Variation in the progression of diabetic nephropathy according to racial origin

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Abstract

Background. In the United Kingdom, diabetic nephropathy is a leading cause of end-stage renal disease. There is a higher incidence amongst subjects of Indo-Asian and African-Caribbean origin compared with Caucasians that is not wholly explained by the differences in the prevalence of diabetes. Therefore, we postulated that this observation could be related to variations in the rate of progression of renal disease according to racial origin.

Methods. We conducted a retrospective case-note review of 1684 adult attendees of the diabetes clinic. Forty-five patients were found with renal impairment (serum creatinine ≥170 μmol/l) due to diabetic nephropathy. The patients were of Indo-Asian (n=10), African-Caribbean (n=11), and Caucasian (n=24) origin. Progression of nephropathy was assessed by analysing (i) the doubling of serum creatinine through construction of Kaplan–Meier curves and (ii) the slope (β) of the rate of change in serum creatinine using linear regression analysis in relation to demographic variables, putative risk factors for nephropathy and antihypertensive drug therapy.

Results. There were no statistically significant differences between systolic and diastolic blood pressure, glycaemic control, smoking habit, baseline proteinuria, and usage of angiotensin-converting enzyme inhibitors between the three groups. The proportion of patients doubling their creatinine was significantly higher in the Indo-Asian compared with the African-Caribbean and Caucasian groups (100, 45 and 50%; P=0.025 respectively). In addition, the mean (95% CI) of β (μmol/l/month) was highest in the Indo-Asian (5.36 (2.21–8.52)) compared with the African-Caribbean (3.14 (0.82–5.46)) and Caucasian (2.22 (1.31–3.14)) groups (P=0.035). The mean ranks of β were highest in the Indo-Asian group (P=0.038) after adjusting for marginal differences in blood pressure age, gender, baseline proteinuria, anti-hypertensive treatment, and smoking habit.

Conclusions. In this small cohort of type 2 diabetic subjects with established renal disease, the rate of decline in renal function is accelerated in Indo-Asian subjects. This observation could be related to differences in renoprotection from antihypertensive therapy.

Keywords: anti-hypertensive therapy; end-stage renal failure; hypertension; nephropathy; racial origin; type 2 diabetes

Introduction

There are marked racial differences in the susceptibility to renal disease. Subjects of African-Caribbean and Indo-Asian origin have a considerably greater risk of developing end-stage renal disease (ESRD) than Caucasians [1–3]. Diabetic nephropathy is rapidly becoming the leading cause for ESRD in countries throughout the Western World, largely due to its increased incidence amongst ethnic groups [4]. In England, the age standardized acceptance ratios for renal replacement therapy have been reported to be respectively 4.2 and 3.7 times higher in African-Caribbean and Indo-Asian compared with Caucasian patients [5]. These epidemiological observations are not simply accounted for by the higher prevalence of type 2 diabetes in people of African-Caribbean and Indo-Asian origin [6]. Therefore, the contribution of other putative risk factors for the onset and progression of renal disease need to be further investigated in these groups.

Hypertension is a major determinant of the progression of renal disease [7,8]. Several studies have shown that effective antihypertensive therapy slows the progression of renal impairment, but paradoxically, the incidence of diabetic renal disease as a cause for ESRD is continuing to rise [8–11]. This is of some importance in the UK since the projected demand for renal replacement therapy amongst the ethnic population may
Racial differences in response to treatment of diabetic nephropathy

outstrip current provision in the near future [12]. Therefore, there is an urgent need to understand how ‘racial factors’ affect the phenotype of diabetic renal disease and the response to therapy.

