Identification and Management of Diabetic Nephropathy in the Diabetes Clinic

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OBJECTIVE — To examine the prevalence and management of diabetic nephropathy in a diabetes clinic.

RESEARCH DESIGN AND METHODS — Characteristics of nephropaths identified by existing screening practice (phase I, albuminuria >20 mg/l in three separate urine samples), were compared with those identified by a nurse-led management program (phase II, in which screening for nephropathy was based on albumin-to-creatinine ratio in a single random urine specimen).

RESULTS — In phase I, 644 patients attended a diabetes clinic over a 6-month period. Microalbuminuria results were available for 485 patients (75%). A total of 115 patients were identified as nephropaths (prevalence 17.8%). Of these patients, 91% had type 2 diabetes. During phase II, prospective analysis of urinary albumin-to-creatinine ratio was carried out in 880 patients over 8 months. A total of 174 patients were identified as nephropaths (prevalence 20%). Of these, 134 patients had been identified by existing screening protocols. Forty had no previous record of microalbuminuria and were therefore newly identified by prospective screening. Systolic blood pressure guidelines were met in only 31% of all known nephropaths and 20% of newly diagnosed nephropaths. Diastolic blood pressure guidelines were met in 36% of all known and 38% of newly diagnosed nephropaths. In the patient group of known nephropaths from phases I and II, 62% were prescribed ACE inhibitors (ACEIs) or angiotensin II receptor (AIIR) antagonists. In the newly identified nephropathy patient cohort from phase II, 48% used ACEIs or AIIR antagonists.

CONCLUSIONS — Introduction of a nurse-led management program significantly improved detection of nephropathy. We are currently evaluating its impact on clinical management.

Diabetic nephropathy is now the commonest cause of end-stage renal disease in the U.K., accounting for 20% of all patients requiring renal replacement therapy, in patients with either type 1 or type 2 diabetes (1). Whereas the prognosis of patients with diabetic nephropathy has recently improved (2,3), there remains an excess mortality of 70–100 times that of an otherwise matched normal population (4). Survival on dialysis remains poor, with up to one-third of patients dying within a year of starting dialysis (4). Furthermore for patients who require renal replacement therapy, morbidity as assessed by hospitalization is two to three times greater than for nondiabetic patients with end-stage renal disease (2).

One aim of the World Health Organization St. Vincent Declaration, published in 1994, was to reduce the incidence of renal failure from diabetic nephropathy by 30% (5). There is now clear evidence from clinical studies that the progression of diabetic nephropathy can be retarded by several therapeutic strategies. These include strict glycemic control (6–9), control of hypertension (10–12), and the early blockade of the renin-angiotensin system (13–17). Despite extensive research into its pathogenesis and the introduction of treatment strategies aimed at delaying the progression of diabetic nephropathy, the incidence of renal failure secondary to diabetes continues to increase.

To date, studies focusing on management of diabetic nephropathy in nephrology clinics have highlighted suboptimal care and late referral (18,19). The implementation of treatment guidelines following referral to specialized clinics, either diabetic renal (18) or nephrology (19) clinics, have been shown to slow the progression of established diabetic nephropathy. The importance of early referral and intervention is also emphasized, since a retardation in the rate of decline in renal function may take up to 3 years (18). It has also been shown that implementation of an intensive multifactorial approach to the diabetic patient leads to retardation in progression of complications other than nephropathy (20). Optimal reduction in the morbidity and mortality of diabetic nephropaths, therefore, requires early identification of at-risk patients allowing instigation of appropriate management protocols known to influence renal and cardiac outcome. In the current study, we have assessed the efficiency of current practice in the early identification and management of diabetic nephropathy. In addition, we have examined the impact of changing screening procedures on identification of the true at-risk population.
RESEARCH DESIGN AND METHODS — All patients enrolled in this study attended the diabetes clinic led by a single diabetologist based at a teaching hospital. Patients in phase I comprised all consecutive patients seen routinely in the diabetes clinic over a 6-month period, and existing prevalent patients were identified from standard protocols. Patients were only included at the time of the first clinic visit during the study, ensuring avoidance of patient duplication. The diagnosis of diabetic nephropathy was made from data recorded in the patient notes or from biochemical laboratory records. Standard screening protocols for the identification of diabetic nephropathy were based on the formal quantification of microalbuminuria on three early morning urine samples on sequential days. Incipient nephropathy was defined as persistent microalbuminuria ranging from 20 to 200 mg/l in the three consecutive urine samples. Overt nephropathy was defined as albuminuria >200 mg/24 h. Patients with impaired renal function in the absence of proteinuria, patients with microscopic hematuria, and patients with known multisystem disease were excluded.

