Relation Between Atherogenic Dyslipidemia and the Adult Treatment Program-III Definition of Metabolic Syndrome (Genetic Epidemiology of Metabolic Syndrome Project)

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Genetic Epidemiology of Metabolic Syndrome is a multinational, family-based study to explore the genetic basis of the metabolic syndrome. Atherogenic dyslipidemia (defined as low plasma high-density lipoprotein cholesterol with elevated triglycerides (<25th and >75th percentile for age, gender, and country, respectively) identified affected subjects for the metabolic syndrome. This report examines the frequency at which atherogenic dyslipidemia predicts the metabolic syndrome of the National Cholesterol Education Program Adult Treatment Panel III (ATP-III). One thousand four hundred thirty-six (854 men/582 women) affected patients by our criteria were compared with 1,672 (737 men/935 women) unaffected persons. Affected patients had more hypertension, obesity, and hyperglycemia, and they met a higher number of ATP-III criteria (3.2 ± 1.1 SD vs 1.3 ± 1.1 SD, p <0.001). Overall, 76% of affected persons also qualified for the ATP-III definition (Cohen's κ 0.61, 95% confidence interval 0.59 to 0.64), similar to a separate group of 464 sporadic, unrelated cases (75%). Concordance increased from 41% to 82% and 88% for ages ≤35, 36 to 55, and ≥55 years, respectively. Affected status was also independently associated with waist circumference (p <0.001) and fasting glucose (p <0.001) but not systolic blood pressure (p = 0.43). Thus, the lipid-based criteria used to define affection status in this study substantially parallels the ATP-III definition of metabolic syndrome in subjects aged >35 years. In subjects aged <35 years, atherogenic dyslipidemia frequently occurs in the absence of other metabolic syndrome risk factors. ©2005 by Excerpta Medica Inc.

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The present report is derived from the Genetic Epidemiology of Metabolic Syndrome project. This is a large, multinational, family-based study exploring the genetic basis of the metabolic syndrome. Two simple lipid-based criteria were used to define the affection status: elevated triglycerides and concomitant low high-density lipoprotein (HDL) cholesterol. These criteria were used because they are (1) primary features of atherogenic dyslipidemia, (2) associated with insulin resistance, (3) detectable early in the development of metabolic syndrome, (4) individually highly heritable, and (5) easy to measure. The essential question addressed was how strongly familial atherogenic dyslipidemia is associated with other components of the metabolic syndrome as defined by the ATP-III.[1] The analysis thus was designed to determine whether most instances of atherogenic dyslipidemia occur together with the metabolic syndrome or as an isolated dyslipidemia.

METHODS

Accrual centers in Australia, Canada, Finland, Switzerland, Turkey, and the United States participated in this study. Analysis was performed in the epidemiology center in Boston University. Caucasian participants (aged 18 to 70 years) were considered affected if they had both plasma triglycerides ≥75th

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TABLE 1 Plasma Triglycerides and High-density Lipoprotein (HDL) Cholesterol Values Corresponding to Triglycerides ≥75th Percentile and HDL in ≤25th Percentile for Specific Ages by Sex and Site*

	Australia		Canada		Finland		Switzerland		Turkey		United States	
	TG	HDL	TG	HDL	TG	HDL	TG	HDL	TG	HDL	TG	HDL
Male Subjects												
Age (yrs)												
20	133	43	130	39	98	46	124	41	109	35	138	39
30	151	39	154	39	148	41	124	41	155	35	159	40
40	195	39	193	39	178	41	133	42	191	35	198	36
50	204	39	202	39	198	40	151	43	189	35	194	37
60	204	39	201	39	190	40	151	43	168	35	184	37
70	195	39	198	39	190	40	151	39	120	35	174	37
Female Subjects												
Age (yrs)												
20	124	46	121	46	94	52	106	54	83	40	116	45
30	115	46	118	46	110	51	106	53	110	40	129	44
40	124	46	120	46	112	50	106	52	136	40	145	44
50	168	46	170	46	133	49	115	54	165	40	183	45
60	186	46	182	46	161	49	124	51	146	40	195	46
70	195	46	197	46	161	49	124	51	145	40	171	46

*The youngest participants in both Switzerland and Australia were 18 years of age.

Despite both Australia and the United States using NHANES data to calculate percentiles, the cutpoints were originally calculated using different age groupings, resulting in slightly different cutpoints by country.