A sub-analysis of the Modification of Diet in Renal Disease Study has shown that despite equivalent achieved mean blood pressure, subjects of African descent still experience a sevenfold greater rate of decline in renal function compared to white subjects [13]. Thus, the absolute levels of blood-pressure reduction may not in themselves comprise adequate renoprotection in certain ethnic groups. Some, but not all authors have reported that the angiotensin-converting enzyme (ACE) inhibitor class of antihypertensive agents has a ‘renoprotective’ action over and above its blood pressure lowering effect [14,15]. These studies have been conducted mainly in Caucasian populations and it is unknown if ACE inhibitor-based antihypertensive regimens afford equivalent protection of renal function for type 2 diabetic patients of different racial origin, we determined the pattern of renal dysfunction due to diabetic nephropathy in these patient groups in relation to current approaches to the management of hypertension.

Subjects and methods

We conducted a retrospective case-note review of patients who attended the Whittington Hospital Diabetes Outpatient Clinic between August 1994 and July 1996. Patients were classified as having type 2 diabetes if they had no history of ketosis and did not require insulin therapy within 1 year from the date of diagnosis. Retinopathy was assessed annually following dilated funduscopy and recorded in a standardized proforma as either background, pre-proliferative, proliferative, or laser treatment effect.

A diagnosis of diabetic nephropathy was assigned only if both persistent clinical proteinuria and diabetic retinopathy were present. Patients with biochemical evidence of non-diabetic renal disease, absent retinopathy, congestive cardiac failure and/or malignancy were excluded from further study. In each case, we examined all the recorded serum creatinine data from routine out-patient visits. Data from hospital admissions for inter-current illnesses were not used.

Renal impairment was considered present if serum creatinine was ≥170 μmol/l. This level of creatinine is at least three standard deviations above the upper limit of the normal in our laboratory (120 μmol/l). This approach reduced the risk of including patients of African-Caribbean origin with normal renal function who tend to have higher comparative values of creatinine due to differences in muscle mass. Furthermore, the coefficient of variation for serum creatinine at 170 μmol/l is <2%, which improved the discriminatory power of the study. This meant that there was a 95% chance that a difference of 10 μmol/l between two sequential measurements of serum creatinine was due to a real change in renal function.

Racial group

Assignment of racial group was according to the patient’s choice of category on the hospital’s coding system. Indo-Asian patients were defined as those who selected either Indian, Pakistani or Bangladeshi, whilst African-Caribbean patients were those who chose Black Caribbean, Black African, Somali or Black other. Caucasian patients were those who selected White. Patients who did not choose a category or selected ‘other’ without further specification were not included in this analysis. Racial coding by this approach was verified by asking patients to provide details of the place of birth and racial origin of both of their parents for which there was complete concordance with the classification.

Clinical and biochemical data

Clinic visits were made 2–3 times/year when a number of routine assessments were made. Sitting blood pressure was measured after rest by mercury sphygmomanometry. Venous blood was sampled for the measurement of haemoglobin A1c by HPLC (Ciba–Corning, Halstead, Essex, UK) and serum creatinine by the modified rate reaction method. Clinical proteinuria was qualitatively assessed by dipstick (Multistix, Bayer, Newbury, UK), and subsequently the protein excretion rate was quantified in a 24-h urine collection. For the purposes of this study, the complexity of antihypertensive treatment was classified as either simple (≤2 agents) or complex (>2 agents). Smoking habit was categorized as either, current smoker, ex-smoker, or non-smoker.

Rate of change in renal function

From the accumulated serum creatinine measurements the decline in renal function was estimated by (i) analysing the time taken for serum creatinine to double and (ii) determining the slope (β) of the rate of rise in serum creatinine by linear regression analysis over a minimum period of 18 months.

