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Comparison of the Rate of Renal Function Decline in Non-Proteinuric patients with and without Diabetes

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Abstract

Background—Patients with diabetes and chronic kidney disease (CKD) without proteinuria are often thought to have a cause of CKD other than diabetes. It was hypothesized that if this is true, the rate of renal function decline should be similar among non-proteinuric patients with and without diabetes.

Methods—Patients seen in the nephrology, endocrinology and general internal medicine clinics at the Medical University of South Carolina between 2008 and 2012 with hypertension and diabetes were identified by ICD9 diagnosis codes. Patients with less than 2 measures of serum creatinine, without urine studies over the study period and with proteinuria were excluded. 472 patients met the inclusion and exclusion criteria and had an initial eGFR between 35 and 80 mL/min/1.73m². The annual rate of decline in eGFR was estimated for each patient from the lowest eGFR in each year by fitting a regression model with random intercept and slope.

Results—In unadjusted analyses the rate of eGFR decline was greater in patients with diabetes than without diabetes (−0.71 vs. −0.30 mL/min/year, p=0.03). After adjusting for age, race, gender, baseline eGFR and use of renin-angiotensin aldosterone system blockade, the rate of decline was

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Conflicts of Interest

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still greater among patients with diabetes than among those without diabetes (-0.68 vs. -0.36 mL/min/year, $p=0.03$).

Conclusions—Patients with diabetes had more rapid decline in kidney function compared to individuals without diabetes, in spite of the absence of proteinuria. These results suggest that even in the absence of proteinuria, diabetes may be associated with CKD.

Keywords

diabetes; renal function decline; chronic kidney disease; proteinuria; hypertension

Introduction

Diabetic kidney disease has significant public health implications. The prevalence of diabetic kidney disease (DKD) in the United States population has increased to 3.3% according to the National Health and Nutrition Examination Survey (NHANES 2005–2008) (1). People with diabetes were considered to have DKD if they had a urine albumin to creatinine ratio (ACR) ≥ 30 mg/g and/or glomerular filtration rate < 60 mL/min/1.73 m². Diabetes is the leading cause of chronic kidney disease (CKD) and end stage renal disease (ESRD) in the US. Patients with ESRD secondary to DKD constituted 44% of incident ESRD patients in the US in 2012 (2). The natural history of DKD as defined from longitudinal studies in the 1980s included 5 stages where the presence of proteinuria was considered a prerequisite for the diagnosis of DKD (3). The five sequential stages were defined as 1) hyperfiltration; 2) morphologic changes; 3) albuminuria in the setting of normal or increased GFR; 4) proteinuria and loss of GFR; and 5) ESRD. The characterization of the stages of DKD was based partly on small longitudinal studies in the 1980s which showed the role of microalbuminuria as predictor of clinical nephropathy. A study by Mogensen et al. (4) on 44 patients with type 1 diabetes with no clinical proteinuria, found that microalbuminuria predicts the development of DKD. In addition to having higher levels of albuminuria, patients who developed proteinuria had a higher glomerular filtration rate. Viberti et al. in a study (5) of 87 patients with type 1 diabetes showed that those with a higher albumin excretion rate at the beginning of the study were most likely to develop frank proteinuria. Microalbuminuria was associated with a 60 to 85 percent increase in risk of development of overt proteinuria within 6 to 14 years. Based on these studies and others, albuminuria is believed to be an early marker for progression of DKD.

More recently, however, it has been established that a non-albuminuric or non-proteinuric type of kidney disease is also prevalent in patients with type 1 and 2 diabetes. A number of studies have demonstrated that CKD can develop in patients without albuminuria or proteinuria. In the United Kingdom Prospective Diabetic Study which included 4031 subjects with type 2 diabetes, 38% developed albuminuria and 29% developed CKD over a median of 15 years of follow up. CKD was defined as Cockcroft-Gault estimated creatinine clearance < 60 mL/min or doubling of plasma creatinine. Among participants who developed CKD, half of them did not have preceding albuminuria and 39% did not develop albuminuria at any time during the study (6). In another study (7), 79 patients with type 1 diabetes and new onset microalbuminuria were followed for 12 years, 23 subjects developed advanced CKD (defined as GFR < 60 mL/min/1.73 m² or ESRD). Only 12 of the 23

progressing patients developed proteinuria which generally did not precede the progression to advanced kidney disease. Other longitudinal studies (8–13) in type 1 and type 2 diabetes, showed the presence of renal function loss without clinical proteinuria.

