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Albumin-to-Creatinine Ratio Predicts Change in Ambulatory Blood Pressure in Normotensive Persons: A 7.5-Year Prospective Study

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Background: The relationship between urinary albumin excretion and blood pressure (BP) has been found to be positive in hypertensive and normotensive subjects. It is not known, in a normotensive and nondiabetic sample, whether elevated urinary albumin levels predict future increases in BP.

Methods: In this prospective study, we followed a cohort of 108 individuals who were initially free of hypertension and diabetes for an average of 7.7 years. Urinary albumin excretion was determined at baseline by radioimmunoassay in a 24-h collection. Ambulatory BP monitoring was used to assess BP at baseline and at 7.5-year follow-up. Regression models were used to evaluate the relationship of baseline urinary albumin-to-creatinine ratio to baseline BP and average rate of change in BP before and after controlling for several potential confounding variables.

Results: Baseline albumin-to-creatinine ratio was not associated with baseline ambulatory BP, but was positively associated with change in ambulatory BP. Before and after controlling for sex, race/ethnicity, age, body mass index at baseline, and change in body mass index, urinary albumin-to-creatinine ratio was found to be a significant independent predictor of change in awake and sleep systolic and diastolic BPs (all $P < .05$). It also independently predicted hypertension status at follow-up.

Conclusions: In healthy normotensive individuals, the urinary albumin-to-creatinine ratio predicts change in ambulatory BPs 7.5 years later. This finding suggests that urinary albumin excretion may be an important marker for processes that increase BP over time. Am J Hypertens 2006;19:220–226 © 2006 American Journal of Hypertension, Ltd.

Key Words: Blood pressure, ambulatory blood pressure, prospective studies, hypertension, urinary albumin excretion, microalbuminuria, cardiovascular risk factors.

Evidence for an association between microalbuminuria and cardiovascular disease (CVD) in patients with hypertension has been accumulating in recent years, with most reports claiming microalbuminuria to be a useful predictor.[1–6] The relationship between urinary albumin level and blood pressure (BP) has been found to be continuous and positive in most,[7,8] although not all,[9,10] cross-sectional studies. We recently reported that this continuous relationship holds separately for both normotensives and hypertensives.[11] Other studies have demonstrated that the risk of death and myocardial infarction increase in patients with an elevated urinary albumin level, even when patients with hypertension are excluded[3,12] or when adjusting for hypertensive status.[13]

Few studies have been conducted in nonhypertensive and nondiabetic samples. In normotensive populations, two studies have reported significant cross-sectional relationships between urinary albumin levels and BP levels,[11,14] but a third found no such association.[15] To our knowledge, there have not been any prospective studies among nonhypertensive, nondiabetic persons on the relationship between urinary albumin and BP. The current study examines the prospective relationship of

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urinary albumin levels to ambulatory BP (ABP) levels and the rate of change in BP during a 7.5-year follow-up in such a sample.

Methods

Participants

The data come from the Work Site Blood Pressure Study (WSBPS) investigating the psychosocial correlates of ABP. The WSBPS is a longitudinal cohort study in which participants were restudied at 3- to 4-year intervals. At initial recruitment into the study, participants were aged 30 to 60 years, had a body mass index (BMI) $\leq$32.5 kg/m^2, had screening BPs less than or equal to 160/105 mm Hg, and were free of CVD, and renal disease. The majority were normotensive, but about one-third had mild hypertension. All participants were literate in English and worked full-time (30+ h/wk) in one of nine organizations. Further details on inclusion and exclusion criteria have been reported elsewhere.[16,17]

