# The Correlation of Arteriosclerosis Obliterans with Lipoproteins in Insulin-Dependent and Non-Insulin-Dependent Diabetes

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**SUMMARY**

**Risk factors for arteriosclerosis, such as age, duration of diabetes, sex, and plasma lipoprotein levels, were correlated with the presence of arteriosclerosis obliterans (ASO) as determined by noninvasive methods in 485 of 506 subjects studied with diabetes mellitus.**

**The diabetic subjects were separated into two major groups for analysis: insulin-dependent diabetes mellitus (IDDM) and non-insulin-dependent diabetes mellitus (NIDDM). The NIDDM group was subdivided into those treated by diet (NIDDM-D), sulfonylureas (NIDDM-S), and insulin (NIDDM-I).**

**Overall, lipoprotein levels in the diabetics were higher than in an age- and sex-adjusted nondiabetic group. Cholesterol levels were elevated in all females and HDL cholesterol levels were depressed in diet- and sulfonylurea-treated females. VLDL levels were most elevated in diet-treated subjects followed by sulfonylurea-treated subjects; VLDL levels in insulin-treated subjects were not elevated.**

**The prevalence of ASO is related to different factors in each group. In IDDM and NIDDM-I subjects, VLDL triglyceride, LDL cholesterol, and duration of diabetes or age are important risk indicators. By contrast, in NIDDM-S subjects, age alone is the significant risk indicator, and in NIDDM-D subjects, inverse HDL cholesterol correlated with ASO. While males have a higher prevalence of ASO than females, the difference is not statistically significant in any group. Other possible factors, such as hypertension, smoking, and obesity, were not considered in this initial analysis.**

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Since the introduction of insulin for diabetic therapy and the subsequent increased longevity of diabetics, the vascular complications of diabetes have appeared as a major cause of morbidity.[1,17] Vascular complications can be divided into two types, microangiopathy affecting glomeruli and retina, and arteriosclerosis involving the cranial arteries, coronary arteries, and peripheral arteries. Involvement of the peripheral arteries frequently leads to claudication, ischemic ulcers, and amputation.

The evaluation of arteriosclerosis obliterans (ASO) has traditionally been done by history, physical examination, and angiography. The first two methods have limited reliability[16] and the third involves considerable pain, risk, and expense. Noninvasive vascular testing, using doppler velocimetry and pre- and postexercise ankle blood pressures, provides a safe, inexpensive, and reliable method for detecting ASO and for evaluating the severity of the disease.

The relationship between the presence of ASO and several risk factors associated with arteriosclerosis is considered in a group including insulin-dependent diabetic subjects and non-insulin-dependent diabetic subjects on various forms of therapy.

## METHODS

A total of 506 diabetics has been evaluated by noninvasive testing for ASO. These subjects were recruited from the diabetic registry of the Diabetes Center in Seattle (20%), an informational mailing by the local American Diabetes Association affiliate (50%), University Hospital and Veterans Administration clinics (20%), physician referrals in response to an informational mailing to members of the local medical society (5%), and referrals from patients and other sources (5%). Every volunteer over 12 yr old was accepted.

In addition to vascular testing, a health history and physical examination with emphasis on detecting vascular disease and neuropathy were obtained from each subject. For measurement of serum electrolytes and glucose (SMA 12) and plasma lipoproteins, 12-h fasting blood samples were drawn.

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Subjects were classified as insulin-dependent diabetes mellitus (IDDM), formerly called juvenile-onset diabetes, or non-insulin-dependent diabetes mellitus (NIDDM), formerly called adult-onset diabetes, by an interviewer on the basis of the following typical presentations. The IDDM patient presents with acute illness, the primary diagnosis is diabetes, and insulin therapy is required because the patient is ketosis prone. The NIDDM diagnosis is made on a screening examination or results from a history of long-standing polyuria. The NIDDM patients may be treated by diet, oral antihyperglycemics, or insulin; but they are not ketosis prone.

Two groups of subjects included in the tabulations were eliminated from the correlation analysis. Fourteen subjects were treated with phenformin and an additional seven with a combination of insulin and oral drugs; these groups were too small for detailed analysis. An additional 26 subjects, who had total triglyceride levels greater than 500 mg/dl, were tabulated separately.

