High levels of foot ulceration and amputation risk in a multiracial cohort of diabetic patients on dialysis therapy.

Running Title: Lower limb complications, Diabetes, Dialysis

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Submitted 29 October 2009 and accepted 27 December 2009.

This is an uncopyedited electronic version of an article accepted for publication in Diabetes Care. The American Diabetes Association, publisher of Diabetes Care, is not responsible for any errors or omissions in this version of the manuscript or any version derived from it by third parties. The definitive publisher-authenticated version will be available in a future issue of Diabetes Care in print and online at http://care.diabetesjournals.org.
**Objective:** To evaluate the prevalence of lower limb complications (LLCs) in a multi-racial cohort of patients with diabetes receiving dialysis.

**Research design and methods:** A cross-sectional study of LLCs in dialysis-treated patients with diabetes in the UK and USA.

**Results:** We studied 466 patients (UK 139; USA 327). The prevalence of LLCs was high (foot ulcers 12%, neuropathy 79%, peripheral arterial disease (PAD) 57%, history of foot ulceration 34% and prior amputation 18%), with no significant ethnic variation, except that foot ulcers were more common in Whites than in patients of African-descent (p=0.013). Ninety-five percent of patients were at-risk of LLCs. Prior amputation was related to foot ulcer history, PAD and hemodialysis modality in multivariable analysis. Prevalent ulceration showed independent associations with foot ulcer history and PAD, but not with ethnicity.

**Conclusions:** All patients with diabetes receiving dialysis are at high risk of LLCs independent of ethnic background.
Amongst individuals with diabetes, significant ethnic differences in lower limb complications (LLCs) have been identified in the United Kingdom (1) and the USA (2). Previous studies linking renal impairment or end stage renal disease (ESRD) to LLCs have been retrospective and have not considered ethnicity (3, 4). We aimed to establish the prevalence of LLCs by ethnic group in dialysis-treated diabetic patients.

RESEARCH DESIGN AND METHODS
This was a prospectively-designed cross-sectional study including patients with diabetes receiving dialysis therapy from centers in Manchester (UK) and Texas (USA). During routine clinic appointments patients were interviewed and had a detailed foot examination including neurological (5, 6) and peripheral arterial disease (PAD) assessment. Data were collected on diabetes and dialysis status, foot conditions, foot care, and footwear. Peripheral neuropathy (DPN) was defined as vibration perception threshold >25V (Neurothesiometer, Horwell Scientific Laboratory Supplies, Nottingham, U.K) and/or a modified neuropathy disability score >3 (5,6). PAD was defined as: ABPI <0.9 (7); a history of peripheral artery revascularization or angiography confirming PAD; non-compressible arteries (ABPI>1.4 with monophasic or biphasic waveforms) (8); or the absence of ≥2 foot pulses on palpation (9). The international working group on the diabetic foot (IWGDF) risk classification was used to assign patients into 4 levels of increasing risk of LLCs (9): no recognizable risk factor (risk category 0); neuropathy and no other risk factors (risk category 1); PAD with or without neuropathy (risk category 2); prevalent foot ulceration, a history of foot ulcer or prior amputation (risk category 3). Patients in risk categories 1, 2 or 3 were considered to be at high risk of LLCs. Ethnicity was based on patient self report. The study received prior approval from relevant ethics committee and review boards. Pearson’s Chi-squared and Fisher’s exact tests were used for between-group comparisons of categorical data. ANOVA was used to assess the influence of ethnic group on LLCs. Proportions of patients with LLC are presented with 95% CI estimated by the modified Wald method. Univariate analysis was performed to identify factors associated with prevalent foot ulceration or prior amputation and variables with significant associations were included in multivariate logistic regression. P<0.05 was considered statistically significant. Analyses were performed using SPSS version 15.0 (Chicago: SPSS Inc.).

RESULTS
We studied 466 patients (UK = 139, USA = 327). Eighty-eight percent were receiving hemodialysis; the remainder received peritoneal dialysis. Recruitment center (UK or USA) was not associated with prevalent foot ulcer or prior amputation in univariate analysis. We observed a high prevalence of PAD and DPN, and a moderately high prevalence of past foot ulceration and amputation that did not vary by ethnicity (Table 1). The only foot complication that varied by ethnicity was current foot ulceration which affected ~one in eight patients; Whites having a higher prevalence than patients of African descent (16.4% versus 4.5%, p = 0.013) but not significantly higher than Asians or Hispanics.

