

Paper

Diabetic nephropathy and chronic kidney disease at a busy diabetes clinic: A study of Outpatient Care and suggestions for improved care pathways at a subspecialty specialist diabetic renal clinic.

Graham UM, Magee GM, Hunter SJ, Atkinson AB

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ABSTRACT

Prior to establishing a specialist diabetic renal clinic in our unit, we studied across 12 months all 1845 patients attending one of our diabetes clinics with a serum creatinine $>150\mu\text{mol/l}$. Diabetic control was examined along with renal function and cardiovascular risk using current audit standards.

74 such patients were identified (male:female 54:20 mean HbA1c 7.8% (sd \pm 1.45) and age 64.2years (\pm 12.8)). 30 patients had creatinine $>200\mu\text{mol/l}$ and 15 $>250\mu\text{mol/l}$. Using the chronic kidney disease classification, 33, 28 and 6 patients were in groups III, IV and V with 7 patients undergoing renal replacement therapy.

65% of patients met JBS2 audit standards of blood pressure using a mean of 2.93 agents (sd \pm 1.43). Ace-inhibitors or angiotensin receptor blockers were used in 81% and 81% were on regular antiplatelet or anticoagulant therapy. Audit standard for total cholesterol and LDL were met in 89% and 97% of patients respectively.

All patients identified in our study were in CKD class III-V and therefore we considered also alternative inclusion criteria. 136 patients had a urinary ACR $\geq 30\text{mg}/\text{mmol}$. Using this and/or the serum creatinine level above identified 197 patients from the clinic.

This study shows that measurement of serum creatinine alone is not sufficiently sensitive but extended criteria identified a 10% subgroup who will now be offered detailed assessments and intensified therapies at a subspecialty in-house renal clinic. eGFR has recently been added to our computerised proforma and will enable us to further refine inclusion criteria.

INTRODUCTION

Diabetes is an increasingly prevalent condition in Northern Ireland. The prevalence of diabetes in Northern Ireland in 2008 was 4.1% of the adult population¹. It is estimated that 9% of all patients with diabetes in Northern Ireland have type 1 diabetes². Approximately one third of patients are managed in hospital with type 1 diabetes making up between 10-35% of hospital clinics². The remaining patients are managed in primary care. Our clinic presently comprises 35% type 1 diabetes and 65% type 2 diabetes.

In Northern Ireland there is a 13.9% prevalence of diabetic nephropathy amongst patients with diabetes¹. Diabetic nephropathy is a major cause of end-stage renal disease affecting 28.9% of new adult patients starting renal replacement therapy in 2007³. In these patients, diabetes is a powerful predictor of increased risk of death after the first 90 days of renal replacement therapy³. The expanding dialysis population and its associated health and resource implications reinforce the need to prevent or delay the progression of nephropathy in our diabetic patients.

A number of risk factors for progression of nephropathy have been identified including poor glycaemic control, hypertension, smoking, genetic susceptibility, age, race and obesity. The DCCT and UKPDS demonstrated that improved glycaemic control reduces the risk of diabetic nephropathy in both type 1 and type 2 diabetic patients^{4,5}. The reduction of proteinuria through the use of ACE inhibitors or angiotensin receptor blockers is also a major intervention shown to reduce progression of renal disease⁶⁻⁸.

The first sign of renal involvement in patients with diabetes is microalbuminuria. This is defined as a urinary albumin creatinine ratio (ACR) $>2.5\text{mg}/\text{mmol}$ (men) or $>3.5\text{mg}/\text{mmol}$ (women) on 2 or 3 occasions⁹. This affects over 20% of type 1 and type 2 diabetic patients 10-15 years after the onset of diabetes and subsequently may evolve to macroalbuminuria or proteinuria (ACR $> 30\text{mg}/\text{mmol}$)^{10,11}. Once macroalbuminuria is present, glomerular filtration rate declines at an average rate of 10-12ml per minute per year in untreated patients¹¹.

