Identifying Risk Factors in a Mostly Overweight Patient Population with Coronary Artery Disease

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Overweight/obesity is a complex multifactorial chronic disorder, and the American Heart Association (AHA) has recently classified as a modifiable risk factor for coronary heart disease (CAD). This study (1) evaluates the association between CAD in a patient population mostly overweight (MOP) and conventional and novel coronary risk factors by using univariate and multivariate logistic regression analysis and (2) seeks to find the best model by comparing univariate and multivariate logistic regression analysis algorithms, which were systematically applied to risk factors by using Hosmer-Lemeshow statistic test. In univariate analysis, there were significant associations between CAD in MOP and conventional and novel risk factors. However, the model's sensitivity, specificity, and accuracy levels were weak. In multivariate analysis, although some risk factors were not found as predictors of coronary artery disease, the model showed good fit to data and had high sensitivity, specificity, and accuracy levels. This was also confirmed by using the Hosmer-Lemeshow goodness of fit test, more specifically.

Introduction

Overweight populations have an increased risk of coronary atherosclerosis. However, until recently the role of obesity as an independent risk factor for coronary atherosclerosis remained controversial; its relationship with coronary atherosclerosis was initially viewed as indirect, because obesity often coexists with other cardiovascular risk factors including hyperlipidemia, hypertension, and diabetes.[1,2] In response to several long-term longitudinal studies that have indicated obesity as an independent predictor of coronary atherosclerosis,[3-6] the American Heart Association (AHA) has reclassified obesity as a major, modifiable risk factor for coronary heart disease.[7,8] Furthermore, Calle et al[9] recently reported higher total-cause and cardiovascular mortality with increasing body weight in both men and women in all age groups. Not only conventional coronary risk factors such as hyperlipidemia, hypertension, and diabetes[1,2] but also the association between obesity and novel risk factors have been studied in case-control and prospective cohort studies.[10-14] The present study was designed to analyze the association of conventional and novel risk factors with

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angiographically proved coronary artery disease (CAD), in a patient population mostly overweight (MOP) variables by using univariate and stepwise multivariate logistic regression algorithms.

Patients and Methods

In our cardiology department, between January 2001 and March 2001, 237 consecutive patients who had been referred for the investigation of chest pain were studied. In total, 124 consecutive patients who had been diagnosed with coronary artery disease by coronary angiograms (at least 1 coronary stenosis > 50%) were enrolled in the study. According to their body mass index (BMI) at the time of the study, the 109 patients who had a BMI of > 25 were overweight (88%), and 15 patients who had a BMI of < 25 were normal weight (12%). The 113 patients with normal-appearing coronary angiograms were taken as control subjects; 28 subjects who had a BMI of > 25 were overweight, 85 subjects who had weight a BMI of < 25 were normal weight. Multiple conventional and novel atherosclerotic risk factors such as age, sex, family history of premature coronary artery disease, smoking, hypertension, and diabetes mellitus, and levels of high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglycerides, C-reactive protein (CPR), fibrinogen, homocysteine, and lipoprotein (a) were identified between the groups.

Definitions

The definition of obesity is based on the BMI, which is defined as weight in kilograms divided by height in meters squared (kg/m^2). This index is independent of height ($r = -0.03$) and strongly related to weight ($r = 0.86$).[15] Recently the AHA has defined obesity as a BMI > 30. A BMI 25 and 30 is considered overweight and normal BMI is < 25.[8] Conventional atherosclerotic risk factors were as follows[16,17]: (1) Age: 45 years or older in men; 55 years or older, or premature menopause without estrogen replacement therapy, in women. (2) Family history of premature CAD: myocardial infarction or sudden death before the age of 55 in father or other male first-degree relative, or before the age of 65 in mother or other female first-degree relative. (3) Current cigarette smoking. (4) Hypertension (≥ 140/90 mm Hg, or use of hypertensive medication). (5) Low HDL cholesterol (< 35 mg/dL). (6) High LDL cholesterol (> 130 mg/dL). (7) High triglycerides (> 200 mg/dL). Novel atherosclerotic risk factors[10-14] were the following: (1) High-sensitivity C-reactive protein; the concentrations of C-reactive protein associated with atherosclerosis are substantially below those of most routine C-reactive protein assays (3 mg/L), and thus are a more sensitive assay procedure termed "high sensitivity" C-reactive protein has been developed.[18] Our laboratory's normal range was between 0 and 4.0 mg/L, and above the 4.0 mg/L level was accepted as a risk factor. (2) Homocysteine: > 15 μmol/L was accepted as a risk factor. (3) Fibrinogen: Our laboratory's normal range was between 200 and 400 mg/dL, and above the 400 mg/dL level was accepted as a risk factor. (4) Lipoprotein (a): > 30 mg/dL was accepted as a risk factor.

