OMS se encontró en 19 sujetos con HFC e IAM, en 11 sujetos con HFC sin IAM y en 6 controles (p < 0,001); hubo diferencias significativas (p < 0,01) al comparar los sujetos con HFC con y sin IAM. No hubo diferencias significativas entre grupos de HFC al estudiar el SM por criterios ATP-III. La HFC es una dislipidemia primaria frecuentemente asociada con resistencia a la insulina y elevado riesgo cardiovascular. En los sujetos con HFC, la presencia de SM según criterios de la OMS es un marcador de riesgo cardiovascular.

Palabras clave: *Hiperlipidemia familiar combinada. Síndrome metabólico. Insulinorresistencia. Infarto agudo de miocardio.*

INTRODUCTION

Familial combined hyperlipidemia (FCH) was described in studies of the family members of individuals who had experienced an acute myocardial infarction (AMI).[1,2] The prevalence of this condition in the general population ranges from 0.5% to 3%, and it is the cause of 10% to 20% of the AMI occurring in individuals under 60 years of age.[3]

The etiology of FCH is unknown and the phenotypic expression is conditioned by genetic, metabolic, and environmental factors.[4] The lipoprotein phenotype varies and mixed dyslipidemia is characteristic, with increased

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low density lipoproteins (LDL), very low density lipoproteins (VLDL), or both, and elevated apolipoprotein B[5]. In many cases, hypertension, abnormal glucose tolerance, and insulin resistance (IR) are also present.[6,7] The insulin resistance is related to a group of metabolic and cardiovascular alterations known as metabolic syndrome (MS).[8]

Our aim was to study the prevalence of MS and the relationship between this factor and cardiovascular disease in individuals with FCH. For this purpose, we compared FCH patients to a control population matched for age, sex, body mass index (BMI) and waist girth.

METHODS

Subjects

The study population included 20 unrelated men who were diagnosed with FCH following a clinical and analytical study of the patients and their first-degree relatives. The diagnosis of FCH was based on described criteria.[7] In addition, the presence of mutations related with familial hypercholesterolemia and familial apo B defect was ruled out in all the families.

Patients with FCH were consecutively included in the study according to the following criteria: no treatment with lipid-lowering drugs or other medication that can alter insulin resistance, non-smokers or ex-smokers for at least one year, baseline glucose concentration <126 mg/dL, acute myocardial infarction occurring more than three months prior to enrollment, and FCH diagnosis established on clinical, electrocardiographic, and enzyme analysis results following hospital admittance. Patients with any of the following criteria were excluded: unstable angina, smokers, diabetes, daily alcohol intake >30 g, intensive physical training or weight loss program, >10% weight change in the last three months, chronic disease, AMI within the last three months, and use at present or in the past month of lipid-lowering drugs, or medication that can modify the degree of IR.

Later, based on the same criteria, we selected 20 age-, sex- and BMI-matched individuals with FCH who were clinically free of coronary disease, as well as 20 healthy controls without hyperlipidemia and with similar exclusion and inclusion criteria, recruited from the healthcare personnel

The study was approved by the Hospital Ethics Committee, and all the individuals involved were informed and gave their signed, written consent to participate in the study.

Laboratory Methods

Following a fast of more than 12 h, determinations were performed for total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), very low density lipoprotein cholesterol (VLDL-C) low density lipoprotein cholesterol (LDL-C), and apo B. In addition, an oral overload of 75 g of glucose was administered to determine plasma insulin and glucose levels according to a previously described method.[7] Insulin resistance was quantified using the formula of the homeostasis model assessment for insulin resistance (HOMA-IR) and the definition of IR was established with the 75 percentile of our population (HOMA-IR =3.2).[8] Metabolic syndrome was defined according to the criteria of the World Health Organization (WHO)[9] and the National Cholesterol Education Program-Adult Treatment Panel (NCEP-ATP-III).[10]

The statistical analysis was done with the SPSS statistics program (SPSS Inc.). Results are expressed as the mean (the standard deviation [SD]). The differences between variables were determined with nonparametric tests (Kolmogorov-Smirnov and Mann-Whitney, and Kruskal-Wallis analysis of variance, including an analysis of trends). Fisher's exact test was used for the comparison between proportions.

