Contribution of Fasting Hyperinsulinemia to Prediction of Atherosclerotic Cardiovascular Disease Status in 293 Hyperlipidemic Patients

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In a cross-sectional study of 293 nondiabetic patients (169 men and 124 women) referred for the diagnosis and treatment of hyperlipidemia, our specific aim was to determine whether fasting serum insulin independently contributes to the prediction of atherosclerotic cardiovascular disease (ASCVD) status. Of the 169 men and 124 women, 65 (38%) and 44 (35%), respectively, had ASCVD with at least one of the following: unstable angina, myocardial infarction (MI), angioplasty, coronary artery bypass graft (CABG), claudication, transient ischemic attack, or ischemic stroke. In addition, 42% and 38% had fasting hyperinsulinemia (≥20 μU/mL). Fasting serum insulin of 20 μU/mL or higher was very common in women (59% to 100%) and men (67% to 88%) when hypertension, obesity, top-decile triglyceride (TG), and bottom-decile high-density lipoprotein cholesterol (HDLC) were concurrent in various combinations. ASCVD events (present or absent) were dependent variables in a stepwise logistic regression model with explanatory variables including age, gender, race, hypertension, cigarette smoking, ASCVD in first-degree relatives at age 55 years or less, Quetelet Index, fasting serum insulin, a gender × insulin interaction term, anticardiolipin antibodies (ACLAs) IgG and IgM, total cholesterol to HDLC ratio, TG, lipoprotein(a) [Lp(a)], and homocysteine. The risk odds ratio for ASCVD (109 events and 184 nonevents) for subjects with top-decile insulin (*v* the bottom nine deciles) was 3.71, with a 95% confidence interval (CI) of 1.62 to 8.9 ($P = .002$). For patients with MI and/or CABG and/or angioplasty ([MCA] 63 events and 184 nonevents), the risk odds ratio for top-decile insulin versus the rest was 5.07 (95% CI, 1.83 to 14.8, $P = .002$). For patients with MCA at age 55 or less, the gender × insulin interaction term was significant ($P = .0004$); the risk odds ratio for men with top-decile insulin was 13.28 (95% CI, 3.82 to 51.65, $P = .0001$). Hyperinsulinemia is very common in nondiabetic hyperlipidemic women and men. Fasting serum insulin, a crude, simple, practical, and inexpensive measure, independently and uniformly improved the prediction of ASCVD status beyond traditional risk factors and lipid variables in patients referred for treatment of hyperlipidemia.

HYPERINSULINEMIA is a significant independent risk factor for coronary heart disease (CHD) and carotid artery atherosclerosis.[1-8] Insulin resistance with concurrent hyperinsulinemia is associated with the atherogenic insulin resistance syndrome that commonly includes hypertriglyceridemia, low high-density lipoprotein cholesterol (HDLC), centripetal obesity, type 2 diabetes, and, often, hypertension.[9-16] The high incidence of myocardial infarction (MI) in type 2 diabetes[17] probably reflects the atherogenic contributions of insulin resistance independent from cholesterol, hypertension, and smoking. In the recent UK Prospective Diabetes Study,[18-20] metformin, an insulin-sensitizing agent that reduces serum insulin levels, significantly reduced macrovascular and microvascular disease. It was speculated that a significant reduction in macrovascular disease by metformin reflects a reduction in the atherogenic effects of hyperinsulinemia or a reduction of the insulin-stimulated high plasminogen activator inhibitor levels.[20]

In a cross-sectional study of 293 nondiabetic patients (169 men and 124 women) referred for the diagnosis and treatment of hyperlipidemia, our specific aim was to determine whether fasting serum insulin independently contributes to the prediction of atherosclerotic cardiovascular disease (ASCVD) status.

SUBJECTS AND METHODS

Patients

Three hundred thirty-seven patients were newly referred from Midwestern states as outpatients to the Jewish Hospital Cholesterol Center for the diagnosis and treatment of hyperlipidemia.[21] They represent a "convenience" sample and were studied in the temporal sequence of their referral without any selection bias. To allow the use of fasting serum insulin as a simple marker of insulin resistance, 44 patients (13%) with type 2 diabetes[22] were excluded from subsequent analyses, leaving 293 patients (169 men and 124 women; Tables 1 and 2). In each patient, by the medical history, physical examination, and review of the referring doctors' and hospital records, ASCVD was characterized by at least one of the following events: unstable angina, MI, angioplasty, coronary artery bypass graft (CABG), claudication, transient ischemic attack, and ischemic stroke. This classification system allows for the possibility that some patients who were presumably free of ASCVD would be classified as positive if they were evaluated by coronary angiograms and carotid, vertebral, and femoral artery Doppler examinations.

