Objective. To study the relationship between the presence of peripheral artery disease (PAD) and the morbidity and mortality at 6 years, and the ankle-brachial index (ABI) as a predictor of morbidity and mortality in type 2 diabetes mellitus.

Design. Retrospective cohort study. Six years follow-up.

Setting. Urban health centre.

Participants. A total of 269 type 2 diabetics, of which 63 had PAD in 1996: 20 were previously diagnosed and 43 had an ABI of ≤0.90.

Principal measurements. An appointed was made with the patients to find out the incidence of fatal and non-fatal microvascular and macrovascular events and the histories were reviewed. Six patients were excluded as all their data were not available.

Results. Thirty nine patients had died, of whom 19 had PAD in 1996 (30.1%) and 20 did not (9.7%) (P=0.001). Seventeen patients died in the group with an ABI of ≤0.9 (32.2%) and 21 (10.1%) in the group with normal ABI values (P=0.001). 7 (13.2%) patients died due to a cardiovascular cause with a pathological ABI, and 8 (3.9%) with a normal value (P=0.009).

The presence of PAD has been associated with a higher probability of having a non-fatal episode of ischemic cardiac disease (P=0.04), a cerebrovascular accident (CVA) (P=0.005) and ulcers (P=0.006). A low ABI has been associated with a higher probability of presenting with a fatal or non-fatal cardiovascular event (P=0.001).

After the multivariate analysis an increase was observed in cardiovascular (odds ratio [OR] >2.3, 95% confidence interval [CI], 1.16-6.79, CVA [OR=1.47], 95% CI, 1.19-10.07), and cardiac failure (OR=6.78, 95% CI, 1.34-33.81), morbidity and mortality in diabetics with an ABI of ≤0.90.

Conclusions. The type 2 diabetics with PAD present with a higher morbidity and mortality. The ABI is a good predictor of cardiovascular disease and heart failure morbidity and mortality.

Key words: Peripheral artery disease. Ankle/brachial index. Type 2 diabetes mellitus. Cardiovascular disease.
Introduction

Peripheral artery disease (PAD) is the name given to arteriosclerotic disease of the lower limbs. Of the 3 important clinical manifestations of arteriosclerosis, it has the most benign prognosis, but it has already been observed in the Framingham study that patients with intermittent claudication had a risk of cardiovascular mortality twice as high as those patients of the same age and gender without claudication. Subsequent studies have also shown that asymptomatic PAD leads to an increased risk of presenting with cardiovascular events and total mortality. The pocket Doppler is an easy to use instrument and helps to make the diagnosis of PAD easier in the asymptomatic patient. With the help of a sphygmomanometer, it is possible to determine the systolic blood pressure (SBP) in the posterior brachial, pedis and tibial arteries and thus be able to calculate the ankle-brachial index (ABI). Many studies have been carried out to evaluate the validity of the ABI and its value as a predictor of total morbidity and mortality. The early diagnosis of PAD, when the patient is still asymptomatic, enables treatment to be started sooner and improves the prognosis. The calculation of the ABI can be particularly useful in the patient with type 2 diabetes mellitus (DM2), who has a high cardiovascular risk. PAD is one of the complications of DM2 and an etiological factor and poor prognosis of diabetes foot. Few studies have been published on the prevalence of PAD in patients with DM2 where the Doppler has been used, and even less follow up studies on these patients to find out their prognosis. For this reason, a study was carried out in Mataró (Spain) in 1996 with the objective of finding out the prevalence of PAD in patients cared for in the health centre with DM2. A Doppler examination was carried out on diabetics without known PAD, to calculate the ABI of each lower limb. The prevalence of PAD was found to be 21.4%, higher than that diagnosed previously. In 2002 we set out to find out the state of the patients studied in 1996 and we began a new study with the objective of assessing the morbidity and mortality of the patients with DM2 after 6 years as regards the presence or not of PAD, and the value of the ABI as a predictor of cardiovascular and total morbidity and mortality in DM2.