**Vascular testing.** Each subject was tested for ASO of the legs by three methods: (1) resting ankle/arm blood pressure ratio, (2) postexercise/preexercise ankle blood pressure ratio, and (3) doppler velocimetry tracing patterns. Subjects with abnormalities by one or more of these methods were classified as having ASO.

The ankle/arm systolic blood pressure ratio was taken in the resting supine position. Right- and left-ankle pressures were referenced to right-arm pressure. In a subject with normal peripheral arterial flow, the systolic blood pressure is higher in the ankle than in the arm. As Carter[6] has shown by correlating ankle pressures with angiography in 258 limbs of patients with ASO, the ankle/arm ratio was less than 1.0 with occlusion. In this study, a subject with an ankle/arm ratio less than 0.95 was classified as having ASO.

Following the measurement of resting ankle systolic blood pressure, every subject who could walk was exercised on a treadmill at 3 km/h for 5 min on a 12% grade. If the subject grew tired, complained of chest or leg pain, or wanted to stop for any other reason, the test was stopped early. After exercise, the subjects were returned immediately to the supine position. Ankle pressures were taken and the post/preexercise ankle ratio was calculated. A subject with a ratio of 0.8 or less was classified as having ASO. Exercise was added because it has been shown by Carter[7] that some patients with stenoses may not have abnormal ankle pressures at rest. However, by adding exercise, it is possible to further detect those patients with lesser degrees of disease.

Finally, an 8-MHz continuous wave directional ultrasonic doppler velocimeter, with a zero crossing frequency meter and strip chart recorder, was used to measure the phasic characteristics of arterial flow. Velocity measurements were taken at the common femoral, posterior tibial, and dorsalis pedis arteries. The tracings were examined for a normal flow pattern, which consists of an initial period of forward flow associated with systole followed by a period of reverse flow associated with diastole. Any velocity pattern that was above zero flow and did not exhibit normal phasic characteristics indicated the presence of ASO proximal to the site of reading.[28] The velocity recordings were added to detect those patients with disease confined to one or more of the tibial arteries. With disease in these locations, resting and even postexercise pressures may be normal.

**Lipoprotein quantification.** A 30-ml blood sample was drawn in EDTA from each subject after a 10–12-h overnight fast for lipoprotein fractionation. Samples were placed on ice immediately after drawing and were centrifuged and decanted within 4 h of drawing. The plasma fractions were prepared by ultracentrifugation with heparin-manganese precipitation and were analyzed by the Northwest Lipid Research Clinic for total, high density lipoprotein (HDL), low density lipoprotein (LDL), and very low density lipoprotein (VLDL) cholesterol and triglyceride.[27]

The subjects, grouped by the presence or absence of ASO, were analyzed for differences in risk factors by SPSS (Statistical Package for Social Sciences).

## RESULTS

**Demography.** A comparison of the demography of the Diabetic Vascular Study (DVS) population with 1970 census data from the greater Seattle area shows a similar race distribution, but the DVS population has more years of education and higher status jobs compared with Seattle as a whole. This is an expected characteristic of a volunteer population. In addition, the DVS population has an excess of males due to 46 male subjects recruited from VA outpatient clinics.

The age ranges and durations of diabetes are listed in

TABLE 1
Age of subjects and duration of diabetes

| Type | Treatment | Sex | Number | Age | | | Duration | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | Mean | Min. | Max. | Mean | Min. | Max. |
| NIDDM (AODM)* | Diet | M | 47 | 58 | 41 | 78 | 6 | 0 | 20 |
| | | F | 43 | 61 | 32 | 79 | 6 | 0 | 19 |
| NIDDM (AODM) | Sulfonylurea | M | 45 | 61 | 42 | 81 | 8 | 0 | 28 |
| | | F | 43 | 61 | 42 | 90 | 7 | 0 | 21 |
| NIDDM (AODM) | Insulin | M | 98 | 58 | 28 | 83 | 13 | 0 | 37 |
| | | F | 61 | 55 | 24 | 81 | 11 | 0 | 34 |
| IDDM (JODM)† | Insulin | M | 77 | 35 | 13 | 71 | 17 | 0 | 59 |
| | | F | 68 | 33 | 13 | 60 | 16 | 1 | 50 |
| | | | 478 | | | | | | |

* AODM, adult-onset diabetes mellitus.
† JODM, juvenile-onset diabetes mellitus.