In phase II of the study, screening for diabetic nephropathy was coordinated and performed by a newly appointed dedicated nurse specialist. Prospective quantification of albumin-to-creatinine ratio on a single random urine sample collected at the time of the clinic visit before seeing the physician, using a CLINITEK 50 Analyzer (Bayer, Elkhart, IN) was carried out for a period of 8 months. This method reports all values >3.4 mg/mmol as abnormal. Subsequently, albuminuria was confirmed by timed urine collection following a discussion with the nurse specialist regarding the probable diagnosis and the benefit of early identification and treatment.

Outpatient assessment included demographic data, serum creatinine, HbA1c, and serum cholesterol. Blood pressure was measured with an automatic digital blood pressure monitor (Omron Healthcare UK, Henfield, West Sussex, UK) after a 5- to 10-min rest (sitting at the clinic). In addition, prescribed medication was recorded, and, in particular, the use of ACE inhibitors (ACEIs), angiotensin II receptor (AIIR) antagonists, aspirin, and cholesterol-lowering medication was noted.

**Table 1—Demographic data for identified nephropaths**

<table>
<thead>
<tr>
<th></th>
<th>Phase I: known nephropaths</th>
<th>Phase II: known nephropaths</th>
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<tbody>
<tr>
<td>n</td>
<td>115</td>
<td>134</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65 (55–71)</td>
<td>66 (58–72)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>37/62.1</td>
<td>37/63</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>90.6</td>
<td>95.1</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0 (7–9.7)</td>
<td>8.2 (7.1–9.4)</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>108 (60–192)</td>
<td>84 (48–156)</td>
</tr>
<tr>
<td>Incipient nephropathy (%)</td>
<td>72.6</td>
<td>75.9</td>
</tr>
<tr>
<td>Overt nephropathy (total) (%)</td>
<td>27.4</td>
<td>24.1</td>
</tr>
<tr>
<td>Overt nephropathy with raised serum creatinine (%)</td>
<td>78.6</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Data are median (interquartile range) unless otherwise indicated.

**Statistical analysis**

Data analysis was carried out using SPSS version 10 for Macintosh (SPSS, Chicago, IL). As appropriate, data were described as mean ± SD and median (interquartile range). χ² and Fisher’s exact test were used to analyze data.

**RESULTS**

**Identification of nephropathy: phase I**

In the initial patient cohort, a total of 644 patient notes and laboratory records were evaluated. All patients were assessed during routine follow-up of nonselected patients to avoid introduction of selection bias. For any patients seen more than once during the study, data were only collected at the time of the first clinic visit, thus avoiding any patient duplication at the diabetes clinic. Microalbuminuria results were available for 485 patients (75%). Of these patients, 115 were identified as meeting the criteria for a diagnosis of diabetic nephropathy, giving an observed prevalence of diabetic nephropathy of 17.8%. Of these, 90.6% were type 2 diabetic subjects. Demographic data for the identified nephropaths are shown in Table 1. Of those identified diabetic nephropaths, 72.6% had incipient nephropathy and 27.4% had overt nephropathy (of whom 78.6% had elevated serum creatinine levels). The mean serum creatinine for the incipient and overt nephropathy groups was 91 (76–145) and 112 μmol/l (109–141) [median (interquartile range)], respectively.

Of the 115 known nephropaths, results of urinary microalbumin or proteinuria quantification were available for the physician at the time of the outpatient consultation in only 53% of the patient case records. The remaining nephropaths were identified from the patients’ laboratory records.

**Identification of nephropathy: phase II**

Prospective analysis of urine albumin-to-creatinine ratio was carried out in 880 patients over an 8-month period. For patients with elevated albumin-to-creatinine ratios, the diagnosis of nephropathy was confirmed by quantification of urinary albumin excretion. In this patient cohort, 174 patients were identified as having diabetic nephropathy, giving a prevalence of nephropathy of 20%. Of these patients, 134 patients had been previously identified as nephropaths by the existing screening practice on the basis of positive urine albumin quantification, recorded in either the patients’ records or the laboratory records. However, 40 nephropathic patients (23%) had no previous record of microalbumin quantification and therefore were newly identified by the prospective screening program.

