Arteriosclerosis Obliterans and Associated Risk Factors in Insulin-dependent and Non-insulin-dependent Diabetes

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SUMMARY

The prevalence of arteriosclerosis obliterans (ASO) of the legs was determined by a battery of noninvasive tests in 141 insulin-dependent and 289 non-insulin-dependent diabetic subjects and in 64 other subjects. The prevalence of detectable ASO ranges from 18% in the younger IDDM group to 41% in the diet-treated NIDDM group.

The prevalence of ASO increases 7.5% per decade, appears to increase 6.5% in the age-adjusted IDDM group, 9% in males, 19% in those with hypertension, and 12% in smokers. No consistently significant correlations with fasting glucose, glycosylated hemoglobin, or obesity were found. After accounting for the effect of smoking, the increased risk for ASO in males becomes nonsignificant. DIABETES 29:882–888, November 1980.

The major causes of morbidity and mortality in patients with diabetes mellitus are related to diseases of the microcirculation and macrocirculation. Microcirculatory changes are most commonly found in the eye, the kidney, and in capillaries in other areas of the body. The disease of the large-sized and medium-sized arteries is atherosclerosis, which appears to be indistinguishable from that observed in nondiabetic patients.[1] However, it is a generally accepted fact that the disease appears at an earlier age in diabetics, is more extensive, and is associated with a higher morbidity and mortality.[2,3]

While there are certain risk factors, such as hypertension, cigarette smoking, and hyperlipidemia, that appear to play a role in the pathogenesis of atherosclerosis, it is not clear to what degree these same factors are operative in diabetes. The purpose of this report is to detail the prevalence of arteriosclerosis obliterans (ASO) in a group of insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) subjects and the correlations between ASO risk factors, including age, sex, fasting glucose, glycosylated hemoglobin, hypertension, smoking, and obesity.

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MATERIALS AND METHODS

Five hundred and twenty volunteers who had been diagnosed as diabetic were evaluated in the study. Each subject was tested for peripheral arterial disease by history, physical examination, and noninvasive procedures. Additional data gathered on each subject included medication, health, and lifestyle history and blood samples for determination of serum electrolytes and glucose (SMA-12), lipoproteins, and glycosylated hemoglobin.

The subjects were recruited from the diabetic registry of the Diabetes Center in Seattle (20%), an informational mailing by the local ADA affiliate (50%), the 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 of age was accepted.

Subjects were divided into six classifications, according to the recommendations of the National Diabetes Data Group:[4]

IDDM—insulin-dependent diabetes mellitus—subjects who are "characterized clinically by abrupt onset of symptoms" and had received daily insulin treatment since diagnosis.

NIDDM-I—non-insulin-dependent diabetes mellitus–insulin treated—insulin-treated subjects, characterized clinically by slow onset of symptoms, who do not require immediate insulin treatment.

NIDDM-S—non-insulin-dependent diabetes mellitus–sulfonylurea treated—sulfonylurea-treated subjects who currently receive no other antihyperglycemic medication.

NIDDM-D—non-insulin-dependent diabetes mellitus–diet treated—subjects with two annual 12-h fasting plasma glucose measurements over 140 mg/dl or a single measurement over 200 mg/dl when no second measurement was available, who receive no antihyperglycemic medication.

IGT—impaired glucose tolerance—subjects failing the NIDDM-D test with the mean of two annual 12-h fasting plasma glucose measurements greater than 120 mg/dl or a single measurement greater than 135 when no second measurement was available, who receive no antihyperglycemic medication.

Not DM—not diabetic—subjects failing the previous tests and receiving no antihyperglycemic medication.

Omitted from the analysis were 25 subjects who were taking combinations of oral antihyperglycemic drugs and insulin and two subjects with pancreatectomies.

Vascular tests. Each subject was screened for arteriosclerosis obliterans (ASO) of the legs by three tests: (1) resting ankle blood pressure, (2) postexercise ankle blood pressure, and (3) continuous wave Doppler velocimetry.

