ELSEVIER

Atherosclerosis 190 (2007) 416–422

ATHEROSCLEROSIS

www.elsevier.com/locate/atherosclerosis

A comparison of the NCEP-ATPIII, IDF and AHA/NHLBI metabolic syndrome definitions with relation to early carotid atherosclerosis in subjects with hypercholesterolemia or at risk of CVD: Evidence for sex-specific differences ☆

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Received 21 November 2005; received in revised form 25 January 2006; accepted 2 February 2006
Available online 17 April 2006

Abstract

The metabolic syndrome is associated with increased risk of cardiovascular disease. However, the association between metabolic syndrome and atherosclerosis in hypercholesterolemic patients remains unknown. We examined the association between carotid atherosclerosis and metabolic syndrome definitions using the NCEP-ATPIII, International Diabetes Federation (IDF) and American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) definitions in 1782 subjects at risk of cardiovascular disease including 926 with hypercholesterolemia (LDL cholesterol ≥160 mg/dL; mean = 203 mg/dL).

Irrespective of definition, carotid intima-media thickness was significantly higher in both men and women diagnosed with the MetS compared to those without MetS. This relationship persists in males with hypercholesterolemia, independently of LDL cholesterol level. Regression analyses, both unadjusted and adjusted for traditional risk factors, indicate that in males the AHA/NHLBI definition, and in females the IDF definition are the strongest predictors of carotid atherosclerosis.

These results highlight important gender differences that exist in the current clinical definitions of the metabolic syndrome, with regards to predicting early atherosclerotic lesions. In addition, this study shows that in males with hypercholesterolemia, MetS is independently associated with increased atherosclerosis, supporting screening for MetS among people at risk of CVD.

Keywords: Metabolic syndrome; Atherosclerosis; Carotid; Intima-media; Hypercholesterolemia

1. Introduction

Approximately 40–50% of individuals aged over 60 years in industrialised countries meet the current criteria for the metabolic syndrome (MetS) [1]. Furthermore, the prevalence of the MetS is expected to increase in union with the current obesity epidemic, especially in younger people [2]. In 2001 the National Heart, Lung, and Blood Institute acting through the National Cholesterol Education Program—Third Adult Treatment Panel (NCEP-ATPIII) proposed a definition for diagnosis of the MetS [3]. This definition is now widely used in both clinical practice and research. In recently issued statements, the International Diabetes Federation (IDF) have proposed a new definition for the clinical diagnosis of the MetS,

☆ This study was partly financed by the "MC2 Club" (Cardiovascular Risk Management Club) of Pfizer France.
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doi:10.1016/j.atherosclerosis.2006.02.019

and the American Heart Association in conjunction with the National Heart, Lung, and Blood Institute (AHA/NHLBI) have proposed a revised version of the NCEP-ATPIII definition [4,5]. These three definitions all use the same five factors to form a diagnosis of the MetS-central obesity, raised fasting glucose, raised triglyceride level, reduced HDL cholesterol, and raised blood pressure. The IDF definition differs from the NCEP-ATPIII definition in the thresholds used for raised fasting glucose and central obesity. Additionally, central obesity (as diagnosed by increased waist circumference) is a compulsory factor of the MetS in the IDF definition [5]. The recent AHA/NHLBI statement makes only minor changes to the NCEP-ATPIII definition, most notably the lowering of the threshold for elevated fasting glucose. Additionally, both the IDF and AHA/NHLBI definitions seek to clarify the use of pharmacological treatments as components of the definition. All three definitions are sex-specific, with different thresholds for both waist circumference and HDL cholesterol between males and females.

The MetS is associated with an increased risk of clinical cardiovascular disease, even in the absence of heart disease and diabetes [6,7]. Both the IDF and AHA/NHLBI statements list identifying individuals at increased risk of cardiovascular events as a key objective in formulating their definitions of the MetS [4,5]. However, while the NCEP-ATPIII definition is associated with increased carotid atherosclerosis [8–11], the association between both the IDF and AHA/NHLBI definitions of the MetS and early carotid atherosclerosis have not yet been reported. Furthermore, there is little evidence as to whether MetS influences carotid atherosclerosis in hypercholesterolemic subjects.

