ORIGINAL RESEARCH

Prevalence and duration of exercise induced albuminuria in healthy people

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Abstract

Purpose: Vigorous exercise increases urine protein excretion. However, whether exercise increases urine albumin enough to reach the threshold for microalbuminuria (2.8 and 2.0 mg/mmol creatinine in women and men respectively) is uncertain. Furthermore, the duration of such albuminuria is unknown. We aimed to estimate the prevalence and duration of exercise induced microalbuminuria in normal healthy volunteers.

Methods: Thirty normal subjects provided a urine sample, then exercised to maximal heart rate, or exhaustion, using the standard Bruce Treadmill protocol. Further urine samples were collected within 15 min of completing exercise, and 24 and 48 hr later. Urine creatinine was measured by the Jaffé method and albumin via immunoturbidometry.

Results: Baseline urine albumin: creatinine ratio (A/C) was 0.5 ± 0.3 (SD) in women (n=14) and 0.4 ± 0.1 mg/mmol in men (n=16). Immediately after exercise A/C increased to 5.6 ± 9.7 (in women) and 7.6 ± 17.6 (in men). Twelve of 30 subjects reached the threshold for microalbuminuria and 2 that for macroalbuminuria. By 24 hr all had returned to baseline and there was no further change at 48 hours.

Conclusions: A short period, 15-20 min, of maximal exercise leads to A/C ratios above the microalbuminuria threshold in a substantial proportion of normal subjects. Physicians should not measure urine albumin in patients who give a history of such activity in the past 24 hr.

Microalbuminuria, defined as 24 hr albumin excretion rates of 30-300 mg, predicts declining renal function in people with and without diabetes.[1,2] More recently, microalbuminuria has been found to predict increased risk for cardiovascular and total mortality (relative risk 1.29 and 1.12 respectively) in the general population.[3] National guidelines recommend measuring albumin excretion in patients with hypertension accompanied by diabetes or renal disease.[4,5,6]

Measurement of 24 hr albumin excretion rate has been largely supplanted by the assessment of the ratio of albumin to creatinine concentrations: the albumin/creatinine (A/C) ratio. Although concerns exist over accuracy, reproducibility and reference ranges[7], an A/C ratio > 2.0 mg/mmol for men and 2.8 mg/mmol for women is generally accepted as abnormal.

Guidelines make the point that several (often 2 of 3) urine A/C measurements should be obtained before labeling the patient with microalbuminuria.[4,5] However, we have noted that some local physicians diagnose microalbuminuria on a single specimen. If microalbuminuria is present, the patient's risk category is elevated. This could lead to unnecessary therapy. Alternatively, a single "positive" sample could lead to collecting two or more further samples. While the cost

of the test has decreased recently, unnecessary testing would waste scarce health care dollars.

Many factors can increase urine albumin excretion: glomerular or tubular kidney disease, bladder or lower urinary tract disorders, fever, heart failure and exercise.[8] Indeed, strenuous exercise has been known for decades to increase protein excretion.[9]

The prevalence of exercise induced proteinuria is uncertain. In one study, all of 13 normal men performing vigorous exercise showed increased albumin excretion. The mean increased from 15 µg per minute (20.6 mg/day) before exercise to 316 µg per minute (455 mg/day) one hour after exercise.[10] The proportion reaching the A/C threshold was not reported. Another group found that 2 of 13 diabetics without microalbuminuria and none of 12 normal subjects reached an A/C ratio of 0.25 mg/mmol after exercising to the anaerobic threshold.[11]

Finally, the duration of exercise induced proteinuria is also not well defined. Poortmans[10] found that albumin excretion rate declined logarithmically after exercise with a half-life of 54 min, while another study suggested that it may last up to four days.[12]

Measuring urine albumin concentration has also undergone change. In the initial studies, urine was concentrated to about 8 g/L via ultrafiltration, followed by radioimmunoassay using rabbit anti-human albumin antibody.[13] This labour intensive method has been replaced in most laboratories by an immunoturbidometric assay (or nephelometry) performed on native urine [14] (see Methods).

We estimated the prevalence and duration of an exercise induced abnormal A/C ratio, using modern laboratory techniques in healthy volunteers.

TABLE 1. Characteristics of the subjects

	Women (n=14)	Men (n=16)
Age (yr)	24±2	28±5
Height (cm)	165.0±6.4	174.1±7.3
Weight (Kg)	59.6±7.8	75.4±9.8
BMI (kg/m^2)	21.9±2.8	24.8±2.3
Waist circumference (cm)	71.3±6.7	82.6±6.4
Resting HR	79±15	65±10
Resting SBP	120±13	132±10
Resting DBP	73±7	77±8

Mean ± standard deviation. BMI, body mass index; HR, heart rate; SBP,DBP, systolic and diastolic blood pressure.

