Association between Retinopathy and Impaired Peripheral Arterial Circulation in Insulin-Dependent Diabetic Patients

Gabriele Riccardi, Olga Vaccaro, Angela Rivellese, Geremia Romano, Vittorio Cambri, Paolo Rubba, Paolo Paucilulo, Giovanni Greco, Ciro Iovine, and Mario Mancini

This study was undertaken to investigate whether, in insulin-dependent diabetic patients, an association exists between microangiopathy (evaluated as retinopathy) and macroangiopathy (evaluated as impaired arterial circulation of the lower limbs). A total of 38 diabetic outpatients with either background (n=25) or proliferative (n=13) retinopathy, plus 18 diabetic outpatients of similar age (46.8 ± 13.4 vs. 43.0 ± 11.0 yrs) and duration of diabetes (16.8 ± 5.8 vs. 14.8 ± 15.1 yrs) without retinopathy were studied. Retinopathy was defined according to fluorescein angiography. The arterial circulation of the lower limbs was evaluated by the ankle/arm systolic pressure index with ultrasonic Doppler end-point detection and echo-Doppler examination of the pelvic vessels. The ankle/arm index was significantly lower in diabetic patients with retinopathy (0.98 ± 0.16 vs. 1.12 ± 0.11, p<0.002) and the percentage of persons with definitely impaired arterial circulation of the legs (ankle/arm systolic blood pressure <0.95) was significantly higher in this group (36.8% vs. 5.5%, p=0.038). Of 14 patients with retinopathy and peripheral arterial disease, only three (21%) had detectable stenoses of the pelvic vessels. The overall profile of cardiovascular risk factors was similar in the two groups. The multivariate analysis indicated that retinopathy was the best correlate of impaired peripheral arterial circulation. In conclusion, in our study population, an association between retinopathy and impaired peripheral arterial circulation of the legs existed independently of major cardiovascular risk factors.

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Macrovascular disease is the leading cause of death in middle-aged patients with insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) diabetes mellitus.1,2,3 A large body of evidence indicates that atherosclerotic vascular complications are, in fact, more frequent and earlier in these patients than in normoglycemic persons.4,5 The reasons for the association between diabetes and macrovascular disease are not completely understood. In fact, although the classical cardiovascular risk factors partly explain diabetic patients' increased susceptibility to atherosclerosis, these risk factors are not always prominent in patients with IDDM.4-6 In these patients, factors associated with diabetes itself or with its treatment may be more important. However, these factors and their mechanisms of action are largely unknown.

A recent in vitro study has clearly demonstrated that an identical stimulus (insulin or insulin-like growth factors) can induce the proliferation of endothelial cells in retinal capillaries and of smooth muscle cells in large arteries. These two processes play a fundamental role in initiating microangiopathy and macroangiopathy, and it is hypothesized that macro- and microangiopathy may share pathogenetic mechanisms in IDDM patients.10

To determine whether an association exists between macro- and microangiopathy in IDDM, we undertook this study in which we evaluated the prevalence of early macrovascular impairment in patients with or without microangiopathy. The confounding influence of the major cardiovascular risk factors was taken into account.

Subjects and Methods

Subjects

Between January and June 1983, a total of 86 IDDM patients ages 21 to 60 years who had had diabetes for at least 10 years were seen at our diabetic outpatients clinic. The referral was based mainly on geographical criteria, since in this country IDDM patients are usually treated at specialized centers and our clinic is the only diabetes care unit in that part of town. The diagnosis of IDDM was made on the basis of clinical records documenting at onset the classical symptoms of diabetes associated with greatly
was also assessed. Fasting blood samples were used to test plasma glucose, plasma lipids, glycosylated hemoglobin, and plasma fibrinogen. Blood pressure was measured after a 5-minute rest in patients who were lying down, and the first and the fifth phases of the Korotkoff sounds were recorded. The average of two measurements taken 2 minutes apart was used in calculations. The presence of autonomic neuropathy was investigated by measuring the heart rate variation during patients' deep breathing. A beat-to-beat variation of 10 beats/min or less was regarded as indicative of autonomic neuropathy. Information on smoking habits and drug consumption was obtained by questionnaire.

All the study procedures were approved by the ethical committee.

**Vascular Investigation**

Both the participants and the observers were blind with respect to the results of the fluorangiography.

