The role of autonomic neuropathy in diabetic foot ulceration

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SUMMARY Five standard, non-invasive tests of cardiovascular, autonomic function were performed in each of four groups of 30 subjects: controls, group 1, diabetics without clinical evidence of neuropathy; group 2, diabetics with neuropathy, but without foot ulceration; group 3, diabetics with neuropathic ulceration of the foot. The results showed a significant impairment of autonomic function in (a) diabetics without clinically demonstrable somatic neuropathy compared with controls (b) diabetics with somatic neuropathy compared with those without (c) diabetics with neuropathic ulceration compared with those with neuropathy without ulceration. Parasympathetic function was more seriously affected than sympathetic. In patients who had only mild sensory neuropathy on clinical assessment, those with ulcers had significantly greater impairment of autonomic neuropathy compared with those with uncomplicated neuropathy.

It is clearly established that patients with diabetic diffuse distal peripheral neuropathy are at risk of developing pedal ulceration, particularly on the sole.1 2 Many factors are involved in the formation of these ulcers,3 the one essential being impaired pain sensation, with the other components of the somatic neuropathy also playing an important role.4 It is also well established that autonomic neuropathy is common in diabetes. Its role in disturbances of many body systems (for example cardiovascular,5–7 gastrointestinal,8 9 genitourinary,9 10 and thermo-regulatory11 12) is increasingly being recognised. However, the extent to which it may contribute to ulceration of the foot is not clearly defined.

The present study was designed to throw further light on the role of autonomic neuropathy in the causation of foot ulceration, by performing a battery of five tests of autonomic function and simple clinical measurements of the degree of sensory neuropathy in groups of patients with and without neuropathy, and/or neuropathic ulcer.

Patients and methods

Ninety diabetic patients (age range 40–67 years) attending either The Middlesex Hospital or The London Foot Hospi-

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tal were studied. The patients were divided into three groups:

Group 1 Diabetics without clinically detectable neuropathy (DM)

Group 2 diabetics with neuropathy but no history of foot ulcers (DMN)

Group 3 diabetics with neuropathic foot ulcers, active or healed (DMU)

The measurement of somatic neuropathy

The degree of peripheral, somatic neuropathy was studied by examination of ankle jerks, pin prick and vibration sense. Neuropathy was graded by assigning a score to each of these signs: Ankle jerks: normal = 0, reduced = 1, absent = 2. Sensation to pin prick: normal = 0, reduced on feet = 1, reduced above ankles = 2. Vibration appreciation: normal = 0, absent on toes = 1, absent at malleoli = 2. The cumulative score for the three signs gave a neuropathy grading of 0–6 for each patient. In all patients the ankle pulses were present.

A control group of 30 volunteers from the hospital staff or surgical inpatients were also studied, each of whom had normal ankle pulses, ankle tendon reflexes and sensation to pin prick and vibration.

The measurement of autonomic neuropathy

Three tests of cardiac parasympathetic activity were performed (a) Heart rate response toValsalva manoeuvre (VR) (b) Beat to beat variation during deep breathing (I–E rate) (c) Heart rate response to standing (30/15 ratio).

Two tests reflecting sympathetic activity were performed (a) Blood pressure rise in response to sustained handgrip (Grip) (b) Blood pressure fall in response to standing (BP stand). An abnormal response to either of these tests indi-
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Table 1  A summary of patient particulars

<table>
<thead>
<tr>
<th></th>
<th>Age years</th>
<th>M:F</th>
<th>Duration of diabetes in years</th>
<th>Type of diabetes</th>
<th>ID %</th>
<th>NID %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cont.</td>
<td>mean 53.7</td>
<td>17:13</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DM</td>
<td>mean 54.0</td>
<td>21:9</td>
<td>10.0</td>
<td>ID</td>
<td>47</td>
<td>53</td>
</tr>
<tr>
<td>range</td>
<td></td>
<td></td>
<td>(1–28)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMN</td>
<td>mean 55.1</td>
<td>19:11</td>
<td>16.5</td>
<td>NID</td>
<td>67</td>
<td>33</td>
</tr>
<tr>
<td>range</td>
<td></td>
<td></td>
<td>(1–45)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DMU</td>
<td>mean 54.2</td>
<td>21:9</td>
<td>18.4</td>
<td></td>
<td>77</td>
<td>23</td>
</tr>
<tr>
<td>range</td>
<td></td>
<td></td>
<td>(0–45)</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