At the initial visit, information was obtained regarding sex, age, race, height and weight, hypertension, diabetes,[22] cigarette smoking, and ASCVD in first-degree relatives at age 55 or less. The Quetelet Index ([kilograms per centimeter squared] × 1,000) was used as an index of body composition; measures of fat distribution were not used. After an overnight fast, blood was drawn for measurement of total cholesterol, HDLC, low-density lipoprotein cholesterol (LDLC), triglyceride (TG), lipoprotein(a) [Lp(a)], homocysteine, methylmalonic acid, and the anticardiolipin antibodies (ACLAs) immunoglobulin G (IgG) and IgM as previously described.[23-25] Apolipoprotein B, another potential predictor of ASCVD status in this cohort, was not measured. ACLA IgA was not measured, since it was previously shown not to discriminate between CHD events and freedom from CHD.[26] Fasting serum insulin was measured by immunoassay with a sensitivity of 2.5 μU/mL and a linearity of 2.5 to 160 μU/mL (Quest Diagnostics, Pittsburgh, PA).[27] The intraassay coefficient of variation for low (9.4 μU/mL), medium (28.4 μU/mL), and high (116.1 μU/mL) pools was 9%, 6.9%, and 13.8%, respectively. The interassay coefficient of variation for low (9.9 μU/mL), medium (29.5 μU/mL), and high (104.3 μU/mL) pools was

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Table 1. Risk Factors for ASCVD in 169 Hyperlipidemic Men, 65 With an Event and 104 Without an Event

Variable	With Event (n = 65)		Without Event (n = 104)		Significance of Difference Adjusted for Age and Race (*P*)
	Mean ± SD	Median	Mean ± SD	Median	
Age (yr)	55 ± 12	54	49 ± 12	48	
Cholesterol (mg/dL)	212 ± 49	213	233 ± 64	227	.05
HDLC (mg/dL)	36 ± 11	33	38 ± 19	37	.3
Cholesterol/HDLC ratio	6.3 ± 2.1	6.1	6.7 ± 2.8	6.3	.4
LDLC (mg/dL)	130 ± 44	138 (n = 40)	143 ± 54	147 (n = 46)	.1
TG (mg/dL)	266 ± 219	210	376 ± 477	219	.2
Lp(a) (mg/dL)	36 ± 48	15	19 ± 26	7	.01
Homocysteine (mg/dL)	10.4 ± 3.4	9.9	10.9 ± 8.1	9.4	.4
IgG (GPL)	14.6 ± 7.3	14.0	14.3 ± 9.6	11.0	.9
IgM (MPL)	4.4 ± 6.1	3.0	3.2 ± 2.5	2.0	.2
Quetelet Index	2.88 ± 0.41	2.88	2.96 ± 0.43	2.91	.5
Insulin (μU/mL)	33 ± 40	20	20 ± 14	16	.006
Race	1 black, 62 white (95%), 2 other		1 black, 102 white (98%), 1 other		$\chi^2 = 1.01$, $P = .3$
Hypertension	38 no, 27 yes (42%)		66 no, 38 yes (37%)		$\chi^2 = 0.4$, $P = .5$
Smoking	57 no, 8 yes (12%)		90 no, 14 yes (13%)		$\chi^2 = 0.05$, $P = .8$
Relatives' ASCVD ≤ age 55	26 no, 39 yes (60%)		54 no, 50 yes (48%)		$\chi^2 = 2.3$, $P = .13$

Abbreviations: GPL, G Phospho Lipid Units; MPL, M Phospho Lipid Units.

12.7%, 7%, and 9.3%, respectively. The assay antibody recognizes proinsulin but has no cross-reactivity with C-peptide. The assay specificity for proinsulin was 2.34 μU(insulin)/pg(proinsulin).

Statistical Analysis

Because there are gender differences in the relationship of obesity to insulin resistance and to hyperlipidemia,[11,28-32] analyses were performed separately for men and women (Tables 1 to 4) except for the stepwise logistic regression,[33] where a gender × insulin interaction term was used to explore gender differences (Table 5). Major ASCVD risk factors were first compared between event and nonevent groups by gender using ANOVA[33] after adjustment for age and race (Tables 1 and 2). Fasting serum insulin was compared between event and nonevent groups after adjustment (ANOVA) for age, race, and the Quetelet Index, with additional comparisons by χ^2 analysis (Table 3).[33] Since most of the data were not normally distributed, Spearman nonparametric univariate correlations[33] were calculated (Table 4).

