ORIGINAL REPORTS: CARDIOVASCULAR DISEASE AND RELATED RISK FACTORS

LOW HIGH-DENSITY LIPOPROTEIN CHOLESTEROL IS ASSOCIATED WITH IMPAIRED ENDOTHELIAL FUNCTION IN ASIAN INDIANS

This study was designed to assess the relationship between plasma lipid levels and endothelial function in Asian Indians without cardiovascular risk factors living in the United States. While traditional risk factors do not account for the increased incidence of coronary heart disease (CHD) in Asian Indians, low high-density lipoprotein (HDL) cholesterol, elevated triglycerides, elevated lipoprotein (a), and insulin resistance are consistently found in Asian Indians with CHD. Endothelial function was measured in 86 healthy Asian Indians (mean age 33 years) free of cardiac risk factors with LDL levels<160 mg/dL. Subjects were divided into two groups on the basis of HDL levels (low HDL<40 mg/dL and normal HDL≥40 mg/dL). Endothelial function during reactive hyperemia was significantly impaired in Asian Indians in the low HDL group. After covariate adjustment, NTG-induced brachial vasodilation was not different between patients in the two HDL groups. These data indicate that low HDL is associated with endothelial dysfunction in this population. (*Ethn Dis.* 2005;15:555–561)

Key Words: High-Density Lipoprotein Cholesterol, Asian Indian, Endothelial Function, Flow-Mediated Dilation

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INTRODUCTION

The development of coronary heart disease (CHD) in Asian Indians living in the United States is more premature and extensive compared to other races.[1] While the traditional CHD risk factors, such as obesity, diabetes, smoking, hypertension, and elevated low-density lipoprotein cholesterol (LDL-C), occur less frequently in Asian Indians than in western European descendants, the prevalence of low high-density lipoprotein cholesterol (HDL-C), elevated triglycerides, elevated lipoprotein (a), and insulin resistance occur more frequently in Asian Indians.[2–11] The increased risk of CHD in Asian Indians living in the United States may be partially linked to overexpression of the polymorphic APOC3 gene, which is associated with hypertriglyceridemia and reduced HDL.[12–14]

Endothelial dysfunction is a well-documented precursor to the development of CHD. Recent studies have demonstrated that endothelial dysfunction is an independent predictor of subsequent atherosclerosis and cardiovascular events.[15–18] Elevated LDL-C is associated with impaired endothelial function.[19–21] Hypercholesterolemia induces endothelial dysfunction by increasing intimal hyperplasia and incorporating lipids into the vascular wall.[22]

It is unknown if the greater prevalence of low HDL and high triglycerides in the absence of elevated LDL in Asian Indians is associated with endothelial dysfunction. The purpose of this study was to assess the relationship between lipid profiles and endothelial function in healthy Asian Indians with no cardiovascular risk factors living in the United States. The relationship between lipid status and endothelial function was evaluated after stratifying subjects into a low-HDL (<40 mg/dL) group and a normal-HDL (≥40 mg/dL) group.

The purpose of this study was to assess the relationship between lipid profiles and endothelial function in healthy Asian Indians with no cardiovascular risk factors living in the United States.

MATERIALS AND METHODS

Subjects

The study group consisted of self-identified Asian Indians >25 years of age with an LDL cholesterol ≤160 mg/dL. Subjects were recruited through local Asian Indian community associations and screened by telephone for known inclusion/exclusion criteria. Individuals who met basic entry criteria underwent a history and physical examination.

Participants could not have any known cardiovascular risk factors including diabetes, treated or untreated hypertension, recent or current use of tobacco, family history of premature CHD, known peripheral vascular disease, body mass index ≥30 kg/m^2, or prior or current use of lipid-lowering medications. Women were excluded if they were pregnant or breastfeeding. Subjects were stratified into two cohorts based on HDL levels: low HDL-C (<40 mg/dL) and normal HDL-C (≥40 mg/dL). Patients who met enrollment criteria provided written informed consent. The protocol was approved by the institutional review board of Creighton University.

Study Protocol

Qualifying subjects had fasting lipid profiles obtained from the antecubital vein and were then stratified into their respective HDL study cohort based on those results. Subjects were asked to fast for at least eight hours before the endothelial function study. All subjects were placed in the supine position in a quiet, temperature-controlled room for 10 minutes prior to the first scan. Baseline blood pressure and pulse were obtained, and electrodes were applied for obtaining a continuous, single-lead electrocardiographic rhythm recording.

