Original Article

The unrecognized prevalence of chronic kidney disease in diabetes

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Abstract

Background. Diabetes mellitus and chronic kidney disease (CKD) are common and exhibit synergistic associations with premature mortality. Current diabetes guidelines in the UK recommend annual urinary albumin and serum creatinine determinations to screen for diabetic kidney disease. The aim of this study was to estimate the burden of CKD in patients with diabetes and examine the ability of serum creatinine and albuminuria to detect clinically meaningful CKD compared with estimated glomerular filtration rate (eGFR).

Methods. All adults known to have diabetes in primary and secondary care in Salford, UK, alive with independent renal function on 1 January 2004 were included in this observational study ($n = 7596$). Demographic and laboratory parameters were obtained from the Electronic Patient Record. eGFR was determined using the 4-variable modification of diet in renal disease (MDRD) formula. Clinically meaningful CKD was defined as an eGFR $<60 \text{ ml/min}/1.73 \text{ m}^2$.

Results. Creatinine and albuminuria were measured in the preceding 2 years in 82.3 and 55.2% of subjects, respectively. In patients with CKD, normoalbuminuria was present in 48.8%, and serum creatinine was normal ($\leq 120 \,\mu\text{mol/l}$) in 54.7%. An abnormal serum creatinine ($\geq 120 \,\mu\text{mol/l}$) had a sensitivity and specificity of 45.3 and 100%, respectively, to identify CKD. The combination of abnormal creatinine and albuminuria had an improved performance but still failed to detect a large number with CKD (sensitivity 82.4%, specificity 75.4%). Serum creatinine failed to identify CKD more often in females (OR 8.22, CI 6.56–10.29).

Conclusions. Undiagnosed CKD is common in diabetes. Current screening strategies, based on creatinine or albuminuria, fail to identify a considerable number of subjects with CKD. Incorporating eGFR into screening for CKD would identify individuals earlier in the natural history of the disease and enable early effective treatment to delay progression of CKD.

Keywords: serum creatinine; estimated glomerular filtration rate; modification of diet in renal disease (MDRD) study equation; diabetic kidney disease; sensitivity

Introduction

Diabetes mellitus is the most common cause of end-stage renal disease (ESRD) in the UK and it has been estimated that 366 million people worldwide will have diabetes mellitus by 2030 [1,2]. Furthermore, diabetes and chronic kidney disease (CKD) exhibit synergistic associations with cardiovascular disease and premature mortality.

Guidelines for diabetes care in the UK recommend annual urinary albumin and serum creatinine determinations, and nephrology referral when serum creatinine levels exceed 150 μmol/l [3,4]. Serum creatinine production is dependent on lean body mass and therefore may not be an accurate reflection of glomerular filtration rate (GFR). At identical GFR levels, older subjects and females have lower muscle mass, lower rates of creatinine production and lower serum creatinine levels [5]. Isotope GFR is the definitive measure of the level of renal function; however, it is logistically unrealistic for population screening. Formulae based on age, sex, race and serum creatinine attempt to correct for differences in muscle mass and have been shown to be comparable to isotope GFR in CKD [6].

Table 1. Prevalence of CKD according to K/DOQI classification

Stage	Description	GFR (ml/min/1.73 m^2)	N	Prevalence %	Age (years) Mean (SD)
0–2	GFR $\geq$60 ml/min/1.73 m^2 without albuminuria data[a]	$\geq$60	2254	36.0	64.7 (13.4)
0	Normal	$\geq$90	1719	27.5	54.1 (12.6)
1	Kidney damage[b] with normal GFR	$\geq$90	168	2.7	48.0 (12.7)
2	Kidney damage[b] with mild $\downarrow$GFR	60–89	391	6.3	59.7 (11.9)
3	Moderate $\downarrow$ GFR	30–59	1547	24.8	72.1 (10.8)
4	Severe $\downarrow$ GFR	15–29	156	2.5	71.9 (12.9)
5	Kidney failure	<15	12	0.2	63.2 (13.9)

[a]Subjects with GFR $\geq$60 ml/min/1.73 m^2 without albuminuria data may have no kidney disease or stage 1–2 CKD.
[b]Kidney damage is defined as structural or functional abnormalities of the kidney manifest by pathological abnormalities or marker of kidney damage such as abnormal urine analysis or renal imaging.

