

Correlates of Abnormal Urinary Albumin Excretion Rates Among Primary Care Patients With Essential Hypertension

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Background: The excretion of small amounts of urinary protein, known as microalbuminuria, among patients with essential hypertension is associated with increased mortality from cardiovascular disease and, possibly, future renal decline. Correlates of microalbuminuria among primary care patients with essential hypertension, however, have not been well described.

Methods: One hundred forty patients enrolled in a large family practice ambulatory care center who had essential hypertension but not diabetes participated in a screening project to document cardiovascular and renal diseases in this population. Patients underwent a brief physical examination and submitted blood and urine samples for analysis.

Results: Twenty-five percent of patients had elevated urinary albumin excretion (UAE) rates, defined as greater than 30 $\mu\text{g}/\text{min}$. Patients with elevated UAE rates did not differ from patients without elevated UAE rates by age, race, sex, duration of hypertension, or type of antihypertensive medication used (if any). Although no patients had abnormally elevated glycosylated hemoglobin, after controlling for age and duration of hypertension, elevated UAE rates were significantly related to higher mean glycosylated hemoglobin levels (odds ratio [OR] = 3.06, 95 percent confidence interval [CI] = 1.11 to 8.41) and to current smoking (OR = 3.14, 95 percent CI = 1.09 to 9.04).

Conclusions: These data are the first in a primary care population to show a threefold increase in risk for elevated UAE rates among patients with essential hypertension who currently smoke or who have above-average glycosylated hemoglobin levels. Although cross-sectional in nature, these data can also point toward subgroups of hypertensive patients who have a worse cardiovascular prognosis. (J Am Board Fam Pract 1997;10:180-4.)

The finding of small amounts of albumin in the urine, or microalbuminuria, is predictive of the development of nephropathy in patients with diabetes mellitus.¹ It is also associated with coronary heart disease risk factors, such as elevated blood pressure and serum lipids, in both diabetic^{2,3} and nondiabetic⁴ patients. In addition, elevated albu-

min excretion (UAE) is associated with an increased mortality from cardiovascular disease among diabetic patients. UAE has recently been described as an independent predictor of mortality from cardiovascular disease in patients with hypertension⁵ and is associated with higher diastolic blood pressure, greater left ventricular mass, and a greater occurrence of hypertriglyceridemia.⁶

Although a relation between UAE and nephropathy has not been established in those persons with hypertension, microalbuminuria has been found to be more common in hypertensive than in normotensive patients.⁷ Five to 15 percent of patients with essential hypertension develop macroalbuminuria and clinical proteinuria and a serious reduction in renal function.^{5,8-14} The appearance of microalbuminuria, therefore, could be an early marker for future renal disease. Al-

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Table 1. Summary Characteristics of Hypertensive Patients by Urinary Albumin Excretion (UAE) Rate.

Characteristic	Nonelevated UAE Rate*†	Elevated UAE Rate*†	P Value‡
Age (years)	58 ± 12	59 ± 13	ns
Black (%)	31.4	48.0	ns
Female (%)	60.0	44.0	ns
Current smoker (%)	14.3	32.0	0.037
Duration of hypertension	11 ± 9	10 ± 9	ns
Medication treatment for hypertension (%)	79.0	72.0	ns
ACEI§ (%)	7.6	12.0	ns
Calcium channel blocker (%)	14.3	16.0	ns
Systolic blood pressure (mmHg)	144 ± 22	150 ± 15	ns
Diastolic blood pressure (mmHg)	88 ± 10	85 ± 9	ns
Mean arterial pressure (mmHg)	106 ± 13	107 ± 9	ns
Body mass index (kg/m ²)	28.2 ± 5.6	29.3 ± 6.4	ns
Waist to hip ratio	0.85 ± 0.19	0.92 ± 0.08	ns
Glycosylated hemoglobin (%)	3.59 ± 1.60	4.44 ± 0.83	0.012
Serum creatinine (mg/dL)	1.04 ± 0.25	1.26 ± 0.52	0.002
UAE rate(µg/min)	8.4 ± 7.0	197 ± 314	0.001¶

*Urinary albumin excretion rate elevated if > 30 µg/min.

†Except for percentages, all values are mean ± standard deviation.

‡P value from the Student t-test for means (unless otherwise noted) or χ^2 for proportions.