After categorizing the patients by the Quetelet Index and TG at or above the age-sex–specific 90th percentile and HDLC at or below the age-sex–specific 10th percentile for the Lipid Research Clinics prevalence population[34] and by the presence of hypertension, the percentage of patients with high fasting serum insulin (≥normal control 95th percentile [20 μU/mL]) was tabulated (Fig 1).

Stepwise logistic regression[33] was performed to assess significant independent determinants of ASCVD events in the 293 patients (Table 5 and Figs 2 to 4). Events or nonevents were the dependent variables, and explanatory variables included gender, fasting serum insulin, a gender × insulin interaction term, the total cholesterol to HDLC ratio,[13,35-38] TG, Lp(a), homocysteine, ACLAs IgG and IgM, age, race, the Quetelet Index, and the presence or absence of hypertension, cigarette smoking, and first-degree relatives with ASCVD at age 55 or less (Table 5). Hypertension was defined by the use of antihypertensive medications and/or systolic/diastolic blood pressure greater than 140/90 mm Hg. The same stepwise logistic regression model was performed separately for 157 patients after excluding 136 patients who were taking lipid-lowering medications at study entry (Table 6).

Table 2. Risk Factors for ASCVD in 124 Hyperlipidemic Women, 44 With an Event and 80 Without an Event

Variable	With Event (n = 44)		Without Event (n = 80)		Significance of Difference Adjusted for Age and Race (*P*)
	Mean ± SD	Median	Mean ± SD	Median	
Age (yr)	58 ± 14	62	50 ± 15	51	
Cholesterol (mg/dL)	236 ± 54	236	252 ± 61	242	.10
HDLC (mg/dL)	42 ± 14	41	50 ± 19	47	.01
Cholesterol/HDLC ratio	6.2 ± 2.6	5.6	5.8 ± 2.6	5.3	.4
LDLC (mg/dL)	146 ± 57	145 (n = 21)	170 ± 48	163 (n = 34)	.2
TG (mg/dL)	385 ± 322	255	290 ± 448	163	.5
Lp(a) (mg/dL)	28 ± 27	16	37 ± 39	25	.06
Homocysteine (mg/dL)	10.1 ± 5.1	9.2	9.1 ± 5.0	8.1	.9
IgG (GPL)	14.1 ± 9.9	12.0	12.1 ± 8.6	10.0	.3
IgM (MPL)	6.3 ± 6.2	3.5	3.6 ± 2.9	3.0	.004
Quetelet Index	2.83 ± 0.49	2.87	2.80 ± 0.60	2.72	.8
Insulin (μU/mL)	31 ± 49	22	17 ± 11	14	.04
Race	2 black, 42 white (95%)		2 black, 78 white (98%)		$\chi^2 = 0.38$, $P = .5$
Hypertension	27 no, 17 yes (39%)		58 no, 22 yes (28%)		$\chi^2 = 1.6$, $P = .2$
Smoking	34 no, 10 yes (23%)		68 no, 12 yes (15%)		$\chi^2 = 1.2$, $P = .3$
Relatives' ASCVD ≤ age 55	15 no, 29 yes (66%)		41 no, 39 yes (49%)		$\chi^2 = 3.4$, $P = .07$

Table 3. Serum Insulin, Percentage of Patients With Serum Insulin ≥20 μU/mL, and ASCVD Events Versus Nonevents in 169 Men and 124 Women

Group	No. of Subjects	Serum Insulin (μU/mL) Median	Serum Insulin (μU/mL) Mean ± SD	P*	Serum Insulin ≥20 μU/mL (%)	χ^2	P†
Men (n = 169)							
No event	104	15.8	20.2 ± 13.6		38		
Any event	65	19.8	32.5 ± 40.2	.002	48	1.40	.24
MCA	50	19.7	32.7 ± 42.6	.001	46	0.79	.37
Any event ≤ age 55	45	21.4	32.5 ± 21.4	.0003	53	2.84	.092
MCA ≤ age 55	35	23.7	33.2 ± 30.8	.0001	54	2.68	.10
Women (n = 124)							
No event	80	14.2	16.6 ± 10.9		29		
Any event	44	21.8	31.1 ± 49.2	.04	55	8.03	.005
MCA	13	24.0	28.7 ± 24.7	.001	69	8.12	.004
Any event ≤ age 55	20	17.5	20.2 ± 11.7	.3	45	1.94	.16
MCA ≤ age 55	6	16.9	17.8 ± 12.0	.6	50	1.20	.27

*Comparison covariance adjusted for age, race, and Quetelet Index (ANOVA).
†χ^2 analysis.