Recent American Diabetes Association guidelines suggest the use of estimated GFR as a superior measure of renal function compared with serum creatinine levels [7].

Studies have shown that a GFR <60 ml/min/1.73 m^2 is a harbinger of premature cardiovascular death [8]. The detection of CKD is therefore important because it identifies patients at high risk of cardiovascular disease, and not merely because it identifies those at risk for progressive kidney disease and its complications.

The aim of this study was to establish the burden of clinically meaningful, but unrecognised, CKD in patients with diabetes and to evaluate the effectiveness of serum creatinine and albuminuria to detect CKD.

Methods

Subjects

Salford is an urban district of Greater Manchester in the UK with a population of 216 000 served by a single teaching hospital. The Salford diabetes Electronic Patient Record (EPR) was introduced in 1992 and is a continuously updated electronic diabetes health care system that incorporates data from primary and secondary care. The EPR was used to define the cohort of all adults with diagnosed diabetes in Salford district. The EPR is part of the hospital electronic patient record system, allowing real-time collection of clinical, biochemical, haematological, clinic visit and hospital admission data.

All patients on the EPR in 2002 were included in this study provided they were still alive on 1 January 2004, except for those on dialysis or with a functioning renal transplant.

The population with diabetes have a skewed distribution with respect to age with a greater number of older subjects compared with the general population. Therefore the prevalence of CKD (GFR < 60 ml/min/1.73 m^2) was examined according to age; $\geq$ or <70 years old.

Definitions of CKD and albuminuria

The most recent serum creatinine and urinary albumin level in the period January 2002 to December 2003 were used for the analysis. Creatinine measurements were performed using an uncompensated modified Jaffé reaction using a Roche diagnostics analyser, Integra 700. GFR was calculated using a validated GFR estimate, the 4-variable modification of diet in renal disease (MDRD) formula (eGFR) [9]:

$$eGFR = 186(sCr/88.4)^{-1.154}$$
$$\times \text{ age}^{-0.203}(\times 0.742 \text{ if female}, \times 1.21 \text{ if black}).$$

The Salford population is predominantly Caucasian (96.1% of the population are Caucasian, 0.6% of black origin). Therefore all subjects were assumed to be non-black for the purposes of GFR calculation. Subjects were classified as having microalbuminuria if the albumin–creatinine ratio (ACR) was >2.5 mg/mmol in males and >3.5 mg/mmol in females and proteinuria if ACR was >30 mg/mmol or 24 h proteinuria >0.3 g/24 h. The term 'albuminuria' includes patients with both micro and macroalbuminuria.

The US National Kidney Foundation's Kidney Disease Outcomes Quality Initiative (K/DOQI) classification was used to define the stage of CKD (Table 1). For the purposes of this study, clinically significant CKD was defined as K/DOQI CKD stages 3–5 (eGFR <60 ml/min/1.73 m^2). The sensitivity and specificity of serum creatinine and albuminuria alone or in combination were compared with eGFR <60 ml/min/1.73 m^2.

This study addresses key audit criteria outlined in the UK NICE (National Institute of Clinical Excellence) guidelines for management of diabetes [3]. All patients gave verbal consent to the storage and use of anonymized data to monitor and improve clinical care.

Statistics

Normally distributed variables are summarized by their means and SDs, median and range are used for skewed data. Analysis of variance and chi-square analysis, respectively, were used for between-group comparisons of continuous and categorical variables, respectively. Logistic regression was used to calculate adjusted odds ratios for (i) the presence of CKD and (ii) the presence of CKD failed to be diagnosed by serum creatinine >120 µmol/l and albuminuria. SPSS version 11.5 was used to perform all the analyses.

