Markers of endothelial dysfunction and inflammation predict progression of diabetic nephropathy in African Americans with type 1 diabetes

Monique S. Roy[1], Malvin N. Janal[2], Juan Crosby[3] and Robert Donnelly[3]

[1]Institute of Ophthalmology and Visual Science, UMDNJ, Rutgers University, Newark, New Jersey, USA; [2]Department of Epidemiology and Health Promotion, NYU College of Dentistry, New York, New York, USA and [3]Department of Pathology and Laboratory Medicine and NJMS Molecular Resource Facility, Rutgers University, Newark, New Jersey, USA

African Americans with early-onset type 1 diabetes mellitus are at a high risk for severe diabetic nephropathy and end-stage renal disease. In order to determine whether baseline plasma levels of inflammatory markers predict incidence of overt proteinuria or renal failure in African Americans with type 1 diabetes mellitus, we re-examined data of 356 participants in our observational follow-up study of 725 New Jersey African Americans with type 1 diabetes. At baseline and 6-year follow-up, a detailed structured clinical interview was conducted to document medical history including kidney dialysis or transplant, other diabetic complications, and renal-specific mortality. Plasma levels of 28 inflammatory biomarkers were measured using a multiplex bead analysis system. After adjusting for baseline age, glycohemoglobin, and other confounders, the baseline plasma levels of soluble intercellular adhesion molecule-1 (sICAM-1) in the upper two quartiles were, respectively, associated with a three- to fivefold increase in the risk of progression from no albuminuria or microalbuminuria to overt proteinuria. Baseline plasma levels of the chemokine eotaxin in the upper quartile were significantly associated with a sevenfold increase in risk of incident renal failure. These associations were independent of traditional risk factors for progression of diabetic nephropathy. Thus, in type 1 diabetic African Americans, sICAM-1 predicted progression to overt proteinuria and eotaxin-predicted progression to renal failure.

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Correspondence: *Monique S. Roy, Institute of Ophthalmology and Visual Science, Rutgers University, UMDNJ, 90 Bergen Street, Room 6164, Newark, New Jersey 07101-1709, USA. E-mail: monique.roy@rutgers.edu*

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African Americans with early-onset type 1 diabetes mellitus are at a high risk for severe diabetic nephropathy and end-stage renal disease.[1–3] For example, in the New Jersey 725 study, 49.8% of type 1 diabetic African Americans had some proteinuria at the baseline examination, 17% progressed over 6 years from no albuminuria to overt proteinuria, and 8.7% progressed to end-stage renal disease.[3] Clinical risk factors for progression of diabetic nephropathy include albumin excretion rate (AER), hypertension, and hyperglycemia.[3] High AER is used clinically as an indicator of progression to overt proteinuria.[4] However, in a significant proportion of type 1 patients, remission from microalbuminuria to normal albumin excretion may occur.[5] Furthermore, renal function may be lost years before proteinuria develops, suggesting an alternative pathway to severe diabetic nephropathy.[5] Thus, there is a need to identify novel predictors of progression of diabetic nephropathy, particularly of advanced chronic kidney disease, in order to better understand the development of diabetic nephropathy and reduce morbidity and mortality from the disease.

In diabetic nephropathy, progressive thickening of the glomerular basement membrane is followed by mesangial cell expansion and gradual progression to glomerulosclerosis and interstitial fibrosis, eventually resulting in renal failure.[6] There is clinical and experimental evidence suggesting that inflammation may be involved in the development or progression of diabetic nephropathy.[7–10] Infiltration of macrophages in the glomeruli and tubular interstitium with overexpression of adhesion molecules and proinflammatory molecules has been documented within the diabetic human kidney and occurs early after induction of experimental diabetes in rat models.[11,12] Compared with diabetic intercellular adhesion molecule (ICAM) $+/+$ mice, ICAM-deficient diabetic mice have lower AER and show less macrophage infiltration of the kidneys, less glomerular hypertrophy, less mesangial matrix expansion, and less fibrosis.[13]

Previously published clinical studies examining the association of inflammatory biomarkers and diabetic nephropathy have been limited by their cross-sectional design, and the few prospective studies have yielded conflicting results.[14–27]

Thus, the purpose of the present study was to use our longitudinal data for the New Jersey 725 cohort to examine whether baseline plasma levels of markers of inflammation or endothelial dysfunction predict progression of diabetic nephropathy and, if so, whether there are different markers of overt proteinuria or renal failure in our African Americans with type 1 diabetes.

RESULTS

Baseline characteristics of the African-American patients by follow-up renal status, progression to overt proteinuria or renal failure, are shown in Table 1. Baseline mean arterial blood pressure (MAP), glycohemoglobin, high-density lipoprotein cholesterol, estimated glomerular filtration rate (eGFR), presence of heart disease or stroke, lower extremity arterial disease (LEAD), and microalbuminuria were associated with an increased risk of progression to overt proteinuria. Older age, longer duration of diabetes, MAP, glycohemoglobin, total cholesterol, low-density lipoprotein cholesterol, eGFR, presence of heart disease or stroke, LEAD, microalbuminuria and overt proteinuria, and the use of angiotensin-converting enzyme inhibitor were associated with an increased risk of incident renal failure.