RESULTS

Patient Characteristics and Major Risk Factors for ASCVD

The 293 patients were predominantly white. Men with ASCVD were older than the event-free men (54 *v* 48 years, $P = .0008$), as were women with ASCVD versus event-free women (62 *v* 51 years, $P = .0009$) (Tables 1 and 2).

After covariance adjustment for age and race, men with ASCVD events had higher Lp(a) and higher fasting serum insulin. Women with ASCVD events had higher ACLA IgM, higher fasting serum insulin, and lower HDLC. Quetelet indices did not differ between patients with and without ASCVD events (Tables 1 and 2).

Of the 169 men and 124 women, 42% and 38%, respectively, had fasting hyperinsulinemia (≥20 μU/mL). After covariance adjustment for age, race, and the Quetelet Index, fasting serum insulin was higher in men and women with ASCVD events

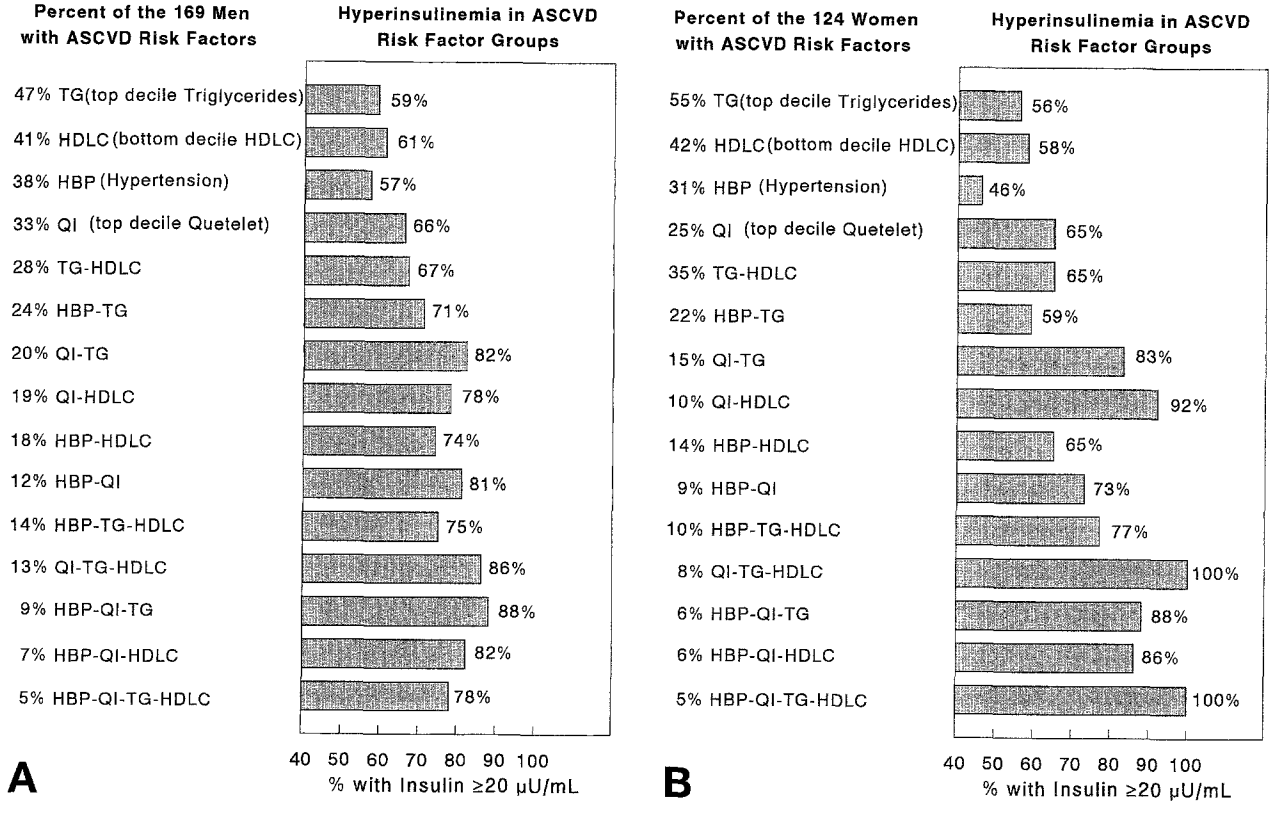

Fig 1. (A) Percentage of 169 men with ASCVD risk factors (top-decile TG, Quetelet index [QI], bottom-decile HDLC, and/or hypertension [HBP]) and percentage of men in ASCVD risk factor groups with fasting serum insulin ≥20 μU/mL. (B) Percentage of 124 women with ASCVD risk factors and percentage of women in ASCVD risk factor groups with fasting serum insulin ≥20 μU/mL.

Table 4. Univariate Correlations Between Insulin and Metabolic Variables

Variable	Men (n = 169)		Women (n = 124)	
	Spearman *r*	*P*	Spearman *r*	*P*
Insulin/HDLC	−.38	.0001	−.53	.0001
Insulin/(TC/HDLC)	.39	.0001	.42	.0001
Insulin/TG	.43	.0001	.50	.0001
Insulin/Quetelet Index	.53	.0001	.48	.0001

Abbreviation: TC, total cholesterol.

versus those who were event-free, including (in both sexes) any ASCVD event and MI-CABG-angioplasty (MCA). Men with any ASCVD event at age 55 or less or MCA at age 55 or less had higher fasting serum insulin than men without events. The percentage of women with serum insulin of at least 20 μU/mL was higher for those with any ASCVD event and MCA versus event-free women (Table 3).