The ultrasound flow-mediated dilation (FMD) method for measuring endothelial-dependent and endothelial-independent brachial arterial dilation was used. The ultrasound B-mode images were obtained with the use of a multi-frequency Trapezoidal Linear Array, L-10-4MHz transducer and a standard Sonos 5500 imaging system. The brachial artery was scanned in the longitudinal plane, 2–15 cm above the antecubital fossa. The center of the artery was identified when the clearest picture of the anterior and posterior intimal layers was obtained, and the transmit was set to the depth of the near wall. Depth and gain settings were set to optimize images of the interface

between the lumen and the arterial wall. Images were magnified with a resolution box function (leading to a video line width of ≈0.065 mm) and were placed in a Cine-loop mode to allow repeated measurements. When a satisfactory transducer position was found, the skin was marked, and the arm remained in the same position throughout the study.

Brachial artery diameter was measured from ultrasound by two independent sonographers blinded to clinical information. The diameter was measured at a fixed distance from the bifurcation with electronic calipers. Measurements were made from anterior to posterior intima-media interface at end diastole marked by the ECG R-wave. Arterial flow velocity was estimated by time-averaging the pulsed Doppler velocity signal obtained from the mid-artery sample volume.

Reactive hyperemia was induced by inflation of a sphygmomanometric cuff around the arm, proximal to the scanned portion of the artery, to a pressure of 60 mm Hg above baseline systolic blood pressure for 4.5 minutes, followed by release. A second scan was performed continuously from 30 seconds before to 120 seconds after deflation of the cuff, including a repeated recording of the flow velocity for the first 15 seconds after release. Diameter was measured at 30, 60, 90, and 120 seconds after release to evaluate the temporal progression of vasodilation. Four cardiac cycles were analyzed per scan.

After a 10-minute recovery period, an additional resting scan was performed. A sublingual nitroglycerin (NTG) tablet (0.4 mg) was then administered to the subject. At four minutes after NTG administration, a repeat scan was performed by using previously described methods.

Statistical Methods

The FMD and NTG-induced vasodilation were calculated by each ob-

server, and the average results were recorded. As indicated earlier, this method is accurate and reproducible for measuring small changes in the arterial diameter with low rates of intra-observer variability. Percent change in brachial artery diameter during reactive hyperemia and in response to NTG was calculated as change in diameter/baseline diameter × 100. Volume flow was calculated by multiplying the velocity-time integral of the Doppler flow signal (corrected for angle) by the heart rate and the cross-sectional area of the vessel (πr^2). The established coefficients of variation between brachial artery diameter and flow measurements in our cardiovascular ultrasound laboratory are 1.76% and 1.33%, respectively.

Age, total cholesterol, LDL-C, triglycerides, resting vessel diameters, resting flow and velocity, and resting resistive index were summarized for each group by their means and standard deviations. Pearson correlation coefficients were calculated to assess the relationship between reactive hyperemia or NTG-induced dilation and lipid parameters, resting vessel diameter, age, and sex. Multivariate analysis of covariance corrected for multiple comparisons using Bonferroni adjustment was then used to evaluate reactive hyperemia by HDL status after correcting for significant covariates. This multivariate analysis was then repeated for percent NTG-induced dilatation. A *P* value <.05 was considered statistically significant.

RESULTS

Clinical Characteristics

Clinical characteristics for the two HDL cohorts are summarized in Table 1. There were no significant differences in age, total cholesterol, LDL cholesterol, and baseline systolic flow velocity between the two groups. A significantly greater proportion of pa-

tients in the low HDL cohort were men compared to the normal HDL cohort (85% vs 45%; *P*=.001). Patients in the low HDL cohort also had significantly higher triglycerides (*P*=.001) and larger baseline brachial artery diameters both prior to reactive hyperemia (*P*<.001) and NTG administration (*P*<.001). The difference in the baseline artery diameter most likely was due to a higher proportion of men in the low HDL group.

Brachial Artery Flow-Mediated Dilation

In both groups, brachial artery dilation was most profound at the 60-second time interval (Figure 1). The FMD, or percent change in brachial artery diameter relative to baseline, was significantly less in the low HDL group for both reactive hyperemia and after NTG administration at all time points.