Gender influences both the aetiology and clinical outcomes of the MetS. The two most-cited aetiological factors underlying the MetS are insulin resistance and obesity, both of which are influenced by gender [12,13]. Male gender is also a strong risk factor for cardiovascular disease [14]. Consequently, there is evidence that the strength of the association between the MetS and atherosclerosis is influenced by gender [11]. However, due to their gender-specific nature, this relationship may differ between definitions.

We thus sought to compare the association between early carotid atherosclerosis and the NCEP-ATPIII, IDF and AHA/NHLBI definitions of MetS in a large cohort of subjects with hypercholesterolemia or at risk for cardiovascular disease. We also examined whether there are sex-specific differences regarding the association between each definition of the MetS and early carotid atherosclerosis, with the goal to ascertain which definition best identifies individuals with increased early atherosclerosis.

2. Methods

2.1. Population

We studied 1782 consecutive patients between 30 and 80 years of age referred to our outpatient Centre for Prevention and Detection of Atherosclerosis in Lyon, France, between 1995 and 2000. All patents possessed at least one conventional cardiovascular risk factor with half of them (52%) being hypercholesterolemic (defined as a LDL cholesterol $\geq$160 mg/dL). All patients provided written informed consent.

2.2. Assessment of cardiovascular and metabolic risk factors

Blood pressure was measured at rest using an automatic sphygmomanometer. The average of three readings was used in these analyses.

Venous blood was sampled using standard venopuncture techniques, after the patient had fasted overnight. Analyses included HDL cholesterol, triglycerides, glucose and fibrinogen. LDL cholesterol was calculated using the Friedewald equation [15], except when triglycerides were >400 mg/dL, in which case LDL subfraction was measured directly.

A structured questionnaire was used to determine medical history, current medication use and smoking status, and was administered by a study physician. For analysis, smoking status was categorised into two groups: (1) subjects who never smoked and those who quit greater than 5 years ago; (2) current smokers and those who have quit within the previous 5 years.

2.3. NCEP-ATPIII metabolic syndrome definition

The NCEP-ATPIII definition of the MetS is defined as the presence of three or more of the following five factors—central obesity (waist circumference >102 cm for men, >88 cm for women), raised triglycerides ($\geq$150 mg/dL), raised blood pressure (BP $\geq$ 130 mmHg/BP $\geq$ 85 mmHg), raised fasting glucose ($\geq$110 mg/dL) and reduced HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women) [3].

Previous diagnosis with type 2 diabetes was included as evidence of raised fasting glucose.

2.4. IDF metabolic syndrome definition

The IDF definition of the MetS consists of the same five factors as the NCEP-ATPIII definition, however with different values for the classification of increased waist circumference and fasting glucose. Additionally, for a diagnosis of the MetS using the IDF definition, central obesity must be present, in addition to two or more of the other four factors. The IDF categories are: waist circumference $\geq$94 cm for men, and $\geq$80 cm for women; triglycerides $\geq$150 mg/dL; systolic BP $\geq$ 130 mmHg or diastolic BP $\geq$ 85 mmHg; fasting glucose $\geq$100 mg/dL; and HDL <40 mg/dL in men, and <50 mg/dL in women [5].

Furthermore, the IDF definition stipulates that all individuals receiving pharmacologic treatment for hypertension, hypertriglyceridemia or low HDL cholesterol, and all individuals previously diagnosed with type 2 diabetes, be considered as possessing those factors. In France, fibrates are principally used to treat hypertriglyceridaemia, and thus fibrate use was treated as evidence of hypertriglyceridaemia only.

2.5. AHA/NHLBI metabolic syndrome definition

The AHA/NHLBI definition of the MetS consists of the same five factors as the NCEP-ATPIII and IDF definitions, with the principal change from the NCEP-ATPIII definition being the use of the same lower threshold for fasting glucose as used by in the IDF definition. Thus, the AHA/NHLBI categories are: central obesity (waist circumference ≥102 cm for men, ≥88 cm for women), raised triglycerides (≥150 mg/dL), raised blood pressure (BP ≥ 130/≥85 mmHg), raised fasting glucose (≥100 mg/dL) and reduced HDL cholesterol (<40 mg/dL for men, <50 mg/dL for women) [4].

