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Metabolic syndrome prevalence and characteristics in Greek adults with familial combined hyperlipidemia☆

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Abstract

Familial combined hyperlipidemia (FCH) is closely related with metabolic syndrome (MetSyn), and coronary artery disease (CAD) is positively associated to MetSyn and FCH. In this study, we evaluated the prevalence of MetSyn and its components between patients with FCH and a control group. We also investigated the role of MetSyn and diabetes mellitus (DM) on the incidence of CAD within the FCH group. Our study population consisted of 463 male and 243 female patients with FCH who were not receiving any hypolipidemic treatment, and 1128 men and 1154 women who came from the same geographical region. The prevalence of MetSyn was 42% and 19.8% among FCH subjects and controls, respectively, whereas MetSyn increased with age in both groups. The prevalence of CAD was 15.3% in the FCH group. Moreover, after dividing FCH patients into 3 subgroups, with and without MetSyn and with DM, CAD prevailed at a percentage of 15.2%, 11.1%, and 26.5%, respectively. However, statistically significant differences in the prevalence of CAD were observed only between FCH subjects with DM compared with the other 2 subgroups, even when an adjustment for age, sex, and smoking was conducted. People with FCH and MetSyn differed in several anthropometric, biochemical, and clinical characteristics, compared with the non-MetSyn subgroup of FCH. MetSyn is more prevalent in the FCH than in the control group. Among subjects with FCH, only DM was significantly associated with an increase in the prevalence of CAD in this subgroup compared with FCH individuals with or without MetSyn.

1. Introduction

Metabolic syndrome (MetSyn), a clustering of abdominal obesity, dyslipidemia, hypertension, insulin resistance, and disturbed glucose metabolism, is a growing health issue that strongly correlates with the increased burden of cardiovascular disease and of diabetes mellitus (DM) [1]. The Third National Health and Nutrition Survey has estimated that 1 of 5 US citizens have this condition [2], a statement that is in agreement with the results from the ATTICA study in a representative sample from the general population in Greece [3]. Metabolic syndrome is presented as a polygenic and multifactorial disorder. The lipidemic profile of this condition, which consists of increased levels of triglycerides, apolipoprotein B (apo B), small, dense low-density lipoproteins (LDL), and of small amounts of high-density lipoproteins (HDL), seems to be the cornerstone of its atherogenic power [4]. Thus, the Adult Treatment Panel III (ATP-III) described MetSyn as a secondary target of the risk-reduction therapy according to the levels of LDL cholesterol (LDL-C) [1]. Furthermore, the profile of MetSyn can be attributed to central obesity and the consequent insulin resistance through various pathophysiologic mechanisms [5-9].

However, the same metabolic abnormalities also characterize familial combined hyperlipidemia (FCH) and type 2 DM [10-12]. FCH is the most common inherited polygenic disorder that affects 1% to 2% of the general population and is associated with a 2- to 3-fold increased risk of coronary artery disease (CAD) [13,14], especially in younger ages.

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The conventional wisdom is that the 2 conditions etiologically overlap; however, only Hopkins et al [15] explored differences in the prevalence of MetSyn between subjects with FCH and controls.

The aim of this work was to compare the epidemiology of MetSyn between people with FCH and a population-based sample of Greek adults, both from the prefecture of Attica, and to investigate the association of MetSyn and DM with the prevalence of CAD in the FCH group.

2. Methods

2.1. Study population

In this study, 706 patients with FCH (463 men and 243 women) were enrolled; they had been referred, for the first time to our lipid outpatient clinic during 1999-2003. Moreover, data regarding 1128 men and 1154 women with FCH (who participated in the ATTICA study) from the general population of the same geographic region were retrieved [3]. The sampling of the ATTICA study was random and multistage (by city) and was based on the age and sex distribution of the province of Attica provided by the National Statistical Service according to the census of 2000.

All subjects were Caucasian and lived in the prefecture of Attica in Greece. On admission to the lipidemic outpatient clinic, the patients with FCH were not under any hypolipidemic treatment (lifestyle interventions, drug therapy). A complete medical history was obtained from all the participants, and a physical examination was performed.