The resting ankle/arm systolic blood pressure ratio was taken in the resting supine position using an ultrasonic velocity detector. Right and left ankle pressures were referenced to right arm pressure. In a subject with a normal peripheral arterial system, the systolic blood pressure is higher in the ankle than in the arm. As Carter[5] has shown by correlating ankle pressures with angiography in 258 limbs of patients with ASO, the ankle/arm ratio was less than 0.98 with occlusion. For the purpose of this study, a subject with an ankle/arm ratio of 0.95 or less on either side was classified as having ASO diagnosed from *decreased ankle blood pressure*.[6]

Subjects with an ankle/arm ratio of 0.90 or less were studied further to determine if the specific arterial segment affected could be identified.[7] Resting systolic blood pressures at the high thigh, above the knee, and below the knee were measured. The aorto-iliac segment was considered to be abnormal if the upper thigh pressure was less than the arm pressure. The lower segments were considered abnormal if the pressure drop between successive segments was greater than 30 mmHg. Subjects with a significant pressure gradient at one or more levels were classified as having *segmental disease*.

All subjects who were willing and able to walk exercised on a treadmill with a 12% grade at 3 km/h for a maximum of 5 min.[8] The treadmill walk was attempted by 88% of the subjects. The walk was terminated before 5 min (25% of the subjects) if the subject complained of shortness of breath (9%), claudication (7%), general fatigue (5%), general leg weakness or pain (2%), or of chest pain or angina (2%). The 5 min treadmill protocol was completed by 63% of all subjects. Supine ankle blood pressures were taken within 1 min after stopping the treadmill walk. A postexercise ankle pressure of 80% of the pre-exercise value or less was classified as abnormal exercise. The remaining 12% of the subjects refused or were unable to walk on the treadmill because of amputations, previous MI, foot ulcers, and other infirmities. In 16 of those subjects who did not walk on the treadmill, a 4 min thigh occlusion reactive hyperemia test was substituted for the exercise test.[9] A post-RHT ankle pressure of 80% of the pre-exercise value was classified as abnormal.

Doppler velocity tracings were recorded on all subjects at the common femoral, posterior tibial (PT), and dorsalis pedis (DP) arteries with a zero-crossing directional Doppler. The velocity waveforms were analyzed for early diastolic flow reversal and the phasic character of the signal.[7] Flow reversal in early diastole in the femoral artery was considered normal. The velocity waveforms from the tibial arteries at the ankle were considered normal if they exhibited flow reversal or had a biphasic contour. A velocity signal at any level which was monophasic and above the zero flow baseline was considered abnormal and was designated *abnormal Doppler*.

Subjects with leg amputation were handled on a patient by patient basis. Of the four subjects with amputation, all are in the NIDDM-I group. ASO was responsible for two amputations; both subjects had segmental disease on the contralateral side. Of the remaining two, one amputation was due to osteomyelitis; the second was due to a saddle embolus. Both subjects had normal studies on the other side and were classified normal.

The tests enabled us to have four diagnostic categories related to the severity of the vascular disease: (1) segmental disease, based on abnormal segmental pressure gradients; (2) decreased ankle blood pressure, based on an ankle/arm index of <0.95; (3) abnormal exercise test, reactive hyperemia test, and/or ankle pressures; and (4) all detectable ASO, based on abnormal Doppler tracings, pressures, RHT, or exercise. Segmental disease is clinically associated with symptoms and complications and, therefore, represents the most severe arterial disease state.

Blood studies. A 30 ml blood sample was drawn in EDTA from each subject after a 10- to 12-h overnight fast for lipoprotein characterization reported previously.[10] An additional 10 ml blood sample was drawn for serum electrolyte and solute analysis (SMA-12). All samples were kept on ice until analysis. Samples which could not be delivered to the laboratory within 15 min were centrifuged to separate erythrocytes from plasma or serum.

