Screening Diabetic Patients for Microalbuminuria

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Abnormal rates of urinary albumin excretion have been shown to predict the development of nephropathy and may signal atherosclerotic disease in diabetic patients. This study demonstrated the feasibility of measuring microalbuminuria in diabetic patients from a large family practice population. Although only one half of the 473 diabetic patients offered free screening took advantage of the testing, those participating did not differ in terms of sex, race, type of diabetes, mean age, systolic blood pressure, and fasting blood glucose levels from those not electing to participate. Over 40% of those screened had abnormally elevated albumin excretion rates as defined as greater than 0.02 g of albumin per gram of creatinine. Those participating in the screening perceived the process as useful and were able to comply with directions for overnight urine collection. Results show that screening for microalbuminuria in diabetic patients cared for by family physicians is feasible, simple, and inexpensive. Interventions to slow or reverse the progression of abnormal microalbuminuria and future risk for nephropathy in those with diabetes are underway.
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Diabetes contributes substantially to the development of premature mortality and morbidity from atherosclerotic disease and is the leading cause of new blindness and end-stage renal disease in the United States. The personal and societal costs of diabetes are enormous. The federal cost of treating end-stage renal disease resulting from diabetes alone exceeds $1 billion a year.[1] Several times that amount are likely to be expended for the care of other diabetic complications such as atherosclerotic disease, neuropathy, and retinopathy.

Diabetic nephropathy is defined by the development of clinical proteinuria (>0.50 g/d) and a decline in renal function. The development of diabetic proteinuria is dependent on the duration of the disease. Although less than one third of all patients who have diabetes for more than 20 years develop frank proteinuria, and only one half of those with proteinuria develop azotemia, once clinical proteinuria does develop, the mean time until end-stage renal disease or death is less than 5 years.[2] The rate of development of renal failure varies inversely with diastolic blood pressure, dietary protein, level of hyperlipidemia, and length of diabetes exposure.[3–5]

Recently investigators have focused on diabetic patients who excrete urinary albumin at levels previously not detectable by routine urine analysis. Urine dipsticks usually have a threshold of detecting 0.200 g/L of albumin. The term *microalbuminuria* has been coined to mean concentrations of albumin between 0.030 and 0.200 g/L.[6] Microalbuminuria is also often used synonymously with abnormal urinary albumin excretion rate (UAER). While microalbuminuria strictly speaking is a urinary albumin concentration below the level detected by dipsticks, UAER is a true excretion rate or ratio and is usually reported in one of three formats: micrograms per minute, grams per day, or grams of albumin per gram of creatinine.

Diabetes is an independent risk factor for the development of atherosclerotic cardiovascular disease.[7] Other known major risk factors for atherosclerosis (age, sex, hypertension, hyperlipidemia, obesity, smoking, and family history) may act synergistically in diabetic patients.[8] Microalbuminuria or increased UAER may also be a marker for diabetic patients with or at increased risk for atherosclerotic disease.[9,10]

Microalbuminuria is a phenomenon not specific for diabetes but is now considered to reflect generalized vascular damage, not just early nephropathy.[11] It is an early predictor of renal involvement and a clinical marker for

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response to steroid therapy in those with lupus.[12] Microalbuminuria is encountered in preeclampsia[13] and essential hypertension and subsides with effective antihypertensive drug treatment.[14] Posture, time of day,[15] and exercise[16,17] may cause the urinary albumin excretion rate to vary. The increase in UAER with exercise, however, is more pronounced in diabetic patients[18] than in normal individuals.

Overnight urinary albumin excretion collections have been advocated to screen for microalbuminuria and increased UAER because this sampling technique is more convenient than 24-hour collections and reduces the variability of UAER that results from physical activity. Quantitative research studies on microalbuminuria often use radioimmunoassay[19] or nephelometric-turbidimetric[20] techniques with high sensitivity and specificity. Watts et al[21] have recently described three qualitative office-based tests now being introduced into general clinical practice: latex bead immunoagglutination, sulphosalicylic acid, and a commercial product, the Micro-bumin Test (Ames Diagnostics, Elkhart, Ind). Although not quantitative for research purposes, these tests are likely to become commonly used for screening in primary care and other clinical settings.

