Acute Effects of Different Intensities of Exercise in Normoalbuminuric/Normotensive Patients With Type 1 Diabetes

JAMES T. LANE, MD[1]
TIMOTHY C. FORD, MS, RCEP, CDE[1]
LUANN R. LARSON, RN, BSN, CCRC[1]
WARD A. CHAMBERS, MD[1]
PASCALE H. LANE, MD[2]

OBJECTIVE — The purpose of this study was to investigate the effect of exercise occurrence and intensity on albumin excretion in normotensive, normoalbuminuric patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS — Eighteen patients (aged 29 ± 2 years, duration of diabetes 14 ± 2 years, blood pressure 120 ± 2/74 ± 1 mmHg, HbA_{1c} 7.0 ± 0.2% [mean ± SE]) without microalbuminuria, hypertension, or anti–angiotensin II therapy participated in two exercise studies in a clinical research center. Exercise intensities were defined as moderate (50% heart rate reserve [HRR]) and intense (75% HRR) and were performed in random order. Subjects collected urine for albumin determination on the days before and after exercise. On the day of exercise, subjects exercised for 30 min on a treadmill at the assigned intensity. Timed urine collections were obtained over the day. Blood pressures were measured using an ambulatory blood pressure monitor.

RESULTS — Moderate exercise demonstrated no changes in albumin excretion. Intense exercise demonstrated a significant increase in albumin excretion during the first 4 h compared with the rest of the day ($P = 0.03$) but returned to normal thereafter. Albumin excretion did not exceed normal levels throughout the study. There was no difference in albumin excretion surrounding days of intense exercise. Ambulatory blood pressures demonstrated nocturnal dipping after moderate and intense exercise ($P < 0.001$).

CONCLUSIONS — We have demonstrated that normotensive, normoalbuminuric patients without anti–angiotensin II therapy do not have elevated albumin excretion following exercise intensities experienced by most patients with type 1 diabetes.

Diabetes Care 27:28–32, 2004

Albumin excretion in the urine defines the presence of nephropathy in patients with diabetes (1–5). The albumin excretion test is confounded by high interindividual variability and false positive readings from concomitant atherosclerotic disease, exercise, high-protein diets, acute hyperglycemia, hypertension, and urinary tract infections (1). Therefore, it is essential to control for these conditions to interpret the results of measurements of albumin excretion. This is especially true because mild increases in albumin excretion trigger therapy with anti–angiotensin II therapy (1).

Exercise may falsely increase albumin excretion (2). Exercise acutely increases intravascular pressure in the arteries and arterioles. This leads to increased glomerular pressure and increases the filtration of albumin across the glomerular basement membrane into the urinary space. The potential for an exaggerated albuminuric response to exercise has led to speculation that albumin excretion during exercise may serve as a prognostic marker for incipient nephropathy (3).

Measuring albumin excretion on a random urine avoids the problems associated with measuring 24-h urine collections. However, this method may overstate the albumin excretion rate when the sample is taken following exercise. It is thus critical to understand the temporal pattern of albumin excretion following exercise. This also includes the intensity of the exercise because it may alter the amplitude of the physiologic response.

Our study characterizes the effect of exercise on albumin excretion in a population of normoalbuminuric, normotensive patients with type 1 diabetes. This group of patients was not treated with ACE inhibitors or angiotensin receptor blockers (ARBs), avoiding the suppression of albumin excretion characteristic of these agents (4–9). We performed a randomized, crossover study in a clinical research center setting that evaluated the amplitude and magnitude of albumin excretion following levels of exercise that would be performed by most patients with type 1 diabetes. The protocol was designed to determine whether these effects differed with the intensity of exercise as well.

RESEARCH DESIGN AND METHODS

— Between 1999 and 2003, 18 subjects, aged ≥19 years, with type 1 diabetes of ≥5 years duration were recruited from the University Diabetes Clinic at the University of Nebraska Medical Center. Subjects had type 1 diabetes as defined by American Diabetes Associa-

From the [1]Department of Internal Medicine, University of Nebraska Medical Center, Omaha, Nebraska; and the [2]Department of Pediatrics, University of Nebraska Medical Center, Omaha, Nebraska.

Address correspondence and reprint requests to James T. Lane, MD, Department of Medicine, 983020 Nebraska Medical Center, Omaha, NE 68198-3020. E-mail: jtlane1@unmc.edu.

