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# The joint diabetic-renal clinic in clinical practice: 10 years of data from a District General Hospital

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## Summary

**Background:** Diabetic nephropathy is the leading cause of end-stage renal failure. Untreated, it causes continuous decline in glomerular function, worsening hypertension and a marked increase in cardiovascular risk. Joint diabetic-renal clinics were established to address these factors and prepare patients for renal replacement therapy.

**Aim:** To determine whether our joint diabetic-renal clinic influenced progression of renal disease, and whether we were able to achieve targets from clinical trials and guidelines in routine practice.

**Design:** Retrospective review.

**Methods:** We collected data using clinical notes and electronic records for 130 patients attending the clinic over 10 years.

**Results:** Our patients had 62% type 2 and 38% type 1 diabetes. Mean duration of diabetes was 24 years

for type 1 and 11 years for type 2 diabetes. At referral, 56% had evidence of vascular disease and 45%, proliferative retinopathy. Baseline median creatinine was 124 µmol/l. Significant improvements were made in systolic BP, diastolic BP and cholesterol ( $p < 0.001$ ), compared to measurements at presentation. We analysed progression of renal disease by linear regression on 45 patients who had follow-up data for 3 years. Rate of decline of GFR was significantly reduced from 1.09 ml/min/month in the first year to 0.39 ml/min/month in the third year, ( $p < 0.004$ ).

**Discussion:** Our findings suggest that the rate of deterioration of renal function can be reduced by aggressive management of risk factors. Joint diabetic-renal clinics appear to be useful in achieving targets in routine clinical practice.

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## Introduction

Diabetic nephropathy (DN) is the leading cause of end-stage renal failure (ESRF) in patients beginning renal replacement therapy (RRT) in the developed world.<sup>1,2</sup> It has been widely accepted that 30% of all diabetic patients develop nephropathy after 30 years of diabetes, but one recent study in type 1 diabetic subjects noted a reduced incidence of 7.8% at 30 years after diagnosis.<sup>3</sup> Only a small proportion of these patients reach ESRF, because of premature cardiovascular

disease, especially in type 2 diabetes. Untreated diabetic nephropathy is characterized by a progressive decline in glomerular filtration rate (GFR), worsening hypertension and a marked increase in cardiovascular risk.<sup>4</sup> Well-controlled blood pressure, treatment of dyslipidaemia and hyperglycaemia, angiotensin-converting enzyme (ACE) inhibition, smoking cessation and reduced dietary protein intake all reduce the rate of progression to ESRF.<sup>5–14</sup>

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Management of these patients with multiple co-morbid factors is challenging in a routine out-patient setting, and hence a multidisciplinary approach has been advocated. The St Vincent's declaration (1992) set down guidelines for the prevention and treatment of diabetic nephropathy,<sup>15</sup> and this was followed by the Scottish Intercollegiate Guidelines Network (SIGN) guidelines in 1997 and 2001 (No. 55), and National Institute for Clinical Excellence (NICE) guidelines in 2002.<sup>16,17</sup> However, patient education, support and motivation are fundamental to achieving a successful long-term outcome.<sup>18</sup> In view of these factors, joint diabetic-renal clinics were set-up in an attempt to reduce the rate of progression to ESRF, with aggressive management of cardiovascular risk and other complications, and prepare patients for renal replacement therapy. Although these clinics help to achieve blood pressure targets, there is little published evidence that they affect the progression of renal disease.

Liew *et al.* studied patients referred to a joint clinic in a tertiary referral hospital, and found that the time to ESRF was increased by an average of 2 years.<sup>19</sup> Joss *et al.* from the same group studied 170 consecutive patients referred from six different diabetic units, and found that patients who were referred early benefited the most from the clinic, and the rate of decline was slowed from 0.52 ml/min/month in the first year to 0.27 ml/min/month in the third year.<sup>20</sup> No longitudinal data have been published on patients attending a joint clinic in a district general hospital, providing secondary care for a single population. Cross-sectional studies and drug trials may be helpful in identifying metabolic defects and effectiveness of new therapeutic interventions, but only longitudinal studies are helpful in understanding the nature and progression of a chronic disease such as diabetic nephropathy.