In daily practice, renal insufficiency in diabetic subjects with no albuminuria or proteinuria is sometimes labeled as non-diabetic kidney disease. It was hypothesized that if this is true, the rate of decline of renal function should be similar among non-proteinuric patients with and without diabetes. Conversely, if the rate of renal function decline is more rapid in non-proteinuric patients with diabetes than in patients without diabetes, it would suggest that diabetes may be causally related to the loss of renal function. In this study, the rate of decline of renal function over a 5-year period was compared between non-proteinuric patients with and without diabetes. All patients had hypertension.

Methods

The electronic medical record (EMR) database was searched for adult patients from the nephrology, endocrinology and general internal medicine clinics at the Medical University of South Carolina (MUSC) who were seen between 2008 and 2012, with an initial mean estimated glomerular filtration rate (eGFR) greater than or equal to $35 \text{ mL/min/1.73 m}^2$ selected using the MDRD eGFR field in the EMR. The search identified 5035 unique patients. January 2008 was chosen as a starting date because MUSC laboratories started to use isotope dilution mass spectrometry (IDMS) traceable creatinine assays for creatinine measurement in mid-December 2007. Patients with an ICD9 diagnosis code for autosomal dominant polycystic kidney disease (ADPKD) were excluded. Patients without a diagnosis code for hypertension were excluded. Other data collected from the EMR included age, gender, race, all serum creatinine values and laboratories related to urine protein or albumin concentration (dipstick, laboratory measurements) over the 5-year period, the use of ACE inhibitors, angiotensin II receptor blockers (ARBs) and spironolactone. Patients who had no urine studies over a 5-year period or had measured serum creatinine values in less than 3 years were excluded. Patients with proteinuria were excluded. Proteinuria was defined as positive dipstick without pyuria (urine white blood cells more or equal to 5), or urine protein to creatinine ratio greater than or equal to 0.2, or 24 hour urine protein greater than or equal to 0.2 gram. Patients with microalbuminuria (ACR 30–300 mg/g) were included in the study. The yearly eGFR for each patient was calculated from the lowest serum creatinine in each year using the CKD-EPI formula.

856 patients had an initial eGFR between 35 and $80 \text{ mL/min/1.73 m}^2$ calculated by CKD-EPI. Patients with eGFR less than $35 \text{ mL/min/1.73 m}^2$ or greater than $80 \text{ mL/min/1.73 m}^2$ were excluded. Twenty-one patients were included in the initial selection because they had an MDRD calculated eGFR greater than or equal to 35 but were excluded because their CKD-EPI calculated eGFR was less than 35. The annual rate of decline in eGFR was estimated by fitting a regression model with random intercept and slope (14). For each subject, a linear regression model of time on GFR (least-squares method) was created, and the slope of the regression line was used to estimate the subject's change in eGFR over time. Results are given as the mean $\pm$ SD unless otherwise stated. The significance of differences between the two groups was determined by Chi-Square tests (or Fisher's exact tests) for

categorical variables and the unpaired *t* test for continuous variables. Multiple linear regression was used to analyze the associations of variables with GFR slope values (or baseline GFR values) controlling for potential confounders. P values under 5% (two-tailed) were considered significant. All analyses were performed with the statistical software package SAS v9.3 (Cary, NC).

The primary outcome measure was a comparison of the annual rate of decline between patients with a diagnosis of hypertension and diabetes to the rate of decline in patients with hypertension who did not have diabetes. The secondary outcome measure was the fraction of patients with early renal function decline defined as rate of eGFR decline $\geq 3.3\%$ per year.