Based on IWGDF risk categories, 95% of all patients were considered to be high-risk. Prevalent foot ulceration showed univariate associations with PAD (OR, [95%CI]: 4.5 [2.1 to 9.4], p<0.0001), foot ulcer history (3.1 [1.7 to 5.4], p<0.0001), retinopathy (4.0 [1.9 to 8.3], p<0.0001), white ethnicity (2.1 [1.2 to 3.7] p=0.008), and failure to wear bespoke footwear (2.1 [1.2 to 3.6], p=0.010). Prevalent
foot ulceration remained independently associated with PAD (4.1 [1.9 to 8.6], p<0.0001) and foot ulcer history (2.8 [1.6 to 5.1], p=0.001) in multivariate analysis. Prior amputation showed univariate associations with foot ulcer history (46 [19 to 110], p<0.0001), PAD (3.8 [2.1 to 6.8], p<0.0001), failure to wear bespoke footwear (3.8 [2.3 to 6.2], p<0.0001), hemodialysis modality (2.9 [1.1 to 8.3], p=0.023), DPN (2.3 [1.1 to 4.7], p=0.016), male sex (1.7 [1.1 to 2.8] p=0.019, and retinopathy (1.6 [1.0 to 2.7] p=0.043). Prior amputation was independently associated with foot ulcer history (42 [17 to 100], p<0.0001), PAD (4.1 [2.9 to 8.4], p<0.0001) and hemodialysis modality (17 [2 to 132], p=0.008) in multivariate analysis.

CONCLUSIONS

We report a high prevalence of LLCs in a large ethnically diverse cohort of diabetic patients on dialysis, with up to 95% of them having at least one recognizable risk factor for foot ulceration. Contrary to previous reports of ethnic variations of foot complications in diabetes (1, 2), we observed no ethnic variation in prevalent foot complications in our dialysis-treated cohort, except for prevalent foot ulceration. This may be due to these patients having a heavy burden of systemic end-stage microvascular and macrovascular disease, such that ethnic differences become relatively insignificant. Diabetic patients with ESRD are likely to have falsely elevated ABPIs (10, 11) and ABPI measurements are less able to detect occlusion in arterial segments distal to the ankle which might be detected by palpation of distal pedal pulses. Therefore we used a combination of criteria to define subjects with PAD. Our data confirm and extend previous reports on diabetic foot disease in the ESRD population (12, 13). The strengths of our study include: the large multi-ethnic sample providing reliable prevalence data; the inclusion of UK and US centers; and a comprehensive assessment of foot pathology. Our study is limited by the small number of patients receiving peritoneal dialysis; and suboptimal information on preventative and therapeutic care. Although this was not an intervention study, we believe that our findings have immediate implications for foot care delivery. Since we found that 95% of dialysis-treated diabetic patients are at high risk for foot problems, we suggest that all such patients should be considered to be high risk. Dialysis-treated patients may fail to attend for appropriate foot care as they are too concerned with the demands of dialysis (14), and therefore scheduling foot evaluation, education and interventions during or immediately following dialysis may be a key component of effective prevention (15).

In summary, diabetic patients treated with dialysis have a high prevalence of foot ulceration, amputation and the ‘high risk foot’ that is similar across all ethnic groups. Comprehensive and multidisciplinary diabetic foot care should be offered to all patients and be integrated within dialysis services.

ACKNOWLEDGEMENT

This project was funded by Diabetes UK and the American Diabetes Association. We acknowledge support from the Manchester NIHR Biomedical Research Centre and Manchester Academic Health Science Centre. MKR was supported by a Higher Education Funding Council for England Clinical Senior Lecturer Award. LV was supported by the NIH/NIDDK R01 DK71066-01A2. Disclosure: The authors declare no conflict of interest to disclose. Lawrence Lavery is on the speaker’s bureau for KCI, Diabetica Solutions, Scientific Ad Board: Diabetica Solutions, LaseCure, National Healing, Advanced Biohealing, Pfizer, Cytomedix, Inc Stock: Diabetic Solutions.
REFERENCES
Table 1. Prevalence of foot ulcers, amputations and risk factors for developing lower limb complications by ethnic groups.