§ACEI - angiotensin-converting enzyme inhibitor.

¶P value derived by Kruskal-Wallis H.

though the relation between microalbuminuria and mortality from cardiovascular disease is established in patients with hypertension, data are limited on the correlates of UAE in these patients.⁶ The purpose of this investigation was to examine factors related to elevated UAE rates in patients with essential hypertension in a primary care setting.

Methods

One hundred forty patients with essential hypertension and without diabetes mellitus were selected from a computerized database at the Family Practice Center of the Bowman Gray School of Medicine as part of a larger project evaluating risk factors for renovascular decline among primary care patients with chronic disease.¹⁵ Hypertension was defined as having a systolic blood pressure at or above 160 mmHg or a diastolic blood pressure at or above 90 mmHg on two or more occasions. Patients were also defined as being hypertensive if they were currently being treated for hypertension detected on at least two previous examinations. Screening of patients occurred between January 1989 and June 1991.

Patients underwent a brief, standardized physical examination. Height, weight, a body mass index (kg/m²) and waist and hip circumferences

were obtained for each patient by 1 research nurse. Blood pressure was measured with a calibrated mercury sphygmomanometer after the patient sat at rest for 5 minutes. Information on smoking status, age, race, sex, duration of hypertension, and antihypertensive medications (if any) was elicited by questionnaire.

After an overnight fast, patients submitted a sample of venous blood for multichannel chemistry measurements and fasting glucose, fasting insulin, total cholesterol, high-density lipoprotein cholesterol, triglyceride, and calculated low-density lipoprotein cholesterol levels. Glycosylated hemoglobin was measured by the affinity columns method, with normal values for our population ranging from 2.9 to 5.1 percent. Patients also submitted an overnight urine collection, recording the time collection started and ended. Urinary albumin levels were determined by immunoturbidity on an automated analyzer, and excretion rates were determined by multiplying urinary albumin concentration by the volume per duration of the urine collection. We defined abnormal UAE rates as greater than 30 µg/min.¹⁶

Mean values between the two groups with normal and elevated UAE rates were compared by the Student t-test or by the Kruskal-Wallis H if variances were not normally distributed. Cate-

Table 2. Logistic Regression Correlates Of Elevated Urinary Albumin Excretion Rate (> 30 µg/min).

Variable	Adjusted Odds Ratio*	95% Confidence Interval
Glycosylated hemoglobin [†]	3.06	1.11 - 8.41
Current smoking [‡]	3.14	1.09 - 9.04

*Model adjusts for age and duration of hypertension.

[†]Glycosylated hemoglobin levels < 5% versus ≥ 5%.

[‡]Current smoking versus never or former smoking.

gorical data were analyzed using chi-square.

In addition to univariate analyses, multivariate analysis was performed with stepwise logistic regression. The dependent variable in the logistic regression model was an elevated UAE rate as defined above. The model simultaneously controlled for age and duration of hypertension (both continuous variables) as potential confounders for abnormal UAE rates. Independent predictors of an elevated UAE rate included race, sex, smoking status (current smoker versus former or never smoker), mean arterial blood pressure, body mass index, waist-hip ratio, glycosylated hemoglobin and insulin levels, and type of antihypertensive therapy used (if any). Backward stepwise logistic regression eliminated nonsignificant variables. All calculations were carried out using the EpiInfo¹⁷ and SPSS-PC¹⁸ statistical software programs.

Results

Summary characteristics of the 140 patients with essential hypertension are listed in Table 1. One hundred fifteen patients (82 percent) had a UAE rate of 30 µg/min or less, whereas 25 patients (18 percent) had elevated UAE levels. The two categories of patients did not vary by age, race, sex, duration of hypertension, number of patients receiving antihypertensive therapy or the percentage on angiotensin-converting enzyme inhibitor or calcium channel blocker therapy, blood pressure levels, anthropometric measurements, or insulin levels. A significantly higher percentage of patients with elevated UAE rates were current smokers (32.0 percent versus 14.3 percent). Additionally, patients with elevated UAE rates had significantly higher glycosylated hemoglobin levels (4.44 ± 0.83 percent versus 3.59 ± 1.60 percent) and serum creatinine levels (1.26 ± 0.52 mg/dL versus 1.04 ± 0.25 mg/dL).