Values are expressed as milligrams per deciliter.

percentile and serum HDL cholesterol ≤25th percentile, both adjusted for age and gender. Those meeting the criteria will be referred to throughout as affected by current criteria. Lipid values were either currently obtained (80%) or obtained up to 3 years before entry (20%). Population values vary in different countries; in particular, HDL levels in Turkey are lower.[2] Thus, cut points were defined by national databases. The following sources were used for different sites: Australia (National Health and Nutrition Examination Survey [NHANES III] survey website [http://www.cdc.gov/nchs/about/major/nhanes/nh3data.htm]); Canada (for subjects ≥18 years, Canadian Heart Health Surveys 1986 to 1992 data,[3] and for younger subjects, Lipid Research Clinics prevalence study),[4] Finland, cardiovascular risk factor data[5]; Switzerland, Geneva database on the epidemiology of cardiovascular risk factors in public servants, Turkey [Turkish Heart Study],[6] and United States (NHANES III survey as mentioned). Age and gender cut points for the 75th percentiles for triglyceride and HDL cholesterol levels for each study site are listed in Table 1.

Subjects were excluded if they (1) had a fasting blood glucose levels ≥126 mg/dl (probands only), (2) had a body mass index ≥35 kg/m^2, (3) were positive for human immunodeficiency virus, (4) were recipients of an organ transplant, (5) had familial hypercholesterolemia, or (6) were heavy alcohol users (>8 U/day). The minimal unit for collection of a family was an affected sib-pair, but larger nuclear or extended families were collected if possible. In a small number of instances, some patients originally believed to be affected, on closer examination turned out not to be affected, leading to a small proportion of families with only 1 affected. An additional 464 singly-ascertained patients were recruited from the same sites with the same lipid phenotype as that used for the family collection. The institutional review board at each participating site approved the protocol and informed consent forms.

A standardized questionnaire was administered to every family member. In addition to demographic data, it captured co-morbid conditions, medications, tobacco, and alcohol. Height, weight, and waist circumference, as well as 3 blood pressure measurements, were obtained for each subject. The average of the second and third systolic and diastolic blood pressure readings was used in the analyses. Blood was collected after a 12-hour fast. Laboratory tests for the lipids and glucose levels were performed according to standard procedures.

Statistical analyses were performed using SAS version 8 (SAS Institute, Cary, North Carolina) and Stata version 8. Descriptive statistics are expressed as number (percent) or mean ± SD, except for triglyceride levels and blood pressure measurements, which are expressed as medians. Statistical significance was determined using univariate logistic regression for continuous variables or a chi-square test for categorical variables. For the linear regression analysis, PROC GLM in SAS (SAS Institute) was used; waist circumference, fasting glucose, and systolic blood pressure were treated as continuous variables and currently affected status was a categorical variable.

RESULTS

In all, 3,273 patients from 504 families were recruited in the study. The 6 accrual centers contributed 33 to 136 families, and the size of the families ranged from 2 to 179. Of 3,273 participants from the family

TABLE 2 Characteristics of Participants Based on the Genetic Epidemiology of Metabolic Syndrome Criteria*

