The Distribution of Peripheral Vascular Disease in a Dutch Caucasian Population: Comparison of Type II Diabetic and Non-diabetic Subjects

A.J.C. Mackaay, 1 P.J. Beks, 2 A.H.M. Dur, 1 M. Bischoff, 3 J. Scholma, 3 R.J. Heine 2 and J.A. Rauwerda 1

1Department of Vascular Surgery, 2Institute for Research in Extramural Medicine and 3Vascular Diagnostic Laboratory, Free University, Amsterdam

Objectives: To study the distribution of peripheral vascular disease and the relationship to diabetes.

Design: Prospective population based study of Dutch caucasian inhabitants.

Methods: From a total of 10 500 subjects aged between 50 and 75 years, 2484 Caucasian inhabitants were screened with respect to their glucose tolerance. Subjects using oral antidiabetic agents or insulin were classified directly as having diabetes mellitus. The other participants were screened using two oral glucose tolerance tests and classified using WHO criteria. A group of 173 people with diabetes and a representative age/sex stratified sample of 288 non-diabetic subjects were seen in the vascular laboratory. Carotid artery disease was investigated with Duplex scanning, arm and leg artery obstructions with real time frequency analysis of continuous wave Doppler signals and indirect blood pressure measurements.

Results: Comparing diabetic with non-diabetic subjects, we found significantly more obstructions of the carotid arteries (8.7% vs. 2.8%), arm arteries (2.3% vs. 0%), as well as leg arteries (31.8% vs. 18.4%). The same holds if only the crural artery obstructions were compared (23.7% vs. 16.0%). Two of the four diabetic subjects with arm artery obstructions had retrograde vertebral flow, three of them had carotid artery obstructions as well and three also had leg artery obstructions. More than half of the subjects with a carotid artery obstruction also had leg artery obstructions.

Conclusions: Peripheral vascular disease is common in diabetes, but most are asymptomatic.

Key Words: Type II diabetes mellitus; Peripheral arterial disease; Carotid artery disease; Epidemiological study

Introduction

Diabetes mellitus type II is associated with a high incidence of peripheral vascular disease. Arterial obstructions tend to be multisegmental with a frequent involvement of the crural arteries. Diabetic subjects have a greater risk of gangrene (10 times) and amputations (15–20 times). The amputation rate may be reduced by screening and early treatment of diabetes with arterial obstructions. Therefore knowledge of the distribution of peripheral vascular disease in the general population and of non-invasive methods to detect arterial obstructions is important. Although peripheral arterial disease does not rank among the main primary causes of mortality, it has been shown to be associated with increased mortality overall and from coronary heart disease. Also cerebrovascular complications are seen more frequently in the presence of diabetes. The clinician needs information concerning the natural history of the disease to assess the effectiveness of a treatment. The importance of such epidemiological information for the vascular specialist was stressed recently. Most of these data concern symptomatic vascular disease in selected populations, predominantly composed of people with diabetes. Much less is known about the prevalence and the location of asymptomatic peripheral vascular disease in diabetics compared with non-diabetics in the general population. Therefore we started a cross-sectional population-based study in the Netherlands.

In epidemiological studies invasive techniques such as angiography or intraarterial blood pressure measurement are not suitable. So investigators are restricted to non-invasive techniques to assess the prevalence of vascular disease. The validity of Duplex scanning is widely accepted for the detection of carotid artery disease. Leg arterial disease can be
studied by Doppler signal analysis, and by measuring the systolic ankle blood pressure or the systolic ankle-brachial index.\textsuperscript{10} Ankle pressure measurements alone can be misleading. Leg arteries of diabetics, especially, may show medial calcification of the whole circumference of an ankle artery ("Monckeberg sclerosis") causing falsely raised ankle pressures.\textsuperscript{17} An obstruction in one or two of the three crural arteries is not necessarily expressed in a low ankle-brachial index. The measurement of toe pressure does not add to the accuracy, mainly because of a poor reproducibility.\textsuperscript{18} The Duplex evaluation of the crural arteries is not validated yet and for epidemiological studies the sensitivity of Duplex scanning is too limited.\textsuperscript{19} In this study we compared the limb arteries of diabetic and normoglycaemic subjects by means of Doppler waveform analysis combined with measurement of the ankle-brachial index.

\textbf{Materials and Methods}

\textit{Study population}

On 1 July 1988 a random sample of 50–75 year-old subjects was taken from the population register of the town of Hoorn (59,000 inhabitants) in the Netherlands. From the total of 10,500 subjects of this age group 3,553 inhabitants were invited to take part in the study. Of these 2,540 (71.5\%) agreed to participate, of whom 56 were excluded from analysis and further study because they were non-Caucasian. Non-participants did not differ significantly from the study population with respect to sex, self-reported diabetes, treatment for hypertension and cardiovascular symptoms.