As stipulated by the definition we included all individuals receiving pharmacologic treatment for hypertension as having raised blood pressure, all subjects receiving fibrates as possessing both raised triglycerides and reduced HDL cholesterol, and all subjects previously diagnosed with type 2 diabetes as having raised fasting glucose.

2.6. Carotid intima-media thickness and presence of plaques

Carotid intima-media thickness (IMT) was investigated as previously described by ourselves and others [16,17]. Briefly, longitudinal scans of both the left and right common carotid arteries were performed using high-resolution ultrasound. IMT was assessed in the segment of artery within 1 cm of the bifurcation. The average of both left and right carotid arteries was used for the statistical analyses. The presence of carotid arterial plaques was assessed in the distal portion of the common carotid artery and the carotid bulb. A plaque was defined as a focal protrusion into the lumen, or an IMT ≥1.5 mm.

These techniques have been previously demonstrated to have good inter- and intra-observer variability in our laboratory [16].

2.7. Statistical analyses

Statistical significance was inferred at $p < 0.05$. The cohort was analysed by gender due to the gender-specific nature of the HDL cholesterol and abdominal obesity components of the MetS definitions. Student's *t*-tests were used to compare continuous variables between MetS and non-MetS groups. Chi-square analyses were used for nominal variables. Multiple and logistic regression analyses were undertaken to determine the influence of both MetS and its individual components on carotid atherosclerosis. Both unadjusted analyses, and analyses using regression models including age, smoking status and LDL cholesterol were performed. To test whether the relationship between MetS and carotid atherosclerosis was modified by gender we used a test of interaction as previously described [18]. Positive and negative likelihood ratios were calculated as previously described [19].

Statistical analyses were undertaken using StatView for Windows (version 5.0, SAS Institute Inc., NC).

3. Results

The MetS was present in 927 of 1782 (52.0%) subjects according to the NCEP-ATPIII definition, 1078 (60.5%) according to the IDF definition, and in 1131 (63.5%) according to the AHA/NHLBI definition. Table 1 presents clinical and biological characteristics of all study participants and in the subgroup with hypercholesterolemia.

Irrespective of definition, carotid IMT was significantly higher in both men and women diagnosed with the MetS compared to those without MetS (Table 2). In men, all definitions of the MetS were associated with a greater incidence of increased IMT (greater than or equal to the sex-specific

Table 1
Patient characteristics for entire cohort and subgroup with hypercholesterolemia

	Entire cohort		Hypercholesterolemic subgroup	
	Males	Females	Males	Females
Number	1101	681	558	368
Age (years)	50.9 (9.6)	54.3 (9.8)	50.0 (9.2)	54.9 (9.9)
Smoking (%)	46.9	26.3	48.0	25.5
Prior CVD (%)	15.3	11.5	11.8	8.7
LDL cholesterol (mg/dL)	165 (51)	170 (53)	202 (42)	205 (44)
BMI (kg/m^2)	28.6 (4.8)	28.5 (6.4)	27.9 (4.5)	27.6 (5.9)
Waist circumference (cm)	101.0 (12.6)	94.3 (16.0)	99.0 (12.1)	92.2 (16.0)
HDL cholesterol (mg/dL)	45 (14)	56 (17)	46 (13)	58 (17)
Triglycerides (mg/dL)	203 (162)	159 (99)	189 (140)	156 (81)
SBP (mmHg)	139.7 (18.2)	136.0 (18.7)	138.4 (18.7)	135.1 (18.5)
DBP (mmHg)	86.5 (11.0)	82.6 (11.1)	85.7 (11.0)	82.0 (10.9)
Glucose (mg/dL)	114 (48)	105 (44)	107 (39)	101 (43)
Fibrinogen (g/L)	3.25 (0.81)	3.41 (0.75)	3.25 (0.84)	3.45 (0.73)

Data presented as mean (S.D.) unless otherwise indicated.