<table>
<thead>
<tr>
<th>Complications and IWGDF risk groups</th>
<th>White</th>
<th>Hispanic</th>
<th>African</th>
<th>Asian</th>
<th>Total</th>
<th>p-value ANOVA for ethnicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>196</td>
<td>165</td>
<td>70</td>
<td>35</td>
<td>466</td>
<td></td>
</tr>
<tr>
<td>Age, years</td>
<td>61 ± 14</td>
<td>61 ± 12</td>
<td>59 ± 13</td>
<td>57 ± 12</td>
<td>60 ± 13</td>
<td>0.363</td>
</tr>
<tr>
<td>Gender (% male)</td>
<td>55</td>
<td>52</td>
<td>53</td>
<td>57</td>
<td>53</td>
<td>0.896</td>
</tr>
<tr>
<td>Diabetes (% type 1)</td>
<td>23</td>
<td>4</td>
<td>6</td>
<td>11</td>
<td>13</td>
<td>0.001</td>
</tr>
<tr>
<td>Time since diagnosis of diabetes (years)</td>
<td>21 ± 11</td>
<td>18 ± 10</td>
<td>21 ± 10</td>
<td>17 ± 9</td>
<td>20 ± 10</td>
<td>0.012</td>
</tr>
<tr>
<td>Glycated haemoglobin (%)</td>
<td>7.4±1.7</td>
<td>6.9±1.4</td>
<td>7.2±1.8</td>
<td>7.6±1.2</td>
<td>7.2±1.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Current foot ulcer (%)</td>
<td>16 (12 to 22)</td>
<td>10 (6 to 15)</td>
<td>4 (1 to 12)</td>
<td>11 (4 to 27)</td>
<td>12 (9 to 15)</td>
<td>0.041</td>
</tr>
<tr>
<td>Past foot ulcer (%)</td>
<td>36 (30 to 43)</td>
<td>34 (27 to 41)</td>
<td>30 (20 to 41)</td>
<td>20 (10 to 36)</td>
<td>33 (29 to 38)</td>
<td>0.277</td>
</tr>
<tr>
<td>Past or present foot ulcer (%)</td>
<td>42 (35 to 49)</td>
<td>39 (32 to 46)</td>
<td>34 (24 to 42)</td>
<td>26 (14 to 42)</td>
<td>38 (34 to 43)</td>
<td>0.276</td>
</tr>
<tr>
<td>Amputation (%)</td>
<td>15 (11 to 21)</td>
<td>20 (15 to 27)</td>
<td>21 (13 to 32)</td>
<td>9 (2 to 23)</td>
<td>18 (14 to 21)</td>
<td>0.286</td>
</tr>
<tr>
<td>PAD (%)</td>
<td>54 (47 to 61)</td>
<td>58 (50 to 65)</td>
<td>63 (51 to 73)</td>
<td>54 (38 to 69)</td>
<td>57 (52 to 61)</td>
<td>0.672</td>
</tr>
<tr>
<td>DPN (%)</td>
<td>82 (76 to 87)</td>
<td>76 (69 to 82)</td>
<td>79 (68 to 87)</td>
<td>89 (73 to 96)</td>
<td>80 (76 to 83)</td>
<td>0.313</td>
</tr>
</tbody>
</table>

IWGDF risk category

| 0: no risk factors (%)              | 5 (3 to 9) | 5 (2 to 9) | 3 (0.1 to 10) | 0 (0 to 12) | 4.5 (3 to 7) |
| 1: DPN only (%)                     | 9 (6 to 13) | 2 (0.4 to 5) | 6 (2 to 14) | 29 (16 to 45) | 7 (5 to 10) |
| 2: PAD ± neuropathy (%)             | 44 (37 to 51) | 55 (47 to 62) | 57 (45 to 68) | 46 (30 to 62) | 50 (45 to 54) | 0.208γ |
| 3: present or past ulcer or amputation (%) | 43 (36 to 50) | 39 (32 to 46) | 34 (24 to 46) | 26 (14 to 42) | 39 (34 to 43) | |

Data are N, mean ± SD, or % (95% CI)
IWGDF, International Working Group on the Diabetic Foot;
PAD, peripheral arterial disease; DPN, diabetic peripheral neuropathy
† Includes all Europeans and similar White origins (UK) and non-Hispanic whites (US). The only native-American (n=1) was included in the White group.
‡ Includes Mexican-Americans and similar Hispanic origins (US)
* Includes people of African-descent in the UK (African-Caribbeans) and US (African-Americans)
β Indo-Asians or similar Asian origin (UK only)
γ Multiple comparison test of variance (Bonferroni correction) confirmed there was no difference between the ethnic groups
a 95% confidence intervals are calculated by the modified Wald method.