Comparison of the demographic data of the known nephropaths identified in phase I with those in phase II revealed no differences in patient characteristics (Table 1) (age, sex, duration of diabetes, HbA1c, percent of type 1 and type 2 diabetes, and incipient and overt nephropathy).

Comparison of patient characteristics in all the known nephropaths and those newly identified in phase II is shown in Table 2. There was no difference in age, sex, HbA1c, duration of diabetes, or incidence of incipient versus overt nephropathy. The serum creatinine for incipient
Screening for diabetic nephropathy

Table 2—Patients characteristics in all known nephropaths and those newly identified in phase II

<table>
<thead>
<tr>
<th></th>
<th>All known nephropaths</th>
<th>Phase II: newly identified nephropaths</th>
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<tbody>
<tr>
<td>n</td>
<td>249</td>
<td>40</td>
</tr>
<tr>
<td>Age (years)</td>
<td>66 (58–73)</td>
<td>66 (58–75)</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>37.5/62.5</td>
<td>45.7/54.3</td>
</tr>
<tr>
<td>Type 2 diabetes (%)</td>
<td>93.3</td>
<td>80</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>8.0 (7.0–9.5)</td>
<td>8.5 (7.8–10.2)</td>
</tr>
<tr>
<td>Duration of diabetes (months)</td>
<td>90 (60–168)</td>
<td>120 (48–180)</td>
</tr>
<tr>
<td>Incipient nephropathy (%)</td>
<td>74</td>
<td>77.4</td>
</tr>
<tr>
<td>Overt nephropathy (total) (%)</td>
<td>25.5</td>
<td>22.6</td>
</tr>
<tr>
<td>Overt nephropathy with raised serum creatinine (%)</td>
<td>65.4</td>
<td>50</td>
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Data are median (interquartile range) unless otherwise indicated.

and overt nephropathy in the newly identified nephropaths was 105 (87–162) and 102 μmol/l (83–159) [median (interquartile range)], respectively. These data may therefore suggest that these patients represent a cohort of patients missed by the standard practice in this clinic.

Risk factor management in known and newly identified nephropaths

Having identified a cohort of patients with diabetic nephropathy, we next sought to examine management of the newly identified nephropaths compared with the known nephropaths according to the National Institute for Clinical Excellence guidelines for the management of renal disease in diabetes.

Blood pressure control

The distribution of systolic and diastolic blood pressure in the known nephropaths and the newly identified nephropaths is shown in Fig. 1. There were no differences in the mean systolic and diastolic blood pressure recordings of the known and newly diagnosed nephropaths. Systolic blood pressure guidelines (<135 mmHg) were met in 31% of all known nephropaths and 26.5% of newly diagnosed nephropaths. Diastolic blood pressure guidelines (<75 mmHg) were met by 36% of all known nephropaths and 38% of newly diagnosed nephropaths. However, the median (25th and 75th centile) measures of both systolic and diastolic pressure reflect the fact that 50% of measurements were fairly tightly grouped (known nephropaths: systolic blood pressure 142 mmHg [133–160], diastolic blood pressure 80 [70–85]; new nephropaths: systolic blood pressure 149 [137–174], diastolic blood pressure 77.5 [70–82]).

Antihypertensive prescription practice in those patients who did not meet either the systolic or diastolic guidelines is shown in Fig. 2. Inadequate blood pressure control was likely to be associated with the use of a low number of antihypertensive agents, indicating inadequate treatment. Of those patients with diabetic nephropathy who did not meet the recommended target blood pressure, 23 patients (8%) had isolated systolic blood pressure (systolic blood pressure >160 mmHg, diastolic blood pressure <80).

Following publication of the Hypertension Optimal Treatment (HOT) study, the clinic protocol for the treatment of hypertension has included prescription of low-dose aspirin to hypertensive diabetic subjects. However, analysis of patient records and direct questioning of patients demonstrated that aspirin was prescribed in only 38% of known nephropaths with hypertension and 43% of newly diagnosed nephropaths with hypertension.

Use of ACEIs

The use of ACEIs is shown in Table 3. In the patient group of known nephropaths from both phases I and II, 62% were prescribed ACEIs or AIIR antagonists. However, of those patients who did not meet the guidelines for blood pressure target of <135/75 mmHg, 24% were not receiving ACEIs or AIIR antagonists (although all were on treatment for hypertension). Use of ACEIs or AIIR antagonists in the newly identified nephropathy patient cohort from phase II was 48%. In this patient cohort, of those who did not meet the guidelines for blood pressure target of <135/75 mmHg, 47% were receiving ACEIs or AIIR antagonists.