This paper reports a study of the feasibility of screening for microalbuminuria and the distribution of increased urinary albumin excretion rates (UAER) and clinical proteinuria in a family practice diabetic population.

METHODS

Computerized encounter data from the Family Practice Center of the Department of Family and Community Medicine, Bowman Gray School of Medicine of Wake Forest University, were obtained for all encounters with patients having a diagnosis of diabetes made between January 1, 1988, and December 31, 1988. During that interval patients were cared for by one of 36 residents, 2 fellows, 11 family physicians, or 3 physician assistant faculty. Personalized form letters were developed and signed by the principal investigator and mailed to invite diabetic patients to the screening program. Those interested in being screened for microalbuminuria called the office and scheduled an appointment for screening.

One week before their scheduled appointment, subjects were sent a packet of questionnaires regarding their health, diet, and activities. A brief one-page instruction sheet explained how to collect urine overnight. The time of voiding before beginning their collection and the time of last voiding upon arising in the morning were recorded. Patients were also asked to be fasting from midnight of the day before their appointment. After 2 months, a postcard reminder was sent to those patients not making an appointment following the first invitation.

Patients were scheduled for screening between January and August 1989. At the beginning of the screening appointment, each patient had blood drawn for a 20-item multichannel serum chemistry profile that included a glycosylated hemoglobin and fasting glucose. Times of beginning and ending urine collection were recorded. The urine volume was measured in milliliters, and a dipstick screening urine analysis was performed for specific gravity, glucose, ketones, blood, protein, and leukocytes. If the dipstick was positive for blood or leukocytes, a microscopic analysis was done on spun urine. A urine culture was also obtained if the urine analysis showed greater than or equal to 2+ leukocytes, 1+ blood, or 10 white or 5 red blood cells per high-power field. A nurse recorded each patient's height, weight, and blood pressure.

Microalbuminuria determinations were made with an Express 550 nephelometer (Ciba-Corning, Oberlin, Ohio) using antialbumin antisera raised in goats (Cappel of West Chester, Pennsylvania) and 4% polyethylene glycol (PEG) in a phosphate buffer, 10 mmol/L, pH 7.4, containing 9 g/L of sodium chloride. The instrument was programmed to add 30 μL of sample to 220 μL of 4% polyethylene glycol. After 20 seconds, the absorbance difference between 340 and 600 nm was recorded, and a 50-μL aliquot of diluted antisera (100 μL antisera in 1000 μL of 4% PEG) was added to the cuvette. After 5 minutes of incubation at 37°C, the absorbance difference at 340 and 600 nm was again recorded. The difference between the two measurements taken at 20 seconds and 5 minutes was used to calculate the concentration of urinary protein after plotting the absorbance difference on semilog paper. Standards were included with each run.[22]

Urinary creatinine was determined by the kinetic Jaffe reaction.[23] Urinary albumin excretion rates were then reported in grams of albumin per gram of creatinine. Where overnight urinary collection times and volumes were available, excretion rates in micrograms of albumin per minute and grams of albumin per day were reported.

On exit from the screening encounter, patients were surveyed about aspects of the screening, such as the manner in which they were contacted and their appointment was scheduled and how difficult it was to remember to fast and collect their urine. The survey was designed to ascertain patients' attitudes toward the protocol, their willingness to attempt compliance with the study, and their enthusiasm for participating in a diabetic control project. As a check on selection bias, the clinical records of those diabetic patients choosing not to attend the screening were audited for date of birth, type of diabetes, last recorded blood pressure, and fasting glucose.

