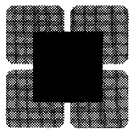

Lipid and lipoprotein abnormalities in lower-extremity arteriosclerosis obliterans

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■ The prevalence of abnormal lipid and lipoprotein values was determined in 125 consecutive patients with lower-extremity arteriosclerosis obliterans, and the lipid and lipoprotein abnormalities in these patients were characterized. Only 13% of the patients had normal lipid/lipoprotein profiles. Forty-eight percent of patients had low levels of high-density lipoprotein cholesterol. High-density lipoprotein cholesterol values were lower in patients with concomitant coronary heart disease compared with those without heart disease. High-density lipoprotein cholesterol values were inversely related to weight, to triglyceride values, and to diabetes mellitus. Twenty-eight percent of patients had "desirable" total cholesterol levels (<200 mg/dL), and 32% had low-density lipoprotein cholesterol values less than 130 mg/dL. Following National Cholesterol Education Program guidelines may be misleading in patients with documented lower-extremity atherosclerosis; therefore, complete lipid/lipoprotein profiles should be performed in these patients.

□ INDEX TERMS: ARTERIOSCLEROSIS OBLITERANS; LEG; LIPIDS; LIPOPROTEINS □ CLEVE CLIN J MED 1992; 59:491–497

THE TOTAL CHOLESTEROL (TC) level is routinely used to screen healthy asymptomatic patients to determine risk of cardiovascular disease. But TC alone is not always a reliable indicator of cardiovascular risk, particularly in certain subsets of patients, such as those with lower-extremity arterial disease.

In 1960, Juergens reported significantly higher TC values in patients with arteriosclerosis obliterans (ASO) compared with normal age-matched controls (256 ± 55 mg/dL vs 198 ± 25 mg/dL).[1] Over the next 20 years, investigators reported various lipid abnormalities in patients with lower-extremity ASO. In these series, the incidence of abnormal lipid profiles in these patients ranged from 17% to 46%.[2–5] These studies did not measure high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C). In 1978, Bradby et al were among the first to demonstrate low HDL-C values in patients with peripheral vascular disease; however, 41% of their patients had normal lipid values.[6]

In 1988, the Expert Panel of the National Cholesterol Education Program (NCEP) published its first report providing guidelines for detecting, evaluating, and treating high cholesterol in adults.[7] The panel recommended that all adults over age 20 be screened

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TABLE 1
DEMOGRAPHIC DATA AND LIPID-LIPOPROTEIN VALUES (MEAN ± SD)

	Male (n = 73)	Female (n = 52)	Total (n = 125)	P value*
Age (years)	63 ± 9	66 ± 10	64 ± 10	.039
Weight (kg)	81 ± 20	68 ± 13	75 ± 18	.0001
Body mass index	26 ± 4	27 ± 5	26 ± 4	NS
Fasting plasma glucose†	7.16 ± 3.5 (129 ± 64)	7.32 ± 3.0 (132 ± 55)	7.27 ± 3.3 (131 ± 60)	NS
Total cholesterol†	6.0 ± 1.4 (233 ± 55)	6.4 ± 1.7 (245 ± 65)	6.2 ± 1.5 (238 ± 60)	NS
Triglycerides†	2.7 ± 2.6 (243 ± 231)	2.7 ± 2.4 (238 ± 216)	2.7 ± 2.5 (241 ± 224)	NS
HDL-C†	0.9 ± 0.3 (36 ± 12)	1.1 ± 0.4 (42 ± 15)	1.0 ± 3 (38 ± 13)	.01
LDL-C†	3.9 ± 1.2 (151 ± 45)	4.0 ± 1.2 (155 ± 45)	4.0 ± 1.2 (153 ± 45)	NS
Normal lipid profile	—	—	16 (13%)	

NS, not significant
*Comparing men to women
†mmol/L (mg/dL)

with a TC measurement. If the patient's TC is less than 200 mg/dL, the panel stated, the test should be repeated every 5 years. If the TC is between 200 and 239 mg/dL, lipoprotein values should be analyzed. Further action is based on the LDL-C: LDL-C values less than 130 mg/dL are considered desirable, values from 130 to 159 mg/dL are borderline elevated, and values of 160 mg/dL or greater are considered abnormal and indicate high cardiovascular risk. In the NCEP guidelines, TC greater than 239 mg/dL is considered high.