The packed erythrocytes from the EDTA samples were washed twice in saline and lysed in equal volumes of distilled water by 2 min of vortex stirring. The cell membranes were extracted with $^1/_3$ vol of carbon tetrachloride by vortex stirring and centrifugation. Fifty microliters of the supernate was placed in an Isolab Fast Hemoglobin chromatograph column and extracted into fast and slow fractions. Dilutions of those fractions were read on a spectrophotometer for hemoglobin concentration. Percent glycosylated hemoglobin was determined by division.

Statistical analysis. Eleven potential risk indicators were examined for relationships with the presence of ASO. These factors were: (1) age, (2) sex, (3) duration of diabetes, (4) glycosylated hemoglobin, (5) fasting plasma glucose, (6) BUN, (7) creatinine, (8) hypertension history, (9) smoking history, (10) Quetelet's index of obesity (wt/ht^2), and (11) skinfold thickness. The statistical procedures used include multiple regression, the chi-square test, and stepwise discriminant analysis from the Statistical Package for the Social Sciences.[11]

RESULTS

Demography. A comparison of the demography of the patients in this study with the 1970 census data from the greater Seattle area shows a similar race distribution, but the study population had 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, there is an excess of males, owing to a group of 40 patients from the Veterans' Administration Hospital. The

TABLE 1
Age and duration of diabetes

Type	Number	Age			Age at Diagnosis			Time Since Diagnosis	
		Min	Mean	Max	Min	Mean	Max	Mean	Max
Not DM*	41	24	56	72	17	51	69	5	17
IGT	23	50	63	79	46	56	73	6	19
NIDDM-D	39	31	59	79	31	53	70	6	20
NIDDM-S	88	42	61	90	31	53	79	8	28
NIDDM-I	162	24	57	83	18	44	72	12	37
IDDM	141	12	34	71	1	17	50	17	50
	494†								

* All subjects studied had been diagnosed as diabetic by their physician at time of entry into study.
† Subjects on multiple antihyperglycemic drugs are not listed.

mean ages and durations of diabetes are listed in Table 1 for the six major groups of subjects.

Prevalence of ASO. Detectable ASO was found in 34% of the NIDDM subjects and 18% of the IDDM subjects. In Table 2, the subjects are separated by type of diabetes, treatment, and the four ASO diagnostic categories used. The use of the most encompassing criteria (all detectable ASO) shows a prevalence of two to three times that noted when only the criteria for segmental disease were used. The majority of subjects with segmental disease had overt signs and symptoms of ASO (claudication, bruit, and absent pulses) while most of the others did not.

The higher prevalence in the NIDDM-D subjects and the lower prevalence in those that are not diabetic are not statistically significant because of the low numbers. Comparisons cannot be made between the IDDM and the NIDDM groups, as ASO is age-related and perhaps also associated with duration of diabetes. The IDDM subjects are much younger and have been diagnosed as diabetic for a longer time (Table 1).

Age, duration of diabetes, and ASO. The relationship between prevalence of detectable ASO and age by decade is shown in Figure 1. If the entire group is taken together and includes all the diagnostic categories, a regression line has a slope of 7.5% per decade. If only those with the most severe disease (segmental category) are considered, the slope is 4% by decade beginning at age 25. No significant difference in slope exists when the IDDM and NIDDM groups are separated; however, the IDDM subjects have a 6.5% greater prevalence of detectable ASO than do the NIDDM subjects of equal age ($P = 0.02$).

In a similar manner, the relationship between duration of diabetes or time since diagnosis can be evaluated. However, the duration of disease in the NIDDM group is, in reality, unknown; the time of detection often follows onset by years. Considering all four groups together, there is a slope of 5% per decade ($P = 0.04$). When a stepwise discriminant analysis is done, controlling for age, this relationship persists ($P = 0.022$). In the NIDDM subjects, 27% who were diagnosed diabetic for less than one year have ASO, while in the IDDM group only 2 of 45 subjects with diabetes for less than 10 yr had detectable ASO—one with an abnormal ankle/arm index, the other with an abnormal ankle blood pressure response to exercise.