Screening for microalbuminuria is an important function of diabetes clinics whether this be in the primary or secondary care setting. Patients with moderate established nephropathy often attend hospital clinics for both diabetic and renal care. Frequently both clinics have overlapping responsibilities with regard to blood pressure control with diabetologists primarily addressing glycaemic targets. This is an unnecessary burden

Regional Centre for Endocrinology and Diabetes

Royal Victoria Hospital

Belfast Health and Social Care Trust, Grosvenor Road, Belfast, BT12 6BA

email: una.graham@belfasttrust.hscni.net

Correspondence to Dr Graham.

on patients many of whom may have other co-morbidities for which they also attend hospital. Therefore a single clinic which addresses both conditions would be of considerable benefit. The complexity of patients with diabetic nephropathy may be difficult to manage in a general diabetes clinic setting and a better solution may be a subspecialty clinic focussing on diabetic nephropathy. This would also help in reducing the number of clinics these patients attend. Diabetologists with well defined links to nephrology services are in an ideal position to manage patients with early or moderate nephropathy. This clinic would be designed through careful liaison with nephrologists to ensure smooth referral to nephrology if kidney disease progresses. Prior to establishing such a subspecialty clinic we reviewed our present patient population to establish initial referral criteria.

KEY WORDS

Diabetic nephropathy, subspecialty clinic, microalbuminuria.

AIM

We performed a study to assess kidney function in a group of diabetic patients attending a general diabetic clinic. This was to enable us to plan for a specialist diabetes renal clinic within our own diabetes service. We aimed to:

- establish the prevalence of chronic kidney disease in our outpatient population
- determine if patients with diabetic kidney disease are receiving treatment to help prevent progression of nephropathy and meet targets as outlined by chronic kidney disease guidelines⁹.

- identify patients for a new specialist diabetic renal clinic to help patients achieve targets, ensure patients are correctly investigated and managed for all aspects of chronic renal care, to provide necessary dietary support and to ensure smooth pathways to the regional services for nephrology in Northern Ireland.

DESIGN AND SETTING

The Regional Centre for Endocrinology and Diabetes at the Royal Victoria Hospital in Belfast has a large outpatient diabetic population. Until recently our patients with diabetic renal disease have been managed as part of general diabetic clinics. Patient information such as regular medication, clinical examination findings and biochemical results are recorded electronically using the Northern Ireland Regional Electronic Patient Record for Diabetes (DIAMOND system). Further information was obtained from patient notes. At the time covered by this study estimated glomerular filtration rate (eGFR) was not routinely recorded on this system.

Study 1

We performed a search of our clinic database to obtain all patients (1845) who had attended the clinic between January 2006 and October 2007 and who had a serum creatinine $>150\mu\text{mol/l}$. This value was chosen based on 2002 NICE guidelines which suggested this as a threshold for referral to nephrology. We aimed to assess our management of these patients with established renal disease in a diabetologist led clinic.

Information obtained from Diamond sheets included patient demographics, type and duration of diabetes, oral antidiabetic therapy, glycaemic control (HbA1c), renal function, involvement in nephrology services, blood pressure, use of antihypertensives and cardiovascular risk profile.

Targets used for blood pressure and cholesterol were based on audit standards as outlined by the JBS2 guidelines¹².

RESULTS

74 patients were identified with serum creatinine $>150\mu\text{mol/l}$. The demographics of these patients are shown in table 1.

Renal function

Renal function was recorded using both serum creatinine and eGFR. All 74 patients had creatinine $>150\mu\text{mol/l}$ with 30 patients having creatinine $>200\mu\text{mol/l}$ and 15 patients $>250\mu\text{mol/l}$. The patients were then grouped into chronic kidney disease classes using eGFR as per national guidelines⁹. There were 33, 28 and 6 patients in CKD class 3, 4 and 5 respectively and 7 patients undergoing renal replacement therapy.

