Non-diabetic microalbuminuria in clinical practice and its relationship to posture, exercise and blood pressure

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SUMMARY

1. The effects of posture and exercise on the relationship between low-level urinary albumin excretion (microalbuminuria) and blood pressure was investigated in two groups of non-diabetic patients at increased cardiovascular risk: 21 otherwise healthy patients with untreated essential hypertension (blood pressure > 160/90 mmHg), and 14 age-matched patients with blood pressure at presentation within the normotensive range (< 160/90 mmHg) attending a cardiovascular clinic for assessment of chest pain.

2. A significant linear relationship between logarithmically transformed 'spot' urinary albumin/creatinine ratio and simultaneous clinic blood pressure existed when data from both groups of patients were analysed ($r = 0.58$, $P < 0.05$). The relationship between the scatter plot of blood pressure and the albumin/creatinine ratio appeared most marked when the mean blood pressure exceeded 120 mmHg.

3. In patients with essential hypertension, clinic systolic blood pressure was related to the albumin/creatinine ratio in simultaneous 'spot' urine samples ($r = 0.69$, $P < 0.05$) and also to the albumin/creatinine ratio in early-morning urine samples ($r = 0.51$, $P < 0.05$). However, the relationship between clinic blood pressure and simultaneous 'spot' urinary albumin/creatinine ratio in the patients with chest pain did not achieve significance when analysed independently.

4. Hourly averaged ambulatory intra-arterial blood pressure was recorded in four of the patients with essential hypertension during normal daytime activity, and a significant correlation with the simultaneous hourly daytime urinary albumin/creatinine ratio was found ($r = 0.65$, $P < 0.01$).

5. Low-level albumin excretion increased in both groups after exercise: peak systolic blood pressure during exercise was related to the rise in albumin excretion (hypertensive patients, $r = 0.68$, $P < 0.01$; normotensive patients, $r = 0.66$, $P < 0.05$).

Key words: ambulatory blood pressure, exercise, hypertension, microalbuminuria, orthostatic proteinuria.

INTRODUCTION

Low-level (10–200 mg/l) albuminuria (or 'microalbuminuria') is an independent predictor of diabetic nephropathy [1], and has been shown to be reversible, together with the decline in renal function, by treatment of mildly raised blood pressure [2]. Microalbuminuria has been shown to be related to the level of blood pressure in non-diabetic patients with essential hypertension [3], but not in normotensive subjects [4]. Although albumin excretion generally returns to normal after adequate anti-hypertensive treatment [5], the basis for the relationship between microalbuminuria and blood pressure is unclear.

Moderate exercise is also associated with an increase in urinary albumin excretion in hypertensive patients [6], but this relationship has not been reported in healthy subjects with normal blood pressure [7], and the role of increased blood pressure during exercise and albumin excretion has not been studied.

Microalbuminuria in hypertension may reflect a hydrostatic effect of increased intra-glomerular pressure, or glomerular or tubular changes in early hypertensive renal disease, or even a more generalized abnormality of endothelial permeability. Such a systemic effect is thought to account for the increase in urinary albumin excretion in certain extra-renal conditions [8–10]. In patients with diabetes mellitus [11] and in non-diabetic populations [12, 13], microalbuminuria appears to be a marker for both the presence and future risk of developing vascular disease.
This study set out to determine the relationship between urinary albumin excretion and blood pressure, posture and exercise in two groups of non-diabetic subjects at high cardiovascular risk and representative of patients seen in a clinical environment: (1) patients referred to a hospital hypertension clinic with untreated essential hypertension, and (2) patients whose presentation clinic blood pressure was within the normotensive range, referred to a cardiovascular clinic for assessment of chest pain.

**PATIENTS AND METHODS**

Fourteen patients (mean age 50.9 years, range 35–68 years, all males) attending a cardiovascular clinic for assessment of chest pain, with a presentation screening blood pressure of less than 160/90 mmHg before entry into the study and negative urinalysis, were recruited. On study days, patients received no therapy apart from sublingual nitrates, if required. Five patients were receiving prior therapy with oral nitrates, and two with calcium antagonists. 'Spot' daytime urine samples were obtained after 5 min of semi-supine rest, simultaneous with blood pressure measurement by a single observer using a mercury sphygmomanometer. After voiding, treadmill exercise (median 6 min) was performed as part of a routine clinical service. During exercise the ECG was continuously monitored and the blood pressure was measured at minute intervals by a single observer using a mercury sphygmomanometer. Exercise continued until the subjects either achieved a target heart rate (210 minus age) or until chest pain or ST depression exceeding 2 mm developed (six patients). A further specimen of urine was obtained after exercise.

Twenty-one untreated patients (mean age 52 years, range 35–71 years, nine males, 12 females), with a screening clinic blood pressure of greater than or equal to 160/90 mmHg at presentation and with negative urinalysis, were recruited from a hospital hypertension clinic. Four of these patients were also studied by intra-arterial blood pressure monitoring using the Oxford ambulatory apparatus [14]. A total of 17 urine samples from these patients were obtained at hourly intervals during daytime unrestricted activity and values for urinary microalbumin excretion were compared with the corresponding hourly averaged intra-arterial blood pressure.