We studied all patients attending the Joint Diabetic-Renal Clinic in our District General Hospital, in Carlisle, UK, established in 1991. This study has the advantage that most of the patients with diabetic nephropathy in our catchment area were being referred directly to this clinic. In addition, at the outset, most patients were already attending separate diabetic or renal clinics, and so duplicating sometimes quite long journeys from home. We present data retrospectively collected on all patients who attended the Joint Diabetic Renal Clinic for at least two consecutive visits in the last 10 years. Our aim was to determine whether targets from clinical trials and guidelines could be achieved through a joint diabetic renal clinic in a District General Hospital, and whether management of this type influenced progression of diabetic renal disease.

## Methods

Data on all patients attending the combined Diabetic-Renal Clinic on at least two consecutive occasions during a 10-year period were collected retrospectively. Patients were referred to the combined clinic from diabetic, renal and general medical clinics, and directly from general practices. The patients were seen by a nephrologist and diabetologist separately during each clinic visit, supported by a diabetic specialist nurse, renal dietician and podiatrist. Patients were seen 3-, 6- or 12-monthly, depending on clinical need. Regularly updated local guidelines based on current evidence were used as targets at the clinic. These were revised regularly in line with published studies, and recommendations were circulated to all General Practitioners, supported by discussion meetings and clinical presentations.

Diabetic nephropathy was defined as the presence of persistent proteinuria with an albumin excretion rate >300 mg/day in a patients with diabetes but no evidence of any other renal disease. Demographic and laboratory data were collected from medical notes and electronic patient records. Data at referral and subsequent 6-month and yearly visits were noted: source of referral, type and duration of diabetes, history of ischaemic heart disease, cerebrovascular disease, peripheral vascular disease, hypercholesterolemia, hypertension, smoking history and presence of retinopathy. Anti-hypertensive, lipid-lowering and glucose-lowering drugs were recorded. Estimated creatinine clearance was calculated using the Cockcroft and Gault formula from serum creatinine measured during or just before the clinic visit.<sup>21</sup> The rate of decline in renal function was calculated by linear regression from the slope of the plot of creatinine clearance vs. time, expressed in ml/min/month. A minimum of three readings for each 12-month period was used to draw the slope and hence estimate the rate of decline in renal function. Proteinuria was measured using 24-h urine collections done at home and sent to the local hospital laboratory. Levels of HbA<sub>1c</sub>, blood pressure, total cholesterol, proteinuria, smoking history, and use of ACE inhibitor drugs were noted at each visit. Blood pressure was measured after 5–10 min sitting, by a physician with a sphygmomanometer. It was rechecked by another physician in the clinic. Results are shown as means and SD or as median and IQR. The significance of difference for various parameters between the groups was determined using the unpaired t test. The paired t test was used to determine the difference in rate of decline with time. A *p* value <0.05 was taken

**Table 1** Patient characteristics at presentation to the diabetic-renal clinic

	All patients	Type 1	Type 2
Mean age (years)	56 (22–84)	42 (22–77)	65 (38–84)
Gender (M:F)	76:54	26:22	50:32
Mean duration of diabetes (years)	16 (1–52)	24 (4–52)	11 (1–29)
Vascular disease (%)	56	41	65
Background retinopathy prevalence (%)	74	41	59
Proliferative retinopathy prevalence (%)	45	55	45
Laser treatment (%)	45	55	45
Insulin treatment (n)	93 (72%)	48 (100%)	45 (56%)

Patient characteristics at presentation. Data are means (range) or percentages.

**Table 2** Smoking history at presentation to the diabetic-renal clinic

	All patients	Type 1 diabetes	Type 2 diabetes
Current smoker (n)	24	11 (24%)	13 (17%)
Ex-smoker (n)	50	12 (26%)	38 (48%)
Non-smoker (n)	51	23 (50%)	28 (35%)

to indicate a significant difference. All statistical analyses used SPSS (version 11.5).

## Results

Between January 1991 and December 2001, 130 patients (76 males, 54 females, mean age 56 years) were referred to the Joint Diabetic-Renal Clinic with diabetic nephropathy. Forty-nine (38%) had type 1 diabetes; the rest had type 2 diabetes (Table 1). General diabetic clinics accounted for 48% of referrals, renal clinics 27%, general medical clinics 6%, and general practitioners 19%.