Subjects and Methods

It is a retrospective follow-up study of a cohort over 6 years. The diabetics studied in 1996 participated in the study. Twenty patients who had signs of calcification, a fact that prevents finding out the intraluminal state of the arteries, were excluded. Also excluded were those diabetics who could not be located and those where it was not known whether they were alive or dead, and in the morbidity study, those who had moved home and could not make the visit. The data was collected from the 1st of July 2002 to the 28th of February 2003. An appointment was made with the patients and they all had an anamnesis performed, including a physical examination, an electrocardiogram, an ophthalmic examination, and a general laboratory analysis. All the clinical histories were reviewed from when the Doppler examination was performed in 1996 up to the last visit to the centre and any new microvascular and macrovascular events were recorded. The diagnostic criteria were the same as those used in 1996:

- PAD: a well documented diagnosis in the clinical history or an ABI of ≤0.90 in at least 1 of the lower limbs.
- Ischaemic heart disease: well documented episode of angina, acute myocardial infarction (AMI), or coronary surgical intervention.
- Ischaemic cerebrovascular accident (CVA): a well documented episode of ischaemic CVA or a stenosis of the supra-aortic trunks of ≤50%.
- Neuropathy: diagnosis present in the clinical history.
- Cardiac failure: diagnosis present in the clinical history.
Peripheral Artery Disease of the Lower Limbs and Morbidity/Mortality in Type 2 Diabetics

Results

Of the 269 patients studied in 1996, 207 did not have PAD.
Of the 62 with PAD, 20 were previously diagnosed and 42 were diagnosed after an examination was made by Doppler. Table 1 shows the patient characteristics according to the ABI obtained. A higher prevalence of high BP and cerebrovascular disease was found among the patients with an ABI ≤ 0.90. Of the patients who did not have signs of calcification, the data of 6 were unknown, therefore they were excluded from the study (in 1996, 2 had a pathological ABI and 4 a normal ABI). The study of mortality was carried out with 263 diabetics. Twenty three diabetics had moved home and were not able to come to the control visit, although it is known that they are alive. Of these, 2 belong to the known PAD group and 21 to the normal ABI group. There were no statistically significant differences between these patients and the patients included in the study as regards age, gender, the presence of PAD, cardiovascular risk factors and the presence of ischaemic heart disease or CVA in 1996. After the exclusion, the morbidity study was carried out with 201 diabetics.

Mortality

Of the total diabetic patients studied, 39 (14.8%) had died, of whom 19 (31.6%) had PAD in 1996 and 20 (9.8%) did not have PAD (P < 0.001). Twenty one patients had died due to a cardiovascular cause, 12 (57.1%) with PAD and 9 (42.8%) without PAD (P < 0.001). Of the 40 patients who had died 16 (40%) had a pathological ABI (≤ 0.90), and 21 (53%) with PAD and 9 (22.5%) with a normal ABI (Table 2). Twenty one patients had died due to a cardiovascular cause and 8 (3.9%) with a normal ABI (Table 2).

Non statistically significant differences were found in the non-cardiovascular deaths.

Morbidity

Of the 201 patients who had been reviewed, those who had PAD in 1996 presented with a significantly higher number of ischaemic heart disease events (P < 0.04), CVA (P < 0.001), and ulcers (P < 0.006), as well as a higher probability of congestive heart failure (P < 0.001), neuropathy (P < 0.05), and retinopathy (P < 0.05). The differences were not significant for nephropathy (Table 3).

Mortality and Morbidity

On analysing the morbidity and mortality together, it was observed that 16 (29.3%) diabetics with PAD 1996 had a coronary event and 34 (61.8%) a cardiovascular event, as compared to 29 (14.6%) (P < 0.01) and 49 (24.6%) (P < 0.001) without PAD (Table 4). The patients who had

TABLE 1 Principal Baseline Characteristics of the Diabetics Studied

<table>
<thead>
<tr>
<th>ABI in 1996</th>
<th>0.51-1.26 (N=203)</th>
<th>0.50 (N=40)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), y</td>
<td>62±3.7</td>
<td>76±3.8</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Male, N (%)</td>
<td>82 (40.8)</td>
<td>19 (47.5)</td>
<td>.28</td>
</tr>
<tr>
<td>Years with diabetes mellitus, mean±SD</td>
<td>7.8±7.8</td>
<td>9.5±6.1</td>
<td>.07</td>
</tr>
<tr>
<td>Smoking, N (%)</td>
<td>82 (30.5)</td>
<td>17 (42.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Hypertension, N (%)</td>
<td>58 (53.6)</td>
<td>29 (72.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Ischaemic heart disease, N (%)</td>
<td>27 (13.3)</td>
<td>7 (17.5)</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Cerebrovascular accident, N (%)</td>
<td>22 (10.8)</td>
<td>14 (28)</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

*ABI indicates ankle-brachial index; CI, confidence interval. **ABI indicates ankle-brachial index; SD, standard deviation.