Sex and ASO. In Table 3, we demonstrate the greater prevalence of ASO in male than in female NIDDM subjects and in those who are not diabetic. This difference does not appear in the IDDM subjects. Such a difference cannot be attributed to age, as the male-female age difference is only 0.3 yr overall (−3.3 for Not DM, −4.2 for IGT, −2.5 for NIDDM-D, +0.2 for NIDDM-S, and +3.1 for NIDDM-I). The greater prevalence of ASO in men as compared with women in the NIDDM groups is statistically significant ($P = 0.009$). A regression analysis, including age, NIDDM vs. IDDM, and sex, shows males have a 9% higher prevalence of detectable ASO than do females.

TABLE 2
Prevalence of arteriosclerosis of the legs in diabetics by type of diabetes, treatment, and test criteria

	Not DM	IGT	NIDDM-D	NIDDM-S	NIDDM-I	IDDM
Segmental disease	2 (5%)	3 (13%)	8 (21%)	12 (14%)	13 (8%)	9 (8%)
Decreased ankle BP*	5 (12%)	5 (22%)	13 (33%)	22 (25%)	32 (20%)	17 (12%)
Decreased ankle BP† and/or abnormal exercise	5 (12%)	6 (26%)	15 (38%)	29 (33%)	41 (25%)	23 (16%)
All detectable ASO‡ (abnormal ankle BP, exercise, and/or Doppler)	8 (20%)	6 (26%)	16 (41%)	30 (34%)	51 (31%)	26 (18%)
Normal	33 (80%)	17 (74%)	23 (59%)	58 (66%)	111 (69%)	115 (82%)
Total	41	23	39	88	162	141

* Includes subjects with segmental disease.
† Includes subjects with decreased ankle blood pressure.
‡ Includes subjects with decreased ankle blood pressure and/or abnormal exercise.

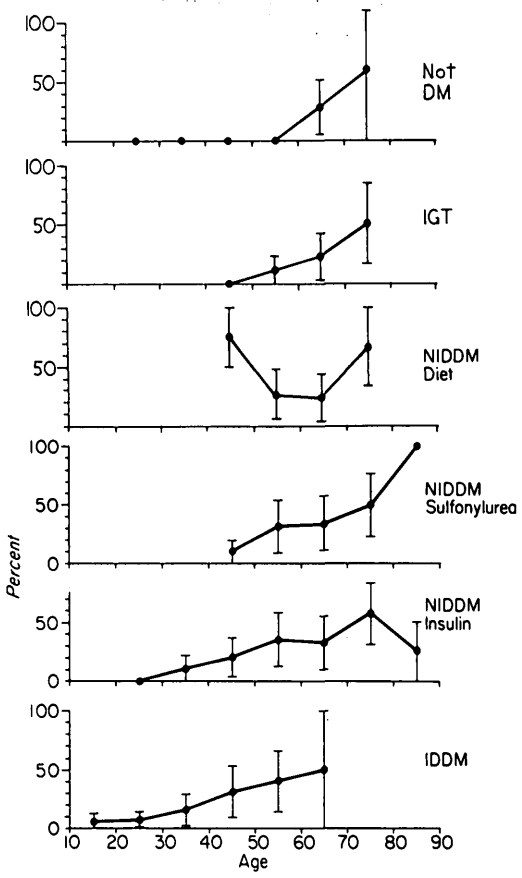

FIGURE 1. Prevalence of detectable ASO in diabetic subjects vs. age. ASO of the legs is diagnosed if resting or postexercise pressures or Doppler velocity tracings are abnormal. The isolated point represents one subject. When the standard error bars include 0%, one subject of the group is abnormal.