Associations of Fasting Serum Insulin ≥ 20 μU/mL With Top-Decile TG and Quetelet Index, Bottom-Decile HDLC, and/or Hypertension

Of the 169 men, top-decile TG[34] and bottom-decile HDLC[34] were present in 47% and 41%, respectively. Hypertension was present in 38% and top-decile Quetelet Index[34] in 33%. Hypertension, top-decile Quetelet Index, top-decile TG, and bottom-decile HDLC were often concurrent in various combinations. The most common two-variable combination was top-decile TG and bottom-decile HDLC in 28% of the 169 men. The most common three-variable combination was hypertension, top-decile TG, and bottom-decile HDLC in 14% of the 169 men (Fig 1A).

Fasting hyperinsulinemia was common in the 169 men with top-decile TG (59%), bottom-decile HDLC (61%), top-decile Quetelet Index (66%), and hypertension (57%). Fasting hyperinsulinemia was very common (67% to 88%) among patients with a combination of top-decile Quetelet Index and TG, hypertension, or bottom-decile HDLC (Fig 1A).

Of the 124 women, top-decile TG[34] and bottom-decile HDLC[34] were present in 55% and 42%, respectively. Hypertension was present in 31% and top-decile Quetelet Index[34] in 25%. Hypertension, top-decile Quetelet Index, top-decile TG, and bottom-decile HDLC were often concurrent in various combinations. The most common two-variable combination was top-decile TG and bottom-decile HDLC in 35%. The most common three-variable combination was hypertension, top-decile TG, and bottom-decile HDLC in 10% (Fig 1B).

Fasting hyperinsulinemia was common in the 124 women with top-decile TG (56%), bottom-decile HDLC (58%), top-decile Quetelet Index (65%), and hypertension (46%). Fasting hyperinsulinemia was very common (59% to 100%) among patients with a combination of top-decile Quetelet Index and TG, hypertension, or bottom-decile HDLC (Fig 1B).

Univariate Correlates: Fasting Serum Insulin With Metabolic Variables

In both sexes, insulin was inversely correlated with HDLC and positively correlated with the cholesterol to HDLC ratio, TG, and Quetelet Index (Table 4).