Table 2 lists the logistic regression model of correlates of elevated UAE rates controlling for age and duration of hypertension. Patients who had higher glycosylated hemoglobin levels or who were current smokers were each approximately three times more likely to have an elevated UAE rate compared with those who had lower glycosylated hemoglobin levels or were nonsmokers (adjusted odds ratio [OR] = 3.06, 95 percent confidence interval [CI] = 1.11-8.41; and adjusted OR = 3.14, 95 percent CI = 1.09-9.04, respectively).

Discussion

Elevated UAE rate, while not necessarily predictive of renal decline in patients with essential hypertension,¹⁹ nonetheless is a marker of widespread vascular damage²⁰ and is predictive of more severe hypertensive complications²¹ including excess mortality from cardiovascular disease.^{6,11} Our results are the first to show a three-fold increase in risk for elevated UAE rates among primary care patients with essential hypertension who also currently smoke or have increased glycosylated hemoglobin levels. These data, which are potentially important to primary care physicians, distinguish a subgroup of patients with essential hypertension who might be at risk for an elevated UAE level and its attendant adverse consequences. It is important to point out, however, that our results are cross-sectional in nature and cannot determine cause-and-effect relations between abnormal UAE rates and cigarette smoking or elevated glycosylated hemoglobin levels.

Blood pressure did not correlate with elevated UAE rates, nor did antihypertensive therapy. This result was surprising and suggests that control of blood pressure, as such, might not be sufficient to decrease vascular damage that underlies abnormal UAE, especially among those patients who smoke or who possess some degree of glucose intolerance. There are at least two possible explanations for the lack of correlation between blood pressure in our patients and abnormal UAE. First, glomerular dysfunction among certain patients with essential hypertension might be less a result of blood pressure than of the presence of insulin resistance.²²⁻²⁴ Second, blood pressures were, on average, relatively normal, and most of our patients were already on antihypertensive therapy. Although angiotensin-converting

enzyme inhibitors²⁵ and calcium channel blockers²⁶ have been associated with a reduction in microalbuminuria apart from their antihypertensive effects, at least in diabetic patients, no such association was noted among our patients with essential hypertension, possibly because of the few patients on either type of medication.

What might be the underlying mechanism for the relation between glycosylated hemoglobin and abnormal excretion of urinary protein? Insulin resistance is associated with increased plasma norepinephrine,²⁷ vascular hypertrophy,²⁸⁻³⁰ and basal vascular tone.²³ In addition, by altering the electrical charge on basement membrane proteins, glycosylated end products make the glomerulus more permeable to serum albumin.³¹ Thus, abnormal UAE rates among hypertensive patients might be the combined renovascular effects of insulin resistance and glycosylated end products. Because hyperinsulinemia might be the most important underlying mechanism for adverse cardiovascular outcomes among patients with essential hypertension, primary care physicians should do everything within their power to improve insulin sensitivity in this group of patients by encouraging aerobic exercise and, if appropriate, weight loss.^{22,23}

These data also corroborate the known relation between cigarette smoking and abnormal UAE rates,³² providing primary care physicians with yet another reason for counseling their patients who have essential hypertension to stop tobacco use.

While the usefulness of screening patients with essential hypertension for abnormal UAE rates has not been firmly established, it is known that abnormal UAE rates predict cardiovascular risk in this group of patients.⁴⁻⁶ At present, it is unclear whether this urinary abnormality is causally linked to renal decline or cardiovascular morbidity or mortality or merely reflects end organ damage from other cardiovascular risk factors. These relations need further prospective study. In the meantime, our data suggest that there is a relation between abnormal UAE rates and hyperinsulinemia and current smoking among patients with essential hypertension. It seems clinically prudent for primary care physicians to address not only blood pressure but other cardiovascular risk factors while monitoring their patients who have essential hypertension. Focusing on weight loss and aerobic exercise as a means to improve insulin

sensitivity^{22,23} and on smoking cessation might be particularly important interventions among these patients already at high risk for adverse cardiovascular outcomes.

Our results are useful not only in predicting which patients with essential hypertension will have abnormal UAE rates; they also underscore the importance of aggressive and simultaneous correction of specific risk factors (eg, elevated glycosylated hemoglobin levels and cigarette smoking) among patients with essential hypertension to avoid renovascular damage and premature mortality from cardiovascular disease.

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