Overnight albumin excretion was assessed in an overnight urine specimen collected immediately after rising. 'Spot' daytime urine specimens were obtained in the clinic after the patients had been resting semi-supine for 5 min, simultaneous with measurement of blood pressure by one observer using a standard mercury sphygmomanometer. After voiding, patients performed bicycle exercise (median duration 6 min) until a target heart rate was achieved. Blood pressure during exercise was measured at minute intervals by one observer and a second urine specimen was obtained immediately after exercise. Nine of the patients in the hypertensive group were unable to exercise and did not provide this specimen. Clinic blood pressure and peak blood pressure during exercise were compared with the urinary albumin/creatinine ratio for both groups of patients.

Urine specimens were collected into plastic receptacles from which 5 ml was taken and stored in glass bottles at −20°C. Urinary albumin was measured by using a sensitive r.i.a. [15]. Results were expressed as the albumin/creatinine ratio to allow for variations in urine flow rate, and were transformed logarithmically to correct for skewing in distribution before statistical analysis.
Microalbuminuria and blood pressure

Twenty-four hour urinary creatinine clearance was measured, and in the hypertensive patients left ventricular mass was estimated from echocardiography [16] and by summated voltage (V1 + V5) in standard ECGs. Linear regression analyses were used to compare the albumin/creatinine ratio with other variables, and the Student's t-test was used to compare values of microalbuminuria in different settings.

RESULTS

The blood pressure and albumin/creatinine ratio data for the patients with chest pain and normal blood pressure at presentation are summarized in Table 1. The relationships between the 'spot' daytime urinary albumin/creatinine ratio and the simultaneous clinic blood pressure did not achieve significance (Table 2), although when data from both groups of subjects were combined the tendency for microalbuminuria to increase at the higher levels of blood pressure (mean clinic blood pressure exceeding 120 mmHg) achieved statistical significance ($r = 0.58$, $P < 0.05$, Fig. 1). No significant difference in either daytime or post-exercise urinary microalbumin excretion was detected in the patients with exercise-induced chest pain or ST-segment depression.

In the patients with essential hypertension, the urinary albumin/creatinine ratio was significantly higher during the daytime than overnight. The blood pressure and the albumin/creatinine ratio during clinic visits are presented in Table 3. There was a significant correlation between both the overnight albumin/creatinine ratio and the daytime albumin/creatinine ratio during clinic visits and the simultaneous clinic systolic and mean blood pressures (Table 2, Fig. 1), although there was no correlation between urinary albumin excretion (overnight or daytime) and the following parameters: diastolic blood pressure, smoking status, age, creatinine clearance and measures of left ventricular mass.

Twenty-four hour intra-arterial studies of ambulatory daytime blood pressure in four of the hypertensive patients confirmed a significant correlation between the hourly albumin/creatinine ratio and the concurrent hourly averaged intra-arterial blood pressure ($r = 0.65$, $P < 0.01$, Fig. 2).

In both groups of patients, urinary albumin excretion increased significantly with exercise. The mean value for the albumin/creatinine ratio obtained after exercise in the patients with chest pain was higher, although the pre-exercise albumin/creatinine ratios for the two groups did not differ significantly. There was a significant correlation between the post-exercise albumin/creatinine ratio and the peak systolic blood pressure during exercise in both groups (Table 2).

DISCUSSION

The urinary albumin/creatinine ratio in different settings correlated with the systolic and mean blood pressures in patients with essential hypertension. This relationship may be due to hydrostatic factors related to systemic blood pressure and glomerular perfusion. The reduced overnight albumin excretion may have been due to lower blood pressure as is seen during normal sleep, or the recumbent posture itself, as seen with orthostatic proteinuria; nevertheless the relationship between overnight albumin excretion and daytime blood pressure was maintained. The closest correlations between blood pressure and albumin/creatinine ratio were found when blood pressure measurements and urine samples were obtained simultaneously. Hourly averaged intra-arterial ambula-
tory blood pressure recorded in four of the hypertensive patients during unrestricted activity (including random posture changes) appeared to confirm a linear relationship between daytime urinary microalbumin excretion and simultaneous blood pressure.

Population studies using 24 h urine collections have shown no correlation between blood pressure and albumin excretion in normotensive subjects, but a tendency for pressure-dependent albumin excretion at higher 'threshold' pressures was found [4]. In our study it is possible to discern a similar effect in those subjects whose mean blood pressure exceeded approximately 120 mmHg (Fig. 1).

In the patients with essential hypertension moderate exercise appeared to be associated with increased urinary albumin excretion, which has been reported previously [3]. An increase in albumin excretion with moderate exercise also occurred in the patients with chest pain and normal blood pressure. In both groups the increase in albumin excretion with exercise correlated with the peak systolic blood pressure. It appeared that the increased albumin excretion at rest in hypertension and during exercise in both groups of patients was most influenced by the level of simultaneous systolic blood pressure.

The variability of microalbuminuria with posture, exercise and the level of simultaneous blood pressure indicate that these factors must be strictly controlled in any future clinical evaluation of microalbuminuria as an independent predictor of cardiovascular risk.

Although this study did not examine the relationship between albumin excretion and blood pressure in diabetic patients, the blood pressure level also appears to influence the degree of microalbuminuria in diabetes mellitus [17]. It is therefore possible that microalbumin excretion in diabetic patients may also be confounded both by the level of simultaneous blood pressure (particularly in the hypertensive range) and by the effects of posture and exercise.

**REFERENCES**