Management of hypercholesterolemia

There was no difference in the median cholesterol, LDL or HDL cholesterol, or triglyceride levels between the known and newly identified nephropaths (Table 4). For the known nephropaths, 28.5% had total cholesterol >5.2 mmol/l. In this group, statins were prescribed for only 31% of the patients. Similarly, elevated cholesterol (total cholesterol >5.2
mmol/l) was documented in 37.5% of newly identified nephropaths, of whom only 9% were prescribed statins.

**CONCLUSIONS** — The ever-increasing incidence of diabetic nephropathy has major implications for both patient welfare and health care resources at a time when renal services are already struggling to cope with current demand. The ominous significance of renal involvement in type 1 diabetes is shown by the comparison of long-term outcome in patients with and without nephropathy. Only 10% of patients with proteinuria survive after 40 years of diabetes, in contrast to >70% of those without proteinuria (21). Furthermore, the mortality rates for diabetic patients on end-stage renal failure programs is roughly twice that for patients with end-stage renal diseases from other causes (2). However, numerous treatment strategies have been identified that delay the progression of renal disease in diabetes, which is also associated with improved patient survival (11,13).

With recent guidelines setting strict targets for the treatment of nephropathy (22), as well as increasing evidence that earlier intervention may benefit this patient group (23), it is clear that we need to develop effective implementation strategies. Any reduction in the prevalence of end-stage renal failure in diabetes will have a major impact on the economics of health care provision. Although aggressive screening protocols, coupled with intensive treatment strategies, are likely to incur additional costs, numerous studies have examined the cost-effectiveness of aggressive management of diabetic nephropathy. The Collaborative Study Group calculated the direct and indirect savings associated with ACEI therapy and blood pressure control compared with blood pressure control alone for diabetic patients with diabetic nephropathy in the U.S. (24). Their economic simulation suggested direct and indirect cost savings of $32,550 and $84,390, respectively, per patient with type 1 diabetes and $9,900 and $45,730, respectively, per patient with type 2 diabetes over a lifetime compared with placebo. Over a 10-year period, this would amount to a cumulative health care cost saving of $2.4 billion. Similarly, data generated from the U.K. Prospective Diabetic Study (UKPDS) suggest that tight blood pressure control was associated with increased end-point free time at a cost of $1,049 per end-point free-years, and life-years gained were at a cost of $720 per life year gained (25). Having instituted a nurse-led program for early identification of diabetic nephropathy, using this patient cohort we can now assess the impact of a nurse-led program of implementation of evidence-based intervention, both on risk factor management and overall cost effectiveness of the program as a whole.

The implementation of evidence-based therapeutic interventions in diabetestes outside the confines of a clinical trial has, however, proved difficult (26). One factor implicated in this is the late referral of diabetic patients to specialist renal clinics, as highlighted by Burton et al. (27). This study demonstrated that the majority of patients were referred at a time when complications of renal failure were already present and late referral was associated with suboptimal clinical management of renal disease. The transfer of care to specialist renal clinics, however, is known to delay the progression of diabetic nephropathy and improve patient morbidity (19).

Our data show that the translation of best practice from both clinical trials and published guidelines into pragmatic clinical practice is difficult and incomplete. One factor suggested to be important is the paucity of resources, especially of nonphysician personnel (28). Many recent initiatives have demonstrated that the use of physician-directed nurse-led case management of patients improves the delivery of diabetes care (26,28–30). A recently published study has shown that although baseline screening rates are improving in the U.S., the introduction of nurse care management can further improve these rates (30). Our results support these observations. In addition to providing added resource in an attempt to capture all patients with the screening program, we also altered and simplified screening practice. Previous studies have demonstrated that the quantitation of the urinary albumin-to-creatinine ratio in a random single voided urine sample is a reproducible alternative to the formal quantification of urinary protein loss significant.

<table>
<thead>
<tr>
<th>Table 3 — Blood pressure and use of ACEIs and AIIR antagonists</th>
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<tbody>
<tr>
<td>Phase I: known nephropaths</td>
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<tr>
<td>-----------------------------</td>
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<tr>
<td>Mean SBP (mmHg)</td>
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<tr>
<td>Mean DBP (mmHg)</td>
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<tr>
<td>Patients on ACEI/AIIR antagonist (%)</td>
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<tr>
<td>Patients with BP &gt; 135/75 mmHg not on ACEI/AIIR antagonist (%)</td>
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Data are median (interquartile range) unless otherwise indicated. BP, blood pressure; DBP, diastolic BP; SBP, systolic BP.