Received for publication 8 May 2003 and accepted in revised form 3 October 2003.

Abbreviations: ARB, angiotensin receptor blocker; CRC, Clinical Research Center; HRR, heart rate reserve.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

tion criteria (10). Exclusion criteria included microalbuminuria (>30 μg/mg creatinine), hypertension (>130/80), therapy with ACE inhibitors or ARBs, proliferative retinopathy, current cigarette smoking, cardiovascular disease, hyperlipidemia, peripheral vascular disease, peripheral neuropathy, autonomic neuropathy, pregnancy, or poor glycemic control as evidenced by screened HbA_{1c} >10.0%. Subjects were screened for HbA_{1c} and for microalbuminuria by random urine samples, and height, weight, and blood pressure were measured. A cardiac stress test was performed on a separate day from the screening using a modified Bruce protocol and interpreted by a cardiologist (11). No subjects were excluded on the basis of a positive exercise stress test for ischemia. The study protocol was approved by the University of Nebraska Medical Center's Institutional Review Board.

After screening, subjects were scheduled to return to the Clinical Research Center (CRC) at the University of Nebraska Medical Center on two occasions. The study utilized a randomized, crossover design. Subjects completed a study sequence following moderate and intense exercise in random order. Intensity of exercise was determined by utilizing the heart rate reserve (HRR), an indicator of $V_{O_{2reserve}}$ (12,13). $V_{O_{2reserve}}$ refers to the maximum oxygen uptake reserve, an indicator of the difference between maximum oxygen consumption and oxygen consumption at rest (12,13). Moderate exercise was defined by reaching an HRR of 50% during exercise on a treadmill. Intense exercise was defined by an HRR of 75% on a treadmill. The formula for HRR is as follows: $HRR = [(HRR_{max} - HR_{rest})(0.5)(0.75)] + HR_{rest}$ (14). HR_{max} was calculated using the formula 220 − age.

Subjects arrived at the CRC by 0800 on the day of exercise. On the day before exercise, subjects collected a 24-h urine sample that concluded at 0900 on the day of exercise. Subjects were not allowed to exercise for 3 days before study. All subjects were instructed by a registered dietitian to eat a normal protein diet consisting of $0.7\ g \cdot kg^{-1} \cdot day^{-1}$ (10% of daily calories) for the week before the study (15). Subjects arrived at the CRC after having fasted for at least 8 h. Subjects were allowed to give their intermediate-acting insulin in the morning and instructed to avoid the use of rapid-acting insulin. Insulin pump users were asked to leave their basal rate the same. A capillary blood glucose was determined, and subjects were not allowed to exercise if their blood glucose was <100 or >250 mg/dl. After a 5-min warm-up period, the walking speed and incline on the treadmill (Marquette Series 2000; Marquette Electronics, Marquette, WI) were increased to reach the planned HRR. The conditions that met the HRR were maintained for 25 min. Subjects were continually monitored with a Polar Heart Rate Monitor (Polar Electro, Kempele, Finland). After exercise, subjects were allowed to check their capillary blood glucose and eat, using their rapid-acting insulin.

Subjects were then confined to the CRC for a series of timed urine collections. Urine specimens were collected every 4 h at 0900–1300, 1300–1700, 1700–2100, and 2100–0100. A final collection was made between 0100 and 0900 the next day. Subjects had their blood pressure continually monitored using an ambulatory blood pressure cuff/monitor (Model 90217–1A; SpaceLabs Medical, Redmond, WA). Subjects were encouraged to hydrate themselves orally to maintain urine output. The session was concluded with a 24-h urine collection on day 3 after discharge from the CRC. The second exercise was completed in an identical manner, except for the HRR measurement, and was completed within 3 months of the first exercise session.

All labs were performed in the Nebraska Health System's Clinical Laboratory. HbA_{1c} was measured by high-pressure liquid chromatography (normal range 4.0–6.0%). Urine albumin was measured by nephelometry. Urine and serum creatinine were measured by enzymatic methods. Urine albumin excretion is expressed as micrograms albumin per milligram creatinine throughout.

Statistical analyses

All values are expressed as means ± SE. All data were examined with repeated measures ANOVA with post hoc Tukey testing if $P < 0.05$ for the ANOVA. In all cases, the comparable nonparametric test was used if the data were not normally distributed. All analyses were performed using SigmaStat 2.0 (SPSS, Chicago, IL).