Table 2 summarizes the Pearson correlation coefficients between lipid parameters and FMD expressed as the percent change from baseline at the various time intervals. High density lipoprotein was significantly correlated to FMD at all time points during reactive hyperemia except at 120 seconds. The total cholesterol/HDL ratio and the LDL/HDL ratio were significantly correlated to FMD during reactive hyperemia at all time points. Triglycerides were significantly correlated to FMD at all time points during reactive hyperemia, but not during NTG-induced vasodilation. Triglycerides, total cholesterol/HDL ratio, and LDL/HDL ratio had significant inverse relationships with reactive hyperemia, while HDL had a positive correlation with both reactive hyperemia and NTG-induced vasodilation. The linear relationship between HDL and reactive hyperemia at 60 seconds is depicted in Figure 2.

Multivariate Analysis

Table 3 summarizes the influence of HDL on the percent change in flow-

Table 1. Baseline clinical characteristics of the two cohorts

	Low HDL	Normal/High HDL	
	HDL<40 mg/dL	HDL≥40 mg/dL	
	n=26	*n*=60	*P* value
Age	34.7 ± 5.5	32.2 ± 6.4	.084
Men/women	22/4 (85%/15%)	27/33 (45%/55%)	.001
TC (mg/dL)	185.4 ± 31.1	182.2 ± 30.9	.670
LDL (mg/dL)	113.2 ± 21.3	107.8 ± 26.4	.360
TG (mg/dL)	186.7 ± 100.0	106.9 ± 52.7	.001
HDL (mg/dL)	33.1 ± 6.4	47.4 ± 3.8	<.001
Pre-reactive hyperemia diameter (cm)	0.45 ± 0.067	0.37 ± 0.056	<.001
Pre-reactive hyperemia systolic flow velocity (m/sec)	0.65 ± 0.16	0.61 ± 0.14	.243
Pre-reactive hyperemia diastolic flow velocity (m/sec)	0.080 ± 0.059	0.056 ± 0.052	.066
Pre-reactive hyperemia RI	0.88 ± 0.082	0.91 ± 0.078	.127
pre-NTG diameter (cm)	0.45 ± 0.064	0.38 ± 0.062	<.001
Pre-NTG systolic flow velocity (m/sec)	0.62 ± 0.10	0.57 ± 0.13	.122
Pre-NTG diastolic flow velocity (m/sec)	0.063 ± 0.054	0.037 ± 0.042	.018
Pre-NTG RI	0.89 ± 0.079	0.94 ± 0.062	.009

HDL=high-density lipoprotein; LDL=low-density lipoprotein; NTG=nitroglycerin; RI=resistive index; TC=total cholesterol; TG=triglycerides.

mediated dilatation after correcting for sex, age, other lipid parameters, baseline vessel diameter, and baseline flow measurements. Reactive hyperemia measurements differed significantly between the HDL groups at each time point (Figure 1). At 30 seconds, the final model included a significant sex effect (*P*=.037), sex by HDL group interaction (*P*=.024), and significant covariate pre-reactive hyperemia diameter (*P*<.001). After correcting for these, the difference between HDL groups remained significant (*P*=.001). At 60 seconds, the final model included the following significant covariates: pre-reactive hyperemia diameter (*P*<.001), pre-reactive hyperemia systolic flow (*P*<.001), and age
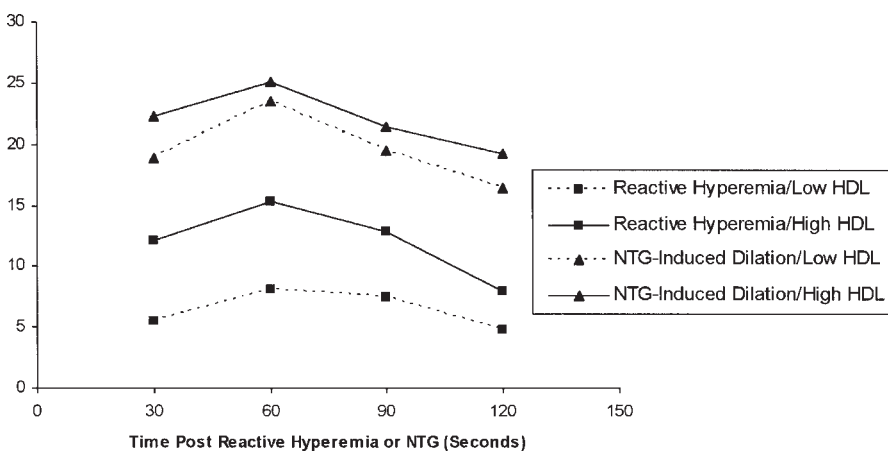
Fig 1. Percent change in artery diameter during reactive hyperemia and NTG-induced dilation over time after multivariate analysis; statistical comparison: * *P*<.001; + *P*=.004; low vs high HDL