Data comparisons were examined for statistical significance using the chi-square test for proportions and *t* tests for the means between independent samples. Because population variances cannot be assumed equal, *t* test

TABLE 1. CHARACTERISTICS OF DIABETIC PATIENTS

Characteristics	Screened (Range) (n = 242)	Not Screened (Range) (n = 231)	P*
Women (%)	54.5	58.6	.393
Black (%)	34.0	33.5	.899
Patients with NIDDM† (%)	89.3	90.5	.660
Age, years‡	55 ± 13 (16 – 86)	54 ± 15 (17 – 89)	.438
Systolic blood pressure, mm Hg‡	131 ± 25 (84 – 205)	134 ± 22 (90 – 208)	.167
Diastolic blood pressure, mm Hg ‡	77 ± 13 (50 – 120)	80 ± 12 (52 – 120)	.012
Fasting glucose, mmol/L‡	10.8 ± 4.4 (4.3 – 24.0)	11.5 ± 5.7 (2.3 – 30.0)	.157
mg/dL‡	195 ± 79 (70 – 432)	207 ± 103 (41 – 540)	

*Chi-square statistic to compare proportions, and t test to compare means.
†Type II, non-insulin-dependent diabetes.
‡Mean ± SD (range).

calculations used the approximate degree of freedom method.[24]

RESULTS

The Family Practice Center computerized encounter data system included 505 individual patients whose encounter form listed diabetes in some way. Excluded from screening were 32 patients, 12 who were incorrectly identified as diabetic, 9 who had died in the interval between their visit recorded in the database and when screening was offered, 5 who had transferred from the practice or were considered inactive (having made no visit in the past 18 months), and 6 who called and forthrightly refused to be screened. The crude prevalence of diabetes in the practice was 2.4%, with 51.2% (n = 242) actually screened of the 473 eligible.

Those patients keeping their appointment are compared in Table 1 with those who did not attend screening for microalbuminuria. Those screened had a mean glycosylated hemoglobin of 7.3% ± 2.2% with a range of 3.0% to 13.0%. Few of those not screened had glycosylated hemoglobin levels recorded in their clinical records.

The mean concentration of urinary albumin for screened patients was 0.11 ± 0.41 g/L with a range of 0 to 3.80 g/L. Nine patients had dipstick-detectable albuminuria exceeding 0.50 g/L, and six of these had concentrations exceeding 1.00 g/L. When those with dipstick-detectable albuminuria (macroalbuminuria greater than 0.20 g/L) were excluded, 49 (21.5%) had microalbuminuria defined as a urinary albumin concentration >0.03 g/L but <0.20 g/L. Although initially all subjects were not requested to record urinary collection times, only 4.5% of those who were requested to do so did not comply. Mean urinary albumin excretion rates for those screened and the percentage meeting or exceeding criteria[25] for increased UAER appear in Table 2. When those with macroalbuminuria are excluded, 40.7%, 28.5%, and 27.8% have abnormal urinary excretion rates measured in grams of albumin per gram of creatinine, micrograms of albumin per minute, or grams of albumin per day, respectively. Figure 1 shows the relative frequency of those with various degrees of microalbuminuria.

Results from the exit screening survey show that 96.5% of the participants perceived that taking part in the screening process was useful to them, 88.0% claimed it was easy to remember to be fasting, and 81.1% said it was not difficult to remember to collect and bring their urine specimens. Of those attending the screening, 76.0% said they would have been willing to make a separate trip to the office to pick up a special container to collect their urine specimens, if requested. Only one patient expressed no interest in participating in a future program to reduce abnormal proteinuria.

DISCUSSION

The 1988 International Symposium on Preventing the Kidney Disease of Diabetes Mellitus[25] has proposed normal albumin excretion rates to be less than 10 μg/min, 0.015 g/d, or 0.01 g of albumin per gram of creatinine; and elevated rates as being greater than 20 μg/min, 0.030 g/d, or 0.02 g of albumin per gram of creatinine.

