Microalbuminuria and Reduced Glomerular Filtration Rate are independent factors for mortality in people with Diabetes Mellitus

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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 [1]. Diabetes mellitus 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 [2].

Globally it is projected that 220 million people will have diabetes by 2010 rising to 330 million in 2025 with type 2 diabetes accounting for 90% of cases worldwide[3].

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. Currently in the UK the mainstay of screening for CKD in the diabetic population is based on annual urine albumin : creatinine ratio (ACR) and serum creatinine levels.

The United States National Kidney Foundation Kidney Disease Outcomes Quality Initiative guidelines (NKF KDOQI) and the American Diabetes Association (ADA) both recommend annual testing for microalbuminuria and serum creatinine at least annually 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 [4;5].

We have previously shown in a diabetic cohort that 19.4% of normoalbuminaemic diabetic patients have a estimated glomerular filtration rate < 60 ml/min (eGFR); of those 54.7% had a "normal" creatinine ≤ 120µmol/l [6].

AIMS OF THE STUDY

There is a paucity of population based studies in the diabetic population concerning cardiovascular risk and mortality based on eGFR and ACR measurements in accordance with the NKF guidelines .

The aim of this study was to assess mortality, cardiovascular disease and progression of CKD in people with diabetes according to their eGFR and presence of albuminuria.

METHODS

Data were collected on all people with diabetes living in Salford UK, where a baseline eGFR (2001/02) could be calculated using the 4 variable MDRD formula (Modification of Diet in Renal Disease) and ACR were available.

Patients were classified as albuminuric if baseline ACR was >3.5mg/mmol.
Data were linked to the Salford diabetes information system to obtain further demographic, metabolic and prescribing data (available for~60%). Four groups were selected based upon eGFR and ACR.

1. eGFR>60ml/min/1.73m² with normoalbuminuria
2. eGFR>60ml/min/1.73m² with albuminuria
3. eGFR<60 ml/min/1.73m²with normoalbuminuria
4. eGFR<60 ml/min/1.73m²with albuminuria

Data were analysed using SPSS version 15 (SPPS Inc, Chicago, IL, USA) and the R open-source software system. Results are presented as mean ± SD for normally distributed data and percentages for categorical variables. Analysis was adjusted for age, smoking, baseline eGFR and ACR. Chi-square and logistic regression were used for categorical data. ANOVA and linear regression were used for continuous variables.

We also fitted a longitudinal mixed effect dynamic regression model to the data. Patients were classified as albuminuric if 2 out of 3 first measurements of ACR were >2.5mg/mmol in men and > 3.5mg/mmol in women. The model fitted includes interaction between each of the parameters and the classification of albumin creatinine ratio, allowing for different parameters for each group of positive and negative ACR. The dynamic part of the model allows us to make predictions of individuals rate of change in eGFR with time (95%CI). The parameters were estimated, and inference was obtained by maximum likelihood.

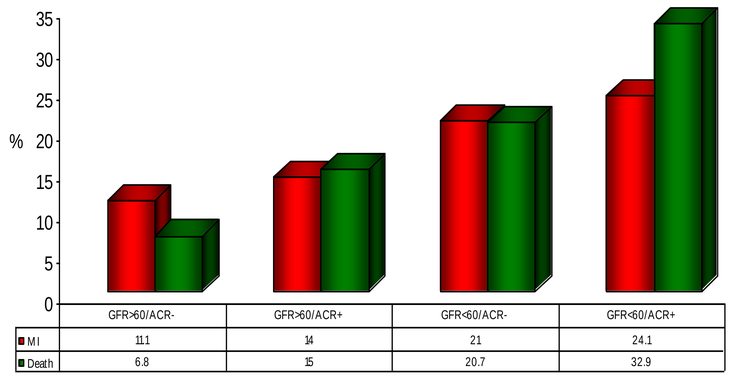
RESULTS

Data were available for 2565 people (n=1557, 414, 357, 237; groups 1-4 respectively).
Mean age was 59, 60, 71and 70 yrs in groups 1-4 (p<0.001), people in groups 3 and 4 being older and with a longer duration DM (p<0.002) than 1 and 2.
There was no difference in usage of ACE / AT2 in groups with or without albuminuria.
Mortality, myocardial infarction (MI) and need for renal replacement therapy (RRT) increased from groups 1 to 4.
Analysis of register data in this cohort showed measurements for albuminuria was recorded in only 39.2% of subjects (2565/6542) at baseline.