In the time since these guidelines were published, lipid and lipoprotein abnormalities have not been characterized as well in patients with lower-extremity ASO as they have in patients with coronary heart disease. The purpose of the present study was to determine the prevalence of abnormal lipid and lipoprotein values in patients with lower-extremity ASO and to characterize these abnormal values in this group of patients.

PATIENTS AND METHODS

One hundred twenty-five consecutive patients with documented lower-extremity ASO were evaluated in a vascular medicine clinic. All patients were studied prospectively. Information was obtained regarding cardiovascular risk factors and whether atherosclerotic disease was present elsewhere. Lipid and lipoprotein values, a fasting plasma glucose level, sequential multiple analysis (SMA-16), urinalysis, and thyroid-stimulating hormone level were obtained for each patient. All patients had a history of intermittent claudication, ischemic ulcerations, or rest pain. All patients had abnormal pulse-volume recordings and Doppler pressures, whether at rest or after treadmill testing. Arteriography was performed in patients being considered for surgical intervention, percutaneous transluminal angioplasty, or atherectomy.

Sixty patients had concomitant coronary artery disease (history of myocardial infarction, coronary artery bypass grafting, or percutaneous transluminal coronary angioplasty), angina pectoris, electrocardiographic evidence of an old myocardial infarction, an abnormal stress test, or greater than 50% stenosis of a coronary artery on cardiac catheterization.

Since diabetes mellitus is associated with both ASO and lipid and lipoprotein abnormalities, patients with normal glucose tolerance were compared with patients with borderline glucose tolerance and diabetes mellitus. Diabetes was classified using a modification of the National Diabetes Data Group criteria. "Normal" glucose tolerance was defined as fasting plasma glucose <6.4 mmol/L (115 mg/dL), "borderline" glucose tolerance was defined as fasting plasma glucose ≥6.4 mmol/L (115 mg/dL) and <7.8 mmol/L (140 mg/dL), and "diabetes mellitus" was defined as fasting plasma glucose ≥7.8 mmol/L (140 mg/dL).[8] Since oral glucose tolerance tests were not performed, this classification may underestimate the incidence of diabetes mellitus and impaired glucose tolerance.

Each patient fasted for 14 hours, after which a complete lipid profile of TC, triglycerides (TG), and HDL-C was performed using Lipid Research Clinics Program standardized techniques.[9] The LDL-C value was calculated when TG was less than 4.52 mmol/L (400 mg/dL), using the following formula: LDL-C equals TC minus HDL-C minus one fifth of TG. When TG was >4.52 mmol/L (400 mg/dL), LDL-C was measured directly.

STATISTICAL ANALYSIS

Differences in values for mean age, weight, body mass index, TC, and LDL-C were assessed by using a *t* test. Values for HDL-C, TG, and fasting plasma glucose failed to meet normality assumptions; therefore, a Wilcoxon rank sum test was used to assess these values. An unpaired *t* test of the difference in mean lipid values was used to compare young patients with older patients; age and lipid values were then correlated.

