Relative Impact of Low-Density Lipoprotein-Cholesterol Concentration and Insulin Resistance on Carotid Wall Thickening in Nondiabetic, Normotensive Volunteers

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The relative effect of an increase in low-density lipoprotein-cholesterol (LDL-C) concentration, as compared with insulin resistance and its manifestations, on intimal medial thickening (IMT) of the common carotid artery was defined in 72 healthy men and women. Insulin-mediated glucose disposal was quantified by the insulin suppression tests, in which the height of the steady-state plasma glucose (SSPG) concentration during the last 30 minutes of a 180-minute infusion of octreotide, insulin, and glucose provides an estimate of insulin resistance. IMT was determined by high-resolution B-mode ultrasonography. Univariate analyses defined statistically significant correlation coefficients between IMT and LDL-C concentration ($r = .25$, $P < .05$), SSPG concentration ($r = .32$, $P < .01$), triglycerides (TG) ($r = .25$, $P < .05$), and high-density lipoprotein-cholesterol (HDL-C) ($r = -.28$, $P < .05$) concentrations (changes associated with insulin resistance) and ratio of waist-to-hip girth ($r = .29$, $P < .05$). When forward step-wise linear regression analysis was used, concentrations of SSPG, LDL-C and HDL-C all emerged as independent predictors of IMT ($P < .05$). Furthermore, the magnitude of their relationship to IMT values was comparable. These results provide evidence that insulin resistance is as significant a predictor of degree of atherogenesis (estimated by IMT) of the common carotid artery as a high LDL-C concentration.

PROSPECTIVE EPIDEMIOLOGIC studies have emphasized that individuals most at risk to develop coronary heart disease (CHD) are those with combined dyslipidemia,[1,2] characterized by having an increase in low-density lipoprotein-cholesterol (LDL-C) and the combination of high triglyceride (TG) and low high-density lipoprotein-cholesterol (HDL-C) concentrations. Although either change by itself increases risk of CHD, there is substantial evidence that the untoward effect of the combination greatly augments the likelihood that CHD will develop. There is also evidence that individuals with combined dyslipidemia or only a high TG and low HDL-C concentration, are insulin resistant and hyperinsulinemic, whereas individuals with only a high LDL-C are not.[3] Thus, it appears that there are 2 fundamental syndromes that play a major role in CHD risk, a high LDL-C, unrelated to insulin resistance, and the combination of a high TG and low HDL-C concentration, which is significantly related to insulin resistance.[1-3] Using ultrasound measures of intimal medial thickening (IMT) of the common carotid artery as the surrogate measure of atherogenesis, either a high LDL-C[4-6] or the combination of a high TG and low HDL-C concentration[7-11] has been shown to be related to early atherosclerosis. Some studies have suggested that both clinical syndromes are predictors of cardiovascular disease.[12-14] However, the relative effects of these 2 fundamental syndromes have been seldom addressed, and in most instances, direct measurements of insulin resistance were not performed. The goal of the present study was to evaluate the relative effects of increase in LDL-C concentration, as compared with direct measurements of insulin resistance and its manifestation, on cardiovascular risk in a cross-sectional study of nondiabetic individuals.

MATERIALS AND METHODS

Volunteers for this study were recruited from individuals attending a health screening center, as well as medical center employees. To be admitted to the study, volunteers had to be between 40 to 60 years of age, in good general health, without a history of diabetes, hypertension, or lipid disorder, nonsmokers, and no medication that would affect carbohydrate or lipid metabolism. Overnight fasting blood samples were obtained for measurement of fasting plasma glucose, insulin, lipoprotein, and uric acid concentrations. In addition, liver and renal function tests were performed, and only individuals with normal liver and renal function enrolled. Finally, measurements were made of blood pressure, body mass index (BMI), and ratio of waist-to-hip (WHR) girth. Volunteers were excluded if they had a fasting glucose concentration greater than 126 mg/dL, a BMI greater than 30 kg/m^2, or a blood pressure greater than 160/90 mm Hg. The volunteers who qualified for further study included 30 men and 42 women of Chinese ancestry, with a mean $\pm$ SD age of 47 $\pm$ 6 years, none of whom were diabetic, hypertensive, or obese.