Statistics

Statistics were computed using the SPSS (version 8) package for MS Windows. Continuous variables were compared with parametric or non-parametric tests according to their distribution. Differences between categorical variables were tested using the Chi-square test. Skewed data were log transformed before analysis. The Bonferroni correction was applied to multiple comparison between groups using ANOVA. Kaplan–Meier survival curves were constructed using ‘doubling of creatinine’ as the end-point and compared using the Log rank test. The Kruskal–Wallis test was used to test whether the ranks of the regression slopes differed significantly between the three groups or were affected by treatment or other putative risk factors for renal disease progression in multivariable analysis. The effect of interaction between variables on the outcome variable of rate of change in creatinine was analysed using MANOVA. All results are reported as mean (SD) unless stated otherwise. A two-tailed P value of <0.05 was accepted as statistically significant.
Results

The records of 45 patients were identified as having established renal impairment due to diabetic nephropathy (Table 1). The frequency of their clinic reviews was every 7.8 (3.2) months. There were no significant differences in the follow-up intervals between the Indo-Asian (A), African-Caribbean (B), and Caucasian (C) groups (6.9±3.2, 7.8±2.0) and 8.2±3.5 months respectively; P=0.53). A total of 293 measurements of serum creatinine were made. The median (range) of total creatinine measurements/patient for the whole group was 6(4–8) measurements. There were no statistically significant, biochemical, or demographic differences initially or on aggregate over the clinic follow-up period between the three groups (Table 2).

Antihypertensive regimens consisted of up to three different agents (ACE inhibitors, β blockers, calcium-channel blockers, α blockers, and/or diuretics). All patients were being treated except for one African-Caribbean patient. More complex regimens tended to be prescribed for group B (P=0.085). An ACE inhibitor was consistently prescribed in 90, 90.9 and 79.2% of groups A, B and C respectively (P=0.242). There were no statistically significant differences in mean systolic and diastolic blood pressure, serum creatinine, and glycated haemoglobin achieved throughout the clinic follow-up period between the three groups (Table 2).

All patients in group A experienced a doubling of their creatinine compared with only 45 and 50% of groups B and C respectively (Log-rank χ²=7.376; P=0.025) (Figure 1). The mean (95% CI) rate of rise in creatinine estimated from the regression of creatinine against time, β, in group A was significantly greater than in groups B and C (5.36 (2.21–8.52), 3.14 (0.82–5.46) and 2.22 (1.31–3.14) (μmol/l/month respectively; ANOVA, F=3.622, P=0.031). The mean log β of group A was significantly greater in comparison to that of group B (P=0.049) and group C (P=0.019). Comparison of the mean ranks of β after adjusting for differences in diastolic blood pressure still showed that the rate of increase of creatinine was faster in group A than groups B and C (31.05 vs 19.40 vs 19.20; P=0.034 respectively). Age was inversely related to β in group C only. However, there was no statistically significant interaction between the rate of change in creatinine and age in multivariable analysis (P=0.073) and no association with variation in treatment regimen (P=0.418), baseline urinary protein

Table 1. Identification of Indo-Asian, Afro-Caribbean and Caucasian patients with type 2 diabetes and established diabetic nephropathy who attended the out-patient clinic between August 1994 and July 1996. Figures in parentheses represent differences in prevalence relative to Caucasians.

<table>
<thead>
<tr>
<th>Patients with Diabetic Nephropathy</th>
<th>Indo-Asian</th>
<th>African-Caribbean</th>
<th>Caucasian</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attendees 1,084</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Number of patients with renal impairment 99
| Indo-Asian 197                    | 11 (1.3)   | 24                 |           |       |
| African-Caribbean 271             |            |                    |           |       |
| Caucasian 914                     |            |                    |           |       |
| Other 302                         |            |                    |           |       |

Exclusions:
- Congestive cardiac failure 19
- No diabetic retinopathy 16
- Other renal disease/malignancy 10
- Insufficient data 9

Table 2. Demographic, biochemical, and clinical parameters measured in Indo-Asian, African-Caribbean and Caucasian patients with type 2 diabetes and established diabetic nephropathy.