Symptoms of impaired arterial circulation of the legs were assessed by the standardized Rose questionnaire on intermittent claudication. The ankle/arm systolic blood pressure (SBP) index with ultrasonic end-point detection was chosen as a sensitive screening test for assessing peripheral arterial disease in asymptomatic patients. The ankle blood pressure was measured in both legs as patients rested in a supine position by an ultrasonic velocity detector placed on the posterior tibial artery. Immediately afterward the right arm pressure was measured and the ankle/arm SBP index was calculated. The lowest value of this index was used in the analysis. All blood pressure measurements were performed twice at one-minute intervals, and the mean value was used in the calculations. Since no fall in arterial blood pressure is expected between the arm and the ankle, the ankle/arm SBP ratio is usually larger than 1. In this study values below 0.95 were considered indicative of impairment of the circulation in the arterial system of the legs. With this method, evidence of marked medial calcification of the arteries can be obtained; a nonsuppressible Doppler signal or a reading of more than 50 mm Hg higher than the arm was interpreted as a sign of medial arterial calcification.

Patients with definite impairment of the arterial circulation of the legs underwent an echo-Doppler examination (duplex scanner ATL Mark V) to better define the sites of hemodynamically significant arterial stenoses. Recordings were taken at the inguinal ligament, which corresponds to the distal end of the external iliac artery. Flow abnormalities due to common or external iliac artery stenoses are detectable by this procedure, which has been extensively validated against angiography.

### Table 1. Pertinent Clinical Data of Participants

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Age (yrs)</th>
<th>Gender (M/F)</th>
<th>BMI (kg/m²)</th>
<th>Years since diagnosis</th>
<th>HbA₁c (%)</th>
<th>FBG (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>Absent (n = 18)</td>
<td>43.0±11.0</td>
<td>8/10</td>
<td>24.8±3.1</td>
<td>14.8±5.1</td>
<td>9.0±1.4</td>
</tr>
<tr>
<td></td>
<td>Present (n = 38)</td>
<td>46.8±13.4</td>
<td>18/20</td>
<td>24.4±3.6</td>
<td>16.8±5.8</td>
<td>8.3±1.7</td>
</tr>
</tbody>
</table>

Values are means ± SD. BMI = body mass index, FBG = fasting blood glucose, HbA₁c = glycylated hemoglobin.
Table 2. Arterial Circulation of Legs in Insulin-Dependent Diabetes Mellitus Patients with or without Retinopathy

<table>
<thead>
<tr>
<th></th>
<th>Absent (n = 18)</th>
<th>Present (n = 38)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ankle/arm SBP (Means ± SD)</td>
<td>1.12 ± 0.11</td>
<td>0.98* ± 0.16</td>
</tr>
<tr>
<td>Ankle/arm SBP &lt;0.95 (%)</td>
<td>1 (5.5)</td>
<td>14† (36.8)</td>
</tr>
<tr>
<td>Claudication (questionnaire) (%)</td>
<td>1 (5.5)</td>
<td>9 (23.7)</td>
</tr>
</tbody>
</table>

*p<0.002, †p=0.038 (Fisher exact test.)

SBP = systolic blood pressure.

Statistical Analysis

Between group comparisons were performed by unpaired Student's t test. Tests for association in 2 x 2 tables were performed by $X^2$ analysis. The Fisher exact probability test was used when observed frequencies were less than 5. All tests were two-tailed; the null hypothesis was rejected when $p<0.05$. The statistical procedure included covariance analysis and stepwise multiple logistic regression from the BMDP statistical package.

Results

Pertinent clinical data from the two groups of IDDM patients participating in the study are given in Table 1. Patients with or without retinopathy were comparable in age, gender distribution, and duration of diabetes. Glycosylated hemoglobin and fasting blood glucose at the time of the study were also similar (Table 1). The reference group of normoglycemic individuals had an almost identical age and gender distribution as the diabetic patients, but their body mass index (BMI) was significantly higher (26.3 ± 1.5, p<0.01 vs. IDDM).

The results of the vascular investigations are given in Table 2. The ankle/arm SBP was significantly lower (worse) in diabetic patients with retinopathy than in patients without retinopathy (p<0.02). The same was observed with definite impairment of arterial circulation of the legs (ankle/arm SBP<0.95) or the presence of intermittent claudication.