The well-known phenotypic variability of FCH leads to a lack of consensus about the diagnostic criteria. There have been several patterns suggested, but we decided to use the following as diagnostic criteria for FCH: (1) plasma levels of total cholesterol (TC) and triglyceride (TG) concentration greater than 90th percentile, as determined by using the age- and sex-related 90th percentile upper levels of the Prospective Cardiovascular Munster study, which was confirmed by at least 2 repeated measurements with a minimum interval of 2 months; (2) the presence of type II-a, II-b, or IV hyperlipidemia in at least one first-degree relative and familial history of early atherosclerotic disease, which are adopted in most of the relative studies [13,14,16].

The MetSyn was defined according to ATP-III criteria [1,2]; a diagnosis can be established when 3 of these risk factors are present: (1) waist circumference greater than 102 cm (40 in.) for men or greater than 88 cm (35 in.) for women, (2) TG level of 150 mg/dL or greater; (3) HDL cholesterol (HDL-C) level less than 40 mg/dL for men or less than 50 mg/dL for women, (4) blood pressure of 130/85 mm Hg or higher; (5) fasting glucose level of 110 mg/dL or greater. Subjects with diabetes were excluded from the MetSyn group, which is in concordance with the methodology of the ATTICA study [3,17].

Finally, we divided subjects with FCH into 3 subgroups: (1) MetSyn subgroup (according to the ATP-III criteria), (2) diabetic subgroup (glucose >125 mg/dL), (3) non-MetSyn subgroup.

2.2. Investigated parameters

Arterial blood pressure was measured 3 times with the subject in sitting position, after participants had rested at least 30 minutes. Blood pressure measurements were taken 3 times by a cardiologist, with the subject's right arm relaxed and well supported by a table, at an angle of 45° from the trunk (ELKA aneroid manometric sphygmomanometer, Von Schlieben, Munich, Germany). The systolic blood pressure level was determined by the first perception of sound (of tapping quality). The diastolic blood pressure level was determined by phase V when the repetitive sounds become fully muffled (disappeared). Changes in loudness were not considered. The mean value of 3 consecutive measurements of blood pressures was taken into account for the analysis that followed. Patients whose average blood pressure levels were greater than or equal to 140/90 mm Hg, who were under antihypertensive medication, or who were told by a physician that they had hypertension but were untreated, or subjects with MetSyn with blood pressure greater than or equal to 130/85 mm Hg were classified as hypertensives.

A 12-hour fasting and abstinence from alcohol and coffee preceded blood sample collection. Blood samples were collected between 8 and 10 AM from the antecubital vein of the individual who was kept in a seated position. The biochemical evaluation was carried out in the same laboratory that followed the criteria of the World Health Organization Lipid Reference Laboratories. All biochemical examinations (serum total cholesterol, HDL-C, TGs, etc) were performed by using a chromatographic enzymic method (Technicon RA-1000, Dade Boehringer, Mannheim, Marburg, Germany). For reasons of validity, an internal quality control was in place for assessing the validity of TC, TGs, and HDL-C assessment methods. The intra- and interassay coefficients of variation of cholesterol levels did not exceed 4%. We also measured apolipoproteins A-I (apo A-I) and apo B, as well as lipoprotein(a), Lp(a). by a latex-enhanced turbidimetric immunoassay (BNII, Dade and Behring, Germany).

LDL-C was calculated by using the Friedewald formula: (total cholesterol) − (HDL-C) − 1/5(TGs), which is valid for TG values less than or equal to 400. For determination of plasma fibrinogen, blood was anticoagulated with 3.8% trisodium citrate (9:1 vol/vol) and was analyzed by nephelometry (BNII, Dade and Behring).

All individuals were classified according to the fasting blood glucose level as: (*a*) normal (glucose level <110 mg/dL), (*b*) with impaired glucose tolerance (glucose level ≥110 and ≤125 mg/dL), and (*c*) diabetic (glucose level >125 mg/dL).