Insulin-stimulated glucose disposal was determined as described previously.[15,16] Briefly, after an overnight fast, intravenous catheters were placed in each arm. Blood was sampled from 1 arm for plasma glucose and insulin concentration, and the contralateral arm was used for administration of test substances. Each subject was given a continuous infusion of octreotide acetate at 30 μg/h following a bolus of 25 μg, insulin at 25 mU/m^2/min, and glucose at 240 mg/m^2/min for 180 minutes. Blood was sampled hourly until 2 hours into the study, and then every 10 minutes at 150, 160, 170, and 180 minutes. These last 4 values were averaged and used as an estimate of the steady-state plasma glucose (SSPG) and steady-state plasma insulin (SSPI) concen-

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trations. Because octreotide inhibits endogenous insulin secretion, the infusion of exogenous insulin resulted in similar SSPI concentration in all subjects. In this situation, the SSPG concentration provides a measure of the efficacy of insulin in promoting disposal of the infused glucose load.

IMT was measured by calculating the distance between the lumen-intima interface and the media-adventitia interface on the B-mode ultrasound image.[17] In our study, the common carotid artery of all subjects was evaluated with high-resolution B-mode ultrasonography (Aspen; Acuson, Mountain View, CA) with a 7.5 MHz transducer, by a single experienced neurologist (C.W. Liou), who was blinded to the results of the metabolic findings of the subjects, and all images were photographed. Scanning of the common carotid artery was performed bilaterally within 30 mm proximal to the bifurcation in anterior oblique, lateral, and posterior oblique views. Six measures (3 from the near wall, 3 from the far wall) were obtained in each view. Eighteen measures from the 3 views of each side were averaged, and the mean of the right and left averages was used in the analysis. The correlation coefficient between repeated measurements was 0.90 for intraobserver analyses.

Plasma glucose concentration was determined on an autoanalyzer (Olympus Reply; Olympus Optical, Mishima, Japan). For other laboratory tests, aliquots of plasma and serum were immediately frozen and stored at –70°C until analysis. Insulin was measured by radioimmunoassay (insulin radioimmunoassay kit; CIS Bio International, France), total cholesterol with a standard enzymatic method (T-CHO(S), Seiken, Tokyo, Japan), triglyceride with the standard GPO (glycerol-3-phosphate oxidase method, Seiken), HDL-C by a selective inhibition assay (HDL-C Auto "DAIICHI"; Daiichi Pure Chemical, Tokyo, Japan), and LDL-C by a 2-step detergent assay (CHOLESTEST LDL; Daiichi Pure Chemical).

Continuous data, including measurements of fasting glucose and insulin concentrations, serum lipid profile, uric acid, BMI, WHR, and blood pressure were expressed as mean ± SD, reported separately for men and women. The significance of gender-related differences was compared by Student's *t* test. Univariate analysis to examine the potential effects of each of the 12 measured variables on IMT was performed by linear regression. The interaction between these risk factors and IMT was then assessed by multiple stepwise regression analysis. Data evaluation was conducted using SPSS 9.0, 1988, for Windows (SPSS, Inc, Chicago, IL). The level of significance was determined as *P* less than .05.

RESULTS

Table 1 presents the demographic and metabolic characteristics of the 32 males and 40 female volunteers recruited for this study. The SSPG values of the 72 subjects varied widely from 50 mg/dL to 304 mg/dL, as did the LDL-C concentration (43 to 166 mg/dL). It can be seen from Table 1 that women had lower values for BMI, WHR, systolic blood pressure, and uric acid concentrations, but higher HDL-C concentrations than men. However, neither SSPG concentration nor IMT varied as a function of gender.

The correlation between degree of IMT and the 12 surrogate estimates of CHD are seen in Table 2. Univariate analysis showed significant correlations between IMT and SSPG concentration ($r = .32$, $P = .006$), WHR ($r = .29$, $P = .02$), and LDL-C concentration ($r = .25$, $P = .03$). Furthermore, IMT was found to be significantly correlated with high plasma TG ($r = .25$, $P = .03$) and low HDL-C ($r = .28$, $P = .02$) concentrations, changes that are associated with insulin resistance (high SSPG).

One approach to evaluate the relative degree of association between IMT and the measured CHD risk factors is to perform multiple stepwise regression analysis of all 12 variables on IMT. The results of the forward stepwise regression approach, which yielded identical results to the backward stepwise regression analysis, is depicted in Table 3, demonstrating that only SSPG, LDL-C, and HDL-C concentrations emerged as significant independent predictors of IMT.