Results

472 patients with an eGFR between 35 and 80 and without proteinuria met the inclusion and exclusion criteria (figure 1). 38% of subjects were male, 37% were African American and 65% had diabetes. Baseline characteristics of patients in each group are shown in Table 1. Baseline eGFR was not different between groups (64 ± 12 in non-diabetic subjects vs. 63 ± 12 mL/min/1.73 m² in diabetic subjects, $P = 0.42$). Patients with diabetes were more likely to be African American but were not different in age or gender. They were also more likely to have microalbuminuria levels tested and to have microalbuminuria but were not more likely to be prescribed ACE inhibitors, ARBs or spironolactone. 180 patients (38%) were tested for microalbuminuria of whom 23% ($n = 41$) were positive, all of whom had diabetes. The number of years in which an eGFR value was available per patient over a 5-year period was not different between the 2 groups (3.9 ± 1.1 in non-diabetic group vs. 4.1 ± 1.1 in diabetic group, $P = 0.08$). The primary goal of the study was to compare the rate of decline in eGFR between groups. The distribution of the overall rate of eGFR decline in the whole population is shown in Figure 2. In unadjusted analyses the rate of eGFR decline across a 5-year period was greater in patients with diabetes than without diabetes (-0.71 mL/min/year, 95% CI $(-0.93, -0.49)$ vs. -0.30 mL/min/year, 95% CI $(-0.60, 0.00)$, $P = 0.03$) (figure 3a). After adjusting for age, race, gender, baseline eGFR and the use of ACE inhibitors, ARBs and spironolactone, the rate of eGFR decline was greater among individuals with diabetes than in individuals without diabetes (-0.68 mL/min/year, 95% CI $(-0.85, -0.51)$ vs. -0.36 mL/min/year, 95% CI $(-0.59, -0.13)$, $P = 0.03$) (figure 3b). When subjects with microalbuminuria were excluded, the rates of decline were -0.64 in diabetic patients vs. -0.34 mL/min/year in patients without diabetes ($P = 0.05$) after adjusting for age, race, gender, baseline eGFR and the use of ACE inhibitors, ARBs and spironolactone. In each group, the fraction of patients who were rapid decliners, defined as a decline in eGFR $\geq 3.3\%$ per year, was examined (14). This value to identify patients with early renal function decline has been used by a number of groups to identify patients who have a greater than expected rate of renal function decline (7, 15–16). There were more decliners among subjects with diabetes than among those without diabetes (34.43% vs. 21.56%, $P = 0.003$). The fraction of patients with a decline in eGFR > 3.5 mL/min/year (17) was also examined and the percent of decliners among subjects with and without diabetes was similar (7.21% vs. 5.99%, $P = 0.61$).

Since risk of renal function loss has been associated with variants in the ApoL1 gene, which is found primarily in African American patients, the rate of decline of eGFR in African Americans was compared with that of white patients. In adjusted analyses, the rate of eGFR decline in the diabetic group was similar in whites and African Americans (-0.70 mL/min/year, 95% CI $(-0.94, -0.45)$ vs. -0.73 mL/min/year, 95% CI $(-1.01, -0.45)$, $P = 0.85$).

Finally, the effect of baseline eGFR on the rate of decline was examined. 36.7% of subjects with diabetes had a baseline eGFR of 60 mL/min/1.73 m² or less. In adjusted analyses the rate of eGFR decline in the diabetic group was much greater in subjects with a baseline eGFR of 60 mL/min/1.73 m² or lower than in those with a baseline eGFR greater than 60 (-2.06 mL/min/year, 95% CI $(-2.38, -1.74)$ vs. 0.07 mL/min/year, 95% CI $(-0.18, 0.32)$, $P < 0.0001$) (figure 4a). In those without diabetes, 38.3% of subjects had a baseline eGFR of 60 mL/min/1.73 m² or less. The rate of eGFR decline in those without diabetes was also much greater in subjects with a baseline eGFR of 60 mL/min/1.73 m² or lower than in those with a baseline eGFR greater than 60 (-1.61 mL/min/year, 95% CI $(-2.00, -1.22)$ vs. 0.52 mL/min/year, 95% CI $(0.22, 0.82)$, $P < 0.001$) (figure 4b).

Discussion

In this retrospective analysis of data from a single center EMR, the rate of decline of eGFR over a 5-year period was compared between non-proteinuric hypertensive subjects with and without diabetes. The primary finding was that patients with diabetes have a more rapid rate of renal function decline, even after adjusting for potential confounders. Although albuminuria is neither a sensitive nor a specific marker of progression of diabetic nephropathy, assessing the albumin excretion rate remains a standard parameter of surveillance in clinical practice. In this study only about 53% of subjects with diabetes had been tested for microalbuminuria across a 5-year period and unexpectedly only about 35% of them were on renin-angiotensin system blockade. The low rate of prescriptions for inhibitors of the renin-angiotensin system may be partly accounted for by the fact that many of the patients had eGFR values greater than 60 and did not have proteinuria although they did have hypertension in the setting of diabetes which was described as a compelling indication for the use of ACE inhibitors or ARBs by the JNC 7 guidelines in place during the study time period (18). The rate of decline of eGFR was found to be higher in individuals with diabetes than in those without diabetes before and after adjustment for age, gender, race, baseline eGFR and the use of ACE inhibitors, ARBs and spironolactone. While the rate of decline of renal function was smaller than has been reported, this may be due to the relatively high baseline eGFR value in both groups (mean 63 and 64 mL/min/1.73 m²). When the rate of decline was compared in those with higher baseline eGFR values to those with lower, the rate of eGFR decline was higher in those with a baseline eGFR of 60 mL/min/1.73 m² or less. Furthermore, when the percent of patients who experienced rapid decline was compared between groups, there were more rapid decliners defined by an eGFR decline 3.3%/year (but not by an eGFR 3.5 mL/min/year) among diabetic subjects than among non-diabetic subjects. These results suggest that even in the absence of proteinuria, diabetes may be associated with a loss of renal function.