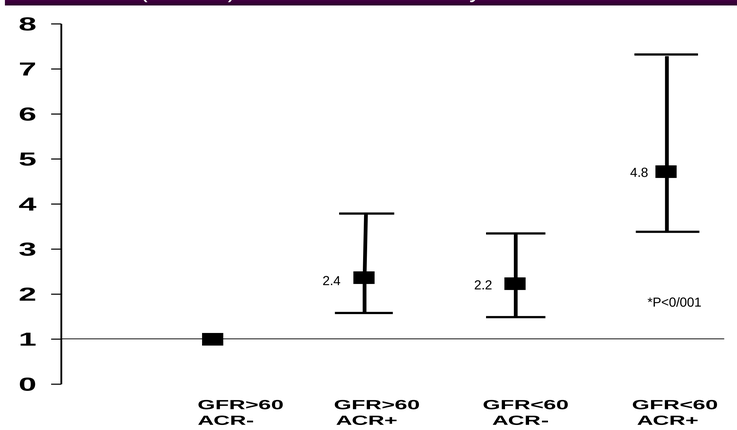
Baseline characteristics of cohort stratified by eGFR and ACR

Group	1 eGFR>60mls/min ACR <3.5mg/mmol (n=1529)	2 GFR>60mls/min ACR >3.5mg/mmol (n=410)	3 GFR<60mls/min ACR <3.5mg/mmol (n=345)	4 GFR<60mls/min ACR >3.5mg/mmol (n=222)	P values
Age (yrs)	59.3 ±13.1	60.8± 13.3	71.3± 9.8.	70.4± 12.7	<0.001
Male Sex (%)	60.4	67.9	36.7	52.3	<0.001
Smoking Never (%)	62.1	55.1	69.9	62.6	NS
Duration DM (mths)	57.9 ± 77.7	53.8 ± 71.4	67.5 ± 92.4	70.3 ± 97.1	<0.002
Baseline eGFR	81.4 ± 13.8	82.0 ± 15.7	48.3 ± 10.0	42.3 ± 12.9	<0.001
Cholesterol (mmol/l)	4.1 ± 1.0	4.1 ± 1.1	4.0 ± 1.0	4.1 ± 1.2	NS
Hba1c (%)	7.7 ± 1.6	8.1 ± 1.9	7.5 ± 1.5	7.8 ± 1.9	<0.001
SBP (mmHg)	132 ± 17	136 ± 20	135 ± 19	138 ± 22	<0.001
DBP (mmHg)	74 ± 10	74 ± 11	72 ± 12	72 ± 12	<0.001
Drugs avail (%)	66.1	64.0	61.3	59.1	NS
ACE (%)	65.6	52.9	49.0	46.4	NS
MI (%)	11.1	14.0	21.0	24.1	<0.001
Death (%)	6.8	15.0	20.7	32.9	<0.001
RRT (%)	0	0.5	1.4	6.3	<0.001

End-point Myocardial Infarction or Death



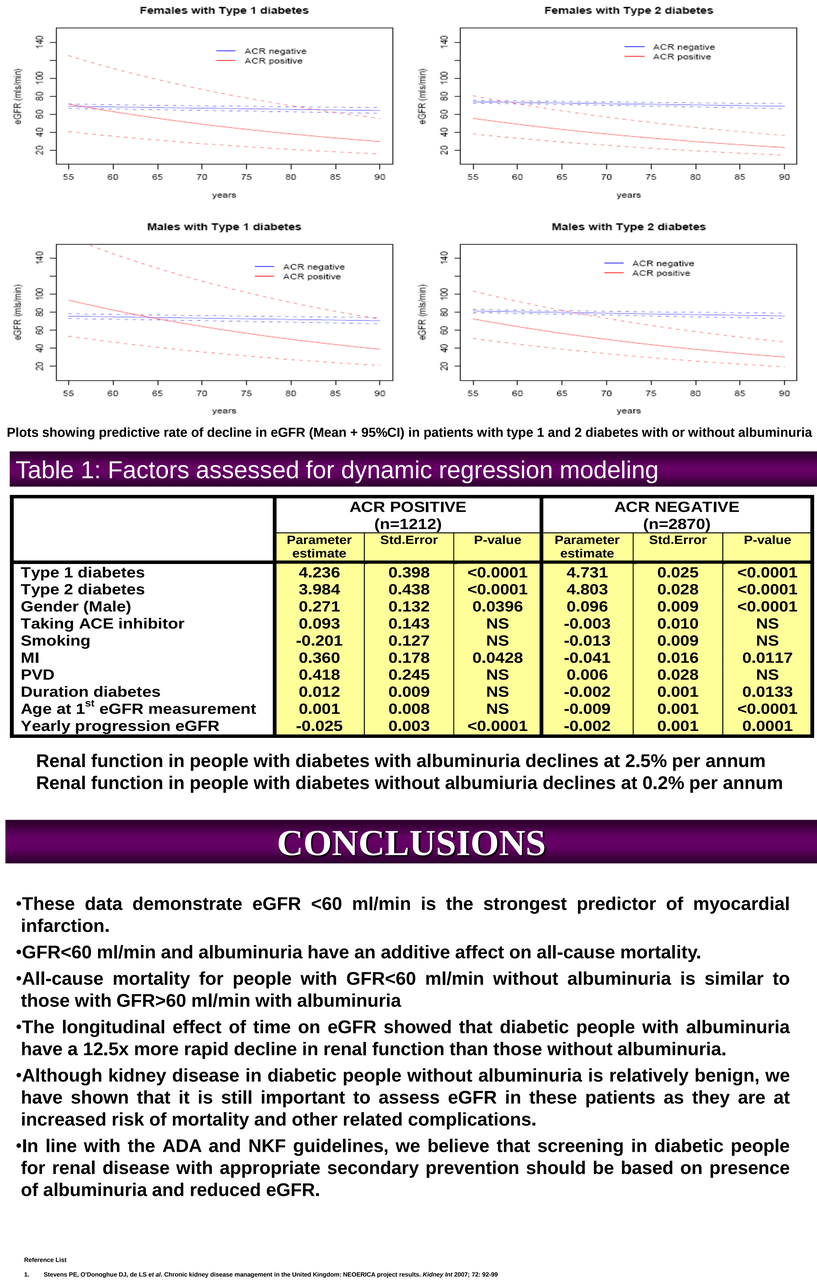
Odds Ratio (95% CI) for All-Cause Mortality



