Microalbuminuria in Patients With Cystic Fibrosis

Melanie Lind-Ayres, MD[1]
William Thomas, PHD[2]
Bonnie Holme, BS[1]
Michael Mauer, MD[1,3]
Maria Luiza Caramori, MD[1,3]
Antoinette Moran, MD[1]

OBJECTIVE—We previously found that microalbuminuria (MA) is present in 14% of patients with long-standing cystic fibrosis–related diabetes (CFRD). However, others have reported much higher rates of MA in CF patients with and without diabetes (32–67%), suggesting this test is not sufficiently specific for diabetic nephropathy screening in CF. We investigated transient (TMA) and persistent (PMA) microalbuminuria in CF patients to resolve these contradictory findings.

RESEARCH DESIGN AND METHODS—We reviewed 1,449 outpatient urinary albumin measurements from 467 patients aged ≥10 years, which were collected over a decade. TMA was defined as a single episode of MA that subsequently was resolved. PMA was defined as two consecutive or two out of three consecutive measurements in the MA range.

RESULTS—The prevalence of TMA that subsequently was resolved in CF patients was similar to the general population. It was found in 7.6% of patients, including 5% of youth (aged 10–17 years) and 9% of adults. PMA was found in 6.1% of the overall CF population, including 2% of youth and 8% of adults. The odds of PMA were increased sevenfold in patients with CFRD (95% CI 2.5–20, $P = 0.0002$) and 48-fold in patients with both CFRD and organ transplant (95% CI 13–177, $P < 0.0001$). The five patients with PMA in the absence of CFRD or transplant included two youths with presumed benign orthostatic MA and three adults with hypertension.

CONCLUSIONS—The spot urine albumin-to-creatinine ratio is specific enough to be a valid screening test for diabetic kidney disease in CFRD.

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Annual urine albumin screening is recommended for people with type 1 and type 2 diabetes to detect early evidence of diabetic kidney disease (1). Elevated urine albumin is also found in patients with cystic fibrosis–related diabetes (CFRD) (2–6). In a study of 192 CFRD patients, we previously reported that microalbuminuria (MA) was present in 14% of those with long-standing (>10 years) CFRD and, as in the general diabetic population, was associated with worse glycemic control (2). Two other groups, however, have questioned the validity of this association because they found MA to be far more common in CF, even in patients without diabetes (7,8). Dobson et al. (7) reported that MA was present in 67% of single urine samples from six CF patients with diabetes and in 32% of 34 samples from CF patients without diabetes. Another European study (8) found a 58% prevalence of MA in 112 children with CF, none of whom had diabetes. Thus, it was suggested that urine albumin excretion (UAE) may not be specific enough to be used as a screening measure for the detection of diabetic kidney disease in CFRD.

The current study attempts to resolve these contradictory findings by determining the prevalence of both transient and persistent MA in CF patients with and without diabetes during routine screening at a large pediatric and adult CF center.

From the [1]Department of Pediatric Endocrinology, University of Minnesota Medical School, Minneapolis, Minnesota; the [2]Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, Minnesota; and the [3]Department of Medicine, University of Minnesota Medical School, Minneapolis, Minnesota.
Corresponding author: Antoinette Moran, moran001@umn.edu.
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RESEARCH DESIGN AND METHODS

—CF patients at the University of Minnesota (UM) CF Center are routinely seen at quarterly intervals, and their clinical and laboratory data are recorded in a database. Annual oral glucose tolerance test screening starts at age 6 years for patients not already on insulin treatment. Additional routine lung function, anthropometric measurement, and blood and urine laboratory studies are performed annually at a time when patients are in their stable baseline state of health. Annual spot urine testing for quantitative albumin determination was introduced as part of routine annual studies starting in 2001, and performance of this measurement became increasingly common over the subsequent decade.

Pediatric patients were defined as <18 years of age. Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg for CF adults, blood pressure consistently above the 95th percentile for age and sex for children, or antihypertensive medication treatment during the study period. Transplant status was recorded.

Review of this prospectively collected data was performed to determine the prevalence of MA during the period between January 2001 and February 2010. All patients and their parents gave informed consent/assent, permitting their records to be reviewed for research purposes. This was approved by the UM Institutional Review Board.

Urine albumin assessment

Urine samples from inpatient hospitalizations and from patients <10 years of age were excluded. Urine albumin and creatinine were measured in the UM Fairview laboratory using nephelometry. MA was defined as an albumin-to-creatinine ratio (ACR) 30–299 mg/g. Macroalbuminuria was defined as an ACR ≥300 mg/g. MA was considered transient or persistent: transient microalbuminuria (TMA) was defined as a single episode that subsequently resolved, while persistent microalbuminuria (PMA) was defined as an ACR in the MA range in at least two consecutive or two of three consecutive measurements. PMA status could not be determined on

two patients with MA who each had only one urinary albumin measurement.