Results

7596 subjects were studied. Table 2 shows their characteristics on 1 January 2004, as well as the proportions receiving measurements of serum creatinine, albuminuria, total cholesterol and blood pressure in the preceding 2 years. Table 1 shows the prevalence of

Table 2. Baseline characteristics

	Number evaluated (%)	%/Mean (SD)
Type 2 diabetes mellitus (%)	7596 (100)	87.7
Male sex (%)	7596 (100)	54.2
Age (years)	7596 (100)	62.6 (14.8)
Primary care (%)	7596 (100)	64.2
HbA1c (%)	6109 (80.4)	7.9 (1.7)
Blood pressure (mmHg)	5797 (76.3)	138/75 (20/11)
Urinary albumin-to-creatinine ratio ratio (mg/mmol)	2898 (38.2)	1.2 (0.5, 3.5)[a]
Urinary albumin-to creatinine ratio (secondary care only) (mg/mmol)	1910 (70.2)	1.3 (0.6, 4.1)[a]
24-hour protein excretion (mg/day)	341 (4.5)	0.3 (0.2, 0.6)[a]
Albuminuria present(%)	3034 (39.9)	30.5
Cholesterol (mmol/l)	5964 (78.5)	4.7 (1.0)
Creatinine (μmol/l)	6247 (82.2)	88 (77, 103)[a]
Creatinine >150 μmol/l (%)	6247 (82.2)	4.9

[a]Non-parametric data expressed as median and inter-quartile range.

Table 3. Diagnostic test performance of serum creatinine >120 μmol/l, albuminuria and proteinuria to detect estimated GFR <60 ml/min/1.73 m^2

	Creatinine >120 μmol/l	Albuminuria[a]	Creatinine >120 μmol/l or albuminuria	Creatinine >120 μmol/l and albuminuria	Proteinuria[b]
Sensitivity	45.3%	51.2%	82.4%	21.0%	19.4%
Specificity	100%	75.5%	75.4%	100.0%	96.1%
Positive predictive value	100%	38.5%	61.7%	100.0%	57.8%
Negative predictive value	82.8%	83.8%	89.9%	80.8%	81.4%

[a]Albuminuria = all proteinuria including microalbuminuria.
[b]Proteinuria = macroproteinuria.

CKD within Salford according to the K/DOQI classification 27.5% (n = 1715) of the population had an eGFR <60 ml/min/1.73 m^2 (stage 3–5 CKD); of these 19.4% (n = 333) had normoalbuminuria; 20.4% (n = 350) had albuminuria, the remainder not having had albuminuria determined. Serum creatinine was normal (≤120 μmol/l) in 54.7% (n = 938) of those with eGFR <60 ml/min/1.73 m^2 i.e. moderate to severe CKD and ≤150 μmol/l in 82.2% (n = 1409). The prevalence of eGFR <60 ml/min/1.73 m^2 was 16% in people <70 years old and 49% if ≥70 years old.

An increased risk of CKD (eGFR <60 ml/min/ 1.73 m^2) was seen with: female sex (adjusted OR 2.11, CI 1.87–2.40); older age (adjusted OR per year 1.09, CI 1.08–1.09) duration of diabetes (adjusted OR per year 1.03, CI 1.02–1.04) and follow-up in a secondary care setting (adjusted OR 1.55, CI 1.34–1.78). The type of diabetes was not associated with an increased incidence of CKD on multivariate logistic regression.

Patients with clinically significant CKD (eGFR <60 ml/min/1.73 m^2) had better glycaemic control (HbA1c 7.8% *vs* 7.9%; P < 0.001), better cholesterol (total cholesterol 4.6 mmol/l *vs* 4.7 mmol/l; P = 0.015), higher systolic blood pressure (BP 140 mmHg *vs* 137mmHg; P < 0.001) and lower diastolic blood pressure (BP 72 mmHg *vs* 75 mmHg; P < 0.001).

Table 3 shows the performance characteristics of an abnormal serum creatinine (>120 μmol/l) and albuminuria to detect an eGFR <60 ml/min/1.73 m^2.

Creatinine >120 μmol/l had a superior predictive value to detect subjects with an eGFR <60 ml/min/1.73 m^2 in the presence of albuminuria than alone; however, it still failed to identify all subjects with eGFR <60 ml/min/ 1.73 m^2. This analysis was also performed for patients attending primary care (low capture of albuminuria quantification) and secondary care (high capture of albuminuria quantification) producing comparable sensitivities and specificities (data not shown).