A detailed medical history, including sociodemographic characteristics (age, sex, mean annual income during the past 3 years, and years of education) and information about the frequency of consumption of various foods and other lifestyle habits, was obtained. Current smokers were defined

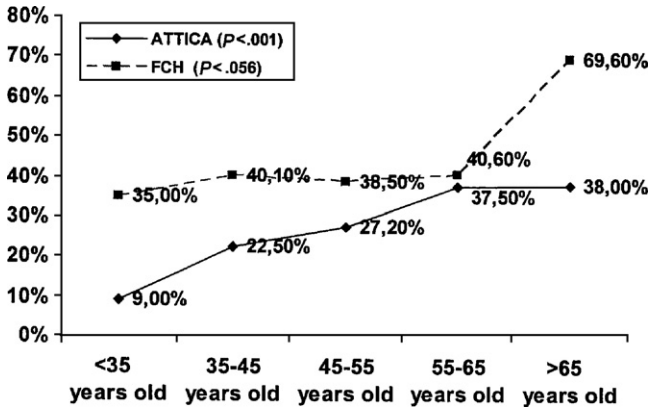

Fig. 1. Age distribution of MetSyn in subjects with FCH and the general population (ATTICA study) (males).

as those who smoked at least 1 cigarette per day; never smokers, those who have never tried a cigarette in their life; and former smokers, those who had stopped smoking for at least 1 year. The number of occasional smokers (less than 7 cigarettes per week) were recorded and combined with that of current smokers. The small number of participants who quit smoking for less than a year and who were enrolled in the former-smokers group could not underscore the power of our analysis.

Coronary heart disease was ascribed to all participants with a medical history of myocardial infarction and surgical or percutaneous coronary revascularization, with positive coronary angiography (stenosis >50% in at least one major vessel), or with symptoms of coronary disease and abnormal findings in thallium stress test. This evaluation was made by experienced cardiologists.

Height and weight were measured, and body mass index was calculated as weight (in kilograms) divided by height (in meters squared).

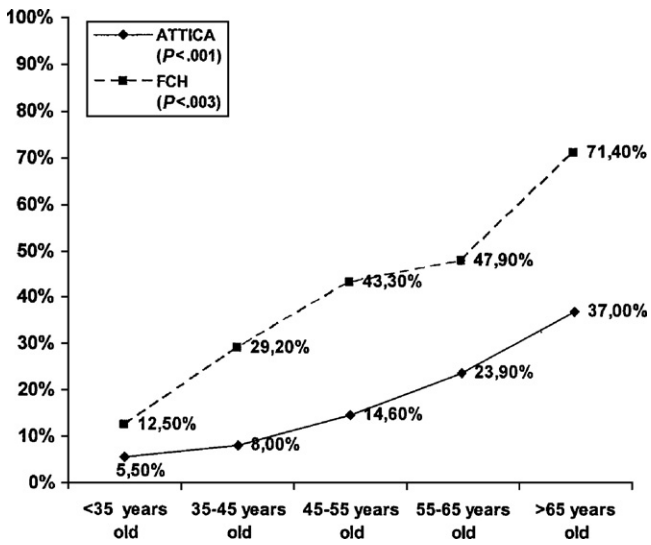

Fig. 2. Age distribution of MetSyn in subjects with FCH and the general population (ATTICA study) (females).

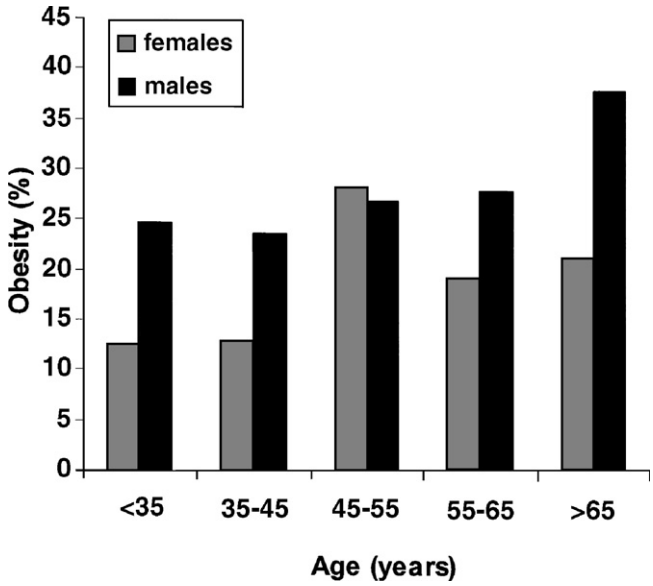

Fig. 3. Distribution of obesity at different age groups of male and female subjects with FCH.