<table>
<thead>
<tr>
<th></th>
<th>Indo-Asian</th>
<th>African-Caribbean</th>
<th>Caucasian</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male:Female 9:1</td>
<td>7:4</td>
<td>13:11</td>
<td></td>
<td>0.63</td>
</tr>
<tr>
<td>Age (years) 58.5 (6.4)</td>
<td>68 (7.2)</td>
<td>67.4 (8.4)</td>
<td></td>
<td>0.022</td>
</tr>
<tr>
<td>Diabetes duration (years) 14.7 (5.9)</td>
<td>12.7 (6.7)</td>
<td>16.2 (8.0)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Follow-up (months) 37 (19–98)</td>
<td>46 (23–127)</td>
<td>51 (23–92)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)* 153.8 (11.1)</td>
<td>159.2 (15.2)</td>
<td>157.4 (14.2)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Diastolic BP (mmHg)* 87.1 (8.9)</td>
<td>90.3 (8.3)</td>
<td>83.4 (8.4)</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Never smoked (%) 38.5</td>
<td>38.5</td>
<td>23.1</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Complex treatment (%) 10</td>
<td>54</td>
<td>29</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>ACE regimen (%) 90</td>
<td>91</td>
<td>79</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Haemoglobin A1c (%)* 8.5 (1.3)</td>
<td>9.1 (1.5)</td>
<td>8.6 (1.6)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Urinary protein excretion/ (g/day) 1.13 (0.73)</td>
<td>3.07 (2.73)</td>
<td>2.07 (2.64)</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Initial serum creatinine (μmol/l) 121.6 (33.0)</td>
<td>146.2 (31.9)</td>
<td>123.9 (32.7)</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

† Mean (range); ‡ measured at baseline only; * average of all measurements.
homogeneous with respect to the diagnosis of diabetic nephropathy because of the careful exclusion of (i) cases with concomitant diseases which could have affected creatinine levels and (ii) of those without diabetic retinopathy who have been shown by renal histology to have a high probability of non-diabetic renal disease [18].

The differences in prevalence of diabetic nephropathy in the cohort we studied is consistent with larger studies. Importantly, our study suggests that racial origin is a determinant of renal disease progression in type 2 diabetic patients. It is possible that the differences we have found are related to sensitivity to hypertension and/or the efficacy of the anti-hypertensive regimens used. However, because of the small sample size and retrospective nature of this study, some caution is required in interpretation. Patients who died early in the course of their renal disease, were lost to follow-up or did not conform to the standardized approach of collecting data in the diabetes clinic would have been excluded and this may have led to bias. We were unable to evaluate the contribution of serum cholesterol and urinary protein excretion rates, as they were not measured consistently throughout follow-up. Hypercholesterolaemia may be associated with the progression of diabetic nephropathy and perhaps treatment with lipid-lowering agents may have a beneficial effect on renal function in the short term [19]. Glucose-dependent differences in lipids were unlikely as glycated haemoglobin was similar between all three groups. Baseline urinary protein excretion rates were similar between the groups and did not confound the differences in progression of renal disease between the groups on multivariate analysis. It is also noteworthy that Koppiker et al. [16] found no effect of protein intake, or excretion rate, on the change in renal function in Caucasian and Indo-Asian type 2 diabetic subjects with advanced renal impairment. Our findings are supported by a recent study showing that the epidemic rise of proteinuria in Pima Indians is occurring in spite of improvements in cholesterol levels, glycaemic control, and blood pressure management [20].

Good blood pressure control limits the progression of renal disease. The ACE inhibitors may have a ‘renoprotective’ effect over and above their blood-pressure lowering effect in diabetic and non-diabetic renal disease [14,15]. But Indo-Asian patients in this study did not appear to benefit from the ‘renoprotective’ action of ACE inhibitors. A theory receiving some attention relates to reduced nephron endowment due to fetal growth retardation, which is more prevalent in developing countries [21,22]. If the constitution of nephrons is limited, then it is conceivable that promoters of renal disease such as hyperglycaemia and hypertension may give rise to faster rates of decline in comparison with subjects with normal nephron number who may have greater ‘renal reserve’. The variation in diabetic renal disease phenotype according to racial origin is an emerging and important clinical challenge. Further studies are required to allow the
development of adjunctive therapies to modulate glucose-induced glomerulosclerosis.

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References

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