RESULTS

The general characteristics of individuals with FCH and the controls are shown in Table 1. Because of the selection criteria, there were no differences between the groups with regard to age, sex, BMI, and waist girth. Nor were there significant differences in the comparison between systolic and diastolic pressure between the groups studied.

Plasma concentrations of TC, TG, LDL-C and apo B were significantly higher in the two groups with FCH (P<.01) relative to the controls. There were no differences between the FCH groups with and without AMI.

No significant differences were found in fasting glucose levels among the three groups. At two hours after glucose overload, blood glucose was similar in the two FCH groups and significantly higher than the controls (Table 1). The study of baseline insulin levels showed significant differences between the groups (P<.01): 22.4 (10.7) #MU/mL in patients with FCH and AMI; 15.0 (2.4) #MU/mL in patients with FCH and no AMI, and 13.9 (3.7) #MU/mL in the controls, with significant differences between the FCH groups with and without AMI (Table 1). Differences in insulin levels were also found in these groups at 2 hours after glucose overload (Table 1). Insulin resistance, as determined with the HOMA-IR index yielded values of 5.4 (2.4) in the FCH plus AMI group, 3.5 (0.8) in the FCH without AMI group and 3.2 (0.9) in the controls. Significant differences were observed (P<.001) between the FCH plus AMI group and the other two groups.

Metabolic syndrome defined according to the ATP-III criteria was found in 18, 14, and 10 individuals in the FCH plus AMI, FCH without AMI, and control groups, respectively, with significant differences between the groups (P<.02) and with a significant trend in the

TABLE 1. **Anthropometric Parameters in Individuals with Familial Combined Hyperlipidemia With and Without Acute Myocardial Infarction Matched by Age and BMI**

T	FCH with AMI	FCH without AMI	Controls	*P* among 3 groups	*P*-trend	*P* between FCH with and without AMI
No. (men)	20	20	20			
Age (years)	51 (7)	51 (7)	51 (7)	.87	.61	.79
BMI	29.4 (2.4)	28.4 (1.6)	29.1 (2.4)	.47	.60	.25
Waist girth (cm)	108.5 (7.5)	106.7 (7.1)	105.4 (9.4)	.23	.21	.39
AMI	20	0	0			
SP (mm Hg)	137 (10)	139 (14)	132 (7)	.14	.137	.69
DP (mm Hg)	87 (10)	85 (10)	81 (7)	.16	.022	.51
TC (mg/dL)	281 (55)	294 (55)	210 (28)	<.001	<.001	.27
TG (mg/dL)	333 (157)	278 (235)	167 (51)	<.001	.002	.11
HDL-C (mg/dL)	37.7 (8.5)	39.2 (8.8)	40.2 (4.2)	.32	.287	.49
LDL-C (mg/dL)	181 (61)	207 (49)	137 (34)	<.001	.009	.07
Apo B (mg/dL)	162 (40)	150 (37)	108 (16)	.036	<.001	.72
FG (mg/dL)	98 (11)	93 (11)	93 (6)	0.21	.072	.16
FG#>110 mg/dL	3	2	0	.28	.089	.63
G 120 min (mg/dL)	148 (40)	129 (27)	93 (21)	<.001	<.001	.20
G 120 min#>140 (mg/dL)	10	6	1	.007	.001	.19
FI (µU/mL)	22.4 (10.7)	15.0 (2.4)	13.9 (3.7)	.008	.001	.020
FI = 14.2 (µU/mL)	10	8	6	.16	.058	.33
I 120 min of OGO	165 (106)	98 (49)	53 (38)	<.001	<.001	.015
HOMA-IR	5.4 (2.4)	3.5 (0.8)	3.2 (0.9)	.002	<.001	.006
HOMA-IR#>3.2	17	11	8	.013	.003	.038
MS ATP-III	18	14	10	.022	.005	.235
MS WHO	19	11	6	<.001	<.001	.003

AMI: acute myocardial infarction; Apo B: apolipoprotein B; BMI: body mass index; HDL-C: high-density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; DP: diastolic pressure; FCH: familial combined hyperlipidemia; FG: fasting blood glucose; FI: fasting insulin; G 120 min: blood glucose at 120 minutes following an oral glucose overload; HOMA-IR; insulin resistance as measured by the HOMA method; I 120 min of OGO: insulin at 120 minutes following an oral glucose overload; MS ATP-III: metabolic syndrome according to ATP-III criteria; MS WHO: metabolic syndrome according to WHO criteria; OGO: oral glucose overload; SP: systolic pressure; TC; total cholesterol; TG: triglycerides.

successive comparison between groups (*P* of the trend=.005); nevertheless, there were no differences between the FCH groups with and without AMI. Metabolic syndrome as defined by the WHO criteria was found in 19 individuals with FCH plus AMI, in 11 individuals with FCH and no AMI, and in 6 controls. Significant differences were found in the comparison between FCH patients with and without AMI (*P*<.01) and the contrast among the three groups was also evident (*P*<.001); there was a well defined trend among the groups compared (*P* of the trend<.001).