TABLE 2 Relationship Between Peripheral Artery Disease Diagnosed Using Doppler in 1996 and Total and Cardiovascular Mortality at 6 Years

<table>
<thead>
<tr>
<th>ABI in 1996</th>
<th>0.91-1.24 (N=203)</th>
<th>0.90≤ (N=40)</th>
<th>Total</th>
<th>Cardiovascular</th>
<th>Non-cardiovascular</th>
<th>Difference of Proportions</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td>8 (3.9)</td>
<td>4 (10)</td>
<td>0.04</td>
<td>-0.04 to 0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>21 (10.3)</td>
<td>16 (40)</td>
<td>0.27</td>
<td>0.12-0.43</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>8 (3.9)</td>
<td>7 (17.5)</td>
<td>0.12</td>
<td>0.01-0.24</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-cardiovascular</td>
<td>10 (4.9)</td>
<td>4 (10)</td>
<td>0.04</td>
<td>-0.04 to 0.14</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*ABI indicates ankle-brachial index; CI, confidence interval. **ABI indicates ankle-brachial index; SD, standard deviation.

– Nephropathy: confirmed presence of microalbuminuria (30-300 mg/dL) or proteinuria (>300 mg/dL) and/or creatinine ≥ 1.3 mg/dL.
– Retinopathy: diagnosis made by an ophthalmologist.
– Ulcers: recorded in the clinical history.
– Non-fatal cardiovascular event: new diagnosis of PAD or ischaemic heart disease or non-fatal CVA.
– Mortality: the passive files of the health centre and the only reference hospital (Mataro Hospital) were consulted to find out the cause of death of the patients who died during the study period. The causes were classified as a) cardiovascular (AMI, ischaemic CVA, PAD, sudden death), and b) non cardiovascular (all the rest).
If the clinical histories were not found in the centre archives, the SIAP (Primary Care Computer System) database was consulted to find out if the patient had died or changed address.

The data was introduced into a computerised database and were analysed using the SPSS/PC, version 12 statistics program.

For the data analysis, the χ2 test and binary logistic regression analysis (stepwise selection of the variables) were used. The variables introduced were: age, gender, years of evolution of the diabetes, blood pressure (BP), smoking habits, blood lipids, value of the ABI, and presence of cardiovascular disease in 1996 (known ischaemic heart disease, CVA, and PAD). As a test of goodness of fit, the Hosmer-Lemeshow test was used in all cases. Patients without PAD in 1996 were compared with those who had PAD (well documented diagnosis in clinical history or ABI ≤ 0.90) and with those who had an ABI > 0.90.

The causes were classified as: a) cardiovascular (AMI, ischaemic CVA, PAD, sudden death), and b) non cardiovascular (all the rest).

No statistically significant differences were found in the non-cardiovascular deaths.

Morbidity

Of the 201 patients who had been reviewed, those who had PAD in 1996 presented with a significantly higher number of ischaemic heart disease events (P < 0.04), CVA (P < 0.001), and ulcers (P < 0.006), as well as a higher probability of congestive heart failure (P < 0.001), neuropathy (P < 0.05), and retinopathy (P < 0.05). The differences were not significant for nephropathy (Table 3).
a pathological ABI showed a higher probability of having a cardiovascular event (P<.001). In the multivariate analysis, a higher risk of cardiovascular morbidity and mortality (odds ratio [OR] =2.81; 95% confidence interval [CI], 1.64-6.78), CVA (OR=3.47; 95% CI, 1.19-10.07), and cardiac failure (OR=6.75; 95% CI, 1.34-33.81) was observed among the diabetics with an ABI ≤0.90 (Tables 6 and 7). If the cardiovascular morbidity and mortality is analysed excluding the patients with known ischaemic heart disease, CVA and/or PAD in 1996, there is still an increased risk in patients with a pathological ABI (OR=3.01; 95% CI, 1.38-6.59; P<.001).