The group of 2,484 participants was screened with respect to their glucose tolerance. Seventy-six subjects using oral hypoglycaemic agents or insulin were directly classified as having diabetes mellitus. Four insulin-treated diabetic subjects were diagnosed before the age of 40 years. Using two oral glucose tolerance tests the other participants were classified according to WHO criteria as diabetic (fasting plasma glucose > 7.8 mmol/l and/or 2 hours post load plasma glucose > 11.1 mmol/l) or normoglycaemic (fasting plasma glucose and 2 hours post load plasma glucose ≤ 7.8). We found 120 newly diagnosed diabetic subjects. All 196 diabetic subjects and a sex/age stratified sample of the normoglycaemic subjects were invited to participate in the study of peripheral vascular disease. The response rate was 89\%.

From November 1989 till March 1992 we investigated the prevalence of peripheral vascular disease in 173 diabetic and in 288 non-diabetic subjects. In order to get a clear contrast between diabetics and subjects with an undisturbed glucose tolerance, the group of 169 subjects with an impaired glucose tolerance is not considered here. Two subjects had undergone a limb amputation, so their data apply to one leg only. Six subjects had undergone a vascular reconstruction.

The study was approved by the medical ethical committee of the Free University Academic Hospital. A written informed consent was obtained from all participants.

\textbf{Non-invasive vascular measurements}

Recording started after a 15 minutes resting period in supine position. Room temperature was kept constant at 23°C. Two experienced vascular technicians not aware of the glucose tolerance data of the participants performed all the investigations.

Using a colour coded Duplex (Acuson-128 with a 7.5 mHz linear array probe, insonation angle 60 degrees), recordings were made on the right and left side from the proximal and distal common carotid artery (RCCA and LCCA), the proximal external carotid artery (RECA and LECA) and the proximal and distal internal carotid artery (RICA and LICA). The recordings were evaluated on-line conform to the criteria of the Seattle group.\textsuperscript{16} We considered a > 50\% diameter reducing stenosis (peak systolic velocity > 125 cm/s) or an occlusion (absence of flow) to be a carotid artery obstruction. In addition the direction of flow in the vertebral arteries was recorded.

Using a 5 or 8 mHz bidirectional Doppler connected to a real-time frequency analyser (MedaSonic), flow velocity tracings were recorded from the radial and ulnar arteries as well as from the femoral, popliteal and crural arteries. Tri- or bi-phasic curves indicate that the arterial inflow to that level was normal. Monophasic or absent tracings were considered abnormal signifying the presence of a severe (haemodynamically significant) arterial obstruction proximal to the examination site.\textsuperscript{10} Multilevel disease could not be evaluated by waveform analysis alone. Obstructions in side branches as the internal iliac or the profunda femoris artery were not considered. Doppler assisted systolic pressure measurements were made from the brachial and ankle arteries using a standard 13 cm arm cuff. The maximal cuff pressure was 250 mm Hg. From the highest ankle and brachial pressure values, the ankle–brachial pressure index at rest was calculated. An ankle–brachial index < 0.90 was considered to be abnormal.\textsuperscript{13–15} A complete set of
normal Doppler waveforms from all lower extremity arteries signified the absence of important peripheral arterial disease. Most of these subjects indeed had ankle–brachial indices > 0.9. Abnormal Doppler signals from the femoral, popliteal as well as the three crural arteries combined with an ankle–brachial index < 0.90 indicated an obstruction at the (aorto)iliac level. A normal femoral Doppler tracing in combination with abnormal tracings from the popliteal and the three crural arteries and an ankle–brachial index < 0.90 indicated an obstruction in the femoropopliteal segment. Abnormal Doppler tracings from the crural arteries were considered to indicate crural obstructions. The absence of a Doppler signal from the peroneal artery in combination with normal tracings from the other two crural arteries and a normal ankle–brachial index was considered to reflect a technical failure. The brachial systolic pressures and Doppler waveforms were used for analysis of obstructions of the arm arteries.

**Statistics**

Data were analysed using the SPSS/PC + (statistical package for the social sciences). Parameters are presented in absolute numbers or percentages. We used Student’s t-test and the $\chi^2$ test (corrected p-value) to evaluate differences between diabetic and non-diabetic subjects. Multivariate logistic regression analyses were performed to assess the contribution of sex, age and diabetes to the risk of peripheral vascular disease. A $p$-value < 0.05 was considered to be statistically significant.