Baseline plasma levels of the inflammatory biomarkers in relation to known risk factors for incidence of proteinuria are presented in Table 2. C-reactive protein was the only biomarker significantly associated with MAP ($r = 0.24$, $P < 0.001$), total cholesterol ($r = 0.16$, $P < 0.01$), and low-density lipoprotein cholesterol ($r = 0.19$, $P < 0.001$).

Incidence of overt proteinuria

Of the 264 patients who had no proteinuria or microalbuminuria at baseline, 51 (19.3%) developed overt proteinuria over 6 years. Baseline plasma levels of the soluble adhesion molecule sICAM-1 were significantly associated with the incidence of overt proteinuria on univariate analysis (Table 3). When sICAM-1 was entered into the multiple regression model as a second step after entering clinical variables, it made an independent contribution to the prediction of overt proteinuria in addition to baseline microalbuminuria and MAP ($P = 0.03$). Relative to the first quartile, sICAM-1 values above the median (164 pg/ml) were associated with a three- to fivefold increase in the risk of incident proteinuria ($P = 0.02$ and $P = 0.006$, respectively, for 3rd and 4th quartiles; Table 4).

Incidence of renal failure

Of the 356 patients who at baseline had an eGFR $\geqslant$ 60 ml/min and did not have end-stage diabetic renal failure requiring dialysis or kidney transplant, 63 (17.7%) developed renal failure over the 6-year follow-up (56 with eGFR < 60 ml/min (14 of whom were on dialysis), 1 had a kidney transplant, and

Table 1 | Baseline characteristics of African Americans with type 1 diabetes (DM) by follow-up renal status

	Overt proteinuria		Renal failure	
Characteristics	None ($N = 213$)	Present ($N = 51$)	None ($N = 293$)	Present ($N = 63$)
Mean (s.d.)				
Age (years)	24.6 (10.2)	27.1 (9.8)	25.5 (10.2)	32.3 (9.5)[a]
Duration of DM (years)	7.9 (7.9)	9.5 (5.8)	8.4 (8.0)	13.8 (7.5)[a]
Age at diagnosis (years)	16.4 (7.7)	17.1 (7.4)	16.8 (7.6)	17.8 (7.1)
BMI (kg/m^2)	26.8 (7.9)	28.8 (9.4)	28.0 (8.8)	27.2 (7.2)
MAP (mmHg)	86.0 (11.6)	91.8 (11.2)[a]	87.8 (12.1)	95.2 (13.0)[a]
Glycohemoglobin (%)	13.8 (4.1)	15.2 (4.3)[b]	13.6 (4.2)	15.7 (4.6)[a]
Total cholesterol (mg/dl)	193.8 (45.4)	203.2 (36.7)	196.1 (43.8)	233.6 (77.0)[a]
HDL-C (mg/dl)	54.8 (17.3)	55.6 (19.2)[b]	54.7 (17.5)	55.1 (18.1)
LDL-C (mg/dl)	99.7 (33.4)	110.6 (32.8)	102.8 (34.4)	116.8 (44.7)[c]
eGFR (ml/min)	108.2 (26.8)	116.1 (22.8)[b]	109.4 (26.5)	95.9 (21.2)[a]
Percentage (%)				
Male/female	39.4/60.6	41.2/58.8	42.0/58.0	36.5/63.5
Heart/stroke (no/yes)	96.2/3.8	86.3/13.7[c]	94.2/5.8	86.0/14.0[b]
LEAD (no/yes)	99.1/0.9	96.1/3.9[d]	97.6/2.4	91.2/8.8[b]
Microalbuminuria (no/yes)	80.8/19.2	58.8/41.2[a]	77.5/22.5	44.1/55.9[a]
Overt proteinuria (no/yes)		—	93.4/6.6	56.7/43.3[a]
ACE medication (no/yes)	94.3/5.7	96.1/3.9	95.2/4.8	84.2/15.8[c]
Statin medication (no/yes)	99.1/0.9	98.0/2.0	98.6/1.4	95.2/4.8

Abbreviations: ACE, angiotensin-converting enzyme inhibitor; AER, albumin excretion rate; BMI, body mass index; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LEAD, lower extremity arterial disease; MAP, mean arterial blood pressure.

Microalbuminuria, AER 20–200 mcg/min; overt proteinuria, AER > 200 mcg/min; renal failure, eGFR < 60 ml/min, dialysis, kidney transplant, or renal failure as the cause of death.

[a]$P < 0.001$.

[b]$P < 0.05$.

[c]$P < 0.01$.

[d]Sample size did not allow for statistical analysis.