2.3. Statistical analysis

Continuous variables are presented as means ± SD, and categorical variables are presented as absolute and relative frequencies. Distributions of continuous variables were assessed for normality by using nonparametric Kolmogorov-Smirnov test. Associations between categorical variables were tested by the use of contingency tables and the calculation of Fisher exact test or Pearson χ^2 when appropriate. Comparisons of normally distributed continuous variables between various subgroups were performed by 1-way analysis of variance after checking for homoscedasticity. Comparisons between skewed variables and genotypes were performed by using the Kruskal-Wallis test. Multiple analysis of covariance was performed to detect differences between groups after adjustment for several factors such as age, sex, etc. Logistic regression models were used to assess the association of dichotomous variables with categorical or continuous variables. All reported P values are based on two-sided tests and

Table 1
Percentage of subjects with abnormal values of the components of MetSyn in subjects with FCH and the general population

	General population	FCH	P
Males			
Waist circumference (%)	31.8	31.5	.899
TG levels (%)	28.4	94.4	<.001
HDL levels (%)	37.6	63.4	<.001
Blood pressure levels (%)	43.7	39.8	.143
Fasting blood glucose level (%)	14.2	15.5	.526
Females			
Waist circumference (%)	29.7	47	<.001
TG levels (%)	12.7	85.2	<.001
HDL levels (%)	37.4	72.1	<.001
Blood pressure levels (%)	34.9	41.6	.049
Fasting blood glucose level (%)	7.7	13.2	.007

Table 2
Differences in the prevalence of CAD among FCH subjects with MetSyn or diabetes or without MetSyn (non-MetSyn) before and after adjustment for age, sex, and smoking

	Prevalence of CAD (%)	*P*	*P* after adjustment for age, sex, and smoking
MetSyn vs non-MetSyn	15.2 vs 11.1	.143	.33
Diabetes vs MetSyn	26.5 vs 15.2	.018	.012
Diabetes vs non-MetSyn	26.5 vs 11.1	<.001	.002

compared to a significance level of .05. SPSS 11.0 software (SPSS, Chicago, IL) was used for all the statistical calculations.

3. Results

In our study, 66% of the subjects with FCH were men, whereas 34% were women. In the ATTICA study, men and women participated, with an equal percentage of 50% according to the distribution of the general population. It should be noted that in both groups, participants were older than 20 years and came from the same geographical region.

The prevalence of MetSyn was 41.8% among subjects with FCH (63% men, 37% women) and 19.8% in the ATTICA study (62.69% men, 37.3% women).

Although the prevalence of MetSyn in men was higher than in women in both groups, a statistically significant increase in the prevalence of MetSyn in the control group was observed by age, starting from 9.4% in men younger than 35 years and increasing to 22.5% in men aged 35 to 45 years, 27.2% in men aged 45 to 55 years, 37.5% in men aged 55 to 65 years, and 38% in elderly men (*P* for trend = .001) (Fig. 1). Similar results were observed in women (Fig. 2). However, in the FCH group, there is an age disparity in the distribution of MetSyn between the 2 sexes. Moreover, 35% of men with FCH younger than 35 years, 40.1% aged 35 to 45 years, 38.5% aged 45 to 55 years, 40.6% aged 55 to 65 years, and 69.6% aged older than 65 years had the MetSyn. In women, the distribution of the prevalence of MetSyn was 12.5%, 29.2%, 43.3%, 47.9%, and 71.4%, respectively. Figs. 1 and 2 present the age distribution of MetSyn by sex in both groups and shows that MetSyn reaches a "plateau" in early ages in men with FCH compared to women.