Table 2
Carotid atherosclerosis by gender and metabolic syndrome definition

	All subjects	NCEP-ATPIII		IDF		AHA/NHLBI	
		Yes	No	Yes	No	Yes	No
Males							
Number	1101	588	513	671	430	724	377
IMT (mm)	0.831 (0.175)	0.843 (0.174)	0.817 (0.174)*	0.843 (0.170)	0.812 (0.180)†	0.841 (0.174)	0.813 (0.175)*
IMT ≥ median (%)	51.9	56.0	46.6†	55.7	45.1‡	55.4	44.3‡
Plaque (%)	32.9	36.2	29.1*	34.8	30.0	35.9	27.2†
Females							
Number	681	339	342	407	274	407	274
IMT (mm)	0.770 (0.162)	0.785 (0.172)	0.755 (0.150)*	0.791 (0.160)	0.740 (0.161)#	0.787 (0.169)	0.746 (0.149)†
IMT ≥ median (%)	52.0	55.3	48.7	57.7	43.4‡	55.8	46.4*
Plaque (%)	26.4	29.9	23.0*	30.2	20.9‡	29.6	21.8*

Data presented as mean (S.D.) unless otherwise indicated.
* $p \leq 0.05$.
# $p \leq 0.0001$.
† $p \leq 0.01$.
‡ $p \leq 0.001$.

median), however only the NCEP-ATPIII and AHA/NHLBI MetS definitions were associated with an increased prevalence of plaques. In female subjects, only the IDF and AHA/NHLBI definitions were associated with IMT greater than the median, whereas all definitions of the MetS were associated with an increased presence of carotid plaques.

In univariate analyses in both sexes, the MetS was significantly associated with carotid IMT using all three definitions (males: NCEP-ATPIII $\beta = 0.026$ [$p = 0.01$], IDF $\beta = 0.031$ [$p = 0.005$], AHA/NHLBI $\beta = 0.028$ [$p = 0.01$]; females: NCEP-ATPIII $\beta = 0.030$ [$p = 0.02$], IDF $\beta = 0.051$ [$p < 0.0001$], AHA/NHLBI $\beta = 0.041$ [$p = 0.001$]). However, in multivariate analysis, after adjusting for age, LDL-cholesterol and smoking status, no MetS definition was significantly associated with IMT in males, and in females only the IDF definition remained statistically significant (males: NCEP-ATPIII $\beta = 0.016$ [$p = 0.10$], IDF $\beta = 0.011$ [$p = 0.27$], AHA/NHLBI $\beta = 0.015$ [$p = 0.13$]; females: NCEP-ATPIII $\beta = 0.013$ [$p = 0.28$], IDF $\beta = 0.029$ [$p = 0.01$], AHA/NHLBI $\beta = 0.017$ [$p = 0.15$]).

Logistic regression analyses indicate that in males the AHA/NHLBI definition, and in females the IDF definition, were the definitions the most strongly associated with IMT ≥ median (males: NCEP-ATPIII OR = 1.46 [95% CI 1.15–1.85, $p = 0.002$], IDF OR = 1.53 [95% CI 1.20–1.95, $p = 0.0006$], AHA/NHLBI OR = 1.56 [95% CI 1.22–2.01, $p = 0.0005$]; females: NCEP-ATPIII OR = 1.30 [95% CI 0.96–1.76, $p = 0.09$], IDF OR = 1.78 [95% CI 1.31–2.43, $p = 0.0003$], AHA/NHLBI OR = 1.46 [95% CI 1.07–1.99, $p = 0.02$]). Furthermore, the AHA/NHLBI definition and the IDF definition were also the strongest definitions for predicting the presence of carotid atherosclerotic plaques in males and females respectively (males: NCEP-ATPIII OR = 1.38 [95% CI 1.07–1.79, $p = 0.01$], IDF OR = 1.24 [95% CI 0.96–1.62, $p = 0.10$], AHA/NHLBI OR = 1.50 [95% CI 1.14–1.97, $p = 0.004$]; females: NCEP-ATPIII OR = 1.43 [95% CI 1.01–2.01, $p = 0.04$], IDF OR = 1.64 [95% CI 1.14–2.36, $p = 0.007$], AHA/NHLBI OR = 1.51 [95% CI 1.05–2.16, $p = 0.03$]). These associations remained significant after adjusting for major cardiovascular risk factors, including LDL cholesterol level (Fig. 1).