**TABLE 3** Relationship Between Peripheral Artery Disease in 1996 and the Mortality During the Follow-Up Period

<table>
<thead>
<tr>
<th>Mortality</th>
<th>ABI ≤0.90 (N=32)</th>
<th>ABI &gt;0.90 (N=188)</th>
<th>Difference of Proportions</th>
<th>95% CI</th>
<th>P</th>
<th>Adjusted to the $\chi^2$ de Hosmer-Lemeshow Model</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischaemic heart disease</td>
<td>21 (65.6)</td>
<td>10 (25.6)</td>
<td>0.12</td>
<td>-0.01 to 0.27</td>
<td>0.13</td>
<td>10.05 &lt;.001</td>
</tr>
<tr>
<td>CVA</td>
<td>19 (58.8)</td>
<td>14 (36.8)</td>
<td>0.24</td>
<td>0.09-0.46</td>
<td>0.13</td>
<td>10.05 &lt;.001</td>
</tr>
<tr>
<td>Cardiac failure†</td>
<td>4 (12.5)</td>
<td>6 (15.3)</td>
<td>0.12</td>
<td>0.11-0.73</td>
<td>0.13</td>
<td>10.05 &lt;.001</td>
</tr>
<tr>
<td>Neuropathy†</td>
<td>17 (51.5)</td>
<td>10 (25.6)</td>
<td>0.15</td>
<td>0.01-0.39</td>
<td>0.13</td>
<td>10.05 &lt;.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1 (3.1)</td>
<td>6 (15.3)</td>
<td>0.11</td>
<td>0.03-0.61</td>
<td>0.13</td>
<td>10.05 &lt;.001</td>
</tr>
<tr>
<td>Retinopathy</td>
<td>32 (9.8)</td>
<td>5 (12.8)</td>
<td>0.7</td>
<td>0.05 to 0.19</td>
<td>0.13</td>
<td>10.05 &lt;.001</td>
</tr>
<tr>
<td>Total mortality†</td>
<td>28 (87.5)</td>
<td>12 (30.8)</td>
<td>13.5</td>
<td>-0.02 to 0.29</td>
<td>0.13</td>
<td>10.05 &lt;.001</td>
</tr>
</tbody>
</table>

*PAD indicates peripheral artery disease; CI, confidence interval; CVA, cerebrovascular accident.
†Dependent variable of each type of mortality. Patients with already known peripheral artery disease in 1996 and deaths by unknown cause (except in the total mortality section).
The pocket Doppler is an easy to use instrument. At 6 years of follow up a higher ankle-brachial index is a good predictor of PAD is a complication of non-insulin dependent diabetes mellitus. The results suggest that the ABI is a good predictor of total and cardiovascular mortality in non-insulin dependent diabetics. As regards morbidity, we have found that the presence of PAD is associated with a higher probability of not only suffering from coronary or cerebrovascular disease already reported by other authors, but also a higher prevalence of congestive cardiac failure, retinopathy, and neuropathy. Although Dolan et al have already described the relationship between PAD and neuropathy, we know of no cohort study carried out only on patients with diabetes where the morbidity associated to the presence or not of PAD was studied.

One of the weak points of the study is the losses that occurred over the 6 years. If we exclude the patients with signs of calcification, only 10.7% of the patients have been lost and 2% in the mortality study.

Another point of conflict is the evaluation of events retrospectively, since the data has been collected basically from the clinical history. However, we believe that the information gathered has been correct, since the health centre has a very stable health staffing levels, and only one reference hospital, which makes the follow up the patient easier.

Another limitation of the study is the number of cases, which was adequate to study the relationship of ABI with mortality but inadequate for the study of the morbidity. It requires a follow-up with a much larger group of diabetics, as has been carried out on a general population, to find out the true value of the ABI as a predictor of complications in Type 2.

Important clinical studies have been published in recent years in the field of cardiovascular diseases. Some of them have newly introduced the use of ABI to make the diagnosis of PAD and to be able to analyse these patients within separate sub-groups, similar to that carried out with ischaemic heart disease and CVA. Others have considered PAD among the principal events studied and, along with other studies, they have also demonstrated the efficacy of the strict control of risk factors for arteriosclerosis in these patients. These studies are the ones that have led to the publication of the most important recommendations for the prevention and treatment of cardiovascular disease by advising the application of secondary prevention measures in the patient with PAD, both symptomatic as well as that diagnosed solely using the ABI. The American Heart Association recommends measuring the ABI on all those over 50 years old, with the intention of identifying patients with a high cardiovascular risk and thus be able to treat them more aggressively, and also to be more active in looking for coronary and cerebral disease.

All this data leads us to emphasise the importance of incorporating the Doppler into Primary Care clinics, thus
being able to identify, with a simple examination, the patients with a higher cardiovascular risk and be able to offer them a treatment which has shown to be efficient.