RESULTS

— Between 1999 and 2003, 20 subjects were screened for participation. Before the exercise treadmill study, two subjects withdrew for schedule reasons. Of the 18 subjects who received exercise treadmill tests, all had normal studies and went on to enter the protocol. One of the 18 subjects completed only the moderate exercise study. The other 17 subjects, all Caucasian, completed both the moderate and intense studies without difficulty (baseline characteristics are summarized in Table 1).

Table 1—*Baseline patient characteristics*

Age (years)	29 ± 2
Sex (M/F)	9/9
Duration of diabetes (years)	14 ± 2
Weight (kg)	83.5 ± 2.1
Height (cm)	175.4 ± 1.6
BMI (kg/m^2)	27.1 ± 0.5
Systolic blood pressure (mmHg)	120.0 ± 2.0
Diastolic blood pressure (mmHg)	74.0 ± 1.0
HbA_{1c} (%)	7.0 ± 0.2
Screening urine albumin (μg/mg creatinine)	8.4 ± 1.4

Data are means ± SE.

Moderate exercise did not result in abnormal albumin excretion on the day of exercise (Fig. 1). Note that two subjects had >30 μg/mg creatinine on the day before exercise, but it did not rise after exercise. On the day of exercise, the albumin excretion was greatest during the first 4 h after exercise, but this value was not statistically different from the other values obtained for the timed urine collections during the subsequent 24 h ($P = 0.21$). Overall, the albumin excretion did not rise above the normal limit of 30.0 μg/mg creatinine.

Intensive exercise resulted in similar levels of albumin excretion when compared with moderate exercise (Fig. 2). Although the mean albumin excretion was slightly higher on the day of exercise compared with the pre- and postexercise days, the difference was not statistically significant ($P = 0.09$). Unlike moderate exercise, intensive exercise resulted in a threefold higher level of albumin excretion during the first 4 h after exercise compared with timed collections throughout the rest of the day ($P = 0.03$). Although the 4-h albumin excretion was higher than that of other time points, this was not statistically different when compared with the same time point after moderate exercise ($P = 0.11$). The increase