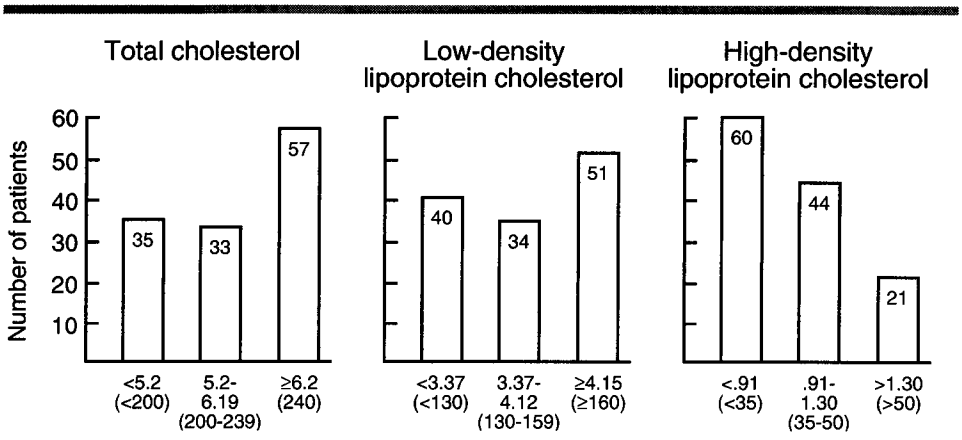

FIGURE. Distribution of total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol in 125 patients (mmol/L [mg/dL]).

A stepwise multiple regression model was used to determine whether low HDL-C or coronary heart disease were associated with other variables (eg, blood pressure, weight, age, and lipid and lipoprotein fractions). Variables that correlated univariately ($P<.2$) were entered into the stepwise selection process. Pearson's correlation coefficient was used to detect correlations among all of the variables.

RESULTS

Lipid and lipoprotein profiles

The demographic data and lipid and lipoprotein values for the entire group, as well as the values for men and women, are shown in *Table 1*. The mean age of the population was 64 ± 10 years. As expected, men weighed more than women, but there was no difference in body mass index between men and women. The lipid and lipoprotein values were identical for men and women except that men had a lower HDL-C (0.9 ± 0.3 mmol/L [36 ± 12 mg/dL]) compared with women (1.1 ± 0.4 mmol/L [42 ± 15 mg/dL]), ($P=.01$).

TC and TG values in the 50th and 90th percentile were higher in our patients compared with a group of patients of similar age in the US population; however, LDL-C values did not differ. The greatest difference between our patients and the US population sample was in HDL-C values: at the 10th, 50th, and 90th percentile, HDL-C values for both men and women were lower in our patients.[10]

Age was related to systolic blood pressure ($r=0.23$, $P=.01$), but there were no other statistically significant relationships among age and fasting plasma glucose, diastolic blood pressure, baseline TC, TG, HDL-C, or LDL-C.

Sixty-one patients smoked cigarettes, and 64 patients were not currently smoking. There was no difference in lipid or lipoprotein values between smokers and nonsmokers. In fact, the HDL-C was 1.0 ± 0.4 mmol/L (35 ± 15 mg/dL) in smokers, compared with 1.0 ± 0.3 mmol/L (35 ± 12 mg/dL) in nonsmokers. There was also no difference in lipid values in patients with hypertension (n=79) compared with patients without hypertension (n=44).

Of the 125 patients studied, only 16 (13%) had a completely normal lipid profile according to NCEP guidelines.

The *Figure* shows the distribution of TC, LDL-C, and HDL-C in the 125 patients with lower-extremity ASO. Thirty-five patients (28%) had TC measurements <5.2 mmol/L (200 mg/dL), and 57 patients (46%) had values >6.2 mmol/L (240 mg/dL). Likewise, 32% of patients had LDL-C <3.37 mmol/L (130 mg/dL). Only 41% had a clear-cut abnormal LDL-C, ie, ≥ 4.15 mmol/L (160 mg/dL). The HDL-C was <0.91 mmol/L (35 mg/dL) in 60 patients (48%).

Low and normal HDL-C

A comparison of patients with low HDL-C (<0.91 mmol/L [35 mg/dL]) and "normal" HDL-C (≥0.91 mmol/L [35 mg/dL]) is shown in *Table 2*. Patients with low HDL-C weighed more and had greater body mass indexes than those with normal HDL-C values. The

TABLE 2
PATIENTS WITH LOW AND NORMAL HDL-C VALUES

	Low HDL-C* (n = 60)	Normal HDL-C† (n = 65)	P value
Age (years)	63 ± 9	66 ± 10	.08
Weight (kg)	80 ± 22	71 ± 12	.01
Body mass index	27 ± 4	25 ± 4	.07
Fasting plasma glucose‡	7.8 ± 4.0 (140 ± 72)	6.8 ± 2.6 (122 ± 46)	.35
Total cholesterol‡	6.2 ± 1.7 (237 ± 65)	6.2 ± 1.4 (239 ± 54)	.90
LDL-C‡	3.8 ± 1.0 (146 ± 39)	4.1 ± 1.3 (160 ± 50)	.08
Triglycerides‡	3.8 ± 3.2 (336 ± 286)	1.7 ± 0.8 (153 ± 75)	.0001