In our group of patients 50 out of 74 had urinary ACR recorded over the proceeding year. Of the 24 patients with no ACR recorded, 7 were undergoing

TABLE 1

	Type 1 Diabetes (n=33)	Type 2 Diabetes (n=41)	Total (n=74)
Patients	33 (45%)	41 (55%)	74
Male/Female	21/12	33/8	54/20
Caucasion	33(100%)	41(100%)	74(100%)
Age (mean±sd)	56.2±12.5	70.6±9.0	64.2±12.8
HbA1c (mean±sd)	8.0±1.5%	7.7±1.4%	7.8±1.5%
Duration of diabetes (mean±sd)	33.5±11.5	17±6.0	24.3±9.4
Retinopathy	27 (82%)	17 (41%)	43 (58%)
Blood pressure (mean±sd)	129/69±17/9	136/72±20/10	133/71±19/10
Patients with uncontrolled BP*	10(30%)	16(39%)	23(31%)
BP in uncontrolled patients (mean±sd)	149/84±5/3	160/88±14/6	156/87±12/5
No. antihypertensives (mean±sd)	2.5±1.6	3.3±1	2.9±1.4
On ACEI/ARB	24(73%)	36(88%)	60(81%)

*Blood pressure $>140/80\text{mmHg}$ as per JSB2 audit standards¹³

renal replacement therapy and 10 were under regular review and assessment at a general nephrology clinic. There were 17 patients with normoalbuminuria, 20 with microalbuminuria and 13 with proteinuria.

Diabetic control and treatment

(see table 1)

45% of patients achieved a HbA1c of <7.5% (audit standard¹²). Eleven patients (16%) were being treated with metformin. Of these patients creatinine ranged from 156 – 212µmol/l and eGFR from 27 – 41ml/min/year. Of patients with type 2 diabetes, 4(10%) were on diet control only with 13(32%) on oral hypoglycaemic agents, 21(51%) on insulin alone and 3(7%) on both insulin and an oral hypoglycaemic agent.

Blood pressure

51 patients (69%) of our group had a blood pressure of <140/80mmHg (audit standard¹²). The number of antihypertensives required for both controlled and uncontrolled patients are displayed in figure 1.

In our group of patients, 14 patients were not taking either an ace-inhibitor or angiotensin receptor blocker. Of this group, 1 patient had developed hyperkalaemia and 2 had renovascular disease. From surveying the hospital notes no apparent reason was identified for the remaining 11 patients.

Cardiovascular risk

The prevalence of ischaemic heart disease and their cardiovascular risk factors are shown in table 2.

Study 2

In order to identify those with significant early modifiable diabetic nephropathy we widened the search criteria in study 1 to include patients with an ACR > 30mg/mmol (macroalbuminuria) and/or creatinine > 150µmol/l. Using this strategy a total number of 197 patients were identified.

DISCUSSION

Although early NICE guidelines recommended renal referral based on serum creatinine >150µmol/l, it is now well recognised that eGFR provides a more reliable measure

of renal function. In study 1, all patients had eGFR <60ml/min/1.73m² equating to CKD class III. eGFR is calculated using the modification of diet in renal disease equation using serum creatinine, age, gender and ethnicity¹³. For a given creatinine, GFR will be lower in those patients who are older, white and female. Of note only 20 of our 74 patients were female which probably reflects the exclusion of many women with significant renal disease but a serum creatinine <150µmol/l. Serum creatinine alone is an insensitive measure of renal function with a rise in creatinine to just above the normal range reflecting the loss of more than one-half of the total glomerular filtration rate. Using a serum creatinine >150µmol/l identified less than half of patients with significant nephropathy.

Comparable with our results, a recent study of renal disease in diabetic patients showed that the sensitivity of abnormal serum creatinine levels in identifying eGFR <60 ml/min/1.73 m² was 45.3%, albuminuria 51.2% and either an abnormal serum creatinine or albuminuria 82.4%¹⁵. Therefore inclusion criteria based solely on creatinine will miss a significant number of patients with early nephropathy. We identified 74 patient with a creatinine > 150µmol/l. Given the prevalence of diabetic nephropathy as 13.9% of the local diabetic population we would have expected to have identified at least 256 patients with nephropathy³. This is defined as microalbuminuria. Clearly the use of creatinine alone will miss a significant number of patients. However for the clinic to be manageable a more stringent criterion would be needed. It is well established that microalbuminuria is predictive of disease progression in diabetic nephropathy and indeed that progression accelerates with development of macroalbuminuria¹¹. We therefore looked at patients with ACR > 30mg/mmol (macroalbuminuria). Including such patients with early modifiable nephropathy alongside our initial group with creatinine > 150µmol/l increased our patient group by more than double from 74 to 197.