Hypertension, renal function, and ASO. The relationship between elevated blood pressure and ASO was evaluated in two ways—first by a history of hypertension and second by a measurement done at the time of the examination. Subjects were classified as hypertensive if their diastolic pressure was greater than 90 mmHg and/or their systolic pressure was greater than 1.5 times the diastolic value.

As noted in Table 4, there were high correlations between a history of hypertension and detectable ASO. While the chi-squared P value is not significant for detectable ASO in every group, the prevalence is 1.5 to 3.3 times higher in those with a history of hypertension. The prevalence of segmental disease is 1.4 to 7.0 times greater in subjects with hypertension, the highest ratio occurring in the NIDDM-S subjects.

A regression of detectable ASO with hypertension, after controlling for age and sex, shows hypertensive subjects have 19% more detectable ASO ($P < 0.0005$), 15% more decreased ankle blood pressure ($P < 0.0005$), and 9% more segmental disease than do subjects with normal systolic blood pressure ($P = 0.001$).

The relationships between levels of creatinine, blood urea nitrogen, and the prevalence of ASO were of interest. Taking creatinine levels of greater than 1.2 mg/dl and BUN greater than 21 mg/dl, there was a greater prevalence of ASO with the higher creatinine levels when all groups were taken together ($P = 0.0182$). The same relationships did not hold for the BUN. The correlations between a history of hypertension and creatinine ($P = 0.0012$) and BUN ($P < 0.00005$) were high.

Smoking history and ASO. The relationships between a history of cigarette smoking and detectable ASO are shown in Table 5. While the Not DM group showed no correlation and a majority of other groups failed to reach statistical significance, the increased prevalence of detectable ASO in smokers was highly significant for the group taken as a whole. In the 49 patients with segmental disease, all but one had been a smoker. In the 96 patients with an abnormal ankle/arm pressure ratio, 78 had smoked (81%) compared with 219 of 384 (57%) without ASO, $P < 0.00005$.

Among those with a history of smoking, those who stopped smoking at least 2 yr before examination had a 30% lower prevalence of detectable ASO than those who continued to smoke. If the more severe disease categories are considered, some interesting relationships appear. In those patients with segmental disease, the prevalence is 19% in the current smokers and 9% in those who had stopped ($P = 0.0206$). Considering decreased ankle BP, 32% of current smokers are abnormal as compared with 20% of those who had stopped ($P = 0.0188$).

Obesity and ASO. Obesity was evaluated in two ways. Skinfold thickness was taken as the sum of the biceps, triceps, subscapular, and supra-iliac measurements. Quetelet's index,[12] weight divided by height squared, was taken as a second index. The correlation between these methods is high ($r > 0.9$). Neither index correlated significantly with ASO.

Fasting glucose, glycosylated hemoglobin, and ASO. Fasting plasma glucose and glycosylated hemoglobin[13,14] were evaluated for possible correlation with the prevalence of ASO. In the diabetic subjects, glycosylated hemoglobin values ranged from 5 to 20, with a mean of 12, and 12-h fasting glucose values ranged from 43 to 46 in the insulin-treated subjects, to 415 in the NIDDM-D group, and 563 in the IDDM group, with means of 200 to 230. No significant correlations were found between either variable and ASO.

Interaction of variables. Correlations between risk factors

TABLE 3
Prevalence of detectable ASO in diabetics by sex

	Not DM	IGT	NIDDM-D	NIDDM-S	NIDDM-I	IDDM
Males						
All detectable ASO	4/18 (22%)	5/14 (36%)	11/21 (52%)	21/44 (48%)	34/99 (34%)	14/75 (19%)
Females						
All detectable ASO	4/23 (17%)	1/9 (11%)	5/18 (28%)	9/44 (20%)	17/63 (27%)	12/66 (18%)

TABLE 4
Prevalence of detectable ASO in diabetic subjects with and without a history of hypertension