*<0.91 mmol/L (35 mg/dL), mean 0.73 ± 0.13 mmol/L (28 ± 5 mg/dL)
†≥0.91 mmol/L (35 mg/dL), mean 1.20 ± 0.28 mmol/L (46 ± 11 mg/dL)
‡mmol/L (ng/dL)

TABLE 3
STEPWISE MULTIPLE REGRESSION MODEL
USING HDL-C AS A DEPENDENT VARIABLE*

	β value	STD error	P value
Weight	−0.01	0.003	.004
Body mass index	0.02	0.009	.04
Triglycerides	−0.03	0.010	.003
Diabetes	−0.12	0.052	.02

*r^2 = 0.22

TABLE 4
FACTORS RELATED TO CORONARY HEART DISEASE

	Patients without known CHD (n = 65)	Patients with known CHD (n = 60)	P value
Total cholesterol*	6.2 ± 1.6 (241 ± 62)	6.1 ± 1.5 (236 ± 57)	.65
Triglycerides*	2.3 ± 2.1 (207 ± 182)	3.1 ± 2.9 (278 ± 259)	.03
LDL-C*	4.0 ± 1.4 (154 ± 52)	3.9 ± 1.0 (152 ± 37)	.79
HDL-C*	1.1 ± 0.4 (43 ± 15)	0.9 ± 0.3 (34 ± 10)	.0001
Cigarette use			
Never	18 (28%)	11 (18%)	
Not current	14 (22%)	21 (35%)	NS
Current	33 (50%)	28 (47%)	
Glucose tolerance			
Normal	39 (60%)	32 (53%)	
Borderline	10 (15%)	12 (20%)	NS
Diabetes mellitus	16 (25%)	16 (27%)	

CHD, coronary heart disease; NS, not significant
*mmol/L (mg/dL)

two groups did not differ in values for fasting plasma glucose, total cholesterol, or LDL-C. However, TG values were higher in the low HDL-C group than in the normal HDL-C group.

Weight, body mass index, TG, and the presence of diabetes mellitus were each independently associated with low HDL-C values, as found with a stepwise multiple regression model (*Table 3*).

Coronary heart disease

Patients with known coronary heart disease had lower HDL-C values than patients without coronary heart disease (*Table 4*). These two groups did not differ in other lipid and lipoprotein values, in number of cigarette smokers, or in the presence or absence of glucose intolerance.

Diabetes mellitus

Patients with diabetes mellitus, borderline glucose intolerance, and normal glucose tolerance were essentially identical in all parameters, except that patients with diabetes had higher TG values and lower HDL-C compared with patients who had either normal or borderline glucose tolerance (*Table 5*). Using multivariate analysis, there was a correlation between fasting plasma glucose and baseline TG (r=0.21, *P*=.02). There was a weak correlation between fasting plasma glucose and HDL-C (r=−0.17, *P*=.06).

DISCUSSION

Characterization of abnormalities

This study prospectively characterizes the various lipid and lipoprotein abnormalities in a consecutive group of patients with documented ASO. Of 125 patients, 87% had abnormal lipid profiles according to NCEP guidelines. Mean values for TC, TG, and LDL-C were elevated compared with age-matched historical controls, and mean HDL-C values were lower than in the controls.[10] As demonstrated in other studies, lipid and lipoprotein values for men were similar to those in women, with the exception that men had lower HDL-C values.

Many of these patients would not be properly characterized if the current NCEP guidelines were followed: While the mean values for TC, TG, and LDL-C were elevated, a significant number of patients had values in the normal or "desirable" range according to NCEP cutoff points.[7] Twenty-eight percent of patients had TC values <5.2 mmol/L (200 mg/dL), and only 46% had TC values that were clearly high, ie, >6.2

mmol/L (200 mg/dL). Therefore, using TC as a screening parameter, nearly one third of all patients at high cardiovascular risk would not be identified.