Laboratory Evaluations

For each participant, blood samples were collected after coronary angiography and centrifuged immediately at 4°C, and the separated plasma was stored at –20°C until assay. Fasting serum total cholesterol, high-density lipoprotein cholesterol, and triglyceride concentrations were measured by using standard enzymatic methods with a fully automated analyzer (Olympus AU 600, Boehringer Mannheim GmbH, Mannheim, Germany). Low-density lipoprotein cholesterol concentration was calculated by use of the Friedewald equation.[19] Fasting serum concentrations of lipoprotein (a) were determined by use of a nephelometric method (Dade Behring 100 Nephelometer, Marburg, Germany), and high sensitivity CRP concentrations were also determined by means of particle-enhanced immunonephelometry using Dade Behring 100. Fibrinogen concentrations were determined by BCT (Behring, Marburg, Germany). Homocysteine serum concentrations were also measured with ELISA (Biomaster, Chemila, Italy) with commercially available kits.

Statistical Analysis

Statistical analysis were performed with SPSS for Windows version 10.0. Age values of CAD and non-CAD groups were expressed as mean ± sd and compared by using unpaired t test. Chi-square test was used for other parameters to determine differences between 2 groups. Univariate and multivariate logistic regression analysis were done to identify the association of the studied

variables with CAD, and $p < 0.05$ was considered to be statistically significant.

Results

Clinical and Biochemical Characteristics

Table I shows the comparison of the clinical and biochemical profiles of the patients with CAD and normal subjects. Body mass index was significantly higher in patients with CAD. There was a significant predominance of men in the CAD group, which may explain the higher body mass index in this group. Conventional and novel coronary risk factors such as diabetes mellitus, hypertension, cigarette smoking, and family history of premature CAD, and levels of HDL, LDL, triglycerides, CRP, homocysteine, fibrinogen, and lipoprotein (a) were significantly different between the 2 groups.

Table II shows the univariate and stepwise multivariate logistic regression analysis of the CAD group. Conventional and novel risk factors were assessed by the univariate logistic regression, and although significant associations were noted between CAD and variables, the model's sensitivity, specificity, and accuracy levels were weak. In the multivariate analysis, the CAD group identified the following as predictors of patients with CAD: age, sex, body mass index, hypertension, diabetes mellitus, smoking, family history of CAD, low concentrations of HDL cholesterol, and high C-reactive protein and homocysteine concentrations. The strongest predictors were the presence of hypertension (odds ratio [OR]: 39.91, 95% confidence interval [CI]: 5.51–280.3, $p < 0.001$), family history of CAD (OR: 38.76, 95% CI: 6.2–242.7, $p < 0.001$), and cigarette smoking (OR: 24.36, 95% CI: 4.1–141.8, $p < 0.001$). The model showed good fit to data and had high sensitivity, specificity, and accuracy value (93.8%, 95.3%, and 93.7%, respectively). Hosmer-Lemeshow goodness of fit test was (χ^2: 3.87, df: 8, p: 0.86).

Discussion

We have investigated the risk variables associated with CAD in MOP compared with non-CAD subjects, classified on the basis of coronary angiography. It is well known that the risk of CAD is higher in patients with diabetes mellitus.[20,21] Although this study was not designed to estimate the risk of CAD conferred by diabetes, because it is well known that obesity often coexists with other cardiovascular risk factors including hyperlipidemia, hypertension, and diabetes,[1,2] the observation of a high proportion of diabetes and a higher prevalence of hypertension in subjects with CAD (66.9% and 58.1%, respectively, $p < 0.0001$) was not surprising to us. Rate of smoking, was statistically different between CAD and non-CAD groups. (74.2% vs 27.4%, $p < 0.0001$).

Both univariate and multivariate analysis showed that body mass index was independently and significantly associated with CAD; this was consistent with the previous outcomes of published studies.[7,9,10] High C-reactive protein was found to be the strongest variable in MOP with CAD (OR: 31.20, 95% CI: 15.3–63.5, $p < 0.0001$), by use of univariate analysis. CRP has been proven to have strong predictive value among obese patients with CAD, and nonpharmacologic methods to reduce CRP include weight reduction and exercise.[12] Univariate analysis also showed that levels of triglycerides, homocysteine, fibrinogen, and lipoprotein (a) and abnormalities in the fractions of cholesterol were significantly associated with CAD.

In the multivariate analysis, hypertension, cigarette smoking, family history of premature CAD, diabetes mellitus, age, sex, and BMI, and levels of homocysteine, CRP, and HDL and LDL cholesterol were found to be strongly and independently associated with CAD. In this study, we could not find a significant association between CAD and levels of triglycerides, fibrinogen, and Lp (a), in the multivariate analysis. Craig et al,[22] in a meta analysis, observed that the separation in values between the cases and controls was not sufficient to allow the use of Lp(a) as a screening test. Because sample storage might affect Lp(a) values, we estimated Lp(a) in freshly collected, fasting serum samples. Several conventional risk factors and CRP and homocysteine were associated with CAD in MOP, but triglycerides, fibrinogen, and Lp(a) showed no association with CAD in this study. Only prospective studies will offer explanations for the major variations seen in the nature of risk variables associated with CAD in overweight patient.