Decline in renal function prior to albuminuria or proteinuria has been observed in longitudinal studies in type 1 and 2 diabetes in different population groups (8–13) although these studies did not compare the rate of decline in patients with diabetes to patients without. Further support for more rapid decline of renal function in diabetic subjects prior to the development of albuminuria can be found in the 2013 USRDS annual data report on Chronic Kidney Disease in the general population. Using data from the 2005–2010 NHANES analyses, the report shows that 19.3% of patients with diabetes have an eGFR < 60 without albuminuria while 12.9% of patients with hypertension meet those criteria (19). These data from a large cohort support the hypothesis that diabetic patients have more rapid decline of renal function compared to a similar population of non-diabetic patients, even in the absence of proteinuria. These results have important clinical implications, as attributing non-proteinuric CKD to a cause other than diabetic nephropathy may lead to a delay in diagnosing and modifying the progression of the kidney disease. A potential confounder in this study is the larger number of African American patients in the diabetic group in our cohort compared to the group without diabetes. Recently, variants in the ApoL1 gene have been identified which place patients at a higher risk of progression of kidney disease (20). Pathogenic variants in ApoL1 are found almost exclusively in African Americans. Therefore, the increased rate of decline in the diabetic group could potentially be accounted for by more pathological ApoL1 variants in the diabetic group since it had a higher proportion of African Americans. However, in this study there was no evidence that the rate of decline in African American patients with diabetes was more rapid than that seen in whites, so ApoL1 variants are unlikely to account for the differences in rate of decline between those with and without diabetes.

A study by Yokoyama (21) in a Japanese population with a median follow-up time of 3.1 year, showed a higher rate of decline in eGFR in non-proteinuric diabetic subjects with CKD than in non-diabetic subjects. He also found that a higher HbA1C contributed to an accelerated decline in eGFR in diabetic patients. Microalbuminuria was checked in diabetic individuals only and those with microalbuminuria were excluded from the study. He separated diabetic and non-diabetic subjects into decliners and non-decliners, based on a GFR slope of less than $-4.0\%/year$. The proportion of decliners was not statistically different between groups (30.1% vs. 26.8%, $P=0.36$). In his study, 76% of non-diabetic patients and 51% of diabetic patients had hypertension making it difficult to assess the role of hypertension in progression. In contrast, the population in this study was selected to include only those with hypertension.

About half of patients with type 2 diabetes may have CKD without proteinuria (6,8). The pathogenesis of diabetic nephropathy is complex and not fully understood. Glomerular lesions typical of diabetic nephropathy have been described in longstanding microalbuminuric patients with type 1 diabetes and a reduced GFR. Why some diabetic subjects have decline in renal function associated with normoalbuminuria or microalbuminuria without the presence of macroalbuminuria is unclear as renal biopsy is commonly not performed in these patients. It has been hypothesized that CKD in diabetic patients without proteinuria could be due to atubular glomeruli or tubular atrophy and interstitial fibrosis rather than classical diabetic glomerulosclerosis (8). A study on 375 patients with type 2 diabetes and normoalbuminuria, microalbuminuria and