(Cont. = Controls; DM = Diabetics without neuropathy; DMN = Diabetics with neuropathy; DMU = Diabetics with neuropathic ulceration.)

Results of 5 autonomic function tests in the four groups of subjects—Controls: Gp 1, DM: Gp 2, DMN: Gp 3, DMU. Figures in brackets are the numbers of subjects with the value at the points indicated. Solid lines are mean values and dotted lines are at 2 SD.
Results

Table 2 summarises the particulars of the patients in the four groups studied. The results of the five autonomic function tests are shown in the figure and summarised in Table 2. There was no significant difference in the age distribution of the four groups. The duration of diabetes in the patients without neuropathy was significantly shorter than in the other two diabetic groups but there was no difference between the neuropathy (DMN) and the ulcer (DMU) group.

In the control group there was a significant negative correlation of age with the Valsalva ratio and the 30/15 ratio (p < 0·05), and with the blood pressure rise with sustained handgrip (p < 0·01), but no correlation was found with the other two autonomic tests. In the neuropathic group (DMN) there was a significant negative correlation of age with the VR (p < 0·05) but no correlation was found with any of the other four tests. In both diabetics without neuropathy (DM) and those with ulcers (DMU) no correlation was found with age in any of the five autonomic tests.

There was no correlation between the duration of diabetes and any of the five tests in any of the three diabetic groups, nor when the three groups were considered together.

The mean and standard deviation of the Valsalva ratio for the controls was 1·73 ± 0·28. There was a significant decrease in the VR between the controls and the diabetics without neuropathy (p < 0·05); between the latter and those with neuropathy (p < 0·001); and between these latter and those with ulcers (p < 0·001).

The mean and standard deviation of the I-E rate for the controls was 22 ± 7·6 beats per minute. A significant decrease was found between the controls

Table 3 Results of autonomic tests in patients with neuropathy and neuropathic ulceration divided into two groups on the basis of the severity of somatic neuropathy. Statistical comparisons were made using the Mann Whitney form of Wilcoxon test

<table>
<thead>
<tr>
<th></th>
<th>Mild (Grades 1 &amp; 2)</th>
<th>Severe (Grades 5 &amp; 6)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DMN n = 15</td>
<td>DMU n = 7</td>
</tr>
<tr>
<td>Valsalva Ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>1·35</td>
<td>1·17</td>
</tr>
<tr>
<td>SD</td>
<td>0·21</td>
<td>0·14</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0·05</td>
<td>NS</td>
</tr>
<tr>
<td>I–E rate (beats/min)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>18·87</td>
<td>7·29</td>
</tr>
<tr>
<td>SD</td>
<td>10·26</td>
<td>5·62</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0·01</td>
<td>NS</td>
</tr>
<tr>
<td>Stand 30/15 ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>1·08</td>
<td>1·02</td>
</tr>
<tr>
<td>SD</td>
<td>0·06</td>
<td>0·04</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0·02</td>
<td>NS</td>
</tr>
<tr>
<td>BP rise on gripping (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>15·47</td>
<td>7·71</td>
</tr>
<tr>
<td>SD</td>
<td>7·18</td>
<td>2·56</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0·02</td>
<td>NS</td>
</tr>
<tr>
<td>BP fall on standing (mm Hg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mean</td>
<td>7·67</td>
<td>11·71</td>
</tr>
<tr>
<td>SD</td>
<td>10·80</td>
<td>6·63</td>
</tr>
</tbody>
</table>
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and diabetics without neuropathy (p < 0.05), between the latter and those with neuropathy (DMN) (p < 0.01), and between these latter and those with ulcers (p < 0.001).