Table 1. Baseline Characteristics (Mean ± SD)

Variable	Male (n = 32)	Female (n = 40)	*P* Value
Age (yr)	47 ± 6	47 ± 5	NS
BMI (kg/m^2)	24.5 ± 2.3	23.4 ± 2.2	<.05
WHR (cm)	0.90 ± 0.04	0.87 ± 0.05	<.03
Systolic BP (mm Hg)	118 ± 10	111 ± 11	<.01
Diastolic BP (mm Hg)	79 ± 8	76 ± 7	NS
IMT (cm)	0.064 ± 0.009	0.062 ± 0.007	NS
Glucose (mg/dL)	95 ± 5	96 ± 8	NS
Insulin (μU/mL)	10 ± 6	8 ± 4	NS
SSPG (mg/dL)	154 ± 65	162 ± 68	NS
Cholesterol (mg/dL)	172 ± 25	170 ± 33	NS
HDL cholesterol (mg/dL)	40 ± 9	46 ± 14	<.05
LDL cholesterol (mg/dL)	108 ± 21	103 ± 31	NS
Triglyceride (mg/dL)	119 ± 60	109 ± 56	NS
Uric acid (mg/dL)	6.8 ± 2.0	5.1 ± 0.9	<.01

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; BP, blood pressure; IMT, intimal medial thickening; SSPG, steady-state plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant.

To further delineate the contribution of these 3 variables to IMT, multivariate analysis of the relationship between pairs of these measurements were performed on IMT. Results from these analyses are shown in Table 4 and indicate that the 3 pair-wise combinations of variables exhibit similar magnitudes of significance in predicting IMT.

DISCUSSION

The hypothesis that led to the initiation of this study was that patients with combined dyslipidemia were at greatest risk for CHD because they suffered from 2 powerful, and independent, metabolic abnormalities, both a high LDL-C concentration and insulin resistance and its metabolic consequences. Furthermore, it was suggested that the untoward impact of insulin resistance and/or its manifestations would be comparable to that of a high LDL-C concentration. The results presented appear to provide an indication for both of these notions. On the other hand, several caveats concerning these results must be addressed to assess the validity of our conclusions.

Perhaps the most obvious shortcomings of our study are its cross-sectional nature and use of noninvasive B-mode ultrasonographic measurement of IMT of the carotid artery as the index of atherogenesis. There is no question that results from a prospective study, with myocardial infarction as the end point, would provide the most useful information. On the other hand, there are certainly data supporting the view that ultrasound estimates of IMT of the carotid artery provide an accurate tool for the in vivo estimate of early atherosclerosis,[17-22] including the ability to predict coronary artery calcification,[22] as well as actual coronary events.[21] Finally, although cross-sectional ob-

Table 2. Univariate Analysis for Relationship Between IMT and Various CHD Risk Factors

Variable	*r*	*P* Value
Age (yr)	0.16	NS
BMI (kg/m^2)	0.18	NS
WHR (cm)	0.29	<.05
Systolic BP (mm Hg)	0.13	NS
Diastolic BP (mm Hg)	0.18	NS
Glucose (mg/dL)	0.10	NS
Insulin (μU/mL)	0.18	NS
SSPG (mg/dL)	0.32	<.01
Cholesterol (mg/dL)	0.22	NS
HDL cholesterol (mg/dL)	−0.28	$P < .05$
LDL cholesterol (mg/dL)	0.25	$P < .05$
Triglyceride (mg/dL)	0.25	$P < .05$
Uric acid (mg/dL)	0.20	NS

Abbreviations: BMI, body mass index; WHR, waist-to-hip ratio; BP, blood pressure; IMT, intimal medial thickening; SSPG, steady-state plasma glucose; HDL, high-density lipoprotein; LDL, low-density lipoprotein; NS, not significant.

servational studies do not have the experimental power of prospective or interventional studies, they can provide information that is useful, per se, as well as providing the insights needed to formulate hypotheses for more definitive studies.

The second issue that must be addressed is the statistical method used to generate our conclusions. The obvious problem in analyzing results of a study such as ours is the multiplicity of variables associated with insulin resistance. This point is made very clear from the results in Table 2, showing that there were significant correlations between IMT and SSPG concentration ($r = .32$, $P < .01$) and concentrations of both HDL-C ($r = -.28$) and TG ($r = .25$); all of which were comparable to the relationship between IMT and LDL-C concentrations ($r = .25$, $P < .05$).

To further refine the relationship between IMT and CHD risk factors, forward stepwise multiple regression was performed with all of the variables in Table 2 entered into the model. When this was done (Table 3), only 3 of the variables entered achieved statistical significance, SSPG concentration, LDL-C concentration, and HDL-C concentration. Furthermore, when the information in both Tables 2 and 3 is considered, it seems that the 3 CHD risk factors appear to be related to IMT to a similar degree. Furthermore, the results in Table 4 demonstrate that the relationship between CHD risk factor and IMT was not particularly enhanced when any pair of the 3 factors were considered.