TABLE 2. URINARY ALBUMIN EXCRETION RATES (UAER)

UAER Measure	Mean ± SD (Range)	Percent with Increased UAER
Grams of albumin per gram of creatinine	0.14 ± 0.48 (0 – 4.12)	44.2
Micrograms of albumin per minute	215 ± 1265 (0 – 15200)	41.6
Grams of albumin per day	0.20 ± 0.79 (0 – 6.77)	40.5

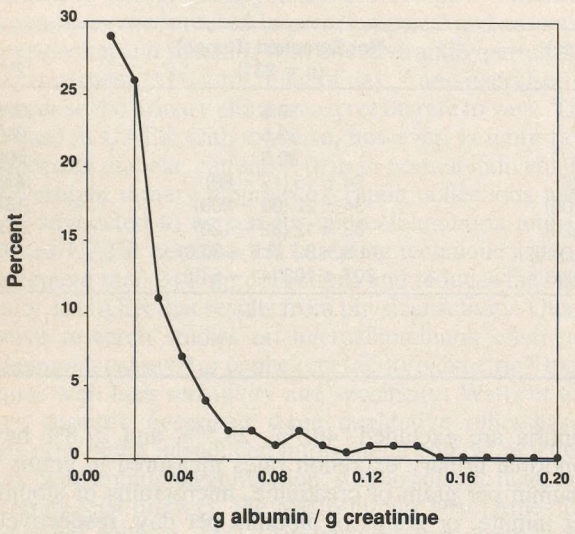

Figure 1. Frequency of degrees of microalbuminuria in diabetic patients, measured in grams of albumin per gram of creatinine.

Microalbuminuria or abnormal urinary albumin excretion is rarely detected in diabetic patients whose duration of disease is known to be less than 5 years, an observation suggesting that microalbuminuria is an early sign of glomerular injury rather than a marker for susceptibility to end-stage renal disease.[26] Nevertheless, the presence of microalbuminuria seems to be a reliable predictor of the risk for end-stage renal disease and atherosclerotic disease as well.

Bennett reported that for those followed an average of 6 to 10 years, the positive predictive value of albuminuria greater than 30 μg/min for developing end-stage renal disease is between 70% and 87% for those with insulin-dependent diabetes mellitus (IDDM), but only about 25% for those with non-insulin-dependent diabetes mellitus (NIDDM).[27] Although elevated albumin excretion predicts renal failure in those with IDDM better than in those with NIDDM, patients with NIDDM with increased UAER have increased mortality rates, perhaps resulting from generalized vascular disease.

Mattock and colleagues[9] have reported that urinary albumin excretion rates were twice as high in patients with adult-onset diabetes with electrocardiographic or symptomatic evidence of coronary disease than those without coronary disease. After controlling for confounding factors of age, body mass index, duration of diabetes, systolic and diastolic blood pressures, glycosylated hemoglobin, plasma glucose, triglycerides, cholesterol, high-density lipoprotein, and smoking and alcohol consumption, only elevated urinary albumin excretion, sex, and systolic blood pressure predicted coronary disease in these diabetics.

Schmitz and Vaeth[10] recently reported on the mortality risk of microalbuminuria in 503 diabetic patients (mostly those with NIDDM) followed for 10 years. Age, morning urine albumin concentration, known duration of diabetes, and serum creatinine predicted mortality, but age at diagnosis, blood pressure, fasting glucose, relative weight, retinopathy, or treatment did not contribute significantly to this prediction. Diabetic patients with urine albumin concentrations greater than 0.040 g/L were twice as likely to have died than those with normal albuminuria, less than 0.015 g/L. Even minor increases in microalbuminuria (0.016 to 0.040 g/L) were associated with a 1.5 increased risk of death ($P = .007$).

Although UAER is less predictive of end-stage renal disease in those with NIDDM as compared with those with IDDM, the majority of diabetic patients who have end-stage renal disease are those with NIDDM. Since the ratio of NIDDM to IDDM patients in the general population is nearly 9:1, detection of abnormal UAER will identify nearly three times as many patients with NIDDM than with IDDM who will progress to end-stage renal disease. How well abnormal UAER predicts increased risk for cardiovascular diseases and retinopathy will require more study.