At presentation, 73 (56%) had a history of vascular disease or clinical evidence of this, including ischaemic heart disease, cerebrovascular disease and peripheral vascular disease. Retinopathy was documented in 96 (75%), of whom 74% had background retinopathy and 45% proliferative retinopathy. Of patients with type 1 diabetes, 55% had evidence of proliferative retinopathy compared to 45% of those with type 2 diabetes. No significant relationship between smoking and the presence of retinopathy was found ( $\chi^2 = 3.78$ ,  $p = 0.052$ ) (Table 2).

Of the 130 patients, 88 were treated with insulin, 34 with oral agents and eight were treated with both insulin and oral agents in combination. Three patients were treated with diet therapy alone. As a

part of renal investigations at the clinic, 113 patients (87%) had ultrasound examination of the kidneys, 15 had an intravenous urogram or DTPA (diethylene triamine pentacetic acid) scan and 16 had a percutaneous renal biopsy. Of those 16, 13 had a biopsy diagnosis of diabetic nephropathy; the other three had IgA nephropathy, renal amyloid and focal segmental glomerulosclerosis, respectively.

At presentation, 54% were taking ACE inhibitor drugs, increasing to 64% by the last visit to the clinic. Contraindications for ACE inhibitor therapy were documented in 28/39 patients (72%) not on such therapy (Table 3). Use of other anti-hypertensives is shown in Figure 1. Anti-platelet therapy (aspirin) was taken by 27% of patients. None was receiving any other anti-platelet agent. Hypercholesterolemia was noted in 43% of patients; 81% of these were treated with a statin, 6% with a fibrate and none was on combination therapy.

Median creatinine at referral was 124 (IQR 92–176)  $\mu\text{mol/l}$  (Table 4), and 16% had a referral creatinine  $>200 \mu\text{mol/l}$ . Estimated median creatinine clearance was 78.1 ml/min (IQR 51.9–104.3) at presentation. The majority of our patients had a history of hypertension (88%), of whom 83% had a blood pressure of  $>140/80 \text{ mmHg}$  on referral. Overall, 91% of patients were on antihypertensive treatment, and 41% achieved their target blood pressure (140/80) by the end of the study period. On referral, mean systolic blood pressure was

158 mmHg (95%CI 153–163) and mean diastolic pressure 84 mmHg (95%CI 82–86). These levels improved to 141 (95%CI 137–146) and 77 (95%CI 75–79) mmHg, respectively, at the last visit to the clinic ( $p < 0.001$ ) (Figure 2).

Mean glycated haemoglobin was 8.4% (95%CI 8.0–8.9) at presentation, and this remained unchanged by the end of the study period at 8.6 (95%CI 8.2–8.9) ( $p = \text{NS}$ ). Mean total cholesterol concentration at presentation improved from 5.9 mmol/l (95%CI 5.6–6.2) to 5.3 mmol/l (95%CI 5.0–5.6) ( $p < 0.001$ ). Proteinuria  $\geq 0.5$  g/24 h was

present in 65% of patients at referral, and 44% of this group had a protein excretion of  $\geq 2$  g/24 h. The rate of decline in renal function was calculated in 45 patients who had data for a minimum of 3 years, by linear regression from the slope of creatinine clearance vs. time (Figure 3). It was reduced from  $1.09 \pm 1.34$  ml/min/month (mean  $\pm$  SD) in the first year to  $0.39 \pm 0.73$  ml/min/month in the third year ( $p < 0.004$ ).

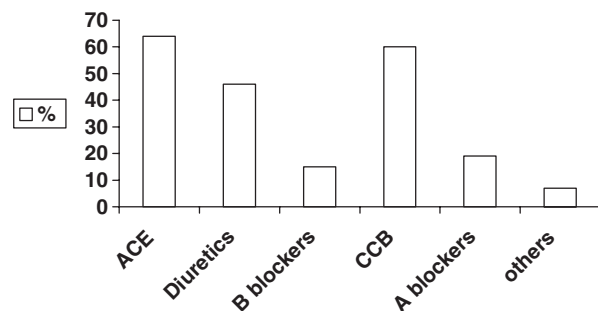
During the study period, 41 (32%) patients died. Mean survival from first clinic visit to death was 47.8 months (95%CI 37.6–57.9). Cardiovascular deaths were the major cause, accounting for 64% of deaths, followed by renal failure in 15%. Other causes accounted for the rest. Twenty-one patients started renal replacement therapy.