Among retinopathic patients, those with proliferative retinopathy (n = 13) had slightly more impaired peripheral arterial circulation than did those with background retinopathy (n = 25), although the difference was not statistically significant (0.93 ± 0.15 vs. 1.0 ± 0.19, p<0.10). The average ankle/arm SBP index and definite impairment in peripheral arterial circulation were similar in diabetic patients without retinopathy and in normoglycemic controls (1.12 ± 0.11 vs. 1.07 ± 0.11, 5.5% vs. 12.0%, respectively).

Retinopathic patients showed a preferential localization of peripheral arterial stenoses below the pelvic vessels: out of 14 patients with abnormal ankle/arm SBP values, only three (21%) had stenoses in the pelvic vessels detectable by an echo-Doppler test and only one was hemodynamically significant (lumen reduction >50%). No patient had foot lesions and only two, one in each group, showed signs of medial arterial calcification.

Figure 1. Blood lipids, blood pressure, and other possible cardiovascular risk factors in insulin-dependent diabetes mellitus patients with or without retinopathy.
The logistic regression analysis with ankle/arm SBP as a dependent variable indicated that retinopathy was the best correlate of impaired arterial circulation of the legs \( (p<0.001) \). Other correlates were plasma triglycerides, followed by BMI and serum cholesterol; for the last two variables, the \( p \) value was not statistically significant. (Table 3).

**Discussion**

The data show that, in our study population, impaired arterial circulation of the legs is associated with retinopathy. This study extends and reinforces previous knowledge on the association between micro- and macroangiopathy, which have until now been investigated only in the heart and kidneys. Moreover, we have demonstrated that, in our group of patients, the association between retinopathy and impaired peripheral arterial circulation is independent of the major cardiovascular risk factors.

Retinopathy was assessed by retinal fluorescein angiography, which has proved to be a reliable and reproducible method in clinical studies.24 The eye was selected for study because retinopathy is the most specific expression of diabetic microangiopathy. The presence of macroangiopathy was assessed by investigating arterial circulation in the legs by use of Doppler velocimetry. The vascular bed of the leg is easily accessible with several noninvasive methods and is, therefore, particularly suitable for epidemiological and clinical investigations.25 The ankle/arm SBP index with ultrasonic Doppler end-point detection has shown a high degree of specificity when validated against angiography.20,21 Although the enrollment of our patients was not population-based, they were in most cases asymptomatic, they were recruited consecutively, and the investigations were performed blindly, thus guaranteeing against possible selection bias.

The association between impaired arterial circulation of the legs and retinopathy could not be explained in our study by any of the more plausible factors related to micro- or macroangiopathy (age, duration of diabetes, body weight, blood lipids, blood pressure, smoking, or plasma fibrinogen) that were investigated. In particular, when multivariate analysis was performed, the impaired arterial circulation of the leg was more closely associated with retinopathy than with the “classical” risk factors for atherosclerosis. Moreover, this association was not explained by the presence of diabetic nephropathy or proteinuria, since this represented an exclusion criterion.

In our patients, the impairment of arterial circulation of the legs was mostly due to stenoses below the iliac arteries. The predilection for a peripheral location of macroangiopathy in diabetic patients has been reported previously.26 It is worth stressing that this preferential involvement of the distal arteries is characteristic of IDDM patients and is not associated with an accumulation of risk factors for atherosclerosis as is the case for more proximal locations.

The possibility of a common pathogenic mechanism for diabetic micro- and macroangiopathy has been recently suggested by two studies in which proteinuria was found to be a predictor of cardiovascular morbidity and mortality.

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**Table 3. Variables Significantly Associated with Impaired Arterial Circulation of Legs* in Insulin-Dependent Diabetes Mellitus Patients**

<table>
<thead>
<tr>
<th>Variable</th>
<th>( x^2 )</th>
<th>( p )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy</td>
<td>14.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Serum triglycerides</td>
<td>7.4</td>
<td>0.007</td>
</tr>
<tr>
<td>BMI</td>
<td>2.9</td>
<td>0.09</td>
</tr>
</tbody>
</table>

This table shows the results of multiple logistic regression analysis.

*Defined as ankle/arm systolic blood pressures < 0.95.

Variables in the equation: retinopathy, triglycerides, body mass index, cholesterol, high density lipoprotein cholesterol, smoking habits, gender, age, duration of diabetes, hypertension, and glycated hemoglobin.