Hypertension	Not DM	IGT	NIDDM-D	NIDDM-S	NIDDM-I	IDDM	All
Yes	5/17 (29.4%)	3/8 (37.5%)	11/20 (55.0%)	21/54 (38.9%)	35/77 (45.5%)	15/41 (36.6%)	90/217 (41.5%)
No	3/24 (12.5%)	3/15 (20.0%)	5/18 (27.8%)	9/34 (26.5%)	16/85 (18.8%)	11/100 (11.0%)	47/276 (17.0%)
Significance	0.3440	0.6805	0.1640	0.3342	0.0005	0.0009	<0.00005

and ASO may not represent direct relationships. Smoking, age, and male gender are all related to ASO, and smoking is correlated with age and with the type of diabetes and male gender. All these factors are well known risk factors for ASO. By stepwise regression analysis, it appears that, after accounting for the effect of age, sex, and type of diabetes, smoking history provides an additional 12% increase in prevalence of ASO ($P < 0.00005$). An alternate indication of the independence of the effects of smoking and age is shown by the discriminant analysis in Table 6. The first column indicates that all five variables are statistically significant ($F > 3.84$). In the second column, after accounting for the effect of a history of hypertension, the additional significance of the variables is little changed, the effect of age and of the IDDM diagnosis decreases somewhat. Adding the effect of age to that of hypertension history causes the effect of an IDDM diagnosis to become not significant. Once hypertension and age are included together, removing the effect of hypertension history would decrease the F value by 24.18; therefore, the effects of age and hypertension contribute independently to the analysis.

The next most significant variable is history of smoking. When smoking history is included, age and hypertension remain significant; however, the effect of male gender drops to the not significant level ($3.50 < 3.84$). Such a result can occur if there is a high correlation between smoking history and male gender. In Table 7, we compare the prevalence of smoking history in males and females. The excess of male former smokers is strikingly evident. A cross tabulation indicates that, of those with a history of smoking, 38% of the males and 28% of the females have detectable ASO as compared with the nonsmokers, in which 19% of the males and 15% of the females have ASO. Controlling for gender, the significance of the correlation with smoking is 0.01; controlling for smoking, the significance of the gender difference is 0.15. The gender difference in ASO prevalence is greater than the smoking history difference in the NIDDM-S group, where 50% of the male smokers and 37.5% of the male nonsmokers have ASO, compared with 29.2% of the female smokers and 10% of the female nonsmokers. Owing to small numbers, these differences are not statistically significant.

DISCUSSION

After the introduction of insulin therapy in 1923, the importance of the long-term sequelae of the disease became apparent. Among these complications, atherosclerosis of the large-sized and medium-sized arteries is a major factor in terms of both morbidity and mortality. There is a general consensus that the atherosclerosis which occurs may develop at an earlier age and be more extensive than in the nondiabetic population. The factors responsible for the development of atherosclerosis have been a source of confusion and debate. Practically every aspect of the diabetic state has been implicated,[2,3,15] including the role of hyperglycemia,[16–19] hyperlipidemia,[20] diets high in fat content, hyperinsulinemia or hypoinsulinemia,[21] the method of treatment,[22–25] the degree of control, genetic defects, and such secondary changes in coagulation as platelet function.[20] In addition, it is not at all clear how such factors as hypertension, cigarette smoking, and obesity may be operative in the patient with diabetes.

A serious, confusing factor in the research done to date is the tendency to lump all patients with diabetes into a single disease category. Thus, while it is now recognized that insulin-dependent and non-insulin-dependent diabetic patients must be analyzed separately,[4] this has not always been the case. Most epidemiologic data have thus been a mix of the two populations, which may tend to further confuse the issues. Also, the studies were made of such rather late end points as claudication, amputation, and radiographic evidence of arterial calcification.