Methods

Subjects

Thirty healthy subjects were recruited through poster advertizing. Their characteristics are shown in Table 1. None had a history of hypertension, diabetes or renal disease and none smoked. They took no prescription or non-prescription drugs, save aspirin (1 subject), a multiple vitamin (3) and oral contraceptives (2). The protocol and consent form were approved by the University of Saskatchewan Biomedical Ethics Committee (#07-168).

Procedures

After signing informed consent, and having age, height, weight and waist circumference recorded, each participant provided a spot urine sample. We then measured resting, seated blood pressure and heart rate, using an Omron HEM-711C automated monitor. We took three readings and averaged the final two to obtain baseline. Subjects then exercised on a variable speed and inclination treadmill, according to the standard Bruce protocol, to a calculated maximal heart rate (220-age in years) or to exhaustion. During exercise we measured heart rate and blood pressure, using a mercury sphygmomanometer, every two minutes. Within 15 min following exercise, we collected another urine sample, then two further samples 24 and 48 hr after exercise. We asked subjects to avoid extreme exertion for 48 hr after the treadmill test, but to continue their normal daily routines.

Measurements

Urine specimens were collected in sterile containers and, then, frozen. They were later analyzed in a single

run. Urine creatinine (Jaffe method) and albumin concentrations were measured in the chemistry laboratory, Royal University Hospital. Albumin was measured using an immunoturbidometric method (Synchron Systems LX, Becton Coulter, Mississauga, ON) in which specific anti-human albumin antibody is added to urine samples and combines with albumin to form insoluble complexes. This results in a decrease in light absorbance (380 nm), which is inversely proportional to the albumin concentration. There is no interference from commonly used drugs or vitamins. The within-assay coefficient of variation is 5.4% and the between-assay 8.0%.[15] Our reference range for albumin to creatinine ratio using these methods is <2.0 mg/mmol for men and <2.8 mg/mmol for women.

Statistical Analysis

We calculated sample size assuming no subject would have microalbuminuria at baseline. We chose 33% as a clinically significant proportion of subjects developing exercise induced microalbuminuria, so that we required 26 subjects for a power of 80% at $\alpha<0.05$ (GraphPad Instat 2.0, Vanderbilt University, Nashville, TN). We compared A/C ratios at all time points using a repeated measures ANOVA (Statmost 3.2, DataMost Corp., Sandy, UT). Finally, we conducted a prespecified post-hoc comparison of subjects who did, or did not develop exercise induced albuminuria using a one-way ANOVA. Data are displayed as mean ± standard deviation.

TABLE 2. Exercise intensity

	Women (n=14)	Men (n=16)
Time on treadmill (minutes)	14.7±2.7	15.5±3.0
METS max	14.8±2.8	12.2±2.9
VO_2 max (ml/Kg/minute)	51.8±7.7	42.8±6.8
HR max	179±10	180±12
SBP max	148±13	168±23

Mean ± standard deviation. METS, metabolic equivalents; VO_2 max, maximal oxygen utilization; HR max, SBP max, HR and SBP at maximal exertion.

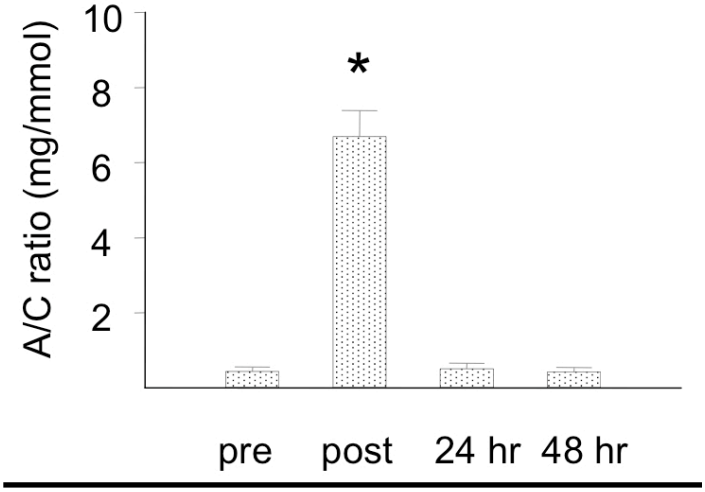

FIGURE 1. Urine albumin/creatinine (A/C) ratio before (pre), immediately after (post), 24 and 48 hour after exercise. *$P<0.001$ compared with baseline.