Moreover, the age distribution of obesity in our FCH group demonstrated a similar plateau among younger men (Fig. 3).

Furthermore, subjects with FCH and controls were compared with each other with regard to several factors of MetSyn, according to sex, as shown in Table 1. It is noticeable that in men, a difference in the percentage of 3 characteristics (waist circumference >102 cm, blood pressure ≥130/85 mm Hg, fasting glucose ≥110 mg/dL) between controls and the FCH group was not found. On the contrary, all 5 metabolic components differed significantly between women with FCH and the control group.

In the FCH group, CAD prevailed in 15.3%. We divided FCH subjects into 3 subgroups: (1) MetSyn (according to the ATP-III criteria), (b) diabetic (glucose >125 mg/dL), and (3) non-MetSyn subgroups. The mean ages of these subgroups were 50.3, 52.2, and 46.6 years old, respectively. The prevalence of CAD in the MetSyn, non-MetSyn, and diabetic subgroups of FCH was found to be 15.2%, 11.1%, and 26.5%, respectively. However, statistically significant differences in the prevalence of CAD were revealed only for comparisons between the diabetic and the other 2 subgroups after adjusting for age, sex, and smoking (Table 2).

In addition, we conducted a more detailed analysis of the former 3 subpopulations of the FCH group, focusing on the differences of several somatometric and biochemical parameters between individuals with and without MetSyn. The mean values of the components of MetSyn among the aforementioned subgroups of the FCH population are presented in Table 3. FCH subjects with MetSyn were older

Table 3
Elements of MetSyn in FCH subjects with MetSyn or without MetSyn (non-MetSyn) or diabetes

	MetSyn	Non-MetSyn	DM	*P* (MetSyn vs non-MetSyn)
Age (y)	50.3 ± 10.9	46.59 ± 10.8	52.23 ± 9.16	<.001
Weight (kg)	83.49 ± 14.5	76.24 ± 11.7	82.2 ± 13.1	<.001
BMI (kg/m^2)	29.15 ± 3.44	26.04 ± 2.9	28.7 ± 3.6	<.001
Waist circumference(cm)	97.6 ± 9.76	88.9 ± 9.4	97.6 ± 10.01	<.001
Smoking (%)	35.2%	42%	37.3%	.009
Hypertension status (%)	68.5	11.8	57.8	.001
TC (mg/dL)	290.9 ± 52.5	290.7 ± 49	285.7 ± 70.9	1.000
TG (mg/dL)	316.2 ± 152.68	265.58 ± 142.5	391.4 ± 207.9	<.001
HDL-C (mg/dL)	38.19 ± 7.9	43.2 ± 10.7	36.48 ± 9.2	<.001
LDL-C (mg/dL)	194.09 ± 55.53	197.79 ± 49.5	182.2 ± 55.7	1.000
Apo A (mg/dL)	139.87 ± 21.4	146.1 ± 25.5	135.32 ± 21.6	.011
Apo B (mg/dL)	178.47 ± 37.6	170.8 ± 35.9	165.4 ± 39.8	.077
Lp(a) (mg/dL)	30.45 ± 33.13	29.78 ± 33.17	24.93 ± 23.7	1.000
FIB (mg/dL)	307.11 ± 60.69	300.0 ± 59.4	304.12 ± 65.2	.555
UA (mg/dL)	5.49 ± 2.417	5.30 ± 2.1	5.52 ± 2.11	1.000
GLU (mg/dL)	102.33 ± 12.95	94.98 ± 15.8	141.1 ± 25.4	.001

Values are presented as mean ± SD. FIB = fibrinogen; UA = uric acid; GLU = glucose.