TABLE 2
Median values of lipoproteins in diabetic subjects

| | NIDDM-D | | NIDDM-S | | NIDDM-I | | IDDM | |
|---|---|---|---|---|---|---|---|---|
| | M | F | M | F | M | F | M | F |
| Cholesterol | 226 | 248 H* | 221 | 219 | 208 | 230 H | 191 | 212 H |
| HDL Cholesterol | 41 | 48 L† | 40 | 46 L | 45 | 54 | 46 | 58 |
| LDL Cholesterol | 144 | 152 H | 142 | 133 | 132 | 145 | 123 | 132 H |
| VLDL Cholesterol | 33 H | 27 H | 24 | 21 | 18 | 18 | 17 | 14 |
| Triglyceride | 188 H | 148 H | 150 H | 154 H | 119 H | 112 | 93 | 98 |
| HDL Triglyceride | 16 H | 19 | 14 H | 16 | 14 H | 17 | 13 H | 16 |
| LDL Triglyceride | 34 H | 40 H | 32 H | 33 H | 33 H | 33 H | 25 | 30 H |
| VLDL Triglyceride | 134 H | 96 | 102 H | 105 | 70 | 65 | 51 | 45 |

* H, Distributions are significantly higher than a healthy, nondiabetic, age- and sex-matched group by the Kolmogorov-Smirnov test.
† L, Distributions are significantly lower than a healthy, nondiabetic, age- and sex-matched group by the Kolmogorov-Smirnov test.

Table 1 by sex for the four major diagnosis and treatment categories. If the subjects not fitting into these categories, i.e., two pancreatectomies, 14 treated with phenformin, and seven on combinations of antihyperglycemics, were included with the NIDDM subjects, they would not change the age and duration values listed.

**Serum lipoproteins.** The lipoprotein distributions skewed to the right, especially the total triglyceride and VLDL cholesterol and VLDL triglyceride distributions. Since median values (the value of the 50 percentile) are more useful in skewed distributions, Table 2 lists median values for the lipoproteins separated by sex, diagnosis, and treatment.

In order to compare the lipid values of the diabetic population with a nondiabetic population, plasma cholesterol and triglyceride fraction data were obtained from the Pacific Northwest Bell Telephone Company Health Survey.[9] Each subject in the Diabetic Vascular Study (DVS) was assigned to the corresponding percentile range for the subject's age and sex. In comparing lipoprotein fractions in the IDDM group with the three treatment groups of NIDDM subjects, the NIDDM-D group had the highest triglycerides and the lowest HDL cholesterol followed by the NIDDM-S group. The NIDDM-I group and the IDDM group were similar and neither could be differentiated from nondiabetic males. Each of the groups of NIDDM diabetics had 8–10 individuals with triglyceride greater than 500 mg/dl; the IDDM group had one individual. NIDDM high values ranged from 2000 to 4000 mg/dl; the IDDM high triglyceride was 558 mg/dl.

**Prevalence of arteriosclerosis obliterans.** Of the 459 diabetic subjects with triglyceride less than 500 mg/dl, one-third were classified as IDDM (Table 3). The prevalence of ASO was 24% in the IDDM subjects and 38% in the NIDDM subjects. Of 12 subjects treated with phenformin, three had ASO. In diabetic males, the overall ASO prevalence was 38% as compared with 29% in females. The sex difference in ASO was barely significant in the NIDDM groups that were not insulin treated ($P > 0.05$, Table 4).

The subjects with and without ASO were compared for risk factors by SPSS multivariate analysis. The risk factors considered were age, sex, duration of diabetes, total plasma triglyceride and cholesterol, LDL cholesterol, VLDL triglyceride, and HDL cholesterol.

In the NIDDM group taken as a whole, the prevalence of ASO was most dependent on age ($P < 0.001$). No ASO was found in the NIDDM subjects under 30 yr old, but the prevalence in those over 75 yr old was 50%. After including the effect of age, no independent effect of duration of diabetes was found. Separating the NIDDM subjects by type of treatment, inverse HDL cholesterol was the most significant risk indicator in the diet-treated group ($P < 0.005$). No other indicators showed significance (Table 4). In the NIDDM-S group, age was the only significant risk indicator ($P < 0.001$). In NIDDM-I subjects, all indicators, except sex, showed statistical significance; however, only VLDL triglyceride exceeded the $P < 0.01$ criteria. In the IDDM group, all indicators except HDL cholesterol and sex surpassed the $P < 0.01$ criterion. The correlations show a similarity to the NIDDM-I group.