Table 5. Significant Independent Determinants of Ratio, ASCVD Events by Logistic Regression (N = 293) With Stepwise Selection on Cholesterol/HDLC Ratio, TG, Lp(a), Homocysteine, Age, Race, Gender, Hypertension, Smoking, Relatives' Events ≤ Age 55, IgG, IgM, Quetelet Index, Insulin, and Interaction Term Gender × Insulin

Dependent Variable	Significant Determinant			Risk Odds Ratio	95% CI	*P*
	Variable	Sign	*P*			
Any event (109 events, 184 nonevents)	Age	+	.0002	1.517	1.240-1.878	.0001
Concordant 74%	Insulin	+	.0001	3.713	1.619-8.896	.002
Discordant 26%	IgM	+	.01	2.475	1.065-5.973	.04
	Relatives' ASCVD	+	.006	2.002	1.193-3.408	.009
MCA (63 events, 184 nonevents)	Age	+	.0001	1.954	1.466-2.672	.0001
Concordant 82%	Relatives' ASCVD	+	.04	2.129	1.081-4.327	.03
Discordant 18%	IgM	+	.03	2.408	0.834-7.063	.1
	Quetelet Index	−	.02	0.410	0.082-1.489	.2
	Gender	+	.0002	4.163	1.931-9.731	.0005
	Insulin	+	.0001	5.070	1.829-14.83	.002
Event ≤ age 55 (65 events, 184 nonevents, age is excluded)	Insulin	+	.0002	3.890	1.559-9.855	.004
	IgM	+	.004	2.602	0.998-6.698	.05
Concordant 73%	Relatives' ASCVD	+	.03	1.966	1.080-3.662	.03
Discordant 26%						
MI ≤ age 55 (27 events, 184 nonevents, age is excluded)	Gender × insulin	+	.006	5.237	1.231-20.24	.02
	IgM	+	.007	3.624	1.036-11.29	.03
Concordant 78%						
Discordant 22%						
MCA ≤ age 55 (41 events, 184 nonevents, age is excluded)	Gender × insulin	+	.0004	13.28	3.818-51.65	.0001
	IgM	+	.005	3.343	1.099-9.674	.03
Concordant 81%	Relatives' ASCVD	+	.02	2.521	1.167-5.830	.02
Discordant 19%	Quetelet Index	−	.05	0.471	0.087-1.775	.3

NOTE. For gender, male = 1, female = 0; for race, white = 1, black/other = 0; for hypertension, yes = 1, no = 0; for relatives' events (≤ age 55), yes = 1, no = 0. Risk odds ratios for IgM, insulin, and Quetelet Index are for top decile *v* the rest. Risk odds ratio for gender × insulin is for men with top decile of male insulin *v* the rest (men and women). Risk odds ratio for age is for increments of 10 years.

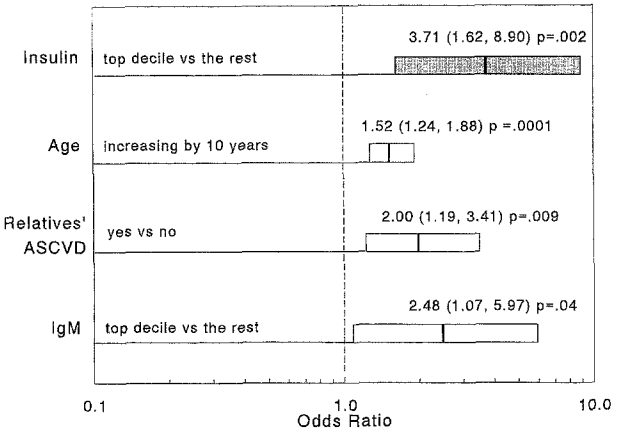

Fig 2. ASCVD odds ratio (95% CI) in 293 patients, 109 with and 184 without ASCVD.

Significant Independent Determinants of ASCVD

Significant independent variables positively associated with ASCVD (109 events and 184 nonevents) included age ($P = .0002$), insulin ($P = .0001$), ASCVD in relatives ($P = .006$), and ACLA IgM ($P = .01$) (Table 5). The risk odds ratio for ASCVD for subjects with top-decile insulin was 3.71, with a 95% confidence interval (CI) of 1.62 to 8.9 ($P = .002$; Table 5 and Fig 2). Top-decile insulin, of all the significant risk factors for ASCVD, had the highest odds ratio for ASCVD (Fig 2). The interaction term gender × insulin did not enter the regression model as a significant independent variable.

For patients with MCA (63 events and 184 nonevents), significant independent variables positively associated with ASCVD included age ($P = .0001$), male gender ($P = .0002$), insulin ($P = .0001$), IgM ($P = .03$), and ASCVD in relatives ($P = .04$). The risk odds ratio for ASCVD for patients with top-decile insulin was 5.07, with a 95% CI of 1.83 to 14.8 ($P = .002$; Table 5 and Fig 3). Top-decile insulin, of all the significant risk factors for ASCVD, had the highest odds ratio for MCA (Fig 3).