**Results**

In our study 225 males (48%) and 236 females (51%) participated. Seventy-six males (44%) and ninety-seven females (56%) had diabetes mellitus (almost all of them non-insulin dependent). The age distribution is given in Fig. 1. There was no significant difference between diabetic and non-diabetic subjects concerning smoking habits whether analysed on a dichotomised scale (ever vs. never smoker, $p = 0.17$) or on a continuous scale (cigarette pack-years, $p = 0.75$). In 346 subjects we found no severe vascular obstructions (carotid, arm or leg arteries) including 114 (66%) diabetics and 232 (81%) non-diabetics (difference statistically significant, $p = 0.001$).

**Carotid artery disease**

Data were gained from 172 diabetic and 287 non-diabetic subjects of whom 436 (95.0%) had no severe carotid disease. Thirty-two severe lesions (Table 1) were found in 15 (8.7%) diabetics and eight (2.8%) non-diabetics (difference statistically significant, $p = 0.009$). Most lesions were found in the internal carotid arteries including 13 severe stenoses and six one-sided occlusions (4 x diabetic) in 16 subjects. One non-diabetic subject had a > 50% stenosis in both common carotid arteries. We found six severe (> 50% diameter reduction) RECA and five severe LECA

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**Table 1. Carotid arteries obstructions**

<table>
<thead>
<tr>
<th>Location</th>
<th>Colour-duplexscanning</th>
<th>&gt; 50 % stenosis</th>
<th>occlusion</th>
<th>subjects DM/non-DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>CCA</td>
<td>2</td>
<td>0</td>
<td>2/1</td>
<td></td>
</tr>
<tr>
<td>ECA</td>
<td>11</td>
<td>0</td>
<td>8/1</td>
<td></td>
</tr>
<tr>
<td>ICA</td>
<td>13</td>
<td>6</td>
<td>10/6</td>
<td></td>
</tr>
</tbody>
</table>

CCA = common carotid artery, ECA = external carotid artery, ICA = internal carotid artery. Numbers include right and left sided obstructions. DM/non-DM = diabetic and non-diabetic subjects, respectively.
stenoses in nine subjects, three diabetics also having an ICA obstruction. The small numbers do not permit further analysis of the correlation with diabetes. Less than 10% of the carotid artery lesions were symptomatic.

Arm artery disease

Four persons, all diabetic (2.3%) and none non-diabetic (difference statistically significant, \( p = 0.038 \)), had abnormal Doppler tracings of the arteries of one arm, the pressure difference between the right and the left arm ranged from 45 to 57 mm Hg. Only two of them had retrograde flow in the ipsilateral vertebral artery.

Leg artery disease

Table 2. Leg artery obstructions (whole study population)

<table>
<thead>
<tr>
<th>Artery</th>
<th>Right</th>
<th>Left</th>
</tr>
</thead>
<tbody>
<tr>
<td>Femoral</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>popliteal</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>crural</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Nr of legs</td>
<td>384</td>
<td>62</td>
</tr>
<tr>
<td>Ankle-brachial index &lt; 0.90</td>
<td>9</td>
<td>10</td>
</tr>
</tbody>
</table>

The results are summarised in Table 2. Based on normal Doppler velocity tracings, 384 (83.5%) right legs and 380 (82.6%) left legs did not show evidence of obstructive disease (355 subjects with two normal legs). In this group we measured an ankle–brachial index < 0.90 in nine right and eight left legs only. Six subjects had an (aorto)iliac obstruction (right side: 4; left side: 3) and 13 a femoropopliteal obstruction (right side 10; left side: 12), based on abnormal Doppler tracings and an ankle–brachial index < 0.90 (seven legs showed an index < 0.50 indicating multilevel disease). In 87 subjects we detected crural artery obstructions based on 189 abnormal Doppler tracings (Table 3). In 24 legs the isolated absence of a Doppler signal from the peroneal artery in combination with a normal ankle–brachial index was interpreted as a technical failure.

Six subjects had previously had a vascular operation. One non-diabetic had a left iliaco-femoral bypass, the Doppler tracings on that side were normal and the ankle–brachial index was 1.02. The other five subjects were diabetic, one had a bifurcation graft (normal Doppler tracings, index 0.86 and 0.85) and three a femoropopliteal reconstruction (all three categorised as abnormal). If we take into account the arterial obstructions of these six subjects, more diabetics had obstructions of the leg arteries than non-diabetics (31.8 vs. 18.4%). Multivariate logistic regression analyses showed that diabetic subjects have a significantly increased risk for peripheral artery disease [Odds ratio (OR) 1.83, 95% confidence interval 1.16–2.87] irrespec-