macroalbuminuria was conducted to investigate the role of intrarenal vascular disease in the pathogenesis of nonalbuminuric renal insufficiency and showed that patients with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$ had a higher resistance index of the renal interlobar arteries (estimated by renal duplex scan) compared to patients with $\text{eGFR} \geq 60 \text{ mL/min/1.73 m}^2$. In the group with $\text{eGFR} < 60 \text{ mL/min/1.73 m}^2$, the resistance index was independent of albumin excretion rates (22). Caramori et al. (23) reported the presence of diabetic glomerulosclerosis on the renal biopsy in 23 patients with type 1 diabetes who had CKD and normoalbuminuria. Budhiraja et al. (24) examined renal tissue from subjects with impaired renal function who underwent nephrectomy for renal cancer and found that diabetic subjects had advanced diabetic lesions even in the absence of albuminuria or proteinuria. Tubules and tubular-interstitium was relatively well preserved. They concluded that diabetic glomerulosclerosis may develop before the proteinuria can be detected and postulated that the absence of proteinuria could be due to the reabsorption of protein by the well preserved tubules. Although the causes of renal function loss in non-proteinuric diabetic patients remain to be established, there is good evidence that CKD may occur in diabetes in the absence of proteinuria.

This study has several limitations. This is a retrospective database review, so data were not collected prospectively and missing values occurred. It was not possible to adjust for BMI because weight and height were not available on all the subjects. Coding information to determine the type of diabetes that the patients had was not available; however, given the mean age of 69, it is likely that the vast majority had type 2 diabetes. It was relied on a single urine test per patient to screen for proteinuria and the test was a urinalysis or urine protein to creatinine ratio or albumin to creatinine ratio or 24 hour urine protein. Nevertheless, this study showed more rapid decline in kidney function in non-proteinuric CKD with diabetes compared to individuals without diabetes. These results suggest that even in the absence of proteinuria diabetes may be associated with a loss of renal function. These findings have important clinical implications for early diagnosis and treatment.

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Figure 1.

Patient selection flow chart. 5035 patients were identified in the initial search of the electronic record who were seen in the nephrology, endocrinology or general internal medicine clinics between 2008 and 2012, with an estimated glomerular filtration rate (eGFR) greater than or equal to 35 mL/min/1.73 m². From this group we selected 472 patients who met all inclusion and exclusion criteria for analysis of the rate of decline of eGFR.

Figure 2.
Distribution of slopes of eGFR decline (mL/min/year) in the total population.

**Unadjusted rate of eGFR change
(mL/min/year)**

Figure 3.

Figure 3a. Rate of eGFR change in patients with and without diabetes (DM) prior to adjustment. In diabetic group the slope is -0.71 mL/min/year 95% CI $(-0.93, -0.49)$. In non-diabetic group the slope is -0.30 mL/min/year 95% CI $(-0.60, 0.00)$; $P = 0.03$.

Figure 3b. Rate of eGFR change in patients with and without diabetes (DM) after adjustment. Adjustment was made for baseline eGFR, age, race, gender, ACE inhibitors, ARBs, spironolactone. In diabetic group the slope is -0.68 mL/min/year 95% CI $(-0.85, -0.51)$. In non-diabetic group the slope is -0.36 mL/min/year 95% CI $(-0.59, -0.13)$; $P = 0.03$.

Figure 4.

Figure 4a. Rate of eGFR change among diabetic patients with a baseline eGFR of 60 mL/min/1.73 m² or lower versus those with a baseline eGFR greater than 60 (−2.06 mL/min/year, 95% CI (−2.38, −1.74) vs. 0.07 mL/min/year, 95% CI (−0.18, 0.32), $P < 0.0001$).

Figure 4b. Rate of eGFR change among non diabetic patients with a baseline eGFR of 60 mL/min/1.73 m² or lower versus those with a baseline eGFR greater than 60 (−1.61 mL/min/year, 95% CI (−2.00, −1.22) vs. 0.52 mL/min/year, 95% CI (0.22, 0.82), $P < 0.001$).

Table 1

Baseline Characteristics of Subjects with and without Diabetes

Variable	HTN (n= 67)	DM and HTN (n= 305)	P-value
Age (yr)	69±11	69±10	0.67
Male (%)	37	39	0.59
AA (%)	25	43	<0.001
Baseline eGFR (mL/min/1.73 m ²)	64±12	63±12	0.42
Microalb. Tested (%)	11	53	<0.001
Microalb. Positive* (%)	0	25	0.01
ACE inhibitors (%)	25	22	0.48
ARBs (%)	11	17	0.10
Spirolactone (%)	6	6	0.92

Values are Mean ± Standard Deviation except when indicated.

* percentage of positive Microalbuminuria in tested patients in each group.

Abbreviations: AA, African American; ARBs, Angiotensin II Receptor Blockers; DM, Diabetes Mellitus; eGFR, estimated Glomerular Filtration Rate; HTN, Hypertension; Microalb., Microalbuminuria; yr, year.