If UAER has predictive value, then screening patients for increased UAER would become an important adjunct to diabetes care as long as treatment of diabetic patients with microalbuminuria can be shown to be efficacious. Such a demonstration would require finding that intensified treatment in those whose abnormal protein excretion was detected early, in an asymptomatic state, not only slowed the progression of abnormally increased UAER but retarded the development of clinical diseases.

Several investigators have already demonstrated that tighter glycemic control can reverse the development of microalbuminuria.[4,28–30] Early results from interventions aimed at reductions in blood pressure[25] and dietary protein[5] are encouraging that the progression of abnormal UAER can also be altered. Further studies are currently in progress to correlate the presence of microalbuminuria and coincident hypertension, hyperglycemia, duration of diabetes, hyperlipidemia, percentage ideal body weight, and other factors related to diabetes control. Large-scale trials are now underway to demonstrate how effective blood pressure and dietary protein control will be in reducing target organ damage, especially related to atherosclerosis and end-stage renal disease.

Whether these interventions will be more efficacious when implemented early for those with identified high-risk status by virtue of an elevated urinary albumin excretion rate is unknown. If early interventions are found to de-

crease the incidence of nephropathy and atherosclerosis, then routine screening for this high-risk marker would be warranted. Such testing could be done periodically as part of planned follow-up appointments for diabetes care, when the patient would be instructed to be fasting and bring an overnight urine specimen. When quantitative microalbuminuria is reported in grams of protein per gram of urinary creatinine or when qualitative screening kits are used, patients would not need to record times, thereby facilitating the urine collection process. Such procedures do not require a blood sample, special containers, or preservatives, though if patients are to be seen late in the day, refrigeration of urine samples would be advisable.

Although research-quality nephelometric procedures were used in this project to detect microalbuminuria, physicians in practice may be able to enlist a commercial or hospital laboratory to use similar quantitative techniques. Where clinical interests are restricted to normal vs abnormal UAER status, such as in screening vs diagnostic procedures, commercial qualitative in-office techniques are also now available. The cost in materials for each determination is less than $1 whether nephelometric or office tablet procedures are used. Factoring in technician time and incidentals would reasonably price these tests at between $5 and $10.

Those who attended screening appeared to follow instructions easily for collecting their specimens. Although it is disturbing, but not surprising, that only one half of those invited actually took advantage of the free screening program, there were no statistically significant differences between those who attended and those who did not as to race, sex, type of diabetes, age, last fasting blood glucose, or systolic blood pressure. Those not screened tended to have slightly higher diastolic pressures; however, the difference of 3 mm Hg between mean diastolic blood pressures may not be clinically significant. These data argue against the likelihood that those patients screened were significantly healthier than those not screened.

It is possible that more patients with diabetes would have taken advantage of the screening had they been sent individual letters from their own physicians, as opposed to the form invitation signed by only one of the 52 providers who see diabetic patients in the Family Practice Center. Personal requests from a patient's own provider at the time of a clinical visit would certainly be more motivating than a letter from an unknown physician. Nevertheless, a large percentage of diabetic patients in this family practice setting had abnormal UAER, identifying a significant proportion of this population who may be developing vascular complications, such as early nephropathy, retinopathy, and atherosclerosis.

Quantitative and qualitative tests for microalbuminuria are now readily available to the primary care family physician, internist, and pediatrician. Furthermore, although this study demonstrated that diabetic patients in a large primary care practice can be screened for microalbuminuria simply and inexpensively, other studies will be needed to determine whether asymptomatic testing for abnormal urinary albumin excretion will satisfy other important criteria for good screening tests.[31] Central among these other criteria will be the demonstration that improved diabetic treatments can not only result in improvements in UAER, but actually reduce the likelihood of future microvascular and macrovascular events. This demonstration will require carefully conceived randomized clinical trials. Until these trials have been completed, the role of UAER might best be in using serial determinations to follow the early decline in renal function for those with diabetes.

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