Table 2. Correlation between lipid parameters and percent change in artery diameter during reactive hyperemia and NTG-induced vasodilation

Lipid Parameter	% Δ FMD @ 30 Seconds	% Δ FMD @ 60 Seconds	% Δ FMD @ 90 Seconds	% Δ FMD @ 120 Seconds
Reactive Hyperemia				
HDL	0.395	0.407	0.372	0.200
	$P<.001$	$P<.001$	$P<.001$	$P=.065$
TG	−0.281	−0.337	−0.303	−0.239
	$P=.009$	$P=.002$	$P=.005$	$P=.027$
TC/HDL ratio	−0.352	−0.403	−0.394	−0.260
	$P<.001$	$P<.001$	$P<.001$	$P=.016$
LDL/HDL ratio	−0.307	−0.345	−0.363	−0.230
	$P=.004$	$P=.001$	$P=.001$	$P=.033$
NTG				
HDL	0.355	0.408	0.337	0.310
	$P<.001$	$P<.001$	$P=.002$	$P=.004$
TG	−0.199	−0.180	−0.201	−0.201
	$P=.066$	$P=.098$	$P=.063$	$P=.064$
TC/HDL ratio	−0.313	−0.299	−0.281	−0.246
	$P=.003$	$P=.005$	$P=.009$	$P=.023$
LDL/HDL ratio	−0.306	−0.283	−0.250	−0.208
	$P=.004$	$P=.008$	$P=.020$	$P=.055$

HDL=high-density lipoprotein; NTG=nitroglycerin; TC=total cholesterol; TG=triglycerides.

($P=.028$). After correcting for these, the difference in HDL groups was significant ($P<.001$). At 90 seconds, the final model included only the covariate of pre-reactive hyperemia di-

ameter ($P=.002$). After adjustment, the difference in HDL groups was significant ($P=.002$). At 120 seconds, the final model included only one covariate of pre-reactive hyperemia di-
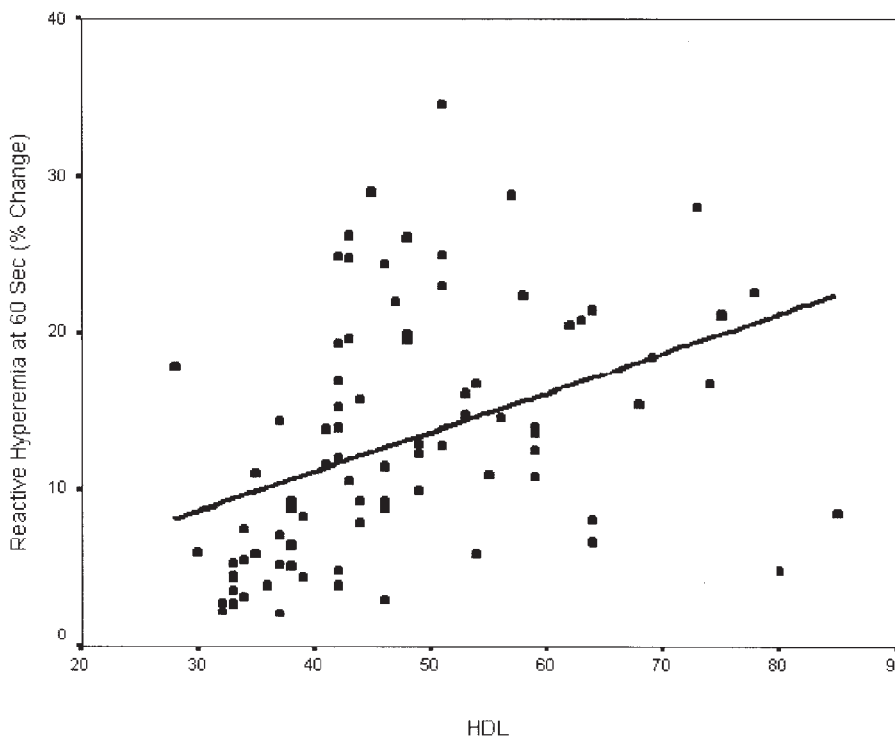
ameter ($P=.028$). After adjustment, the difference in HDL groups was significant ($P=.040$).