All-cause mortality for people with GFR<60 ml/min without albuminuria is similar to those with GFR>60 ml/min with albuminuria

For the analysis of the population average progression of eGFR, biochemical as well as ACR data and drug prescribing were available in 4082 people including those patients with results not available at baseline.
1212 patients were ACR positive, of which 92 had Type 1 diabetes and 1120 had Type 2 diabetes.
2870 patients were ACR negative of which 283 with Type 1 diabetes and 2587 with type 2 diabetes.

Plots of population average progression of eGFR showing the rate of change of eGFR with time in people with type 1 and 2 diabetes according to presence / absence of albuminuria



Plots showing predictive rate of decline in eGFR (Mean + 95%CI) in patients with type 1 and 2 diabetes with or without albuminuria

Table 1: Factors assessed for dynamic regression modeling

	ACR POSITIVE (n=1212)			ACR NEGATIVE (n=2870)		
	Parameter estimate	Std.Error	P-value	Parameter estimate	Std.Error	P-value
Type 1 diabetes	4.236	0.398	<0.0001	4.731	0.025	<0.0001
Type 2 diabetes	3.984	0.438	<0.0001	4.803	0.028	<0.0001
Gender (Male)	0.271	0.132	0.0396	0.096	0.009	<0.0001
Taking ACE inhibitor	0.093	0.143	NS	-0.003	0.010	NS
Smoking	-0.201	0.127	NS	-0.013	0.009	NS
MI	0.360	0.178	0.0428	-0.041	0.016	0.0117
PVD	0.418	0.245	NS	0.006	0.028	NS
Duration diabetes	0.012	0.009	NS	-0.002	0.001	0.0133
Age at 1st eGFR measurement	0.001	0.008	NS	-0.009	0.001	<0.0001
Yearly progression eGFR	-0.025	0.003	<0.0001	-0.002	0.001	0.0001

Renal function in people with diabetes with albuminuria declines at 2.5% per annum
Renal function in people with diabetes without albumiuria declines at 0.2% per annum

CONCLUSIONS

- These data demonstrate eGFR <60 ml/min is the strongest predictor of myocardial infarction.
- GFR<60 ml/min and albuminuria have an additive affect on all-cause mortality.
- All-cause mortality for people with GFR<60 ml/min without albuminuria is similar to those with GFR>60 ml/min with albuminuria
- The longitudinal effect of time on eGFR showed that diabetic people with albuminuria have a 12.5x more rapid decline in renal function than those without albuminuria.
- Although kidney disease in diabetic people without albuminuria is relatively benign, we have shown that it is still important to assess eGFR in these patients as they are at increased risk of mortality and other related complications.
- In line with the ADA and NKF guidelines, we believe that screening in diabetic people for renal disease with appropriate secondary prevention should be based on presence of albuminuria and reduced eGFR.

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