For the 65 subjects with an ASCVD event at age 55 or less, insulin was a significant positive explanatory variable ($P = .0002$), with a risk odds ratio of 3.89 (95% CI, 1.56 to 9.86, $P = .004$; Table 5 and Fig 4). Top-decile insulin, of all the significant risk factors for ASCVD at age 55 or less, had the highest odds ratio for ASCVD (Fig 4).

For MI at age 55 or less and for MCA at age 55 or less, the gender × insulin interaction term was significant ($P = .006$ and $P = .0004$; Table 5). Men with top-decile insulin were more likely to have events.

At study entry, 89 of 293 patients (30%) were taking statin medications to decrease LDLC, 28 (9.6%) were taking TG-lowering agents, and 19 (6.5%) were taking both. Only one patient was taking nicotinic acid. Exclusion of the 136 patients on lipid-lowering agents did not affect the appearance of insulin as a significant independent predictor of ASCVD in the remaining 157 patients (Table 6).

DISCUSSION

In the present study, fasting serum insulin, a crude, simple, practical, and inexpensive measure, independently and uniformly improved the prediction of ASCVD status beyond traditional risk factors and lipid variables in nondiabetic patients referred for treatment of hyperlipidemia. The associations of insulin with MI or MCA at age 55 or less were present for men but not for women, suggesting gender differences[11,28-32] in the association of insulin with ASCVD. The study limitations include the convenience patient sample, cross-sectional design, lack of estimation of centripetal and peripheral adiposity, lack of measures of apolipoprotein B, and use of lipid-lowering agents at study entry in 46% of the patients. However, after exclusion of patients who were taking lipid-lowering medications, insulin remained as a highly significant explanatory variable for ASCVD events.

Hyperinsulinemia probably augments the risk for ASCVD directly and via its inverse effects on HDLC and positive associations with type 2 diabetes, the Quetelet Index, TG, plasminogen activator inhibitor activity, and hypertension.[1-20,27,39-41]

The gold standard for assessment of in vivo insulin sensitivity is the glucose clamp technique; however, it is associated with substantial measurement error.[42] Fasting serum insulin has been used as a surrogate index of insulin sensitivity,[5,43-45] but it explains only 30% to 40% of the variance in glucose clamp–

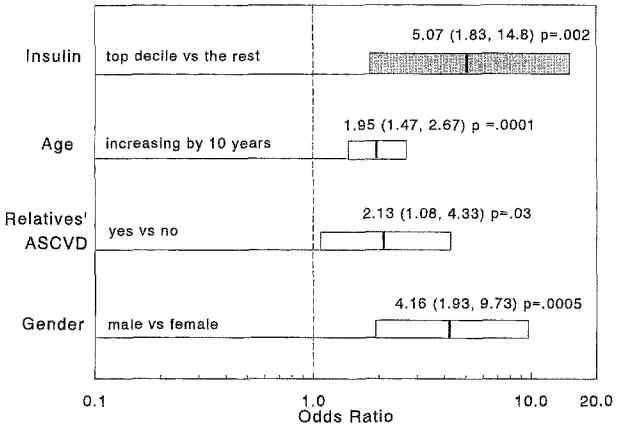

Fig 3. ASCVD odds ratio (95% CI) in 247 patients, 63 with and 184 without events (MI or CABG or angioplasty).

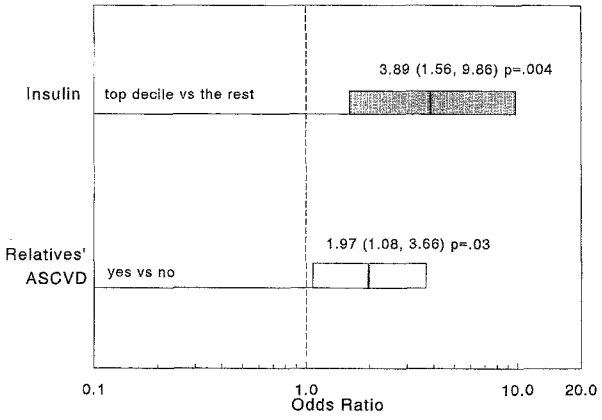

Fig 4. ASCVD odds ratio (95% CI) in 249 patients, 65 with an event at ≤ age 55 years and 184 without an event.