In conclusion; when conventional and novel risk factors were assessed by univariate logistic

Table I. Clinical and biochemical characteristics of subjects with and without CAD.

	CAD Group (n = 124)	Non-CAD Group (n = 113)	p Value
Age (years)	55.6 ±4.01	54.5 ±3.24	<0.02
Men/women	104/20 (83.9%)	35/78 (31.0%)	0.000
BMI (kg/m^2)			
≥ 25*	109 (87.9%)	28 (24.8%)	0.000
< 25†	15 (12.1%)	85 (75.2%)	
Hypertension*	72 (58.1%)	16 (14.2%)	0.000
Diabetes mellitus*	83 (66.9%)	22 (19.5%)	0.000
Cigarette smoking*	92 (74.2%)	31 (27.4%)	0.000
Family history*	76 (61.3%)	18 (15.9%)	0.000
HDL (mg/dL)			
≤ 35*	70 (56.5%)	37 (32.7%)	0.000
> 35†	54 (43.5%)	76 (67.3%)	
LDL (mg/dL)			
> 130*	89 (71.8%)	35 (31.0%)	0.000
≤ 130†	35 (28.2%)	78 (69.0%)	
Triglyceride (mg/dL)			
≥ 200*	41 (33.1%)	13 (11.5%)	0.000
< 200†	83 (66.9%)	100 (88.5%)	
CRP (mg/L)			
≥ 5*	105 (84.7%)	17 (15.0%)	0.000
<5†	19 (15.3%)	96 (85.0%)	
Fibrinogen (mg/dL)			
> 400*	100 (80.6%)	32 (28.3%)	0.000
≤ 400†	24 (19.4%)	81 (71.7%)	0.000
Lipoprotein (a) (mg/dL)			
> 30*	100 (80.6%)	26 (23.0%)	0.000
≤ 30†	24 (19.4%)	87 (77.0%)	0.000
Homocysteine (nmol/mL)			
> 15*	98 (79.0%)	32 (28.3%)	0.000
≤ 15†	26 (21.0%)	81 (71.7%)	

HDL, high density lipoprotein; LDL, low density lipoprotein; BMI, body mass index; CRP, C-reactive protein; *risk factor; †not a risk factor.

Table II. Univariate and multivariate predictors of patients with CAD.

Variables	Odds Ratio			
	Univariate		Multivariate	
	(95% CI)	p Value	(95% CI)	p Value
Age	1.07 (1.01–1.1)	<0.001	1.11 (1.01–1.30)	0.013
Sex*	12.31 (6.5–23.1)	<0.001	4.32 (1.07–17.2)	0.035
BMI*	22.05 (11.0–43.8)	<0.001	5.40 (1.10–26.5)	0.033
Hypertension*	8.39 (4.4–15.8)	<0.001	39.91 (5.51–280.3)	<0.001
Diabetes mellitus*	8.37 (4.6–15.2)	<0.001	9.41 (1.67–51.9)	0.01
Cigarette smoking*	7.60 (4.2–13.5)	<0.001	24.36 (4.1–141.8)	<0.001
Family history*	8.35 (4.4–15.5)	<0.001	38.76 (6.2–242.7)	<0.001
HDL*	2.66 (1.5–4.5)	<0.001	7.03 (15.1–31.8)	0.014
LDL*	5.66 (3.2–9.9)	<0.001	8.84 (13.04–34.08)	<0.001
Triglyceride*	3.80 (1.9–7.5)	<0.001		
CRP*	31.20 (15.3–63.5)	<0.001	13.41 (2.45–71.7)	0.002
Homocysteine*	9.5 (5.2–17.3)	<0.001	7.0 (1.49–31.6)	0.013
Fibrinogen*	10.5 (5.7–19.3)	<0.001		
Lipoprotein (a)*	13.9 (7.4–26.2)	<0.001		

*Risk factor.

regression, although significant associations were noted between CAD and variables, the model's sensitivity, specificity, and accuracy were weak. However, when we analyzed by using a multivariate logistic regression model, although some risk factors were not found as predictors of CAD in a patient population mostly overweight, the model showed good agreement on predictors and had high predictable sensitivity, specificity, and accuracy. More specifically, this was confirmed by using the Hosmer-Lemeshow goodness of fit test. Therefore, multivariate logistic regression may be useful for analysis of outcomes of studies that have the advantage of high predictable ratio.

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