Variable	Men		Women	
	Affected (n = 854)	Unaffected (n = 737)	Affected (n = 582)	Unaffected (n = 935)
Age (yrs)	45.9 ± 14.0	40.4 ± 18.4§	45.3 ± 16.4	42.1 ± 18.0§
Ever smoked	541 (63%)	392 (53%)§	244 (42%)	326 (35%)‖
Current smoker	229 (26%)	210 (29%)§	105 (18%)	151 (16%)
No. of cigarettes/d	21.2 ± 14.3	19.3 ± 13.1	15.5 ± 11.3	12.5 ± 9.4‖
No. of alcoholic drinks/wk	5.5 ± 6.7	5.3 ± 6.4	3.6 ± 3.8	4.1 ± 5.5
Waist circumference (cm)	100.2 ± 12.0	90.0 ± 14.4§	91.5 ± 14.0	81.7 ± 12.9§
High waist circumference >102 cm (M), 88 cm (F)	333 (41%)	121 (17%)§	332 (60%)	270 (30%)§
Waist-to-hip ratio	0.94 ± 0.06	0.89 ± 0.08§	0.85 ± 0.08	0.82 ± 0.09§
Body mass index (kg/m^2)	28.2 ± 3.9	25.1 ± 4.4§	28.1 ± 4.7	24.7 ± 4.5§
Body mass index ≥30 kg/m^2	291 (34%)	96 (13%)§	211 (36%)	128 (14%)§
Diagnosed diabetes mellitus	75 (9%)	25 (3%)§	60 (11%)	19 (2%)§
Diagnosed systemic hypertension	275 (32%)	110 (15%)§	198 (34%)	148 (16%)§
Taking blood pressure medication	208 (24%)	74 (10%)	165 (28%)	108 (12%)§
Blood pressure (median, mm Hg)	133/84	128/80§	131/83	129/79§
Elevated blood pressure†	583 (69%)	378 (53%)§	380 (67%)	422 (46%)§
Taking lipid-altering medication	282 (33%)	64 (9%)§	140 (24%)	60 (7%)§
Total cholesterol (mg/dl)	211.9 ± 56.1	188.2 ± 46.0§	210.0 ± 49.6	192.6 ± 43.9§
HDL cholesterol (mg/dl)	32.4 ± 5.4	46.0 ± 11.4§	37.3 ± 6.5	57.0 ± 14.0§
HDL cholesterol <40 mg/dl (M), <50 mg/dl (F)	829 (97%)	221 (30%)§	573 (98%)	290 (31%)§
LDL cholesterol (mg/dL)	118.2 ± 40.5	118.1 ± 39.9	121.8 ± 42.8	114.8 ± 38.1‖
Triglycerides (median, mg/dl)	265.5	109.0§	215.0	88.7§
Triglycerides (≥150 mg/dl)	796 (93%)	190 (26%)§	476 (82%)	129 (14%)§
Fasting glucose (mg/dl)	99.6 ± 23.5	91.9 ± 17.9§	99.0 ± 31.3	88.3 ± 16.8§
Glucose ≥110 mg/dl‡	143 (17%)	52 (7%)§	84 (15%)	32 (3%)§

*The Genetic Epidemiology of Metabolic Syndrome plasma lipid criteria: triglycerides ≥75th percentile, HDL cholesterol ≤25th percentile (age-adjusted, country and gender-specific).
†Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg.
‡Does not include treated diabetics
§p ≤0.05; ‖p ≤0.01; §p ≤0.001 versus affected subjects.
Values are expressed as number (%) or mean ± SD.
ATP-III criteria to define metabolic syndrome are depicted in italics.

TABLE 3 Characteristics of Singly-ascertained Cases

Variable	Cases (n = 464)
Men	340 (73%)
Age (yrs)	50.6 ± 8.6
Ever smoked	295 (64%)
Current smoker	109 (24%)
No. of cigarettes/d	21.0 ± 13.3
No. of alcoholic drinks/wk	NA
Waist circumference (cm)	97.6 ± 15.3
High waist circumference >102 cm (M), >88 cm (W)	230 (50%)
Waist-to-hip ratio	0.92 ± 0.07
Body mass index (kg/m^2)	28.9 ± 3.3
Body mass index ≥30 kg/m^2	179 (39%)
Diagnosed hypertension	160 (34%)
Blood pressure (median, mm Hg)	132/81
Elevated blood pressure	279 (60%)
Taking lipid medication	206 (45%)
Total cholesterol (mg/dl)	221.9 ± 45.3
HDL cholesterol (mg/dl)	35.7 ± 6.2
HDL cholesterol <40 mg/dl (M), <50 mg/dl (W)	429 (92%)
LDL cholesterol (mg/dl)	132.1 ± 45.3
Triglycerides (median, mg/dl)	310.7
Triglycerides ≥150 mg/dl	443 (95%)
Fasting glucose (mg/dl)	96.1 ± 11.2
Glucose ≥110 mg/dl	43 (11%)

Values are presented as number percentage or mean ± SD.
LDL = low-density lipoprotein.

dataset, 1,436 (44%) were considered as affected using the current definition, 1,672 (51%) were unaffected, and the remaining 165 patients (5%) were considered unknown due to absence of reliable measurements of either HDL cholesterol or triglycerides and thus were excluded from analysis. The clinical characteristics of the 1,436 (854 men/582 women) affected and the 1,672 (737 men/935 women) unaffected family members, as well as the proportion of these patients who met each patient ATP-III criterion, are listed in Table 2. Age, waist circumference, waist-to-hip ratio, body mass index, the proportion of obese patients, blood pressure, and the proportion of hypertensive subjects, blood glucose levels, and proportion of persons with blood glucose levels >110 mg/dl were all significantly higher among affected versus unaffected men and women ($p < 0.001$). These differences were not due to differences in alcohol consumption or current cigarette smoking. In addition, a separate set of 464 unrelated patients was ascertained based on the same criteria as the familial subjects, except that they were not required to have an affected relative. The characteristics of this singly-ascertained group are listed in Table 3.