Univariate ANOVA was used to test relationships between mortality and parameters including age, HbA<sub>1c</sub>, blood pressure, total cholesterol and proteinuria. High initial total cholesterol ( $p = 0.012$ ,  $r^2 = 5.3\%$ ), high final total cholesterol ( $p = 0.010$ ,  $r^2 = 7.7\%$ ) and age at presentation ( $p = 0.041$ ,  $r^2 = 3.3\%$ ) all predicted mortality.

**Table 3** Recognized contraindications to ACE inhibitors

Contraindication	<i>n</i>
Renal vascular disease	14
Hyperkalaemia	7
Cough	3
Anaphylaxis	2
Others	2

Contraindications were documented in 28 (72%) of 39 patients not taking ACE inhibitors.



**Figure 1.** Classes of anti-hypertensive agents used in patients with diabetic nephropathy.

## Discussion

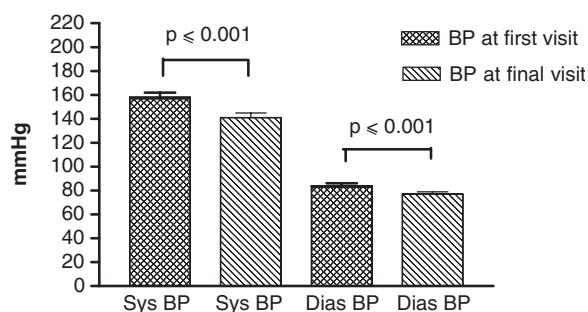
Diabetic nephropathy is the most common single cause of ESRF in the developed world, and the increasing incidence has followed the epidemic of type 2 diabetes and the improved survival of patients with both type 1 and type 2 diabetes. Moreover, patients with diabetic nephropathy are now more readily accepted for renal replacement therapy.<sup>4</sup> However, challenges in managing this group of patients include the increasing costs of renal replacement therapy, increased cardiovascular risk and limited availability of organs for transplantation. Primary prevention of diabetic nephropathy would be an ideal solution, but is currently unachievable. It is therefore prudent to identify and manage diabetic nephropathy early, in order to delay

**Table 4** Comparison of clinical parameters at presentation and last visit

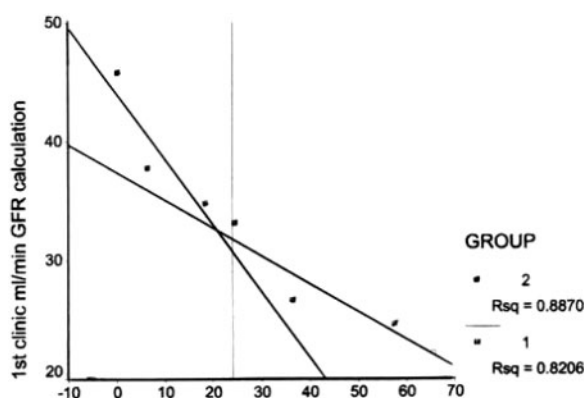
	At presentation	Last visit	<i>p</i>
Mean HbA <sub>1c</sub> (%)	8.4 (8.0–8.9)	8.6 (8.2–8.9)	0.89
Mean systolic BP (mmHg)	158 (153–163)	141 (137–146)	<0.001
Mean diastolic BP (mmHg)	84 (82–86)	77 (75–79)	<0.001
Mean cholesterol (mmol/dl)	5.9 (5.6–6.2)	5.3 (5.0–5.6)	<0.001
Mean proteinuria (g/24 h)	2.2 (1.7–2.7)	2.4 (1.7–3.1)	0.21
Median serum creatinine ( $\mu$ mol/l) [IQR]	124 [92–176]	155 [109–245]	<0.001

Data on clinical parameters at presentation and last visit to the clinic. Data are means (95%CI) or median [IQR] as appropriate.





**Figure 2.** Improvements in blood pressure (BP). Mean systolic BP at referral was 158 (95%CI 153–162)mmHg, improving to 141 (137–145)mmHg at final visit. Mean diastolic BP improved from 84 (82–86)mmHg to 77 (75–79)mmHg ( $p < 0.001$  for both).