Figure 1 shows the distribution of the major cardiovascular risk factors for diabetic patients with or without retinopathy. Plasma lipid concentrations were similar in the two groups (total cholesterol 184 ± 41 vs. 189 ± 47, triglyceride 107 ± 44 vs. 123 ± 77, high density lipoprotein cholesterol 41 ± 11 vs. 45 ± 15 mg/dl) as was the proportion of treated hyperlipidemic patients (8% vs. 11%, respectively).

No significant differences were detected in either SBP or diastolic blood pressure between diabetic patients with and those without retinopathy, although the former group had slightly higher SBP values (140 ± 22 vs. 130 ± 21 mm Hg), as well as a higher proportion of treated hypertensives (24% vs. 11%). There were no significant differences between the groups in the number of smokers (33% vs. 25%) and ex-smokers (7% vs. 9%). However, the daily tobacco consumption for smokers was higher in retinopathic patients, and the difference was of borderline statistical significance (19.3 ± 12.5 vs. 11.1 ± 5.4 cig/day; \( p<0.1 \)). The daily insulin requirement and plasma fibrinogen levels were also similar in the two groups.

To account for the small, nonsignificant differences in blood pressure between patients with and those without retinopathy, the ankle/arm SBP was compared in the two groups after adjusting for blood pressure by covariance analysis. Adjusted ankle/arm SBP values were still significantly lower in diabetic patients with retinopathy (0.98 ± 0.17 vs. 1.11 ± 0.16, \( p<0.01 \)). The same was observed after adjusting for the number of cigarettes smoked per day; the adjusted means were 0.99 ± 0.18 vs. 1.13 ± 0.18, \( p<0.02 \), respectively, in retinopathic and non-retinopathic patients. Significantly lower ankle/arm SBP values were also found in retinopathic patients when the analysis excluded treated hypertensives (0.97 ± 0.20 vs. 1.12 ± 0.12, \( p<0.01 \)) or current smokers (0.99 ± 0.17 vs. 1.14 ± 0.12, \( p<0.01 \)) in an attempt to correct for differences between the groups in these variables.

Since a higher proportion of individuals with autonomic neuropathy was detected among retinopathic patients, the ankle/arm SBP values were compared in the two groups after excluding patients with a beat-to-beat variation during deep breathing of less than 10 beats/min. Once again, significantly lower values were found in retinopathic patients (0.99 ± 0.17 vs. 1.10 ± 0.11, \( p<0.001 \)).
in IDDM patients. However, in these studies the link between micro- and macroangiopathy, although hypothesized, was not proved. In fact, the possible confounding role of the major cardiovascular risk factors could not be excluded.\textsuperscript{27,28,29}

Since the association between retinopathy and impaired peripheral arterial circulation in our patients is independent of the major cardiovascular risk factors, it is possible that diabetes itself or some factor related to the disease or its treatment may have caused a generalized vascular damage to the arterial wall.

Various mechanisms to explain the coexistence of micro- and macroangiopathy in IDDM patients could be proposed. Abnormalities of platelet function, blood clotting, and fibrinolysis often associated with diabetes might enhance atherogenesis and, at the same time, facilitate the occurrence of retinal ischemia. This hypothesis is supported by the fact that, in patients with retinopathy, platelet adhesiveness is not only increased but is also more difficult to correct with drugs in comparison with diabetic patients without retinopathy.\textsuperscript{30}

Another possibility is that a generalized angiopathy is associated with diabetes although with different morphologic characteristics in small and large arteries. This angiopathy might be due to the ill effect of hyperglycemia on the vascular system.\textsuperscript{31,32}

The role of genetic factors should also be considered: HLA apolipoproteins, insulin gene polymorphism, and many different genetic markers have been associated with increased vascular susceptibility in patients with IDDM or NIDDM.\textsuperscript{33} It is, therefore, possible that hyperinsulinemia, hyperglycemia, high platelet adhesiveness, or another metabolic abnormality associated with diabetes might cause ill effects only on the vascular systems of genetically predisposed individuals.

Further research is needed to clarify the role of these variables and of other hormonal and genetic factors that may be underlying mechanisms for the association between micro- and macrovascular disease in IDDM. We believe that efforts in this direction will give us a better understanding of the etiopathogenesis of the vascular complications of diabetes.

References


Index Terms: retinopathy • peripheral vascular disease • insulin-dependent diabetes mellitus • microangiopathy
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