To be eligible for this study, subjects had to have had an evaluation between 7/24/1989 and 7/1/1991, the only period during which 24-h urine samples were assayed for albumin. For some subjects this was their first evaluation, but most subjects had been first evaluated between 1985 and 1988 and this was their second assessment. Of the 227 eligible individuals evaluated during this period, hereafter referred to as baseline, 21 did not collect urine and 17 samples were inadvertently not assayed, resulting in 189 individuals with valid albumin data. Five participants with albumin data who had been diagnosed with diabetes, one who did not complete the ABP monitoring protocol, and 56 who were taking antihypertensive medications or whose mean awake ABP at the time of the albumin assessment was 135/85 mm Hg or higher were excluded from further analyses. All subjects were free of CVD (according to self-report, 12-lead electrocardiogram (ECG), *and* echocardiogram) at the time albumin was assayed. Thus, 127 participants met the inclusion criteria and were eligible for this prospective study.

Of these 127 participants, 19 did not participate in the final follow-up, which took place between 1996 and 2000. There were no significant differences between the 108 who did versus the 19 who did not complete the final follow-up with regard to sex, race/ethnicity, age, mean awake and sleep systolic and diastolic ABPs, or urinary albumin-to-creatinine ratio (all $P > .10$); however, BMI was greater in those who were followed compared to those who were not (mean 25.3 *v* 23.7 kg/m^2; $P < .04$). In summary, this study examines the change in ambulatory and clinic BPs of 108 individuals who were CVD-free and classified as normotensive according to their ABPs at the time their albumin was assessed.

The protocol and written consent form were approved by the Committee on Human Rights in Research of The New York Presbyterian Hospital–Weill Medical College of Cornell University. All participants gave written informed consent at the time of each evaluation.

Procedures

BP Measurements Using a mercury sphygmomanometer and an appropriately sized arm cuff (based on arm circumference), casual BPs were taken at the work site or clinic by a trained technician using the American Heart Association protocol.[18] After a 5-min rest period three BP measurements were taken in a sitting position, 1 to 2 min apart, and the average of the last two was used as the measure of casual BP. Systolic and diastolic BPs were defined by the first and fifth Korotkoff phases, respectively. These casual BPs were taken either before fitting the participant with the 24-h ABP or during the cardiovascular examination that occurred shortly thereafter.

Participants wore a SpaceLabs 90202 (baseline) or SpaceLabs 90207 (follow-up) ABP monitor (Hillsboro, OR) at baseline and follow-up evaluations for 24 h during a normal weekday (a work day if employed), using procedures described previously.[16,17] The monitor was fitted either while the participant was at work or during a research visit to The New York-Presbyterian Hospital Hypertension Center and calibrated by comparison of five successive systolic and diastolic readings against simultaneously determined auscultatory readings taken by a trained observer with a mercury column. Agreement of the averages to within 5 mm Hg was considered acceptable. The monitor was programmed to take readings at 15-min intervals during the day and at 30- or 45-min intervals during sleep, and the participant was instructed to proceed through a normal day. Each participant was asked to remain as motionless as possible each time the monitor took a reading during waking hours and then to record his or her location, position, activity, and mood in a diary. The average numbers of awake and sleep readings per subject were 51 $\pm$ 11 (mean $\pm$1 standard deviation) and 7.5 $\pm$ 2.7 at baseline and 58 $\pm$ 9 and 9.2 $\pm$ 2.6 at follow-up. All awake and sleep averages were based on a minimum of 10 and 4 readings, respectively.

Urinary Albumin Measurement On the day of the cardiovascular examination, a 24-h urine specimen was collected. Urinary albumin excretion was determined by the Hypertension Center Laboratory at Weill Medical College of Cornell University, New York, using a double-antibody radioimmunoassay technique, with a coefficient of variation ranging from 8% to 11% depending on the level of albumin.[19] Urinary creatinine was determined from the same 24-h specimen using the Jaffe rate calorimetry method (Beckman Astra, Brea, CA). From these measurements, the ratio of urinary albumin-to-creatinine (in milligrams per gram) was computed. Because the distribution of urinary albumin-to-creatinine ratio was severely positively skewed, the values were logarithmically transformed before performing all analyses.

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