In performing these studies, we identified 17 patients (23%) with creatinine >150µmol/l who were also normoalbuminuric. This result confirms the lack of specificity of elevated creatinine in identifying diabetic nephropathy. It has been reported that about 20% of patients with diabetes have reduced GFR but normal ACR¹⁶. These patients are typically women with a shorter duration of diabetes, a low prevalence of retinopathy, a non-smoking history and a higher haemoglobin and HDL level. It is difficult to identify an underlying cause of renal impairment in these patients. However they typically have a low risk of CKD progression or death¹⁶. In some cases the kidney disease may relate to hypertension or ischaemic nephropathy secondary to renal artery stenosis. In contrast to the benefits of ACEI/ARB therapy in diabetic nephropathy, treatment in patients with significant renal artery stenosis is associated with an over 30% rise in serum creatinine which is reversible on stopping the drug¹⁷. The prevalence of renal artery stenosis detected by MRA in patients with type 2 diabetes is 17%¹⁸. Although not all structural defects are associated with clinically significant disease, this highlights the need to screen for kidney

TABLE 2

	Type 1 diabetes (n=33)	Type 2 diabetes (n=41)	Total (n=74)
Known IHD	11(33%)	20(49%)	31(42%)
Regular antiplatelets/ anticoagulants	23(70%)	37(90%)	60(81%)
Cholesterol <5mmol/l*	29(88%)	36(88%)	65 (88%)
LDL <3mmol/l*	32(97%)	40(98%)	72(97%)
Statin therapy	19(58%)	36(88%)	55(74%)
Smokers	4(12%)	0	4(5%)
Ex-smokers	5(15%)	14(34%)	19(26%)

*denotes audit standards as outlined by the JBS2 guidelines¹³

disease in diabetic patients using a combination of both creatinine (or eGFR) and ACR.

Now that eGFR is being used more commonly, this, combined with estimation of urinary albumin, will be a useful means of identifying patients with early nephropathy for inclusion in a specialist diabetic clinic. All of the patients in study 1 were in CKD class III and one possibility is to include all patients with this stage of kidney disease in specialist diabetes renal clinics. On screening of general practice populations without diabetes, approximately 5% of patients have CKD stage III-V with 97% of these patients in CKD class III¹⁴. However in a group of patients with diabetes, this percentage will be much higher. Indeed in one study, 27.5% of patients with diabetes have clinically significant CKD, as defined by an eGFR <60 ml/min/1.73 m²¹⁵. This study included patients from both primary and secondary care. At our centre, to include up to one third of our diabetic population in a specialist renal clinic, may exceed the capacity of service provision and therefore we plan to screen initially using creatinine and ACR.