Table 3. Crural artery obstructions

<table>
<thead>
<tr>
<th>Nr of diseased arteries</th>
<th>3</th>
<th>2</th>
<th>1</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nr of legs</td>
<td>18</td>
<td>26</td>
<td>83</td>
<td>127</td>
</tr>
<tr>
<td>Diabetic subjects</td>
<td>41 (23.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-diabetic subjects</td>
<td>46 (16.0%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>difference</td>
<td>( p = 0.025 )</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Multivariate logistic regression analysis of peripheral artery disease

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>(95% CI)</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0.84</td>
<td>(0.54–1.32)</td>
<td>0.447</td>
</tr>
<tr>
<td>Age (per year)</td>
<td>1.07</td>
<td>(1.03–1.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.83</td>
<td>(1.16–2.87)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

The increased risk by age (OR 1.07 per year, 95% CI 1.03–1.10) was confirmed in our group; sex had no significant influence in this respect (OR 0.84, 95% CI 0.54–1.32). Of those vascular lesions the frequency of (aorto)iliac plus femoropopliteal obstructions was higher in diabetics than in non-diabetics (8.1 vs. 2.4%, \( p = 0.004 \)). The same holds if only the crural lesions are compared (23.7 vs. 16.0%, \( p = 0.025 \)). In diabetic subjects 19.3% of the crural artery disease involved all three crural arteries compared with 9.2% in non-diabetics (\( p = 0.167 \)). By far
the majority of the leg artery lesions were asymptomatic (94.4%).

**Combined lesions**

In the group of 23 subjects with carotid artery lesions, two had an (aorto)iliac obstruction, one had a femoropopliteal obstruction and ten showed crural obstructions as well. The four persons with an arm artery obstruction also had severe lesions elsewhere; two had a carotid artery and a lower extremity artery obstruction as well, one also had a carotid artery lesion, and one also had obstructions of all six crural arteries.

**Discussion**

Peripheral vascular disease is an important cause of morbidity and mortality of non-insulin-dependent diabetics. Our study confirms that the prevalence of atherosclerotic lesions, including carotid arteries, arm arteries as well as leg arteries, is significantly higher in diabetics aged 50-75 years, 34% versus 19%. Many data in the literature come from studies of populations with a high prevalence of diabetes. Our subjects are representative of a Dutch Caucasian population and concern an age/sex stratified sample of non-diabetics and known as well as newly diagnosed diabetics, mostly non-insulin-dependent.

Some authors report the prevalence of vascular disease of leg arteries in terms of claudication, pulse deficits and lower limb amputations. However in the general population most lesions are asymptomatic. Others used a low ankle-brachial index (<0.9) as an indicator for leg artery obstruction. Epidemiological studies concerning the localisation of the obstructions in the leg arteries are scarce. As most lesions in diabetic subjects are found in the crural arteries, non-invasive tests should be able to discriminate between proximal and distal leg artery obstructions. Duplex can discriminate between central and femoropopliteal lesions but is not validated for crural obstructions. We chose the qualitative evaluation of continuous wave Doppler velocity waveforms as an additional non-invasive test as we use it in daily practice. The measurements can be performed quickly and easily without discomfort for the participant. Severe, haemodynamically significant arterial obstructions can be identified and located by means of a qualitative analysis of the Doppler signals. With this technique we found the prevalence of proximal lesions as well as of distal lesions in lower extremity arteries to be significantly higher in diabetic than in non-diabetic subjects. Combining these data with the systolic blood pressure measurements revealed that only 17 of the 764 legs without abnormal Doppler tracings (2.2%) had an ankle-brachial index < 0.90 whereas this was the case in all 29 legs with (aorto)iliac and femoropopliteal obstructions. However, an abnormal ankle-brachial index was found in only 24 of the 127 legs (19%) with diseased crural arteries. The difference may be explained by a loss of compressibility of the ankle arteries (Monckeberg sclerosis). In addition, an obstruction of a crural artery may be obscured because the ankle-brachial index is calculated from the highest pressure reading of the ankle arteries. So we conclude that in epidemiological studies the prevalence of severe arterial obstructions is underestimated if defined only by an abnormal ankle-brachial index. The Doppler waveform analysis is a necessary adjunct to the ankle pressure data in assessing peripheral vascular disease.

In Dutch diabetics, the prevalence of peripheral vascular lesions was 31.8% which is comparable to that described for Seattle, U.S.A. also based on abnormal Doppler signals and ankle pressures. Data of Munich, Germany, and Southampton, U.K. show lower prevalences but in those studies peripheral arterial disease was determined only by the measurement of a low ankle pressure. Comparing diabetic and non-diabetic subjects, we demonstrated a three times higher prevalence of serious lesions in the carotid arteries. In the leg arteries the prevalence was nearly two times higher. The four subjects with arm artery obstructions were all diabetic. Most of those vascular lesions identified were asymptomatic.

**References**


*Accepted 6 May 1994*