**Figure 3.** Rate of decline in renal function calculated using linear regression in a single subject. The slope of the plot of creatinine clearance vs. time is expressed in ml/min/month. A set of three readings for each 12-month period was used to draw the slope.

or prevent ESRF, and reduce the associated cardiovascular risk.

Managing these patients within a busy general diabetic or renal clinic is challenging. Intensified multifactorial intervention in patients with type 2 diabetes and microalbuminuria delays progression to nephropathy, retinopathy and autonomic neuropathy.<sup>22</sup> Combined diabetic-renal clinics were therefore set up to provide high-quality care and individualized treatment to these patients with multiple risk factors. Our joint clinic was among the first to provide such a service in a busy District General Hospital in the UK, and was aided by the development and use of widely circulated local guidelines, in which General Practitioners were actively involved. The clinic continues to serve a population of approximately 188 000. However, there have been very few publications showing a

positive benefit of these multidisciplinary clinics in the management of diabetic nephropathy,<sup>19,20,23</sup> and as far as we are aware, no published studies from a District General Hospital providing secondary care for patients with diabetic nephropathy.

The number of patients with type 2 diabetes in our cohort exceeds those with type 1 diabetes. Mean age at presentation in patients with type 1 diabetes was lower when compared with type 2 diabetes, but with a longer duration of diabetes, similar to published data, suggesting that our study group was a representative population.<sup>23</sup> The prevalence of retinopathy was high: at least 75% of patients had documented background retinopathy and almost half had proliferative retinopathy. All patients with proliferative retinopathy received laser photocoagulation. Absence of retinopathy was not used as a criterion for renal biopsy in our group of patients. Smoking is an important modifiable risk factor affecting the progression of renal disease, and also has an adverse effect on cardiovascular risk. We were unable to reduce the significant proportion of patients who continued to smoke during the period of follow-up in the clinic. In a recent study, smoking cessation had benefits in addition to blood pressure control and ACE inhibition, in reducing the progression of diabetic nephropathy.<sup>13</sup> Patients should be made aware of the benefits of smoking cessation at clinic visits by physicians and nurses, and if possible, offered direct access to smoking cessation clinics.

Reduction of blood pressure is crucial to the management of diabetic nephropathy.<sup>5,6</sup> Various guidelines have recommended a target blood pressure of <140/80 mmHg, and a level of <130/80 mmHg has recently been suggested in patients with diabetic nephropathy.<sup>4,15,16</sup> Our patients had a high prevalence of hypertension, and most were on anti-hypertensive treatment on referral. Even though most referrals were from specialist diabetic and renal clinics, 83% of subjects had a blood pressure >140/80 mmHg, and only 41% achieved their modest target of 140/80 mmHg at the clinic. These results are consistent with published studies, showing that only a small percentage of patients achieve these targets, despite intensive management.<sup>23,24</sup> On the other hand, patients improved their systolic and diastolic blood pressure significantly, compared to their blood pressures on referral. Patients required at least 2–3 anti-hypertensives to achieve their target blood pressure. Large prospective studies including UKPDS<sup>25</sup> also showed that patients required multiple drug regimens to reduce blood pressure significantly.

The use of ACE inhibitor drugs improved marginally at the clinic, but contraindications to therapy

were well-documented in most patients not taking treatment. Co-existing renal vascular disease was the most common contraindication in almost half of the patients not receiving ACE inhibitor drugs, followed by hyperkalaemia in approximately 20%. This may reflect a reluctance in some clinicians to use ACE inhibitors in the presence of renal insufficiency, more so with a suspicion of renal vascular disease. However, it is important that ACE inhibition in this high-risk group be increased; evidence is accumulating that this offers protection against further deterioration of renal function, independent of blood pressure reduction,<sup>26–29</sup> and may also help to reduce cardiovascular risk.<sup>30</sup> Aggressive investigation and management of renal vascular disease may be an option to increase the number of subjects on ACE inhibition, rather than relying on a clinical suspicion of renal vascular disease. Dietary advice on restriction of potassium intake from a specialist dietician might be useful.<sup>31</sup> Angiotensin II receptor antagonists, with their favourable side-effect profile and once-a-day treatment, might also improve patient compliance.

