The use of Estimated Glomerular Filtration Rate and Albumin Creatinine Ratio to predict decline in renal function in people with Diabetes

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BACKGROUND

The global epidemic of chronic kidney disease (CKD) is a significant public health issue affecting up to 10% of the adult population in the United Kingdom . Diabetes mellitus (DM) remains the most common cause of end-stage renal failure (ESRF) in the developed world and diabetic nephropathy the leading specific primary renal diagnosis for patients commencing renal replacement therapy (RRT) in the UK .

The increased cardiovascular risk and premature mortality engendered by the combination of diabetes and CKD imposes a significant burden on both patients and health care resources.

In the UK until recently the mainstay of screening for CKD in the diabetic population was based on annual urine albumin : creatinine ratio (ACR) and serum creatinine levels. New National Institute for Clinical Excellence (NICE) guidelines published in September 2008 recommend annual assessment of eGFR and ACR in line with the United States National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (NKF KDOQI) and the American diabetes association (ADA) who both recommend annual testing for microalbuminuria and serum creatinine for estimation of glomerular filtration rate (GFR) in all adults with diabetes regardless of the degree of urine albumin excretion to aid early detection and prevention of progression in patients with early kidney disease.

Progression of DKD in single large populations is not well described. Decline in eGFR varies considerably between individuals with diabetes; ranging from < 1 ml/min/year in slowly progressive disease to between 10-18 ml/min/year in more rapidly progressive kidney disease. Somewhat surprisingly given the high prevalence of type 2 DM most of the observational data regarding the epidemiology of progression of DKD is sparse. Much of our current understanding comes from studies in type I diabetics, small investigative cohorts or limited to particular ethnic group.

AIMS OF THE STUDY

Progression of diabetic kidney disease within a single population, with predictive modeling, has not been well described .The aim of this study was to investigate the rate of progression of chronic kidney disease (CKD) in people with diabetes according to their estimated glomerular filtration rate (eGFR) and presence of albuminuria, in line with NICE, ADA and K/DOQI guidelines.

METHODS

Data for this longitudinal study were collected using a population based district diabetes register in Salford, Greater Manchester, UK. The Salford diabetes Electronic Patient Record (EPR) is a continuously updated electronic health care system which assimilates information from primary and secondary care. It was used to obtain data between 2001-2007 on all adults with diabetes in Salford district where both an eGFR (calculated using MDRD formula) and ACR were available.

Patients were classified as normoalbuminuric if baseline measurement of ACR was <2.5mg/mmol in men or <3.5mg/mmol in women, microalbuminuric if ACR was 2.5-25mg/mmol in men or 3.5-35mg/mmol in women and macroalbuminuric if ACR was >25mg/mmol in men and >35mg/mmol in women.

For the predictive progression of diabetic kidney disease we fitted a longitudinal mixed effect dynamic regression model to the data (See below). Results are presented as parameter estimates ± standard errors (table 1).The first measurement of ACR was used as we have shown that this measurement is consistent with following measurements within the first 3 months in this cohort (Plot 1).

$$Y_{ij} = \alpha_1 \text{ If(Type 1 diabetes)} + \alpha_2 \text{ If(Type 2 diabetes)} + \text{alpha\_3 If(male)} + \alpha_4(\text{duration diabetes}) + \alpha_5(\text{Age at baseline}) + \alpha_6(\text{longitudinal effect with time}) + U_i + \text{integral} + Z_{ij}.$$

The model was fitted to each of the 3 classifications of ACR allowing a different model mean for each group. The dynamic part of the model allows us to make robust predictions of population average rate of change in eGFR with time, while allowing for correlations between repeated measurements of eGFR within individual subjects. The parameters were estimated, and inference was obtained by maximum likelihood

RESULTS

For the analysis of the population average progression of eGFR, biochemical as well as ACR data and drug prescribing were available in 4082 people with mean age 59.2 years, 57.2% were male and 55.2% non-smokers.
2832 were normoalbuminuric of which 283 (10%) had type 1 and 2549 (90%) type 2 DM.
1059 were microalbuminuric of which 75 (7.1%) had type 1 and 984 (92.9%) type 2 DM.
191 were macroalbuminuric of which 17 (8.9%) had type 1 and 174 (91.1%) type 2 DM.