The mean and standard deviation of the 30/15 ratio for the controls was 1.14 ± 0.09. There was a significant decrease in this ratio between the controls and the diabetics without neuropathy (p < 0.001); between the latter and those with neuropathy (p < 0.01), and between diabetics with neuropathy and the ulcer group (p < 0.05).

The mean and standard deviation of the blood pressure rise with sustained handgrip was 18.0 ± 3.1 mm Hg. There was a significant difference in the rise of blood pressure in the controls compared with the diabetics without neuropathy (p < 0.002) and in those with neuropathy compared with the ulcer group (p < 0.002) but not between diabetics with and without neuropathy.

The mean and standard deviation of the blood pressure fall on standing was 2.3 ± 4.8 mm Hg. There was a significant difference in the fall in blood pressure with standing between diabetics with and without neuropathy (p < 0.05) but not between controls and diabetics without neuropathy nor between diabetics with neuropathy and those with ulcers. There was, however, a significant difference between those with ulcer and controls (p < 0.001) and those with ulcer and no neuropathy (p < 0.001).

There was no significant difference in sensory impairment between the neuropathy and the ulcer group. The autonomic tests were compared in subjects whose sensory neuropathy was mild (grades 1 and 2) on clinical testing and also in those whose neuropathy was severe (grade 5 and 6). The results are shown in Table 3. In the patients with mild sensory neuropathy those in the ulcer group showed significantly greater impairment of autonomic function than those with neuropathy but no ulcer (DMN), but in patients with severe sensory neuropathy there was no such difference.

Discussion

These findings confirm the previous studies that diabetics with peripheral somatic neuropathy consistently have evidence of autonomic dysfunction. There was no significant difference in the degree of sensory neuropathy as judged clinically between those with neuropathy and those with ulcers. There was, however, a statistically significant deterioration of parasympathetic function in sequence in all three tests between the four groups from controls to the ulcer group. The tests of sympathetic function showed a sequential impairment from controls to diabetics with ulcers, but there was not a consistent significant difference between all the groups, though the response to both tests (blood pressure rise on handgrip; fall on standing) in the ulcer patients was significantly different both from controls and from diabetics without neuropathy. This confirms the findings that in diabetic neuropathy sympathetic function is affected later than parasympathetic.14

The finding that the impairment of autonomic function was greater in the patients with neuropathic ulceration does not necessarily imply that this impairment has a causative role in the formation of the ulcer. The tests performed indicate an impairment of the central, cardiac functions of the autonomic system, and it may be that the impairment of function they demonstrate and the development of pedal ulceration are independent indices of the severity of the neuropathy. However, it is of interest that comparing those patients with a mild degree of sensory neuropathy and no ulceration with those with a similar degree of neuropathy but with ulceration showed that the degree of impairment of autonomic function was significantly greater in those with ulceration, suggesting that this component of the neuropathy may indeed be a factor in the development of neuropathic ulceration.

There are a number of ways in which impairment of the autonomic supply to the foot could contribute to the formation of an ulcer. It is known that in patients with neuropathy there is decreased circulatory transit time in the foot,15 and this may well diminish tissue oxygenation. Further, it probably results in impairment of the vascular response to trauma and infection. Impairment of autonomic sudomotor function16 is responsible for the characteristic dry foot of the patient with neuropathy, and this may well contribute to the formation of the characteristic callosus which develops at the site of high mechanical stress.

The findings of this study may also be of practical importance. It is now clear that in the management of the diabetic patient with neuropathy it is important to detect those patients who are particularly at risk of developing ulceration so that their feet can be protected by the use of special insoles and other measures. The use of one of the simple, non-invasive tests of autonomic function used in this study may well be of value in this context.

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References

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