Results

All subjects achieved 90% or more of their estimated maximal heart rate (Table 2).

None complained of chest discomfort or light-headedness. All had the expected increase in systolic blood pressure with exercise.

Prior to exercise, all subjects had a normal A/C ratio: 0.5 ± 0.3 mg/mmol in women and 0.4 ± 0.1 in men. None reached the nominal threshold for microalbuminuria. Immediately after exercise, all subjects showed an increase in A/C ratio to a mean of 5.6 ± 9.7 in women and 7.6 ± 17.1 in men ($P<0.001$ for both). The mean A/C increased 11-fold and 19-fold respectively. The percent increase, while numerically higher in men, was not statistically significant between the sexes. By 24 hr after exercise, and while carrying on their usual activities, all subjects returned toward their baseline A/C ratio (Figure 1) and none had sustained microalbuminuria.

Twelve subjects, 8 men and 4 women, reached the nominal, sex-standardized A/C ratio for microalbuminuria after exertion, and two subjects, 1 man and 1 woman, developed frank proteinuria: 70.7 and 31.7 mg/mmol. Table 3 compares subjects who developed microalbuminuria with those who didn't. There were

TABLE 3. Subjects who did, or did not, manifest post-exercise microalbuminuria

	Microalbuminuria (n=12)	No microalbuminuria (n=18)
Sex (m/f)	4/8	12/6
BMI	23.6±3.2	23.4±2.7
Waist	78.1±9.1	75.4±9.8
METS max	14.4±2.3	13.1±3.2
HR max	175±3.2	182±2.9
SBP max	166±22	153±23

Mean ±standard deviation.
Abbreviations same as in Tables 1 and 2.

no differences in the parameters measured between these groups. In particular, there was no correlation between the maximal systolic blood pressure during exercise and the post-exercise A/C ratio (r=-0.04; *P*=0.748).

Discussion

We showed that a substantial proportion of normal, fit, people develop microalbuminuria after a single, short bout of intense exercise. In fact, 40% of our thirty subjects had microalbuminuria and two of thirty developed frank proteinuria. All resolved within 24 hr. Physicians should ask about recent vigorous exercise and delay measuring urine albumin excretion for 24 hr in the presence of same. Our subjects were students and medical personnel who are fairly active in everyday life, but did not develop albuminuria on three successive days of normal activity. Furthermore, we were unable to predict, using easily measurable clinical parameters, subjects whose urine protein excretion would reach the threshold. Our subjects varied substantially in age, but were not obese. Perhaps a group with a wider range of BMI, waist circumference or resting blood pressure might show a correlation between one or more of these parameters and albumin excretion with exercise.

Our study offers no insight into the mechanism of exercise induced increases in A/C. Vigorous exercise causes a 30% decrease in renal blood flow (notwithstanding an increase in mean arterial pressure)[16], but a lesser decrease in glomerular filtration rate[17] so that creatinine clearance (and excretion) decreases minimally. Protein excretion, on the other hand, increases several fold, apparently due to both increases in filtered load and relative decreases in tubular absorption.[18] In general, low molecular weight proteins such as β_2 microglobulin (molecular weight 11 kD) show a greater increase in urine after exercise than albumin (molecular weight 69 kD).[18] This suggests that differential reabsorption occurs and that smaller proteins can saturate their reabsorption mechanisms at lower urinary concentrations. However, increased glomerular permeability to protein also occurs. One possible explanation is an increase in intraglomerular pressure due to angiotensin induced efferent arteriolar contraction. Indeed, short term angiotensin converting enzyme inhibition with captopril reduces exercise induced albuminuria in diabetics to a greater extent than nifedipine.[19]

Our study has limitations. We chose to study normal volunteers who were capable of vigorous exercise, not the group generally tested for microalbuminuria; those with hypertension and diabetes or renal disease. We speculate that patients with these conditions would show the same or an even greater response. Also, we chose only two intensities of exercise: maximal and that obtained in everyday medical duties. Whether there is a threshold for exercise induced microalbuminuria between these extremes is uncertain. We showed that the A/C ratio returns to baseline within 24 hr (actually 18-20 hr); whether a shorter recovery period is possible is unknown. Finally, as mentioned above, the homogeneity of our study population mitigates against finding correlations between increases in A/C ratio and body mass index, waist circumference, resting blood pressure or other clinical parameters.

In summary, we have shown that even a short period of strong dynamic exercise causes microalbuminuria in healthy subjects. Physicians should ensure

the absence of recent vigorous exercise in the preceding 24 hr before sending a specimen to the laboratory.

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