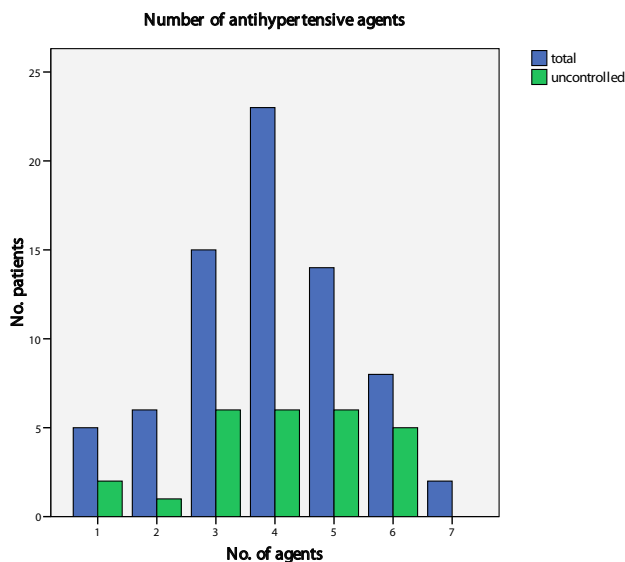


Figure 1

As discussed above patients with diabetic nephropathy have significantly increased cardiovascular risk and therefore attention to cardiac risk factors is an essential part of their care. Only 65% of our patients met recommended audit standards for blood pressure in our general diabetes clinic. This could be improved with increased focus on blood pressure control at a subspecialty clinic. To achieve blood pressure control our patients required an average of 3 antihypertensive agents. Good blood pressure control often needs 2 or more agents. In a study comparing intensive and conventional blood pressure management, the UKPDS group found that 29% of patients in the intensive group required 3 or more agents to achieve targeted blood pressure control¹⁹. Figure 1 displays the number of antihypertensives used for patients with both controlled and uncontrolled blood pressure. Of note 9 patients with uncontrolled blood pressure were taking 0-2 agents and thus were not being treated aggressively enough. This highlights the need for strict blood pressure control through introduction and titration of new agents if

necessary. Cholesterol was well controlled in our study with good use of statin therapy.

It was more difficult to attain audit standards for HbA1c with just 45% achieving HbA1c of <7.5%. However the mean HbA1c in our study was 7.8±1.5% which is similar to mean HbA1c after longterm follow up (8-10years) in other studies such as Steno-2 and UKPDS^{20,21}.

This study demonstrates a need to improve our focus on cardiovascular risk reduction in this high risk group of diabetic patients. This can be achieved through ongoing education of medical staff and early and appropriate use of antihypertensives, statins and antiplatelets. Rather than refer many patients to a specialised nephrology service we feel that the skills within a diabetes centre should also allow us to intensify and improve glycaemic control and delay progression of renal disease. We feel that this can best be achieved with a subspecialty clinic.

Other guidelines are also in place for patients with CKD stage III-V⁹. In addition to the measures outlined above, patients with established kidney disease require further monitoring, investigation and management. It is recommended that all patients with CKD stage III should have annual measurement of haemoglobin, calcium and phosphate. Those patients who are anaemic may benefit from treatment with iron and/or erythropoietin. In addition, patients at this stage are at risk of renal bone disease. Therefore parathyroid hormone should be checked and if elevated (with an associated low vitamin D level), treatment with vitamin D should be initiated. It is also recommended that patients are referred for a renal ultrasound scan if they describe lower urinary tract symptoms, have refractory hypertension or an unexpected progressive fall in eGFR. Patients should also be immunised for influenza and pneumococcus.

Before this study these measures were not included as part of our diabetic clinic. Thus patients not attending a nephrologist were not routinely screened for these complications of renal disease. As they attend our diabetic clinic on at least a biannual basis, this care can be included as part of their routine review at a specialist diabetic renal clinic.

STRATEGIES FOR CHANGE

We have now established a specialist diabetic renal clinic to run alongside our general diabetic clinic. We have initially included patients with serum creatinine >150µmol/l and/or ACR>30mg/mmol. It is also likely that we will develop additional criteria based on eGFR which is now widely available on biochemistry reports and on our Diamond system. Patients at this clinic will benefit from input from a multidisciplinary team of diabetologists, specialist nurses and dieticians with specialist interests in both hypertension and diabetes. This clinic has been established in collaboration with nephrology ensuring that appropriate referral criteria are set and that patients who perhaps do not need to attend a nephrology clinic can have a "virtual review" if there are any concerns regarding their renal function.

Given the high cardiovascular disease risk of these patients, all risk factors will be addressed during the clinic. In addition, a protocol for screening for complications of renal disease such as anaemia and bone disease has been prepared. This will help

guide clinicians to ensure appropriate treatment. By having a well established renal diabetic clinic, this should enable smooth referral to nephrology if renal disease is progressing towards likely end-stage.

CONCLUSION

In conclusion the results of this survey confirm the lack of sensitivity and specificity of measurement of serum creatinine in the diagnosis of diabetic nephropathy. The use of serum creatinine and with time eGFR alongside ACR significantly improves the identification of patients with diabetic nephropathy and non-diabetic chronic kidney disease. The move to a subspecialty clinic will enable greater focus on aggressive management of cardiovascular risk factors combined with assessment and treatment of chronic kidney disease associated issues such as anaemia. We believe a diabetologist led clinic has the power to enhance patient care although liaison with nephrology remains a key priority.

The authors have no conflict of interest.

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