To explore the concordance between the current and the ATP-III definitions for metabolic syndrome,

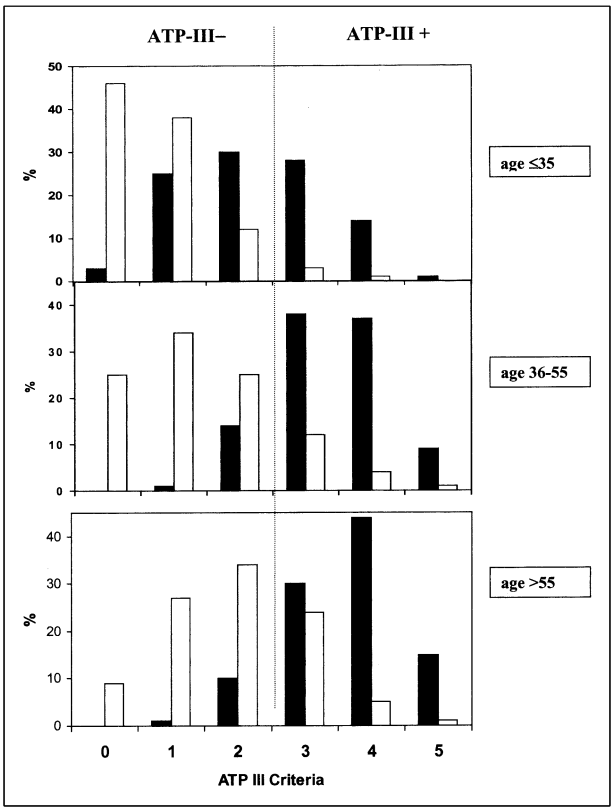

FIGURE 1. Frequency distribution (percent) of genetic epidemiology of metabolic syndrome-affected *(closed bars)* and -unaffected *(open bars)* patients according to the number of ATP-III criteria and age. (ATP-III criteria to define metabolic syndrome are listed in Table 1.) The diagnosis of metabolic syndrome is made if ≥3 of these criteria are met (corresponding to *right side of dotted line*).

we first partitioned 3,030 subjects from the family dataset who had sufficient information for ATP-III classification according to these 2 definitions. Among those affected by current criteria, 76% met the ATP-III definition for metabolic syndrome, whereas 85% of those unaffected by current criteria were also negative for the ATP-III definition, with a Cohen's κ of 0.61 (95% confidence interval [CI] 0.59 to 0.64), indicating overall substantial agreement. To establish how much of the discordance between the 2 definitions was due to our different criteria for dyslipidemia, and how much was due to coexistence of dyslipidemia with other metabolic syndrome factors, we repeated this analysis after replacing the absolute thresholds for triglyceride and HDL cholesterol in ATP-III with the current thresholds to create a pseudodefinition and again looked for concordance with the current definition. Among those positive for both definitions, 81% also met the ATP-III definition for metabolic syndrome, whereas 91% of those unaffected by current criteria were also unaffected by ATP-III, with a Cohen's κ of 0.72 (95% CI 0.69 to 0.74). Thus, overall concordance was increased, and only a small proportion of subjects (4.7%) affected by current criteria did not achieve ATP-III status due to differences in the lipid thresholds.

We next stratified the participants in this study according to the number of ATP-III criteria they met and by age categories (Figure 1). In this figure, solid bars located left of the dotted line correspond to "false positives," whereas solid bars on the right correspond to "true positives," if the ATP-III definition is used as the "gold standard" to define metabolic syndrome. This analysis revealed that in the age group ≤35 years old, >50% of the participants (58%) who were affected by current criteria were not affected by ATP-III. In contrast, the rate of false positives decreased to 14% in those aged 36 to 55 years and to 12% in older subjects. The overall agreement between the 2 criteria as described by the Cohen's κ showed a similar pattern, with only moderate agreement in those <35 years (κ 0.42, 95% CI 0.36 to 0.48), but substantial agreement in both those 35 to 55 years (κ 0.66, 95% CI 0.60 to 0.71) and in those >55 years (κ 0.58, 95% CI 0.51 to 0.65).