Unidentified CKD, defined as the presence of an eGFR <60 ml/min/1.73 m^2 but without any evidence of an abnormal creatinine (i.e. serum creatinine ≤120 μmol/l) was significantly greater in females compared with males adjusting for age, type of diabetes and secondary care setting (OR 8.22, CI 6.56–10.29). Using albuminuria as a screening test also failed to identify CKD in females (OR 2.22, CI 1.63–3.03). The presence of abnormal serum creatinine and albuminuria to identify CKD continued to display a significant bias against females (OR 7.58, CI 5.44–10.57).

Discussion

This study shows that 27.5% of the population with diabetes have clinically significant CKD, as defined by an eGFR <60 ml/min/1.73 m^2. Current screening techniques based upon albuminuria and/or abnormal serum creatinine would fail to detect a significant

number of subjects with an eGFR $<60 \, \text{ml/min/1.73 m}^2$. The sensitivity of abnormal serum creatinine levels in identifying eGFR $<60 \, \text{ml/min/1.73 m}^2$ is 45.3%, albuminuria is 51.2% and either an abnormal serum creatinine or albuminuria is 82.4%. In this study 60.6% have CKD stage 3 with a normal serum creatinine. Therefore, without eGFR reporting the clinician may not be alerted to the presence of CKD and be falsely reassured that renal function is normal. This study suggests that current screening for CKD could be improved by incorporating eGFR reporting.

Serum creatinine is the most commonly recognized marker of renal function; it is quick and easy to perform and inexpensive. Creatinine is produced by skeletal muscle and its plasma concentration is therefore proportional to muscle mass. Formulae such as the Cockcroft–Gault equation and the 4-variable MDRD equation attempt to correct for factors affecting the muscle mass, such as age, body size, gender and race.

Microalbuminuria assessment by an albumin creatinine ratio (ACR) remains an essential component of diabetes care as an indicator of the development of diabetic nephropathy and the rate of progression of chronic kidney disease. This study highlights the practical difficulty in quantifying albuminuria in population based diabetes care. Albuminuria was determined in only 39.8% of subjects with an eGFR $<60 \, \text{ml/min/1.73 m}^2$ over the 2-year period of our study despite current recommendations in the UK for annual screening. A greater proportion of subjects (70%) receiving diabetes management in a secondary care setting had albuminuria quantified and this figure is comparable with other diabetes centres. However, this leaves a significant number failing to have any measurement [10]. When the sensitivity and specificity of albuminuria for detecting CKD was calculated for those patients in secondary care, similar results were obtained, suggesting that the low ascertainment of albuminuria does not appear to influence the sensitivity or specificity of this test. Furthermore, albuminuria was absent in 52.6% of subjects with CKD stage 3 in whom a measurement was obtained, reinforcing the need for a simple functional measurement of GFR, as provided using the eGFR.

Diabetic nephropathy represents only a proportion of the aetiology of chronic kidney disease in diabetes; a number of subjects will have ischaemic renal disease or other renal pathologies [11]. The low positive predictive value of albuminuria to detect eGFR $<60 \, \text{ml/min/1.73 m}^2$ is unsurprising given that the presence of microalbuminuria does not necessarily correlate with impaired renal function. Proteinuria, a marker of overt nephropathy, had an improved positive and negative predictive value in detecting eGFR $<60 \, \text{ml/min/1.73 m}^2$ compared with albuminuria, however, with a greater number of false negative results.

In our study population, the prevalence of CKD is higher in females and older age groups as well as in patients receiving their diabetes management in a secondary care setting. This study shows that the current practice of using serum creatinine and albuminuria to determine that CKD is biased against females; this may translate to late diagnosis of kidney disease, late presentation to renal services, and subsequently crash landing onto dialysis. The combination of ACR and eGFR would lead to earlier detection of kidney disease in diabetes and eliminate this gender bias. Early detection of kidney disease enables intensive blood pressure control, institution of an angiotensin converting enzyme inhibitor or angiotensin 2 receptor blocker and meticulous control of glycaemia; factors which have all been shown to slow progression of CKD in diabetes [12].