The NCEP suggests initiating treatment based on LDL-C values. If this recommendation were followed in our patient population, the 32% of patients with LDL-C values <3.37 mmol/L (130 mg/dL) would be considered to be at low cardiovascular risk. Only 41% of our patients had clearly elevated LDL-C values. Furthermore, 48% of our patients had an HDL-C below 0.91 mmol/L (35 mg/dL). These data underscore the importance of obtaining a complete lipid profile in every patient with atherosclerosis so that appropriate modification of cardiovascular risk factors can be initiated.

TABLE 5
LIPID/LIPOPROTEIN VALUES (MEAN ± sd) AND GLUCOSE TOLERANCE

	Fasting plasma glucose			
	Normal* (n = 71)	Borderline† (n = 22)	Diabetic‡ (n = 32)	P value§
Age (years)	63 ± 10	64 ± 9	66 ± 10	NS
Weight (kg)	76 ± 14	68 ± 15	80 ± 26	NS
Body mass index	26 ± 5	24 ± 4	27 ± 4	NS
Total cholesterol‖	6.3 ± 1.5 (242 ± 59)	6.1 ± 1.2 (235 ± 46)	6.0 ± 1.8 (232 ± 69)	NS
Triglycerides‖	2.6 ± 2.5 (229 ± 218)	2.4 ± 1.8 (211 ± 157)	3.2 ± 3.1 (286 ± 270)	.06
HDL-C‖	1.0 ± 0.4 (40 ± 15)	1.1 ± 0.3 (41 ± 12)	0.9 ± 0.2 (33 ± 10)	.01
LDL-C‖	4.0 ± 1.2) (156 ± 45)	4 ± 1.1 (155 ± 44)	3.8 ± 1.2 (145 ± 48)	NS

NS, not significant
*<6.4 mmol/L (115 mg/dL)
† ≥6.4 mmol/L (115 mg/dL) and <7.8 mmol/L (140 mg/dL)
‡ ≥7.8 mmol/L (140 mg/dL)
§Comparing diabetic patients with normal and borderline patients
‖mmol/L (mg/dL)

Low HDL-C and coronary heart disease

An interesting and unexpected finding was the lower HDL-C demonstrated in patients with known coronary heart disease compared with those without known coronary heart disease. Not all patients underwent stress testing or cardiac catheterization; therefore, some patients with "silent" coronary artery disease may actually be in the group with no known coronary disease (*Table 4*). Since those groups did not differ with regard to smoking and glucose tolerance, the low HDL-C values appear to be directly related to known coronary heart disease. However, normal and low values for HDL-C are arbitrarily defined and cannot actually be divided into two distinct groups. HDL-C and cardiovascular risk is a continuum with no clear normal or abnormal values.

Previous studies

Table 6 summarizes some of the more important studies relating lipid values to peripheral vascular disease. Many of these reports[2-5] suggest that only 17% to 45% of patients have abnormal lipid profiles. As shown in *Table 6*, the mean values for TC, TG, and LDL-C, when available, were similar to the values obtained in the present study. The percentage of patients with abnormal lipid values is considerably lower in previous studies than in the present study. This merely reflects how the "normal" value for each lipid component has changed over the last 20 years. These mean values may be misleading in that many patients may have one or more lipid and lipoprotein fractions which are completely normal.

The Framingham Study confirmed that a higher TC increases the likelihood of intermittent claudication; however, the exact characteristics of the lipid abnormalities were not fully defined.[14,15] Also, the Lipid Research Clinic Coronary Primary Prevention Trial[16] demonstrated that using cholestyramine to lower the mean TC from 280 mg/dL to 257 mg/dL decreased coronary heart disease mortality by 24% and intermittent claudication by 15%.