Nitroglycerin-induced vasodilation did not differ significantly between the HDL groups at any of the time points after correcting for significant covariates and sex. At 30 seconds, the final model included a significant sex by HDL effect ($P=.019$) and pre-reactive hyperemia diameter ($P<.001$). The difference between HDL groups at 30 seconds was not significantly different ($P=.178$). At 60, 90, and 120 seconds, the final model included pre-NTG diameter ($P<.001$) as the only significant covariate. After adjustment, the difference in HDL groups was not statistically different.

DISCUSSION

Our study is the first to assess the relationship between HDL levels and endothelial function in a relatively large sample of Asian Indians without cardiovascular risk factors living in the United States. We demonstrated that endothelial function as measured by FMD during reactive hyperemia is significantly impaired in Asian Indians with low HDL levels. The maximal vasodilatory response in both cohorts was seen at 60 seconds following release of vessel occlusion which is consistent with previously reported data.[23,24] After covariate adjustment, NTG-induced

We demonstrated that endothelial function as measured by FMD during reactive hyperemia is significantly impaired in Asian Indians with low HDL levels.

Fig 2. Relationship between HDL and flow-mediated dilation at 60 seconds

Table 3. Multivariate analysis of covariance

| | Low HDL | Normal/High HDL | |
| | HDL<40 mg/dL | HDL≥40 mg/dL | |
	n=26	*n*=60	Significance
Reactive Hyperemia			
Gender interaction			*P*=.024
Men	10.22 ± 1.70	12.22 ± 1.25	
Women	0.72 ± 3.32	12.03 ± 1.30	
% Δ at 30 seconds	5.47 ± 1.77	12.13 ± 0.89	*P*=.001
% Δ at 60 seconds	8.09 ± 1.16	15.26 ± 0.72	*P*<.001
% Δ at 90 seconds	7.44 ± 1.35	12.82 ± 0.84	*P*=.002
% Δ at 120 seconds	4.82 ± 1.22	7.99 ± 0.76	*P*=.040
NTG			
Gender interaction			*P*=.019
Men	22.90 ± 2.08	20.37 ± 1.58	
Women	14.89 ± 4.14	24.22 ± 1.66	
% Δ at 30 seconds	18.89 ± 2.22	22.30 ± 1.10	*P*=.178
% Δ at 60 seconds	23.49 ± 1.46	25.11 ± 0.92	*P*=.374
% Δ at 90 seconds	19.41 ± 1.55	21.45 ± 0.97	*P*=.291
% Δ at 120 seconds	16.42 ± 1.56	17.25 ± 0.98	*P*=.668

HDL=high-density lipoprotein; NTG=nitroglycerin.

brachial vasodilation was not correlated with HDL levels. We also found a significant inverse relationship between reactive hyperemia and triglycerides, total cholesterol/HDL ratio, and LDL/HDL ratio. This is of particular interest as hypertriglyceridemia has previously been shown not to be associated with endothelial dysfunction.[25] These data indicate that low HDL is an independent risk factor for endothelial dysfunction in this ethnic population.

Reduced production of nitric oxide (NO) by the endothelium is thought to induce endothelial dysfunction in patients with dyslipidemia.[26] Studies with lipid-lowering medications have demonstrated normalization of endothelial function, increased NO-mediated vasodilation, reduced reactive oxygen species, and reduced proinflammatory markers such as intracellular adhesion molecule-1 (ICAM-1), E-selectin, P-selectin, and tissue plasminogen activator antigen (tPAag).[27–37]

In addition to modulating NO release, low HDL with or without high triglycerides in the absence of elevated LDL in Asian Indians may result in endothelial dysfunction through other mechanisms. A normal or high HDL may inhibit endothelial dysfunction by binding free transition metals, shuttling reactive hydroperoxides from the endothelium to the liver for excretion via intrinsic antioxidant enzymes, and limiting the endothelial toxicity of very low-density lipoprotein (VLDL) remnants.[38] High density lipoprotein has also been shown to inhibit the expression of the adhesion molecules, ICAM-1 and VCAM-1, which prevent interactions between leukocytes on the endothelium.[39] Likewise, HDL has been shown to prevent oxidized LDL generation and to reverse oxidized LDL-induced impairment of endothelial relaxation.[40–42] Other proposed vasoprotective effects of HDL include modulation of endothelin secretion, endotoxin lipopolysaccharide (LPS) adsorption, decreased platelet activation, and modulation of COX-2 and PGI_2.[43] Triglycerides, on the other hand, may facilitate the progression of endothelial dysfunction by increasing the oxidative burden, stimulating endothelial cell plasminogen activator inhibitor-1 (PAI-1) production, activating Factor VII, and increasing endothelial cell expression of adhesion molecules.[38]