Whilst the patients with CKD had statistically better glycaemic and cholesterol control, in reality the clinical significance of this is negligible, with the difference in HbA1c being 0.2% and cholesterol being 0.1 mmol/l. It is, however, worth noting that the metabolic control achieved in both groups was sub-optimal with respect to glycaemic control and blood pressure targets, whilst acceptable for total cholesterol. This emphasizes the need for improvement in diabetes management in all patients and especially in those with CKD [3].

Late referral to renal services may have serious consequences for the individual patient, having been shown to be associated with greater use of temporary dialysis access, increased hospitalization, mortality and access to transplantation waiting lists [13,14]. In the United States third National Health and Nutrition Examination survey (NHANES III), less than 10% of subjects with CKD stage 3 had any awareness of having 'weak or failing kidneys' with women having less awareness than men, which may reflect the bias in CKD detection using serum creatinine [15]. Mortality is high in diabetic kidney disease. According to the UKPDS study group, patients with macroalbuminuria have a greater annual risk of dying than of progression of nephropathy or development of ESRD (4.6% vs 2.3%) [16]. Comparable data from the US observed Medicare system demonstrate that patients with diabetes and CKD are five times more likely to die than develop ESRD in a 2-year follow-up period compared with those without CKD [17]. Diagnosing CKD is the first step to improving the poor prognosis.

The 4-variable MDRD formula for estimated GFR was used in this study, as opposed to the Cockcroft–Gault formula suggested in the ADA guidelines, as it relies on age, sex, race and serum creatinine only. Consequently, this formula is quick and easy to calculate on all patients using the demographic data routinely provided when requesting a serum creatinine measurement and can be automatically reported by clinical biochemistry laboratories.

The 4-variable MDRD formula was derived from isotope GFR measurements in 1628 patients with CKD. The equation has been validated on large populations with CKD, including subjects with diabetic nephropathy, however, it may underestimate GFR in subjects with normal renal function or GFR $\geq 60 \, \text{ml/min/1.73 m}^2$ [6,18]. The Cockcroft–Gault formula requires the knowledge of the patient's weight and therefore is a less convenient method. Furthermore the Cockcroft–Gault formula has also been shown to be

less accurate than the MDRD formula in CKD patients with diabetes [6]. The MDRD formula is widely used in population-based studies and the recently published National Service Framework for Renal Services in the UK supports the routine use of eGFR in clinical practice [19].

This is an observational study of diabetes care within Salford, therefore as one would expect the entire local population with diabetes did not undergo serum creatinine measurements and other relevant investigations. Consequently, the exact prevalence of CKD in diabetes may differ slightly from our estimates, however, at least 23% of the population would have CKD stages 3–5 (eGFR <60 ml/min/1.73 m^2). We have not attempted to determine the number of subjects who may have had transient deterioration in kidney function rather than chronic kidney disease and the kinetics and clinical significance of this warrant further investigation. In addition, in line with the observational nature of this study, not all the serum creatinine and albuminuria tests will have been concurrent, allowing a potential source of error. The number of subjects who have had their albuminuria successfully treated with angiotensin converting enzyme inhibitors or angiotensin 2 receptor blockers were not examined and potentially could impact on our results.

Population prevalence studies in the United States have reported the prevalence of stage 3–5 CKD to be 15.1% in subjects with diabetes which is significantly higher than those without diabetes (3.9%), but less than our reported prevalence [20]. The difference in reported prevalence may be due to differences in case-mix or differences in creatinine assays and calibration.

The diabetes and hospital electronic patient registers in Salford are well established and validated to capture all subjects with diabetes in the local population, including investigations and consultations initiated outside of the diabetes care setting. It provides a true picture of current practice in screening for CKD in diabetes.

This study demonstrates the burden of chronic kidney disease in a large population-based cohort with more than 25% having moderate to severe CKD (eGFR <60 ml/min/1.73 m^2). Current recommendations for screening using serum creatinine and presence of albuminuria fail to identify subjects with moderate to severe CKD, and in particular discriminate against women and older age groups. Incorporating eGFR into screening for CKD in diabetes would enable clinicians to identify individuals with CKD earlier in the natural history of the disease, enabling early effective treatment to delay the progression of CKD.

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