<table>
<thead>
<tr>
<th>Table 4 — Cholesterol and triglyceride levels in known and newly identified nephropaths</th>
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<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
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<tr>
<td>Triglycerides (mmol/l)</td>
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<tr>
<td>HDL cholesterol (mmol/l)</td>
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<tr>
<td>LDL cholesterol (mmol/l)</td>
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Data are median (interquartile range).
(31). Using this method, we identified a cohort of diabetic patients with nephropathy in which the diagnosis was not made by existing clinical practice; therefore, appropriate intervention could not have been initiated. Interestingly, there were no significant differences between the nephropaths diagnosed by the existing protocol and the additional newly identified group of patients detected by the nurse-led screening program. Specifically, the newly identified group did not comprise those with recent onset of diabetes but rather the same population as those who were known nephropaths and therefore may truly have been “missed.” The discrepancy in the assumed and true prevalence of diabetic nephropathy has identified numerous levels at which our screening practice was failing to identify patients with diabetic nephropathy. Although screening was targeted to all patients, compliance in terms of return of urine samples resulted in numerous missed patients. Furthermore, failure of documentation, even in those in which the screening program did lead to a diagnosis of nephropathy, led physicians to be unaware of the diagnosis at the time of patient consultation.

Introduction of structured care protocols is also hampered by poor patient compliance. Recent studies aimed at starting an intensive lipid-lowering strategy in patients with diabetes demonstrated the importance of patient perceptions of treatment benefits, as only 12% of their patients participated in the study (32). Nurse-led initiatives in diabetes care in general practice, however, have shown benefit to patients in terms of clinical management and patient satisfaction (29). After instigation of prospective screening, we used albumin-to-creatinine ratio, which was determined at the time of clinic to target those patients for quantification of urinary albumin excretion. To improve patient compliance, all patients with raised urine albumin-to-creatinine ratios in the random urine samples were seen by the designated nurse and counseled as to the importance of further urine albumin quantification. Furthermore, patients who failed to provide urine samples for formal quantification of urinary albuminuria were contacted again by the nurse.

The excess morbidity and mortality in diabetic patients requiring renal replacement therapy are explained by high cardiovascular comorbidity, and survival on dialysis is largely determined by predialysis care (4). In terms of minimizing cardiovascular risk, analysis of the diabetic subgroup of the HOT trial and UKPDS have provided clear evidence that control of blood pressure reduces the risk of cardiovascular complications (12,33). Furthermore, analysis of diabetic patients recruited into the Heart Outcomes Prevention Evaluation (MICRO-HOPE) study suggested a specific cardioprotective action of drugs that block the renin-angiotensin system (34). Secondary analysis in secondary prevention studies also suggests beneficial effects of treatment of hypercholesterolemia (35,36). Aspirin also prevents cardiovascular events in both hypertensive (33) and diabetic (37) individuals. Our data demonstrate that in a cohort of patients identified as diabetic nephropaths and therefore at high cardiovascular risk, prescription of therapeutic measures aimed at both delaying the rate of progression of renal disease and targeting cardiovascular risk is poor. From the point of view of progression of renal disease, it is of particular note that a large proportion of our patients did not meet published blood pressure guidelines. Furthermore, the use of ACEIs in the group of patients with suboptimal blood pressure control is also low and represents a missed opportunity in terms of minimizing risk of progression of renal disease and addressing cardiovascular risk factor management. It is likely that documentation in the patient records of positive urinalysis in only 50% of cases partially explains the low ACEI prescription rates in known diabetic nephropaths. However, it is not unexpected that in those “missed” nephropaths identified after change of practice, ACEI usage was particularly poor. The significant omission of ACEIs in the subgroup of hypertensive “missed” nephropaths, however, further emphasizes the need for a comprehensive and effective screening program. Publication of numerous studies that have clearly demonstrated the benefit of treatment strategies based on blood pressure management and blockade of the renin-angiotensin system in patients with diabetic nephropathy has led to the publication of numerous treatment guidelines, such as those issued by the National Institute for Clinical Excellence (22). Interestingly, one recent study has demonstrated that without added resources, patient care may in fact deteriorate following publication of guidelines (18). It is clear, therefore, that publication of treatment guidelines in itself, without allocation of additional resources, does not improve patient care.

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References
9. UK Prospective Diabetes Study Group: Intensive blood glucose control with sulphonylurea or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes.