Treatment targets for total cholesterol levels have been gradually reduced throughout this long study period. Though there are no large randomized studies in this area, a recent meta-analysis found that lipid reduction may preserve glomerular filtration rate and also decrease proteinuria in patients with renal disease.<sup>8</sup> It is now widely accepted that dyslipidaemia in chronic renal failure should be aggressively managed with statin therapy, due to the increased cardiovascular risk. Furthermore, for a group of patients with a high risk of atherosclerotic vascular disease, only 27% took aspirin as an antiplatelet agent. We were unable to identify any valid reasons for the low prescription rate of aspirin in this study. Glycaemic control remained unchanged during the study period. On the other hand, HbA<sub>1c</sub> levels in this group are similar to those in previously published studies, and did not change with declining renal function.<sup>20,24</sup>

In this observational study, we estimated creatinine clearance using the Cockcroft and Gault equation. We are aware that this method overestimates creatinine clearance,<sup>32</sup> but nevertheless, it correlates well with measured creatinine clearance.<sup>33</sup> We have assumed that this overestimation will be insignificant because of the longitudinal nature of our study. We used linear regression to calculate the decline in renal function; similar methods have been used for audit purposes by other groups.<sup>20</sup> Parving *et al.* showed that in intensively-treated type 1 subjects with nephropathy, the rate of decline of renal function could be reduced from 0.89 ml/min/month to 0.22 ml/min/

month.<sup>34</sup> As far as we know, these results have not been reproduced in routine clinical practice in diabetic patients with nephropathy, nor in clinical trials. Joss *et al.* studied a group of subjects in a joint clinic with early diabetic nephropathy, and showed that the rate of decline could be reduced from 0.52 ml/min/month in the first year to 0.27 ml/min/month in the third year. They suggested that for audit purposes, a joint clinic should aim to achieve a rate of decline of renal function of <0.25 ml/min/month in at least 70% of patients with early nephropathy.<sup>20</sup> The rate of decline of GFR in our study was reduced from 1.09 ml/min/month in the first year to 0.39 ml/min/month in the third year. For example, in a patient with a creatinine clearance of 50 ml/min/year, the improvement in the rate of decline in renal function in our study would extend the nephropathy stage, independent of dialysis, from 4 years to 11 years, with all the attendant savings and potential for reduced cardiovascular risk. However, our initial rate decline of GFR was significantly high, and remains unexplained despite moderate control of risk factors. One possibility could be initiation and titration of ACE inhibitors in the first year after referral to the combined clinic. Our analysis could also be vulnerable to sudden changes in serum creatinine, most commonly secondary to incurrent illness. The latter is unlikely to have been a major factor, since most of our readings were done in the clinic setting when patients were well.

One third of our patients died during the 10-year study period. Of these deaths, 64% were due to cardiovascular disease, followed by renal failure and others. Coronary artery disease was the major contributor accounting for most of the cardiovascular deaths. The mean survival in our group of patients who died was only 4 years from their first clinic visit, which is comparable to metastatic tumours of the lung.<sup>35</sup> Haffner *et al.* showed that patients with type 2 diabetes without a history of previous myocardial infarction, carry the same cardiovascular risk as non-diabetic patients with a previous history of myocardial infarction.<sup>36</sup> Mild renal insufficiency alone may directly promote atherosclerosis, and this increases with advancing renal failure.<sup>37</sup> This increased cardiovascular risk is further aggravated by non-traditional risk factors such as the increased proportion of atherogenic small dense LDL, raised homocysteine and inflammatory markers such as C-reactive protein, which are associated with chronic renal impairment.<sup>38,39</sup> Survival on renal replacement therapy appears to be worse for patients with diabetes,<sup>40</sup> partly because of the increased cardiovascular disease associated with the end stages of renal disease. The challenge for the future will be improved patient management

in the earlier stages of diabetic nephropathy to prevent progression, as well as cardiovascular complications.<sup>41</sup>

The audit value of this study has allowed us to make improvements to the protocols and guidelines used in our clinic. In summary, management of our patients with diabetic nephropathy in a District General Hospital joint diabetic-renal clinic significantly delayed the rate of decline in renal function and extended the time to renal support, in patients with early diabetic nephropathy. This clinic also helped somewhat to achieve targets in blood pressure control and improve total cholesterol, as suggested by established guidelines in the treatment of diabetic nephropathy, although optimal blood pressure remains difficult to achieve for many patients. This study provides important data regarding the natural history of diabetic nephropathy in a single population attending a district general hospital, which may be valuable for future resource planning and management.

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