Data analysis

Observations were collected over a period of 10 years, and many were repeated measurements from the same patient. For the analysis, we used the first urine collection from patients with all normal ACRs, the first urine collection with ACR ≥30 mg/g for patients with TMA, and the second (confirmatory) urine collection with ACR ≥30 mg/g for patients with PMA. The study sample was divided into three ACR groups: those with all normal ACRs, those with TMA, and those who met PMA criteria.

There were three deceased patients who underwent lung transplants and for whom only pretransplant urine albumin data were analyzed. They are therefore reported in the no-transplant group. They included one male subject who died the day of the transplant and two others who developed persistent renal failure unrelated to diabetes as a complication of a difficult postoperative course.

Cumulative prevalence of MA was estimated by dividing the number of subjects in each ACR group by the total number of patients. Continuous variables were compared among groups by ANOVA, and categorical outcomes were compared using χ^2 tests. P values < 0.05 were considered statistically significant. Separate analyses were performed by CFRD and transplant status. Odds ratios were calculated using a generalized logit model for probabilities of the three ACR categories (9). All computations were performed using SAS version 9.2.

RESULTS

Cumulative prevalence of MA

During the study period, 2001−2010, there were 1,449 ACR measurements recorded on 467 patients, comprising 75% of all patients aged ≥10 years seen during this period. One-third of the study patients were youth aged 10–17 years at the time of the first urine collection, and there were equal numbers of males and females. Seventy-six percent of the study cohort had at least two or more recorded urine collections.

The cumulative prevalence of TMA that subsequently resolved was 7.6% in all patients, 5% in youth, and 9% in adults. The cumulative prevalence of PMA was 6.1% overall, 2% in youth, and 8% in adults. Prevalence rates varied greatly depending on CFRD and transplant status. Patients with CFRD with no history of lung or liver transplant (n = 149) had no increase in odds of TMA (95% CI 0.5–2.4), but sevenfold greater odds of PMA (95% CI 2.5–20, P = 0.0002). Patients with a history of organ transplantation (n = 20, 19 of whom also had CFRD and 1 with impaired glucose tolerance) had nearly fourfold greater odds of TMA (95% CI 1.0–16, P = 0.044) and a 48-fold increase in the odds of PMA (95% CI 13–177, $P < 0.0001$). Only five patients with PMA (17%) did not have either CFRD or a history of transplant. Two of these were adolescents with intermittent MA, which was presumed to be benign orthostatic microalbuminuria. The other three were adult patients with hypertension, a known risk factor for MA.

Prevalence of macroalbuminuria and kidney failure

There were 14 patients (3%) with at least one urine collection in the macroalbuminuric range. Only two of these patients did not have CFRD and/or a history of transplant. Both patients were youth who had macroalbuminuria on only one occasion with subsequent improvement (one into the normal range and one into the MA range).

A 48-year-old man with an 18-year history of poorly controlled diabetes developed diabetic nephropathy and received a kidney transplant. He is the third CF patient ever to require dialysis for diabetic nephropathy at UM, and the first to receive a renal transplant. Of 20 patients followed during the study period who had a history of lung or liver transplant, 8 developed chronic kidney disease, which was felt to be secondary to nephrotoxic antirejection medications rather than to diabetes. Two of these patients received kidney transplants between 2 and 5 years after their initial organ transplant, and another is currently on the transplant list.

Patient characteristics

Clinical characteristics were compared among patients with normal ACR, TMA, and PMA (Table 1). For patients who did not have CFRD or an organ transplant (n = 298), apart from a higher prevalence of antihypertensive medications in TMA, there were no statistically significant clinical differences between ACR categories. Among CFRD patients with (n = 20) or without (n = 149) transplant, those with TMA and PMA were older and tended to have higher mean blood pressures, higher serum creatinine values, and worse lung function compared with those in the normal ACR group, although these differences did not always reach statistical significance.

CONCLUSIONS—In the U.S. adult general population, the prevalence of MA on random screening has been reported to be 6–7% in patients without known risk factors such as diabetes or hypertension (10–12). In healthy adolescents aged 11–17 years in the general population, the prevalence of MA was 8% on single urine samples but decreased to 0.8% upon repeat testing (13). Similarly, routine clinic screening of youth and adults with CF over a period of 10 years showed TMA that subsequently normalized in 7.6% of patients. PMA was found in 6.1% of CF patients, primarily in those with CFRD and especially in those with both CFRD and a history of transplant. Thus, contrary to some previous reports (7,8), excessive UAE is not unusually common in CF patients.