All three definitions were then incorporated into the same regression analyses to determine if one definition was superior to the others with respect to the association with atherosclerosis. In males, no definition had a significantly greater association with either IMT or IMT ≥ median (IMT: NCEP-ATPIII $\beta = 0.012$ [$p = 0.44$], IDF $\beta = -0.001$ [$p = 0.97$], AHA/NHLBI $\beta = 0.006$ [$p = 0.73$]; IMT ≥ median: NCEP-ATPIII OR = 1.10 [$p = 0.64$], IDF OR = 1.04 [$p = 0.85$], AHA/NHLBI OR = 1.33 [$p = 0.21$]). However there was a statistical trend towards a relationship between carotid arterial plaques and the AHA/NHLBI definition in males (NCEP-ATPIII OR = 1.19 [$p = 0.44$], IDF OR = 0.71 [$p = 0.08$], AHA/NHLBI OR = 1.56 [$p = 0.08$]). In contrast, the IDF definition was strongly associated with IMT and IMT ≥ median in females (IMT: NCEP-ATPIII $\beta = -0.015$ [$p = 0.48$], IDF $\beta = 0.061$ [$p = 0.01$], AHA/NHLBI $\beta = -0.024$ [0.37]; IMT ≥ median: NCEP-ATPIII OR = 0.70 [$p = 0.23$], IDF OR = 3.39 [$p = 0.001$], AHA/NHLBI OR = 0.54 [$p = 0.12$]). A similar trend was evident for the association with carotid plaques, however this was not statistically significant (NCEP-ATPIII OR = 1.18 [$p = 0.61$], IDF OR = 1.71 [$p = 0.17$], AHA/NHLBI OR = 0.69 [$p = 0.37$]).

We used a test of interaction to formally test whether these associations between each MetS definition and atherosclerosis were modified by gender. There was no evidence to suggest that the association between the NCEP-ATPIII definition and carotid atherosclerosis was different between males and females (IMT $p = 0.30$, IMT ≥ median $p = 0.22$, plaque $p = 0.98$). In contrast the relationship between the IDF definition and all three endpoints was modified by gender (IMT $p = 0.03$, IMT ≥ median $p = 0.005$, plaque $p = 0.04$). There was also evidence of interaction by gender for