An examination of Pearson correlations between risk indicators and of partial correlations between some risk indicators and ASO, while controlling for other variables, reveals some additional insights. The correlation between age and duration of diabetes in the IDDM group is 0.65. The partial correlation between ASO and duration of diabetes, controlling for age, is not significant ($P = 0.193$), nor is the partial correlation between ASO and age, controlling for duration ($P = 0.059$).

The Pearson correlation between VLDL triglyceride and total triglyceride is 0.99 and between VLDL triglyceride and VLDL cholesterol is about 0.9. Those three risk indicators are therefore interchangeable. The correlation between HDL cholesterol and VLDL cholesterol is about −0.42. In those groups where both indicators have significant Pearson correlations with ASO, controlling for either one decreases the partial correlation between the other and ASO.

TABLE 3
Prevalence of arteriosclerosis obliterans in diabetics with triglyceride less than 500 mg/dl

| Type | Treatment | Sex | Normal | ASO | % with ASO | Total |
|---|---|---|---|---|---|---|
| NIDDM (AODM) | Diet | M | 21 | 19 | 48 | 40 |
| | | F | 28 | 12 | 30 | 40 |
| NIDDM (AODM) | Sulfonylurea | M | 22 | 18 | 45 | 40 |
| | | F | 31 | 12 | 28 | 43 |
| NIDDM (AODM) | Insulin | M | 55 | 40 | 42 | 95 |
| | | F | 37 | 20 | 35 | 57 |
| IDDM (JODM) | Insulin | M | 57 | 20 | 26 | 77 |
| | | F | 52 | 15 | 22 | 67 |
| | | | | | | 459 |

TABLE 4
Pearson correlations between risk indicators and arteriosclerosis obliterans in subjects with triglyceride less than 500 mg/dl

| | NIDDM-D | NIDDM-S | NIDDM-I | IDDM |
|---|---|---|---|---|
| Age | 0.168 (0.069) | 0.328 (0.001) | 0.109 (0.025) | 0.228 (0.003) |
| Duration of diabetes | 0.081 (0.237) | 0.011 (0.460) | 0.177 (0.015) | 0.201 (0.008) |
| Sex | −0.180 (0.055) | −0.178 (0.054) | −0.070 (0.197) | −0.046 (0.293) |
| LDL Cholesterol | 0.125 (0.135) | 0.119 (0.142) | 0.181 (0.013) | 0.209 (0.006) |
| HDL Cholesterol | −0.284 (0.005) | −0.109 (0.162) | −0.144 (0.038) | 0.051 (0.270) |
| VLDL Triglyceride | 0.162 (0.076) | −0.082 (0.231) | 0.205 (0.006) | 0.307 (0.001) |

Significance values (P) are in parentheses.

The 33 hyperlipemic subjects (TG > 500 mg/dl) constitute a special group. One subject is IDDM and the rest are uniformly distributed between the three NIDDM treatment groups. Of the seven subjects on a combination of insulin and oral treatment, five have elevated triglyceride (>500 mg/dl). Of the 14 subjects treated with phenformin, two have elevated triglyceride. Correlations between lipoprotein fractions in this group indicate that a large fraction of the cholesterol is in the VLDL fraction rather than in the LDL fraction. This is consistent with the possibility of a reduction in lipoprotein lipase activity, which retards the breakdown of VLDL lipoproteins. In this lipemic group, 53% of the males and 43% of the females have ASO.