(50.3 vs 46.6 years old, $P = .03$) and had higher levels of apo B (178 vs 170.8 mg/dL, $P = .077$), lower levels of apo A (139.8 vs 146.1 mg/dL, $P = .011$), and lower prevalence of smoking (35.2% vs 42%, $P = .09$), as shown in Table 3. As far as apo B is concerned, we repeated the analysis, after adjusting for age, sex, and obesity, and the significant difference persisted. However, in this subanalysis, differences in sex ($P = .338$) and levels of TC (290.9 vs 290.7 mg/dL, $P = 1.0$), LDL-C (194 vs 197.7 mg/dL, $P = 1.0$), Lp(a) (30.4 vs 29.8 mg/dL, $P = 1.0$), fibrinogen (307 vs 300 mg/dL, $P = .555$), and uric acid (5.5 vs 5.3 mg/dL, $P = 1.0$) did not reach a level of statistical significance.

4. Discussion

We evaluated the prevalence of MetSyn and its components in FCH patients and in people from the general population, from the same geographical region. Furthermore, we investigated the impact of MetSyn and DM on the prevalence of CAD among subjects with FCH.

According to the results of this study, the prevalence of MetSyn was 42% in the FCH group, which is 2-fold higher than the prevalence found in the control group (19.8%). Hopkins et al [15] reported a higher prevalence (65%) of MetSyn among FCH subjects compared with the 40% suggested in our study. This can be attributed to the higher mean age of the participants enrolled in the former study (52.9 years vs 48.9 years in our study) and the interethnic heterogeneity concerning obesity and energy intake and expenditure. Furthermore, the Hopkins et al study, unlike our study, included diabetics in the MetSyn group, which could overestimate the prevalence of MetSyn among individuals with FCH. The positive association of age with the prevalence of MetSyn is well known. Several investigators report that approximately 1 of 2 subjects aged older than 55 years meet the criteria for MetSyn [2,3]. In our study, the prevalence of MetSyn shows a linear increase by age in both groups; whereas it is significantly higher among all FCH subjects, with an exception in the subgroup of male FCH subjects, where a plateau of the prevalence of MetSyn was observed. However, this could be partly explained by the relationship of MetSyn with obesity, which is in accordance with the results of our study (Fig. 3) and by the fact that FCH relies on a more genetic basis (thus, it is expressed in younger ages), whereas MetSyn mainly depends on several lifestyle habits. Both Pairitz et al [18] and Austin et al [19] have depicted genetic mechanisms resulting in the elevation of apo B levels and of small dense LDL particles, respectively. The interaction of genetics with lifestyle habits for the manifestation of FCH is reinforced by Bredie et al [20] who reported nonobese FCH subjects presenting with insulin resistance and by the observation, that apo B levels were higher in FCH patients than controls with similar BMI, visceral fat and metabolic status [21].

The prevalence of MetSyn in the control group was 19.8%, which is similar, but quite lower compared with other studies [2-4,22]. Thus, it is lower than the reported 22% in the National Health and Nutrition Examination Survey [2] and the observed 25.8% in a multiethnic population in Canada [22]. The data from the ATTICA study [3,17] suggest that this can be partially attributed to the high frequency of the adoption of the Mediterranean diet (40%) in this part of the Greek population, which seem to be inversely associated with the prevalence of MetSyn. It should be noted that in the ATTICA study DM was excluded from MetSyn, which could underestimate the overall prevalence of MetSyn. However, MetSyn in our control group prevailed at a quite higher percentage compared with that in a Chinese population (13.7%) [23].

Several studies have implicated the etiologic overlap between MetSyn and FCH [10]. The main metabolic similarities consist of insulin resistance, small and dense LDL-C and TG particles, small amounts of HDL-C, and high levels of apo B [20,24]. Furthermore, numerous genome loci have been involved with FCH and MetSyn, but there is a lack of consensus about the genetic nature of these 2 similar entities [25-27].

This overlap is confirmed in our study through the clustering of MetSyn in the FCH group and the higher prevalence of MetSyn observed in the age groups of FCH compared with the general population. The population of our survey was extracted from the same geographical region as the ATTICA study; thus, the beneficial effect of the adoption of the Mediterranean diet to the MetSyn [3], as mentioned above, and the lower age of subjects with FCH with MetSyn provide further explanations about these results.