Because currently defined status was fairly well correlated with ATP-III status overall, it was interesting to explore which nondyslipidemic components of ATP-III (waist, fasting glucose, and systolic blood pressure) were most closely associated with the current definition of dyslipidemia. A linear regression analysis performed on waist circumference, fasting glucose, and systolic blood pressure is presented in Table 4. The parameter estimates correspond to the mean increase in the trait under evaluation in affected subjects by current criteria compared with unaffected subjects. Univariate analysis indicates unadjusted association, whereas model 1 adjusts for standard confounders (age, gender, center, smoking, and low-density lipoprotein cholesterol), and model 2 further adjusts for metabolic syndrome-associated factors. Affection status by current data was closely associated with each of the 3 traits in the univariate analysis, and the association remained significant after adjustment for confounders, although with a reduced magnitude of effect for both waist circumference and fasting glucose levels. In contrast, after adjustment for factors related to metabolic syndrome, systolic blood pressure was no longer associated with status by current criteria, suggesting that the observed association with current data was a secondary effect of ≥1 of the syndromic factors. Further analysis showed that waist was the specific variable that ablated this association (data not shown).

To assess if the concordance between the 2 definitions was influenced by the familial nature of dyslipidemia in the present study, the same comparison was performed in the additional set of 464 patients affected by current criteria who were singly ascertained. Overall, 75% of these sporadic cases also were affected for ATP-III metabolic syndrome, a figure similar to that observed in the family sample. Thus, the level of concordance between the 2 criteria does not appear to have been substantially affected by the familial nature of affected family members.

TABLE 4 Association of the Genetic Epidemiology of Metabolic Syndrome Criteria With Systolic Blood Pressure, Waist Circumference, and Fasting Glucose

	Systolic Blood Pressure (mm Hg)			Waist Circumference (cm)			Fasting Glucose (mg/dl)		
	Parameter Estimate	95% CI	p Value	Parameter Estimate	95% CI	p Value	Parameter Estimate	95% CI	p Value
Univariate	7.1	5.6–8.6	<0.0001	11.3	10.3–12.3	<0.0001	9.5	7.9–11.1	<0.0001
Model 1*	3.8	2.4–5.1	<0.0001	8.2	7.3–9.1	<0.0001	7.0	5.4–8.6	<0.0001
Model 2†	0.6	−0.9–2.2	0.43	7.0	6.0–7.9	<0.0001	3.6	1.8–5.3	<0.0001

*Adjusted for age, gender, center, smoking, and LDL cholesterol.

†Systolic blood pressure further adjusted for waist, fasting glucose, and hypertension medications; waist circumference further adjusted for systolic blood pressure, fasting glucose, and hypertension medications; fasting glucose further adjusted for waist, systolic blood pressure, and hypertension medications.

DISCUSSION

In our family collection, 86% of Caucasian patients aged >35 years affected with atherogenic dyslipidemia met the ATP-III definition for metabolic syndrome. A similar high association was present in sporadic cases of atherogenic dyslipidemia. Thus, most middle-aged subjects who have atherogenic dyslipidemia seemingly will have it as a component of the metabolic syndrome. This supports our contention that atherogenic dyslipidemia, whether familial or sporadic, is a robust identifier of predisposition for the syndrome. The strongest association was with abdominal obesity. The weaker concordance between atherogenic dyslipidemia and ATP-III metabolic syndrome before age 35 years may signify a particularly strong predisposition to an isolated lipid disorder, but in many cases, it likely foreshadows the development of the metabolic syndrome later in life.

The relation between dyslipidemia and systolic blood pressure was less striking, suggesting a weaker causal linkage. This corroborates well with published findings, where a factor analyses investigating metabolic syndrome shows that blood pressure often falls out as a distinct factor,[7] although it often correlates with obesity.[8] Elevated plasma glucose was also not strongly associated, but here it is known that compensatory hyperinsulinemia can prevent the development of overt hyperglycemia for many years in persons with the metabolic syndrome. Finally, it is known that the metabolic syndrome manifests differently in different populations, and the essential findings obtained in the current Caucasian population will not necessarily be applicable to other populations, notably blacks, Hispanics, and Asians.

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