The identification of HDL-C and SSPG concentrations as independent risk factors for IMT suggests that the relationship

Table 3. Stepwise Multiple Regression Analysis for Determinants of IMT

Variable	Coefficient	*t*	*P*
SSPG	0.238	2.1	.039
LDL	0.280	2.6	.012
HDL	−0.245	−2.1	.036
$R^2 = .18$			

Abbreviations: SSPG, steady-state plasma glucose; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol.

Table 4. Multivariate Analysis for Pairwise Combination of Determinants of IMT

Variable Pair	R^2	*F*	*P*
HDL and LDL	.14	6.84	.002
HDL and SSPG	.12	5.60	.006
LDL and SSPG	.14	6.74	.002

Abbreviations: HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SSPG, steady-state plasma glucose.

between HDL-C concentration and IMT is unlikely to be due entirely to the well-known link between SSPG and HDL-C concentrations.[23-25] The fact that there is a relationship between SSPG concentration and IMT is independent of HDL-C concentration does not necessarily mean that insulin resistance, per se, is atherogenic. For example, SSPG and TG concentrations are closely related,[26,27] and it could be argued that the identification of SSPG concentration, and not TG concentration, in the multiple regression analysis is simply because of the greater inter- and intraindividual variability of TG concentrations as compared with SSPG concentrations.[28] Furthermore, SSPG concentrations are significantly correlated with smaller and denser LDL particles,[29] higher concentrations of plasminogen activator inhibitor-1,[30] increase in concentration of partially oxidized LDL particles,[31] and higher remnant lipoproteins concentrations[32]; all of which have been viewed as CHD risk factors.[33-36] Thus, caution should be exercised in concluding that insulin resistance, as contrasted to its related variables, is responsible for the increased IMT.

Finally, it is necessary to put our results in the context of other cross-sectional studies that have evaluated the relationship between insulin resistance and carotid IMT. If we first focus on results of studies in subjects without either type 2 diabetes, hypertension, or clinically established CHD, the first published report that used specific measures to assess the relationship between resistance to insulin-mediated glucose disposal and asymptomatic carotid IMT reported that 30 middle-aged subjects with evidence of atherosclerosis were insulin resistant as compared with 13 control subjects.[37] Similar findings in a relatively small case-control study of 25 men were found by Agewall et al.[38] A more recent study of 104 clinically healthy 58-year-old men of Swedish ancestry showed that common carotid IMT correlated significantly with insulin sensitivity assessed by the clamp technique.[8] The conclusion of the only large population-based study[39] was that insulin-resistance was an independent predictor of IMT in Hispanic and non-Hispanic whites, but not in African Americans. Our study population is a body of nondiabetic, normotensive subjects, and we have defined the correlation of IMT and clinical correlates at an early stage of atherosclerosis in this normal population. We plan to continue this study to fully assess the effects of insulin resistance and dyslipidemia on the development of cardiovascular disease.

The general conclusion that insulin resistance is an independent predictor of IMT is also supported by results in patients with high blood pressure,[7] vasospastic angina,[40] and type 2 diabetes.[41,42] However, not all studies in nondiabetics have defined relationships between measurement of insulin resis-

tance[41] or plasma insulin concentration[43,44] and carotid IMT. On the other hand, even the studies that have emphasized the lack of a relationship between insulin resistance/hyperinsulinemia and IMT have not concluded that the 2 variables are unrelated, but rather that their association was not an independent one.

Although there is not a total consensus as to the relationship between insulin resistance and carotid IMT, there seems to be considerable support for the view that insulin resistance is an independent predictor of carotid IMT in healthy volunteers without either type 2 diabetes or high blood pressure. Furthermore, our results demonstrating that SSPG, HDL-C, and LDL-C concentrations all independently predicted IMT are consistent with the results recently published by Jeppesen et al[45] in the Copenhagen Male Study. These investigators reported on the incidence of clinical ischemic heart disease in 2,910 men followed for 8 years, using the combination of a high TG and low HDL-C concentrations, the characteristic dyslipidemia of Syndrome X,[3,23-25] as a marker of insulin resistance. Their results demonstrated that insulin resistance, thus defined, was at least as powerful a predictor of ischemic heart disease as a high LDL-C concentration. The results of the Copenhagen Male Study, in conjunction with the results we presented, plus our review of other data using IMT as an indicator of CHD, provide substantial support for the view that insulin resistance, and/or its manifestations, is as significant a predictor of IMT as high LDL-C concentrations.

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