Approximately 26% of the patients in the present series had diabetes mellitus, and 18% had impaired glucose tolerance. These figures are similar to those previously reported.[17,18] In our series, lipid or lipoprotein values did not differ in patients with normal glucose tolerance compared with patients with borderline glucose tolerance. However, patients with diabetes mellitus had higher plasma TG values and lower HDL-C values than patients with either normal or borderline glucose tolerance. These data are similar to those reported in other series of patients with diabetes mellitus.[17,19-24] Patients with diabetes mellitus

TABLE 6
STUDIES OF LIPID AND LIPOPROTEIN VALUES
IN PATIENTS WITH ARTERIOSCLEROSIS OBLITERANS

Study/year	N		Values in mmol/L (mg/dL)*			
			Total cholesterol	Triglycerides	HDL-C	LDL-C
Juergens[1]/1960	520		6.6 (255)	—	—	—
Newall[2]/1971	65		5.1 (197)	—	—	—
Greenhalgh[3]/1971	116		5.6 (216)	2.1 (186)	—	—
Vyden[4]/1975	28		6.5 (251)	2.2 (195)	—	—
Hughson[5]/1978	54		6.3 ± 0.2 (243 ± 7.72)	2.32 ± 0.19 (205 ± 17)	—	—
Bradby[6]/1978	100	male	6.03 ± 1.33 (233 ± 51)	1.89 ± 0.88 (167 ± 78)	0.71 ± 0.19 (27 ± 7)	—
		female	6.75 ± 1.14 (261 ± 44)	2.61 ± 2.78 (231 ± 246)	0.76 ± 0.27 (29 ± 10)	—
Trayner[11]/1980	32	male	6.69 ± 1.03 (258 ± 40)	2.1 ± 1.0 (186 ± 89)	1.04 ± 0.20 (40 ± 8)	—
		female	6.79 ± 0.89 (262 ± 34)	1.8 ± 0.7 (159 ± 62)	1.11 ± 0.32 (43 ± 12)	—
Dionyssion[12]/1985	15		6.19 (239)	2.24 (198)	1.18 (46)	4.15 (160)
Pauciullo[13]/1985	20		7.29 ± 0.33 (281 ± 13)	1.74 ± 0.20 (154 ± 18)	1.30 ± 0.08 (50 ± 3)	5.2 ± 0.30 (201 ± 12)
Olin/1992	125		6.2 ± 1.5 (238 ± 60)	2.7 ± 2.5 (241 ± 224)	1.0 ± 0.3 (38 ± 13)	4.0 ± 1.2 (153 ± 45)

HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol
*mean ± SD

did not differ in weight or body mass index compared with nondiabetic patients.

Falko et al[19] demonstrated a relationship between increased TG and low HDL-C in patients with noninsulin-dependent diabetes compared with controls. Interestingly, these authors also demonstrated no difference in lipid profiles in the control group compared with patients with impaired glucose tolerance. The same findings were demonstrated in our patients with ASO: all of our diabetic patients were type 2, noninsulin-dependent. Almost all had low HDL-C values; some also had elevated plasma TG. The TC and LDL-C may be normal in diabetic patients. The exact pathogenesis of ASO in this group of patients is unclear: it may be related to the low HDL-C values, increased plasma TG values, or elevated circulating levels of insulin.

CONCLUSION

While screening healthy asymptomatic patients for TC may be a valid means of determining cardiovascular risk,[7,25] a complete lipid profile is important in determining treatment for patients with lower-extremity ASO or, for that matter, any manifestation of atherosclerosis. TC and LDL-C are unreliable in assessing cardiovascular risk, since these values may be normal in up to 32% of patients with atherosclerosis. In this series, 87% of patients had at least one abnormality in their lipid profile. This report also underscores the limitations of the NCEP guidelines. The result of simply following LDL-C levels to determine therapy would be that as many as 32% of patients with documented atherosclerosis would go untreated. In addition, 48% of patients had low HDL-C, but the NCEP does not use HDL-C levels when formulating a treatment plan.

Therefore, we propose that all lipid and lipoprotein parameters be taken into consideration when initiating treatment in patients with documented atherosclerosis. This will be particularly important if future studies support the benefit of raising HDL-C levels in patients with lower-extremity ASO.

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