DISCUSSION

Familial combined hyperlipidemia is considered the most common and most poorly characterized atherogenic dyslipidemia, conferring a cardiovascular risk status between three- and ten-fold higher than that of the general population. Metabolic syndrome is common in western populations (prevalence of 12%-35%), and also represents a state of elevated cardiovascular risk.

Familial combined hyperlipidemia and MS share certain clinical and biochemical characteristics, such as abdominal obesity, hypertension, high cardiovascular risk, and dyslipidemia. Nonetheless, these conditions differ in other important aspects, such as apo B elevation, which is moderate in MS and considerable (apo B>120 mg/dL) in FCH. In the current study, we included male FCH patients with and without AMI who met the diagnostic criteria for MS according to the two most commonly used standards, those proposed by the WHO and those of the NCEP-ATP III. Our aim was to assess the risk of coronary disease in individuals with FCH depending on the presence or not of MS, and to compare the risk with that observed in a control group adjusted for sex, age, BMI and abdominal circumference.

Our results showed no significant differences in the lipid profile of individuals with FCH who had experienced an AMI and those who were clinically free of coronary disease. Thus, the characteristic hyperlipidemia of FCH did not explain the presence of coronary disease in a group of individuals.

Several authors have reported detection of IR in FCH,[11,12] and this factor has been related with cardiovascular death after a follow-up of 5 to 15 years.[13-16] In a previous study, our group demonstrated a high prevalence of IR in individuals with FCH, regardless of the grade of abdominal obesity or the pattern of dyslipidemia; insulin resistance is an important predictive factor of cardiovascular disease in FCH.[17] In this study

we measured IR in FCH patients and controls, and found significant differences in insulin levels ($P<.01$) between the three groups as compared to baseline, at two hours following an oral glucose overload, and in the HOMA-IR index, even though the groups were comparable for several factors that have a considerable influence on IR (age, sex, BMI, and waist girth). Significant differences in the IR parameters were also seen between FCH patients with and without an AMI: HOMA-IR was 5.4 (2.4) in the FCH group with AMI, a value significantly higher ($P<.01$) than that seen in the other two groups (HOMA-IR 3.5 [0.8] in the FCH group without AMI and 3.2 [0.9] in the controls).

Several studies have indicated that the presence of MS (WHO or ATP-III criteria) is the best predictor of cardiovascular risk in the general population, in diabetic patients, and in non-diabetic individuals, whether obese or not.[18-22] The comparison of the prevalence of MS as detected by the two definitions (WHO and ATP-III) showed significant differences among the groups. However, when comparing FCH patients with and without AMI, we found significant differences ($P<.01$) in the frequency of IR (HOMA-IR) and MS by the WHO criteria, but no differences in the prevalence of MS by the ATP-III criteria (Table 1). Thus, in FCH patients with dyslipidemia and (frequently) abdominal obesity, MS as defined by the WHO criteria, which includes the presence of IR, is a more sensitive parameter. In contrast, MS as defined by the ATP-III criteria does not make a particular distinction regarding FCH; these criteria place more importance on the lipid parameters (hypertriglyceridemia and HDL-C decrease), which, by definition, are more prevalent in FCH.

In conclusion, FCH is a primary dyslipidemia frequently associated with IR and an elevated risk of cardiovascular disease. The presence of MS, defined according to the WHO criteria, is an important independent marker of cardiovascular risk in individuals with FCH. Larger prospective studies are needed to better delimit the additional degree of cardiovascular risk that MS implies in FCH patients. This study has a limitation related to the small number of individuals analyzed, which was difficult to resolve because of the characteristics of the group (untreated patients with dyslipidemia and AMI). Nevertheless, the study design gave a clear indication of the prognostic value of MS determined according to the WHO criteria in individuals with FCH.

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