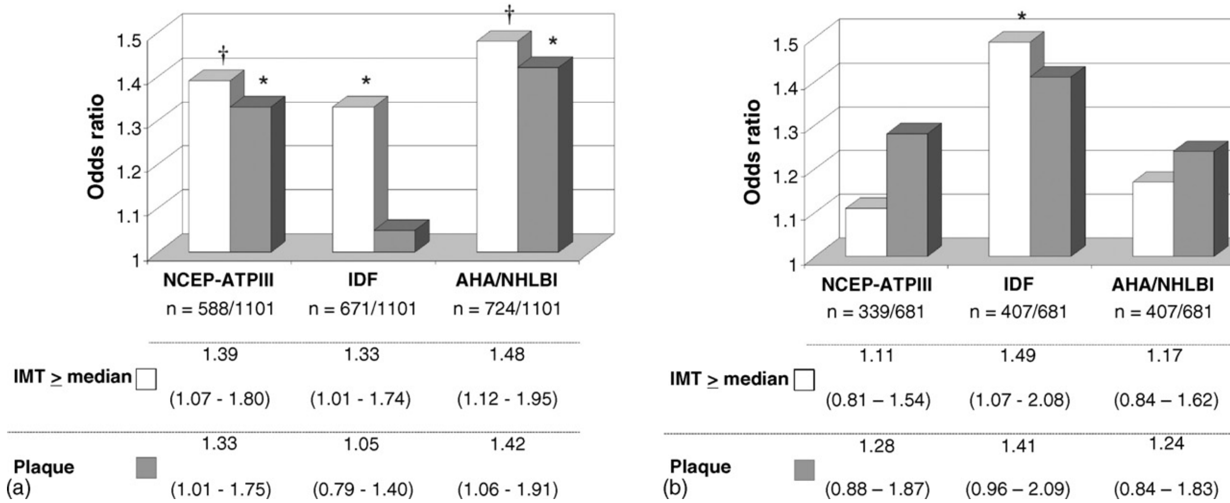

Fig. 1. Association of IDF, NCEP-ATPIII and AHA/NHLBI metabolic syndrome with carotid atherosclerosis in (a) males, and (b) females. IMT ≥ median and plaque analysed using logistic regression analyses. All models include age, smoking status and LDL cholesterol. Results displayed as OR (95% CIs). $^{*}p \leq 0.05$, $^{\dagger}p \leq 0.01$.

the association between the AHA/NHLBI definition and IMT ≥ median and possibly the presence of plaques (IMT $p = 0.34$, IMT ≥ median $p = 0.05$, plaque $p = 0.10$).

We calculated both the positive and negative likelihood ratios for the three definitions using unadjusted IMT ≥ median and presence of plaque data. In males there was little evidence for any differences between the three definitions, except that the IDF definition appeared weaker in the plaque analyses (IMT ≥ median: NCEP-ATPIII 1.19/0.82, IDF 1.18/0.77, AHA/NHLBI 1.16/0.75; plaque: NCEP-ATPIII 1.16/0.84, IDF 1.09/0.87, AHA/NHLBI 1.14/0.76 for positive/negative likelihood ratios). In females, the IDF definition has both a higher positive and lower negative likelihood ratio than the other definitions for both increased IMT and presence of plaques (IMT ≥ median: NCEP-ATPIII 1.14/0.88, IDF 1.26/0.71, AHA/NHLBI 1.16/0.80; plaque: NCEP-ATPIII 1.20/0.82, IDF 1.21/0.74, AHA/NHLBI 1.17/0.78 for positive/negative likelihood ratios).

Excluding subjects with previous cardiovascular disease from the analyses did not alter the general trend of the results. For example, the IDF definition was still the strongest definition for predicting increased IMT in females (NCEP-ATPIII: OR = 1.17; IDF: OR = 1.56; AHA/NHLBI: OR = 1.20 after adjustment for age, smoking status and LDL cholesterol), as was the AHA/NHLBI definition for predicting the presence of carotid plaques in males (NCEP-ATPIII: OR = 1.26; IDF: OR = 0.98; AHA/NHLBI OR = 1.34 after adjustment for age, smoking status and LDL cholesterol). Similarly, altering the IDF definition such that the use of fibrates fulfils both the reduced HDL cholesterol and raised triglycerides criteria, as in the AHA/NHLBI definition, resulted in only minor changes to these results (males: IMT ≥ median OR = 1.34, plaque OR = 1.05; females: IMT ≥ median OR = 1.40, plaque OR = 1.37, after adjustment for age, smoking status and LDL cholesterol).

To provide insight on possible explanations for these differences between definitions, multivariate regression analyses incorporating the five components of the MetS were used to identify which components from each definition were independently associated with carotid atherosclerosis. These analyses identified blood pressure as the primary MetS component associated with atherosclerosis in both males and females (males: IMT and plaque $p < 0.0001$ for all definitions, IMT ≥ median $p < 0.001$ for all definitions; females: IMT and IMT ≥ median $p < 0.0001$ for all definitions, plaque NCEP-ATPIII $p = 0.02$, IDF $p = 0.003$, AHA/NHLBI $p = 0.001$). In males but not females, the impaired fasting glucose component was also strongly associated with carotid atherosclerosis (males: $p < 0.0001$ for all definitions; females: $p > 0.10$ for all definitions). Additionally abdominal obesity using the IDF criteria was associated with IMT ≥ median in females ($p = 0.05$). In contrast, in males both the abdominal obesity and HDL cholesterol components were negatively associated with the presence of carotid arterial plaques (abdominal obesity: NCEP-ATPIII $p = 0.007$, IDF $p = 0.09$, AHA/NHLBI $p = 0.003$; HDL cholesterol: NCEP-ATPIII $p = 0.01$, IDF $p = 0.02$, AHA/NHLBI $p = 0.17$). All other associations were non-significant ($p > 0.10$).