References

Peripheral Artery Disease of the Lower Limbs and Morbidity/Mortality in Type 2 Diabetics

Both symptomatic and sub-clinical peripheral artery disease causes a large decrease in functional capacity and quality of life, leads to limb amputations and increases the risk of death. These patients most probably have other ischaemic cardiac diseases, such as myocardial infarction or stroke. It is, in fact, a marker of atherothrombotic disease in other vascular regions.

In patients with diabetes, the presence of arterial disease is increased. It is particularly localised in distal zones (femoral, popliteal, and tibial area), unlike other risk factors such as smoking and hypertension, associated with disease in the aorta-iliac-femoral vessels. Owing to this localisation of the disease and its association with neuropathy, which reduces the sensitivity of the lower limbs, patients with diabetes are diagnosed later with peripheral artery disease. By the time the symptoms appear they have a higher risk of amputation and other fatal cardiovascular diseases.

The study by Bundó et al characterises the vascular risk of the diabetic patient with symptomatic or asymptomatic peripheral artery disease very well. It is a study carried out in Spain in a primary care setting, with a follow-up of 6 years on patients with diabetes and peripheral artery disease, in which it demonstrated the increased prevalence of clinical and sub-clinical disease, which goes from 6.9% to 21.4% on measuring the ankle-brachial index (ABI), on all known diabetics in their health centre. The follow-up of these patients showed an increase in the morbidity/mortality to be seen and a higher probability of microvascular and macrovascular complications of diabetes: ischaemic heart disease, stroke, cardiac failure, neuropathy and retinopathy as well as skin ulcers. An increase in nephropathy was not found, perhaps because this association required a larger number of cases in the study. Finally, the incorporation of this technique into daily clinical practice is recommended.

The ABI is a non-invasive, quantitative and reliable diagnostic method, as well as a prognostic predictor of peripheral artery disease. It is validated in relation with the diagnostic reference, angiography, with a sensitivity of 95% and a specificity of almost 100% for a cut off point of abnormality of <0.91. This method also has limitations, on giving false negative results in some symptomatic patients with moderate aorta-iliac stenosis and in people who have calcified, difficult to compress arteries, as happens in older people and in some patients with diabetes.

The American Diabetes Association recommends measuring the ABI in patients >50 years old with diabetes and a repeat test every 5 years if it is normal, with the purpose of obtaining an early sub-clinical diagnosis and to begin applying preventive measures which may prevent an amputation. However, according to the PAPPS (Preventive Activities and Health Promotion Program) recommenda-
tions (adaptation of the European Cardiovascular Prevention Guide) a few changes should be made, as regards aggressive therapy and special care of the feet, whether the patient with diabetes, may have arterial disease or not.3 We should remember that the guide places non-insulin dependent diabetes and insulin dependent diabetes with microalbuminuria in the high cardiovascular risk group, with treatment recommendations similar to established peripheral artery disease. The general impression is that these recommendations are sub-optimal and that the diagnosis of artery disease reinforces a more aggressive attitude by the doctor. In the SMART study, screening of asymptomatic cardiovascular disease is carried out with non-invasive imaging techniques in patients classified as high or low risk according to the European Cardiovascular Prevention Guide. In this, an ABI<0.90 was only found in 5 patients out the 545 initially classified as low risk. In other words, only 0.91% of the low risk patients were reclassified to high risk by the sub-clinical diagnosis of artery disease.4 The measurement of ABI in primary care is feasible. The technique takes 10-15 minutes to perform, but to be used routinely it would be necessary for the nursing staff to assume this task. The ABI enables a diagnosis of artery disease to be made, to establish the baseline value and to make a prognostic staging of the disease. Its follow-up enables us to understand the evolution of the disease and it is a prognostic factor of cardiovascular mortality (Bundó et al). In any case, it is difficult to recommend it as a screening test, since the diagnosis of artery disease should not change the therapeutic approach, unless diabetes with arterial disease in future investigations is classified as very high risk and may change the treatment objectives or different treatments may be used for this diabetic group. To insist that the doctor complies with the recommendations of the guides, it would be more logical to introduce this test as a screen now. Future lines of investigation is the presence of an abnormal ABI in patients with impaired fasting glucose or glucose intolerance.5 These have lower vascular risk and an abnormal ABI could lead to a change in the therapeutic approach. Another possible line is the prognostic significance of a high ABI, since in some studies it has also been associated with an increase in cardiovascular mortality.6

References