Plot 1: Plots for First ACR measurement vs Second ACR measurement in cohort

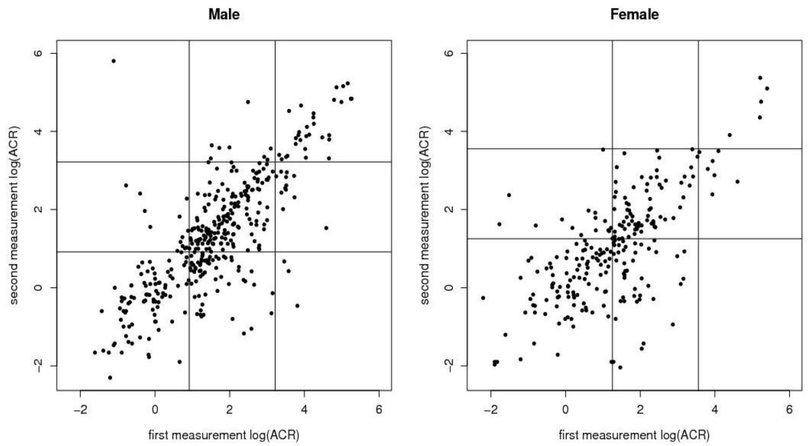


Table 1: Parameter estimates from dynamic regression model

	Normoalbuminuria (N=2832)			Microalbuminuria (N=1059)			Macroalbuminuria (N=191)		
	Parameter estimate	Std.Error	P-value	Parameter estimate	Std.error	P-value	Parameter estimate	Std.Error	P-value
Type1Diabetes	4.760	0.022	<0.0001	4.472	0.186	<0.0001	4.206	0.283	<0.0001
Type2Diabetes	4.828	0.025	<0.0001	4.091	0.108	<0.0001	4.423	0.294	<0.0001
Gender(Male)	0.095	0.010	<0.0001	0.274	0.117	0.0193	NS	NS	NS
Duration Diabetes (yrs)	-0.002	0.001	<0.0389	NS	NS	NS	NS	NS	NS
Age at first eGFR measurement	-0.010	0.0004	<0.0001	NS	NS	NS	NS	NS	NS
Yearly progression log eGFR	-0.004	0.001	<0.0001	-0.017	0.002	<0.0001	-0.055	0.010	<0.0001

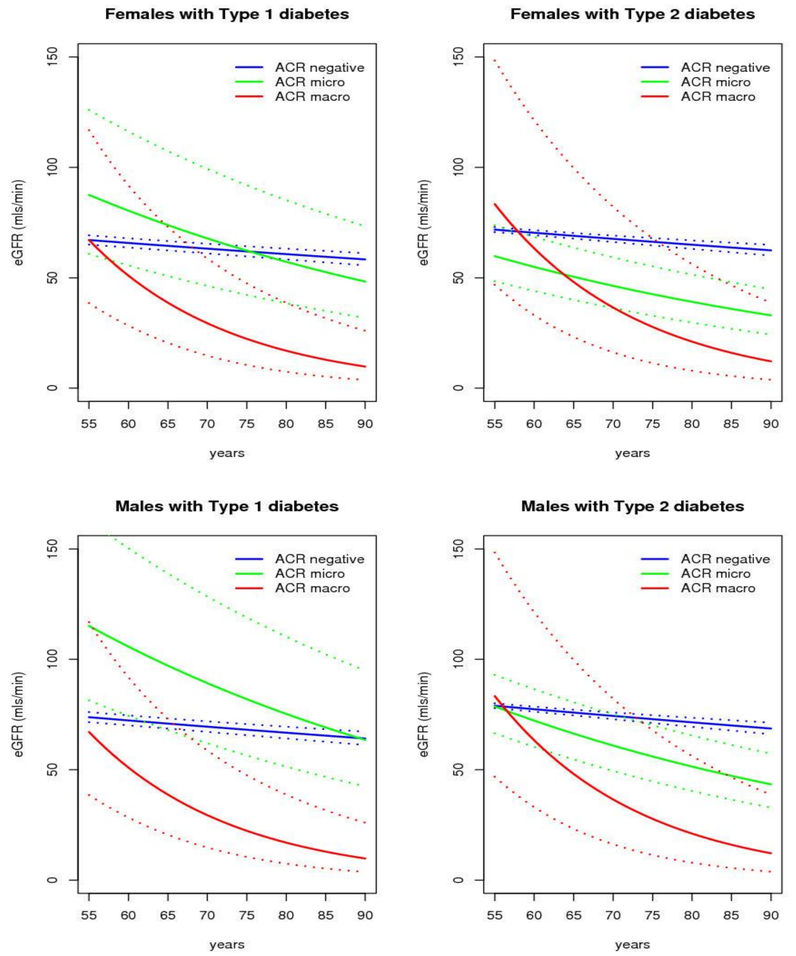
Males with normoalbuminuria and microalbuminuria had a statistically significantly higher eGFR (PE 0.095, 0.274, P<0.0001). This was not observed in people with macroalbuminuria. In the normoalbuminuric group the duration of diabetes was associated with a lower initial eGFR at 0.2% per year(PE -0.002, P=0.0389).

Similarly in the normoalbuminaemic cohort the later the first measurement of eGFR in this cohort the lower the expected eGFR by 1% per year (PE-0.010, P<0.0001).

The longitudinal effect over time revealed that on average, eGFR in people with diabetes and normoalbuminuria decline at 0.4% per year, those with microalbuminuria at 1.7% per year and macroalbuminuria at 5.5% per year.

When substituting the parameter estimates in table 1 into the model for both male and female patients with type 2 diabetes starting at age 55, the average predictive decline in eGFR can be plotted against time (Plot 2)

Plot 2:Predicted progression of eGFR in people with type 1 and 2 diabetes according to presence / absence of albuminuria



CONCLUSIONS

The longitudinal effect of time on eGFR showed that individuals with diabetes and macroalbuminuria have an estimated 13.75x more rapid decline in renal function than those without albuminuria (5.5% per annum vs 0.4% per annum).

Individuals with microalbuminuria also have a significantly increased estimated rate of decline of eGFR (3.3x greater) compared to people with normoalbuminuria .

This study provides robust estimates of progression of CKD in a large diabetic population, enabling clinicians to more accurately predict decline in renal function in patients with diabetes based on ACR and eGFR measurements.

Using this dynamic regression model in individual patients with DM will aid physicians in estimating progression of CKD, enabling them to identify those with more rapidly progressive disease and target these individuals for therapeutic intervention at the earlier stages of CKD.

We believe in line with K/DOQI ,NICE and ADA guidelines it is essential to screen diabetic people for renal disease with annual eGFR and ACR measurements.