Table 6. Significant Independent Determinants of ASCVD Events by Logistic Regression (n = 157, TC/TG-lowering agent users excluded) With Stepwise Selection on Cholesterol/HDLC Ratio, TG, Lp(a), Homocysteine, Age, Race, Gender, Hypertension, Smoking, Relatives' Events ≤Age 55, IgG, IgM, Quetelet Index, Insulin, and Interaction Term Gender × Insulin

Dependent Variable	Significant Determinant			Risk Odds Ratio	95% CI	P
	Variable	Sign	P			
Any event (43 events, 114 nonevents)	IgM	+	.009	3.984	1.257-13.18	.02
Concordant 76%	Insulin	+	.009	2.630	0.819-8.253	.1
Discordant 23%	Relatives' ASCVD	+	.01	2.607	1.205-5.930	.02
	Age	+	.04	1.410	1.078-1.882	.01
MCA (15 events, 114 nonevents)	Age	+	.0009	3.312	1.845-6.924	.0003
Concordant 91%	Gender × insulin	+	.004	9.755	1.061-79.01	.03
Discordant 9%	Relatives' ASCVD	+	.02	4.317	1.192-19.23	.04
Event ≤ age 55 (28 events, 114 nonevents, age is excluded)	IgM	+	.008	4.778	1.325-17.36	.02
	Insulin	+	.01	2.585	0.683-9.015	.1
Concordant 78%	Relatives' ASCVD	+	.01	3.272	1.320-8.953	.01
Discordant 22%						

NOTE. For gender, male = 1, female = 0; for race, white = 1, black/other = 0; for hypertension, yes = 1, no = 0; for relatives' events (≤ age 55), yes = 1, no = 0. Risk odds ratio for IgM and insulin is for top decile *v* the rest. Risk odds ratio for gender × insulin is for men with top decile of male insulin *v* the rest (men and women). Risk odds ratio for age is for increments of 10 years.

determined insulin sensitivity.[46] The moderate shared variance between fasting insulin and insulin resistance can be explained in part, by measurement errors associated with both measures.[42,46] In the present study, having excluded patients with type 2 diabetes mellitus, fasting serum insulin is a simple, practical, and inexpensive correlate of insulin resistance.

Other methodologies have been used to measure insulin resistance. The short-term insulin tolerance test accounts for 65% of the variance in insulin sensitivity,[47] and 30% to 50% of the variance in insulin sensitivity can be explained by the intravenous glucose tolerance test analyzed with the minimal model.[48,49] A computer-modeled homeostasis model has been used to estimate insulin sensitivity for epidemiologic studies.[50] The progression from impaired glucose tolerance to type 2 diabetes is thought to reflect a decline in insulin secretion rather than an increase in insulin resistance.[51]

The rate of hyperinsulinemia in the current study of patients referred for the diagnosis and treatment of hyperlipidemia (42% of men and 38% of women) is similar to that in the population study by Bonora et al (45%).[52] In the present study, hyperinsulinemia was very common (59% to 100%) when hypertension, obesity, low HDLC, and high TG were present in various combinations. Insulin resistance is ubiquitous when several metabolic disorders cluster within the same individual as in the present study and previous studies,[52] whereas it is rarer when the various metabolic disorders are isolated.[28,52-54] Hyperinsulinemic "healthy" subjects[28,45,52] may later become hyperlipidemic, develop the full-blown insulin resistance syndrome, and be at high risk for atherothrombotic disease. In an 8-year prospective study, Haffner et al[45] showed that fasting hyperinsulinemia precedes the development of multiple metabolic risk factors for ASCVD.

In the current study, ACLA IgM was a significant independent uniform determinant of ASCVD events, similar to two prospective studies[55,56] and one recent cross-sectional study.[57]

The failure of homocysteine to be a significant determinant of atherosclerotic events in the present study, while not in agreement with our previous report on hyperlipidemic patients,[24] is similar to the findings in a recent prospective study by Folsom et al.[58]

Insulin may be a relevant marker of atherothrombotic abnormalities that increase the risk of CVD which are not inclusively assessed by traditional risk factors and lipid variables. Assessment of the risk for atherothrombosis probably should be broadened beyond "traditional" risk factors to include fasting serum insulin, homocysteine,[24] Lp(a),[25] and ACLAs.[55-57] By reducing insulin levels, the insulin-sensitizing agent, metformin may speculatively have promise in the primary and secondary prevention of ASCVD not only in type 2 diabetics[18-20] but also in euglycemic hyperinsulinemic subjects.[27]

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