In the subgroup with marked hypercholesterolemia (mean LDL cholesterol of 203 mg/dL), MetS was associated with an elevated IMT and the presence of carotid plaques, however this is dependent on the definition of MetS used (males IMT: NCEP-ATPIII $p = 0.02$, IDF $p = 0.004$, AHA/NHLBI $p = 0.04$; males plaque: NCEP-ATPIII $p = 0.06$, IDF $p = 0.45$, AHA/NHLBI $p = 0.05$; females IMT: NCEP-ATPIII $p = 0.65$, IDF $p = 0.008$, AHA/NHLBI $p = 0.10$; females plaque: NCEP-ATPIII $p = 0.06$, IDF $p = 0.18$, AHA/NHLBI $p = 0.32$).

Regression analyses in the hypercholesterolemic subgroup reveal that in males the predictive value of the MetS after adjustment for other risk factors, was similar to that exhibited by the entire cohort (IMT ≥ median: NCEP-ATPIII OR = 1.45 [95% CI 1.01–2.07, p = 0.04], IDF OR = 1.35 [95% CI 0.94–1.92, p = 0.10], AHA/NHLBI OR = 1.52 [95% CI 1.06–2.18, p = 0.02]; plaque: NCEP-ATPIII OR = 1.35 [95% CI 0.93–1.97, p = 0.12], IDF OR = 1.01 [95% CI 0.69–1.47, p = 0.97], AHA/NHLBI OR = 1.42 [95% CI 0.97–2.10, p = 0.07], after adjustment for age, smoking status and LDL cholesterol). However, in hypercholesterolemic females, the associations between MetS and carotid atherosclerosis were generally weaker than those seen in the entire cohort (IMT ≥ median: NCEP-ATPIII OR = 0.76 [95% CI 0.49–1.19, p = 0.24], IDF OR = 1.18 [95% CI 0.75–1.84, p = 0.48], AHA/NHLBI OR = 0.84 [95% CI 0.54–1.32, p = 0.46]; plaque: NCEP-ATPIII OR = 1.34 [95% CI 0.80–2.25, p = 0.27], IDF OR = 1.13 [95% CI 0.66–1.91, p = 0.66], AHA/NHLBI OR = 1.02 [95% CI 0.60–1.72, p = 0.95], after adjustment for age, smoking status and LDL cholesterol).

4. Discussion

The present study investigated for the first time the association between the recently proposed IDF and AHA/NHLBI definitions of the MetS with early carotid atherosclerosis in a large cohort of subjects either with hypercholesterolemia or at risk of cardiovascular disease.

As with previous studies, assessment of MetS using the IDF criteria identified a higher number of subjects than the NECP-ATPIII definition [20–22]. In comparison with the IDF definition, the AHA/NHLBI definition diagnosed a similar number of females, and a greater number of males.

In addition to diagnosing increased numbers of subjects, our findings show that individuals diagnosed using the IDF or AHA/NHLBI definitions of the MetS have greater subclinical carotid atherosclerosis than those without MetS, suggesting a greater risk of cardiovascular disease. Similar results were observed when considering the diagnosis of MetS according to the NCEP-ATPIII definition, which is in agreement with a large body of evidence showing increased early atherosclerosis in subjects with NCEP-ATPIII MetS [8–11].