In the current study, we recruited subjects without regard to the presence of either arterial disease or the type of treatment employed. Further, instead of depending on the history and physical examination, noninvasive tests were employed, which are capable of detecting disease down to the level of the tibial vessels in the foot.[26,27] The particular tests selected have been shown by such independent methods as arteriography to be reliable in objectively providing evidence of the disease, its location, and the baseline data for future comparison.[5–9]

In clinical terms, arteriosclerosis obliterans is a segmental disease which tends to affect specific areas of the arterial system of the lower leg. These can be divided roughly

TABLE 5
Prevalence of detectable ASO in diabetic subjects with and without a history of smoking

Smoking history	Not DM	IGT	NIDDM-D	NIDDM-S	NIDDM-I	IDDM	All
Yes	5/26 (19.2%)	6/17 (35.3%)	13/25 (52.0%)	25/60 (41.7%)	37/107 (34.6%)	20/73 (27.4%)	108/325 (33.2%)
No	3/15 (20.0%)	0/6 (0%)	3/13 (23.1%)	5/28 (17.9%)	14/55 (25.5%)	6/68 (8.8%)	32/194 (16.5%)
Significance	0.7269	0.2493	0.1717	0.0508	0.3146	0.0087	0.0001

TABLE 6
Stepwise discriminant analysis (F statistic) on subjects with/without detectable ASO

	Variables entered			
Variables	None	BP HX†	BP HX† Age*	BP HX† Age* SMOKE HX†
BP HX†	38.60		24.18§	22.24§
Age*	33.69	19.41		15.98§
SMOKE HX†	19.32	15.15	11.75	
Male/female†	7.48	7.64	7.04	3.50
IDDM/NIDDM†	9.92	4.29	1.75	2.28

* Continuous variable.
† Binary variable.
§ F to remove;
others, F to enter.

into the aorto-iliac vessels, the femoro-popliteal segment, and the tibial-peroneal arteries. Atherosclerosis can affect any of these areas either singly or in combination. Thus, the noninvasive test must be sensitive enough to make this distinction. Also, they should be able to detect disease which may not yet have progressed to total occlusion.

A measurement of the ankle/arm systolic pressure can objectively relate to the extent of disease, as determined by arteriography. As Carter demonstrated, an index of <0.98 is likely to be associated with total occlusion.[5] We arbitrarily chose an index of 0.95 as the cutoff point to allow for some variation in the pressures at the time of measurement. Further, by using the detection of an abnormal segment gradient, we further identified the area occluded and, because of this fact, consider this to represent the most advanced disease.

It is recognized that a stenosis may be present which is not significant at rest, i.e., the resting pressures may be normal. Carter has also shown that some of these lesions may be "unmasked" by adding stress, which was also done in our study.[8] This allows the detection of additional patients, who may not appear to be abnormal when studied in the resting state.

Finally, disease may be present in the tibial arteries alone, which does not result in an abnormal resting pressure or become apparent with exercise. This is due to the fact that disease distal to the popliteal trifurcation does not produce claudication, but will be reflected in either absent velocity signals or abnormal flow patterns, as estimated with the Doppler technique. Velocity patterns which are monophasic and above the zero-flow level are only seen with proximal stenosis or obstruction.

By using the above tests, it is possible to increase the sensitivity of the diagnostic approach and to provide as complete a survey of the limb as is currently feasible, short of arteriography. Furthermore, these tests can be used repetitively to document disease progression, even though the history and physical findings may remain unchanged.

The separation of insulin-treated subjects into the IDDM and NIDDM groups is somewhat arbitrary, as are the definitions of the two groups as stated by the National Diabetes Data Group.[4] In their description of IDDM, they include ketosis proneness, HLA antigens, islet cell antibodies, abrupt onset of disease, and dependence on insulin to sustain life. In discussing NIDDM, they include slow or silent onset, ketosis only under stress, and both abnormally high and low levels of insulin. They specifically warn against the use of age at diagnosis and of the glucose tolerance test in the diagnosis of diabetes and the differentiation as to type. Therefore, short of using immunologic tests and/or insulin withdrawal to differentiate NIDDM from IDDM, history (though, perhaps, unreliable) is the only method available to differentiate these groups.