Previous studies investigating the relationship between lipids and endothelial function have utilized traditional and FMD methods of assessment. The relationship between lipoproteins and acetylcholine-induced coronary vasoreactivity was assessed in 27 American men and women.[44] While no correlation was found between total cholesterol, LDL, or total cholesterol/HDL ratio, there was a positive correlation between HDL and normal acetylcholine-induced coronary vasoreactivity in both angiographically smooth ($r=0.59$, $P<.001$) and diseased ($r=0.62$, $P<.02$) segments. Likewise, variables affecting atherosclerotic plaque load and local epicardial vasoreactivity in 26 German men and women were evaluated.[45] Patients with high HDL ($n=11$) had a significantly blunted constrictor response to acetylcholine ($P<.01$) in the left anterior descending coronary compared with patients with low HDL ($n=15$). A significant correlation was also found between LDL and LDL/HDL ratio and arterial endothelial function in 241 healthy Australian men and women using FMD.[46]

The relationship between HDL and endothelial function in 20 healthy young Finnish men found that FMD was significantly correlated with HDL levels.[47] A similar study was conducted in 105 Chinese men and women with normal total cholesterol, 71 with known CHD and 34 without CHD.[48] The degree of FMD significantly correlated with HDL, but not LDL or total cholesterol.

Abnormalities in endothelial function were assessed in 26 Asian Indians (Punjabi Sikh) and 18 European Caucasian males living in London, England.[49] While no differences existed between baseline brachial artery diameters in Asian Indians and Caucasians or in brachial artery dilation in response to sublingual nitroglycerin, FMD was significantly reduced in Asian Indians.

Several studies have assessed pharmacologic means of increasing HDL

and its effect on endothelial function. Endothelial function was measured in patients from the United States Armed Forces Regression Study by FMD.[50] Patients had to have angiographic evidence of CHD with normal or modestly elevated LDL (<160 mg/dL) and low HDL (<40 mg/dL). Patients were treated for 30 months with gemfibrozil ± niacin ± cholestyramine or placebo. Despite a 24% reduction in LDL and a 27% increase in HDL, lipid lowering therapy failed to improve FMD or nitroglycerin-induced dilation. The effect of six months of treatment with bezafibrate on endothelial function in 16 Spanish males with known CHD, isolated low HDL (<35 mg/dL), LDL <160 mg/dL, and endothelial dysfunction has also been reported.[51] Bezafibrate produced a 28% increase in $cHDL_2$, a 26% increase in $cHDL_3$, and a 14% increase in apolipoprotein A-I. Mean FMD increased after bezafibrate therapy from 2.5 ± 4.2% to 12.3 ± 7.1% (*P*=.0004) and normalized or improved in 75% of the participants. It has also been recently shown that an infusion of recombinant HDL in healthy hypercholesterolemic men increases plasma HDL levels and normalizes endothelial function.[52]

Whether newer modalities that increase HDL, such as cholesterol ester transfer protein (CETP) inhibitors, will lead to improvements in endothelial function and subsequent reductions in CHD risk continue to be investigated.[53]

While baseline clinical characteristics for the two HDL cohorts were generally similar, more men than women were in the low HDL group. In addition, subjects in the low HDL group had greater baseline brachial artery diameters. This most likely resulted from the relatively larger vessel size found in men. It is uncertain if conclusions about endothelial dysfunction and low HDL levels in women can be reached. Subjects in the low HDL group also had significantly higher triglycerides. Likewise, other potential

cardiovascular risk factors such as insulin resistance and LDL particle size were not evaluated. We also did not quantify changes in HDL subclass.

The measurement of endothelial function and its association with lipid profiles in Asian Indians with no cardiovascular risk factors living in the United States had not been previously assessed. These data indicate that a low HDL is an independent risk factor for the development of endothelial dysfunction and potentially for the development of CHD in this ethnic population. Because endothelial dysfunction occurs prior to angiographic evidence of atherosclerosis, our findings strongly suggest that HDL levels should be assessed in the screening of cardiovascular risk.[54] Further research is needed to assess the association between low HDL and endothelial dysfunction in other ethnic populations. The ability of risk factor modification and pharmacologic intervention to raise HDL, reverse endothelial dysfunction, and decrease cardiovascular events will also require further investigation.

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