In the general population, several nonrenal and renal factors can elevate UAE. Nonrenal factors that transiently increase urine albumin include fever, illness, daytime collection (benign orthostasis), and heavy exercise. Renal disease risk factors to which CF patients are prone include diabetic microvascular disease, nephrolithiasis, and exposure to nephrotoxic agents such as aminoglycoside antibiotics or posttransplant antirejection drugs (14). In the current report, PMA was found in about half of patients following lung or liver transplant. The etiology in these cases is likely multifactorial, including complications of surgery, nephrotoxic antirejection medications, diabetes, and hypertension. Macroalbuminuria was rare, and there was only one case of diabetic nephropathy requiring kidney transplant.

Other studies that described much higher rates of MA in CF patients, including patients without diabetes, had much smaller sample sizes and limited or no follow-up data (7,8). Dobson et al. (7) suggested that the elevated ACR was because of the combination of both increased urinary albumin due to chronic infection and reduced urine creatinine related to low muscle mass. This may be less relevant in the current report because ACR was evaluated during routine annual studies, which are always done during a period of stable health, and because CF patients at UM are generally well nourished.

The current study has some limitations. Urinary measurements were obtained at clinic visits, which might lead to higher ACR values compared with morning void or overnight urine collections. Thus, we may have overestimated the prevalence of MA by including patients with a postural component to their increased ACR values. The

Table 1—*Demographic and clinical characteristics of patients with normoalbuminuria (normal ACR), TMA, and PMA, stratified by CFRD-transplant status*

	Normal ACR	TMA	PMA	*P* value
Neither CFRD nor transplant (*n*)	271	22	5	—
Female (%)	44	59	80	0.13
Adult (age >17 years) (%)	57	64	60	0.82
Age (years)	23 ± 1	27 ± 3	24 ± 5	0.29
ACR (mg/g)	4.5 (4–5)	65 (49–85)	121 (69−210)	—
Serum Cr (mg/dL)	0.76 ± 0.01	0.84 ± 0.05	0.66 ± 0.10	0.18
SBP (mmHg)	108 ± 1	114 ± 5	115 ± 13	0.50
DBP (mmHg)	65 ± 1	63 ± 3	74 ± 6	0.29
Hypertensive medication (%)	0.4	9	0	0.0004
FEV1 (%)	79 ± 2	68 ± 6	64 ± 12	0.11
CFRD only (*n*)	122	11	16	—
Female (%)	46	45	63	0.39
Adult (age >17 years) (%)	83	100	94	0.22
Age (years)	27 ± 1^a	34 ± 3^b	35 ± 2^b	0.002
ACR (mg/g)	5 (4−6)	71 (43−117)	260 (170−394)	—
Serum Cr (mg/dL)	0.8 ± 0.04^a	1.2 ± 0.1^b	1.5 ± 0.2^b	<0.0001
SBP (mmHg)	112 ± 2^a	127 ± 6^b	127 ± 7^b	0.01
DBP (mmHg)	66 ± 1^a	74 ± 4^{ab}	76 ± 4^b	0.02
Hypertensive medication (%)	4	9	19	0.06
FEV1 (%)	65 ± 3^a	51 ± 8^{ab}	45 ± 7^b	0.01
Transplant (*n*)*	9	3	8	—
Female (%)	67	33	63	0.68
Adult (age >17 years) (%)	89	100	100	0.48
Age (years)	36 ± 4	36 ± 6	35 ± 4	0.99
ACR (mg/g)	8 (4−15)	35 (10−125)	108 (50−235)	—
Serum Cr (mg/dL)	1.3 ± 0.3	1.9 ± 0.7	2.0 ± 0.4	0.43
SBP (mmHg)	126 ± 6	141 ± 12	134 ± 6	0.48
DBP (mmHg)	75 ± 4	81 ± 8	79 ± 4	0.73
Hypertensive medication (%)	83	67	100	0.26
FEV1 (%)	79 ± 4	—	82 ± 6	0.74

Values are mean ± SE or percentage; ACR is reported as a geometric mean (95% CI). Cr, creatinine; DBP, diastolic blood pressure; FEV1, percent predicted expiratory volume in 1 s; SBP, systolic blood pressure. *a*,*b*, means with no shared letters were significantly different ($P < 0.05$); means with shared letters were not significantly different. *All patients in this stratum also had CFRD except for one patient with impaired glucose tolerance.

study might have been enhanced by a prospective collection of data on antibiotic use, number and timing of pulmonary exacerbations, and formal measurements of glomerular filtration rate.

In summary, we evaluated a large, well-described CF outpatient clinic population over a period of about 10 years. TMA was no more common than in the general population. PMA was found in only 6.1% of patients, the majority of whom had diabetes. Thus, as in the general diabetic population, the spot urine ACR is specific enough to be a valid screening measure for the assessment of diabetic kidney disease in patients with CFRD.

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M.L.-A. researched data and wrote the manuscript. W.T. completed the statistical analyses. B.H. organized and collected data. M.M. and M.L.C. edited the manuscript. A.M. devised the study and edited the manuscript.

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