## DISCUSSION

Since the introduction of insulin and the resultant prolongation of life in diabetics, an increase of cardiovascular complications has been reported.[1,17] Numerous studies of these arteriosclerotic complications have examined risk factors such as serum lipid values, dietary habits, and treatment regimens. In these studies, no differentiation is made between cardiac disease, cranial artery disease, and arteriosclerosis obliterans. ASO in past studies has been identified by physical evidence of advanced ischemia eliciting a history of intermittent claudication or loss of peripheral pulses.[13,20]

Work done in our laboratory has shown that a history of claudication and the physical examination are unreliable as screening methods for the detection of ASO.[16] A history of claudication has a sensitivity of 22% and a specificity of 96%, while physical examination has a sensitivity of 67% and a specificity of 70%, when using noninvasive testing as the standard.[16] The validity of the resting ankle/arm pressure index, the postexercise ankle pressure response, and the velocity recordings in detecting ASO has been extensively investigated and correlated with angiography by Carter[6,7] and Yao et al.[28]

In reviewing the relationships between identified risk factors, diabetes mellitus, and arteriosclerosis, the following conclusions have been published: (1) Diabetics and others with abnormal glucose tolerance have a higher prevalence of arterial disease of all kinds than do nondiabetics.[4,12,17,21,24] (2) Diabetic subjects have a higher prevalence of other risk factors for arteriosclerosis including elevated total cholesterol[4,20] and total triglyceride,[4,15,19] elevated LDL cholesterol,[20] and decreased HDL cholesterol.[3,20] (3) Diabetic subjects with arteriosclerotic disease have increased triglyceride,[1,3,15,22] cholesterol,[22] and VLDL triglyceride.[3,22]

The studies cited above have all been done on diabetic populations containing both juvenile- and adult-onset diabetics. No attempt to separate these two groups or to evaluate the effects of the form of therapy was made, even though it is recognized that there are great differences in other aspects of the disease in these patients. In the present study, separation of patients with IDDM and those with NIDDM has allowed the elucidation of the differences in risk factors for each group.

While not explicitly stated in the literature, the association of hyperglycemia with arterial disease implies that the longer a patient has diabetes, the greater the risk for arterial disease. This possible correlation is clouded by the relationships between age and duration of diabetes, age and arterial disease, and age and lipoprotein levels, which all appear to be independent risk indicators for arterial disease.

Partial correlation analyses, which control for age and duration of diabetes in our data, reveal little change in the relationships between lipoprotein and ASO compared with Pearson correlations. This implies that the lipoproteins are risk indicators that are independent of age and duration of diabetes. If one accepts $P < 0.05$ as the desired level of significance, only the NIDDM-D does not have age as a significant indicator.

With regard to the duration of diabetes, the only group in which this is known with any degree of certainty is the IDDM group. In the NIDDM group, onset of diabetes antedates diagnosis by an undetermined period, as diagnosis of diabetes is often an incidental finding on routine checkup. The observation that duration of disease is, in fact, significant in NIDDM subjects who are insulin treated is of interest, particularly since it does not appear to be significant in the remainder of the NIDDM group regardless of the form of therapy. This suggests that this group may bear a closer relationship to the IDDM group than might have been expected.

For the NIDDM group treated by diet alone, the relationship between HDL cholesterol and ASO would appear to agree with the current theories on the relationship between this lipoprotein and atherosclerosis in nondiabetic subjects.[20] This risk indicator is also noted to be of importance ($P < 0.038$) in the NIDDM-I group.

In the NIDDM-S groups, none of the lipoprotein fractions approached significance in relationship to ASO, yet the prevalence appears to be nearly the same as in other NIDDM subjects. This suggests that other risk indicators, as yet unidentified, may be important in this subgroup or that perhaps sulfonylureas alter lipoprotein patterns.

It is of great interest that the NIDDM-I group and the

IDDM group have very similar results. As noted earlier, the only difference is in the HDL cholesterol, which does not appear as significant in the IDDM subjects. It may be that the addition of insulin in the NIDDM group results in the appearance of different lipoproteins as potential risk indicators.

Clearly there are other important risk indicators that may have a bearing on some of our findings. A difference with regard to sex in incidence of ASO is noted particularly in the NIDDM group treated with diet and sulfonylurea. While of marginal significance ($P = 0.055$, NIDDM-D and $P = 0.054$, NIDDM-S), it is in contrast with the insulin-treated groups. In the IDDM subjects, the prevalence is nearly identical in males and in females.

While further study of these parameters will be required as they relate to other factors, it is clear that it is not acceptable to relate ASO to any suspected risk indicators unless the type of diabetes and its form of therapy are considered. The marked differences that can and do occur in these subgroups are apparent from our study.

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