Our findings highlight some gender-related differences in the extent of subclinical atherosclerosis associated with the different MetS definitions. In males the IDF definition diagnosed substantially more patients than the NCEP-ATPIII definition. Yet in the regression analyses, the IDF definition was arguably a weaker predictor of carotid atherosclerosis. On the other hand, the AHA/NHLBI definition not only diagnosed substantially more patients than the NCEP-ATPIII definition, but also the regression analyses revealed that this definition was a strong predictor of carotid atherosclerosis in men. These results indicate that the AHA/NHLBI definition best identifies males with increased carotid atherosclerosis and therefore who are at a high risk of CVD. A different pattern is evident in females. The IDF and AHA/NHLBI definitions both diagnosed the same number of females with the MetS, although these were not all the same subjects. The AHA/NHLBI definition provided similar results in the regression analyses to the NCEP-ATPIII definition, both of which were not as powerful at predicting carotid atherosclerosis as the IDF definition. This is supported by the likelihood ratios analyses, where the IDF definition consistently performed better than either of the other definitions. Thus our results suggest that the IDF definition of the MetS may be a better tool for the identification of females with elevated atherosclerosis than either the NCEP-ATPIII or AHA/NHLBI definitions. This may relate to the inclusion of abdominal obesity as a prerequisite for diagnosis of the MetS according to the IDF definition. Indeed the abdominal obesity component of the IDF definition was independently associated with increased IMT in females, but not in males. Thus the inclusion of abdominal obesity as a prerequisite in the IDF definition should act to strengthen the association between the MetS and increased IMT in females.

A recent report showed gender differences in the relation between MetS and subclinical atherosclerosis, with MetS being a stronger risk factor for carotid atherosclerosis in women than in men [6,7]. However, in this study, MetS was only defined according to the NCEP-ATPIII definition and the authors did not compare the predictive value of each definition.

Our findings relating to the associations between the IDF and AHA/NHLBI definitions with early carotid atherosclerosis are of clinical importance as both definitions have been designed specifically for clinical use to identify those subjects at risk of cardiovascular disease, a role previously filled by the NCEP-ATPIII definition. To our knowledge, there are no previous reports that describe the cardiovascular predictive value of these recently proposed MetS definitions.

The present study also shows that the presence of MetS is associated with increased atherosclerosis burden among males with marked hypercholesterolemia. These findings suggest that the MetS may be considered as a valuable cardiovascular disease risk marker in men both with and without severe hypercholesterolemia, and thus support the use of clinical screening for MetS among males already known to be at risk of cardiovascular disease. In females, the MetS was a weaker predictor of carotid atherosclerosis in hypercholesterelemic subjects compared with the entire cohort. Thus, in contrast to our findings in males, our results suggest that in hypercholesterolemic females screening for the MetS provides little benefit in identifying subjects at risk for cardiovascular disease. While our study provides no mechanistic explanation for this gender disparity, it is tempting to speculate that this finding may relate to either gender-specific differences in the association between LDL cholesterol and atherosclerosis [23], or a lower impact of insulin resistance on cardiovascular events in women than in men [24]. This latter argument is supported by our findings that the impaired fasting glucose component of the MetS was only an independent predictor of carotid atherosclerosis in males.

The present study has several limitations. Our cohort consists of patients at risk of CVD with at least one cardiovascular risk factor referred to an “atherosclerosis detection and prevention” clinic. Correspondingly, the proportion of individuals with MetS is also greater in our cohort than observed in the French population [25]. Thus, our findings relate to subjects at increased risk for both elevated levels of atherosclerosis and cardiovascular events and may not be applicable to the general population.

While carotid IMT is used extensively as a measure of subclinical atherosclerosis and is related to future risk of clinical cardiovascular events [26,27] additional prospective clinical studies are required to determine the ability of each of these MetS definitions to predict the occurrence of ischaemic heart disease in both males and females.

In conclusion, the MetS is associated with early carotid atherosclerosis in subjects at risk of cardiovascular disease including those with hypercholesterolemia, suggesting a clinical role for identifying people with subclinical atherosclerotic lesions. However, important sex-specific differences exist, with the AHA/NHLBI definition being more strongly associated with carotid atherosclerosis in males, and the IDF definition being a better predictor of early atherosclerosis in females.

Acknowledgments

We are indebted to the nurses (P. Serra, G. Chany), dieticians (E. Gallindo, J. Masson) and the medical staff who were in charge of the patients at our Centre (S. Bernard, C. Bully, L. Groisne, D. Honnorat, F. Labrousse, S. Marsot, L. Perrot, C. Sagot).

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