With regard to prevalence of ASO, type of diabetes, and method of diabetes' treatment, ASO prevalence is higher in the NIDDM group, but this is a reflection of the difference in the age of the patients. In fact, when either method of age correction is used, the IDDM subjects have a 6% to 12% higher prevalence of ASO. Also, as shown in the IDDM subjects, only two patients who had IDDM for less than 10 yr had detectable ASO.

With regard to sex and ASO, the latter has largely been considered a disease of males, which appears to be the case in all four groups of NIDDM patients. However, the sex difference is not at all evident in the IDDM patients.

The issue of diabetes control and complications has been hotly debated. The major problem in this debate is that no practical method of monitoring control is available for broad uniform use in diabetes care and research. Glycosylated hemoglobin and fasting plasma glucose, usually done at a single point in time, do not accurately predict the mean plasma glucose levels during the day. The relationship between control and such complications as ASO must await the availability of better methods of defining this critically important point.

Hypertension is accepted as a major risk factor in atherosclerosis in the nondiabetic, with the same being noted in our study population. The strong correlation between ASO and the serum creatinine levels certainly tends to link the presence of hypertension with renal disease in these patients. This is further substantiated by the high correlation between a history of hypertension and the levels of creatinine and blood urea nitrogen.

TABLE 7
Smoking history of diabetic subjects

	Males	Females	Not DM	IGT	NIDDM	IDDM
All	271	224	41	23	290	141
Ever smoked	198	110	26	17	193	73
	(73.1%)	(47.7%)	(63.4%)	(73.9%)	(66.6%)	(51.8%)
Smoked in the last 2 yr	87	67	7	10	96	41
	(32.1%)	(29.9%)	(17.1%)	(43.5%)	(33.1%)	(29.1%)
Now smoking	69	53	5	10	77	30
	(25.5%)	(23.7%)	(12.2%)	(43.5%)	(26.6%)	(21.3%)

The importance of cigarette smoking as a risk factor is no less significant in patients with diabetes. In fact, it is striking that, of 49 patients with segmental disease, all but one had been a cigarette smoker. The beneficial effect of stopping smoking is most evident in those patients with the more advanced disease. Whether smoking is a greater risk factor than it is in nondiabetics cannot be ascertained from this study without age-matched and sex-matched controls, but its obvious importance cannot be overemphasized.

A most difficult problem in studies of this type is to determine the relationships between apparent risk factors. As noted in Table 6, a stepwise discriminant analysis provided some interesting results. When accounting for a history of hypertension, the importance of age and IDDM decreases somewhat. When age is added to the effect of hypertension, the importance of being an insulin-dependent diabetic falls below significant levels. When smoking is added to the analysis, age and hypertension remain significant, but the effect of being a male drops to nonsignificant levels. The excess of male smokers is clearly evident, as noted in Table 7. A cross tabulation indicates the prevalence of ASO in male and female smokers is much higher (38% for males; 28% for females) than it is in the nonsmokers (19% for males; 15% for females).

An important question not answered by this study is the contribution of diabetes itself to the development of ASO. This might have been answered by the inclusion of age-matched and sex-matched controls, but this was not possible given the resources available. An interesting finding which will require further study was that the prevalence of ASO in diet-treated subjects was twice that in normoglycemic patients and was higher than that found in the drug-treated and insulin-treated NIDDM groups (Table 2). The relevance of these observations will require study.

CONCLUSION

By this study of the prevalence of arteriosclerosis obliterans in patients with diabetes mellitus as related to multiple risk factors, we can draw certain conclusions. It is clear that any analysis must take into account the type of diabetes and the method of management. The most important risk factors include cigarette smoking and hypertension. Evidence is presented that cessation of smoking is associated with a decrease in the prevalence of ASO. It also appears that the difference in smoking habits accounts for the greater prevalence of the disease in males. A history of hypertension correlates highly with both abnormal renal function and arterial disease.

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