The data of our study demonstrate a higher incidence (15.3%) of CAD among FCH individuals compared with the estimated 3.8% in a population-based sample of 3042 individuals from the same geographical region [17]. It is well established that FCH exerts a 2- to 3-fold increase of the coronary risk [13]. The abnormal lipidemic profile of high levels of very low-density lipoprotein particles and TGs and low levels of HDL-C could be implicated in the former observation [28-30].

Concerning the role of MetSyn and of diabetes as a cardiovascular risk factor, Alexander et al [31] reported the highest prevalence of CAD (19.2%) among people older than 50 years with DM and MetSyn. In the same study, the prevalence of CAD was 13.9% and 8.7% in the MetSyn/no DM and no MetSyn/no DM groups, respectively. This positive association of MetSyn with CAD is observed in several similar studies [32,33]. On the contrary, the data from the San Antonio Heart Study [34], which enrolled subjects with a high predisposition for cardiovascular disease, reported that the excessive risk for cardiovascular disease could be attributed to diabetes and not to MetSyn.

There are few data exploring the association of MetSyn and DM with CAD among FCH subjects. Although reports from a recent study, which enrolled 133 FCH subjects, have speculated that MetSyn could increase the burden of

cardiovascular disease in FCH patients [15], the results of our study showed that among FCH subjects, MetSyn did not exacerbate the prevalence of CAD. This lack of association could be ascribed to the small sample population, the younger ages of our group (thus CAD might not have been expressed), and the potential protective effects of the Mediterranean diet and of physical activity on CAD, although they have not been taken into account. DM in FCH patients seems to be significantly associated with the manifestation of CAD, which is consistent with the recent implications of the National Cholesterol Education Program [1] considering DM as a coronary heart disease equivalent.

The detailed examination of FCH subjects with and without MetSyn revealed that beyond the factors that compose the definition for MetSyn (waist circumference obesity, glucose, hypertension, lipidemic profile), the levels of apo B and apo A were not significantly different. The results of our study demonstrated that apo B level was higher (not statistically significant) in FCH patients with MetSyn than those without, which is in line with the data from a population-based sample from the same geographical region, whereas the difference reached a level of statistical significance [3]. Apo-B plays a substantial role in the pathogenesis of FCH [11,14] and is reported to be associated with abdominal fat among FCH individuals [21]. Several investigators have discovered the positive association of apo B with MetSyn and insulin resistance [21,35,36], but none, a specific gene [21]. However, the potential impact of lifestyle habits on the metabolic elements of MetSyn and FCH is demonstrated by O'Donovan et al [37], who stated that physically active subjects had lower levels of apo B compared with their sedentary counterparts. The lower levels of apo A among FCH subjects with MetSyn could be explained, from the proportionally lower levels of HDL particles, by definition of MetSyn.

FCH and MetSyn are highly overlapping entities, the treatment of which is quite similar. The results of our study demonstrated that the prevalence of MetSyn is higher among FCH patients than among the general population. In the FCH group, the prevalence of CAD was statistically positively related to DM. According to the data of our study, DM seems to further increase the already high cardiovascular burden of FCH, which implicates the screening of the general population for FCH and MetSyn. Moreover, the diagnosis and early treatment of DM and MetSyn (which is a precursor of DM) in all patients should be a physician's top priority.

4.1. Limitations

In both groups, diabetic patients were not included in MetSyn group. Subjects from the control group (ATTICA study) for whom there was evidence for cardiovascular disease (through the medical history) were excluded from the study population. This exclusion criterion might underestimate the prevalence of MetSyn; thus, subjects with CAD are more likely to meet the ATP-III criteria for MetSyn. However, the ATTICA study reported an overall prevalence of CAD of 3.8%; hence, the small number of the aforementioned subjects minimize this potential bias. In addition, the small number of FCH subjects (1% of the general population) who might have participated in the ATTICA study could not weaken the power of our statistical analysis.

It should be noted that lifestyle habits and the energy intake and expenditure were not taken into account in our study, which might underestimate the prevalence of obesity especially among older ages.

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