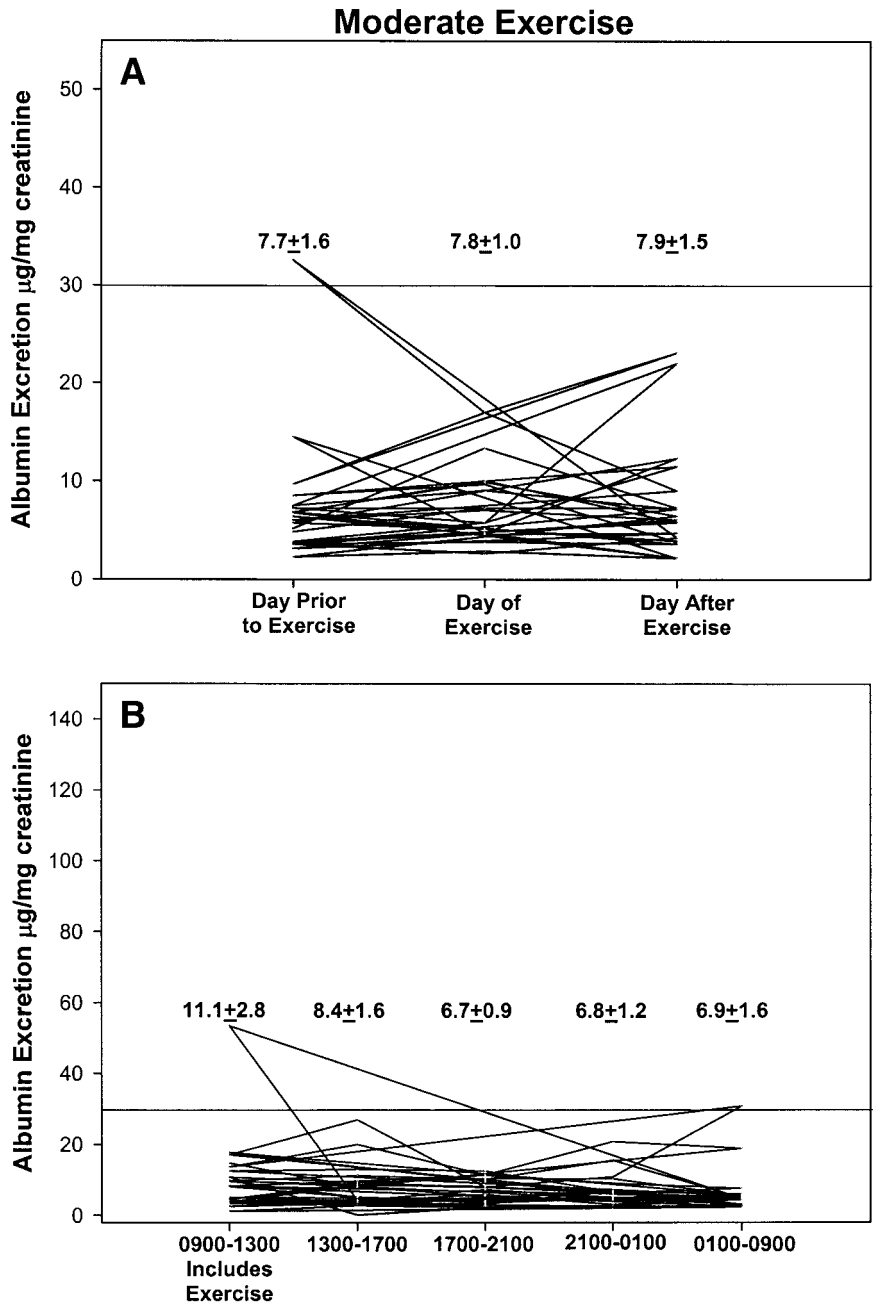

Figure 1—*Effect of moderate exercise on urine albumin excretion.* A*: Albumin excretion in micrograms per milligram creatinine on 3 successive days around exercise.* B*: Albumin excretion on timed urine collections during the day of exercise. Data for individual subjects are presented with the mean ± SE for the group above each collection point. There was no difference in albumin excretion throughout the day of exercise* (P = *0.21). The solid horizontal line represents the upper limit for albumin excretion (30 µg/mg creatinine).*

seen immediately after intense exercise was due to increased values in 4 of the 18 patients. No differences in age, duration of diabetes, sex, BMI, blood pressure, HbA_{1c}, or baseline albumin excretion were demonstrated when these patients were compared with the 14 who remained normoalbuminuric.

Blood pressures were not different for patients with the moderate or intense protocol, and there were no differences in blood pressure following exercise between levels of intensity. There were no differences in blood pressure following exercise between levels of intensity. There was a significant fall in pressure during the night following both levels of exercise. Daytime values (pre-exercise, 10 min, 60 min, 1100, and 0800) were compared with overnight readings (0001 through 0600). For moderate exercise, daytime blood pressure averaged 91 ± 1 mmHg, whereas overnight blood pressure averaged 80 ± 1 mmHg ($P < 0.001$). Similar values were demonstrated for the intense protocol (90 ± 1 vs. 80 ± 1 mmHg; $P < 0.001$). The maximum fall in mean arterial pressure was 15 mmHg after moderate intensity exercise and 14 mmHg after the intense protocol.

CONCLUSIONS — Patients with type 1 diabetes who are normotensive and normoalbuminuric show no significant change in albumin excretion with exercise. With intensive exercise, there is a higher level of albumin excretion within the first 4 h after exercise. Although the rise in albumin excretion was statistically significant after intensive exercise, albumin excretion did not rise above normal levels. The spectrum of the exercise intensity in this study should correspond to the level of exercise attained by most patients with type 1 diabetes. For patients with type 1 diabetes who exercise at intense levels for prolonged durations, it would still be appropriate to put limitations on exercise before screening because less is known about the interpretation of results in this setting. This conclusion differs from previous recommendations (16) that only early morning urine specimens should be used for baseline albumin excretion determinations.

The results of our study cannot be extended to patients with elevated albumin excretion or who are receiving anti–angiotensin II therapy. Patients who already have microalbuminuria have been shown to have more pronounced albumin excretion in response to exercise when compared with normoalbuminuric patients (17,18). Patients with microalbuminuria have also been shown to have an exaggerated rise in systolic blood pressure with exercise (18). However, by the time patients develop microalbuminuria, current clinical recommendations encourage the use of anti–angiotensin II therapy with ACE inhibitors or ARBs (1).

Previous studies have shown that patients on ACE inhibitor therapy have decreased levels of albumin excretion. In a randomized, double-blind, placebo-controlled study, Tuominenet, Ebeling,

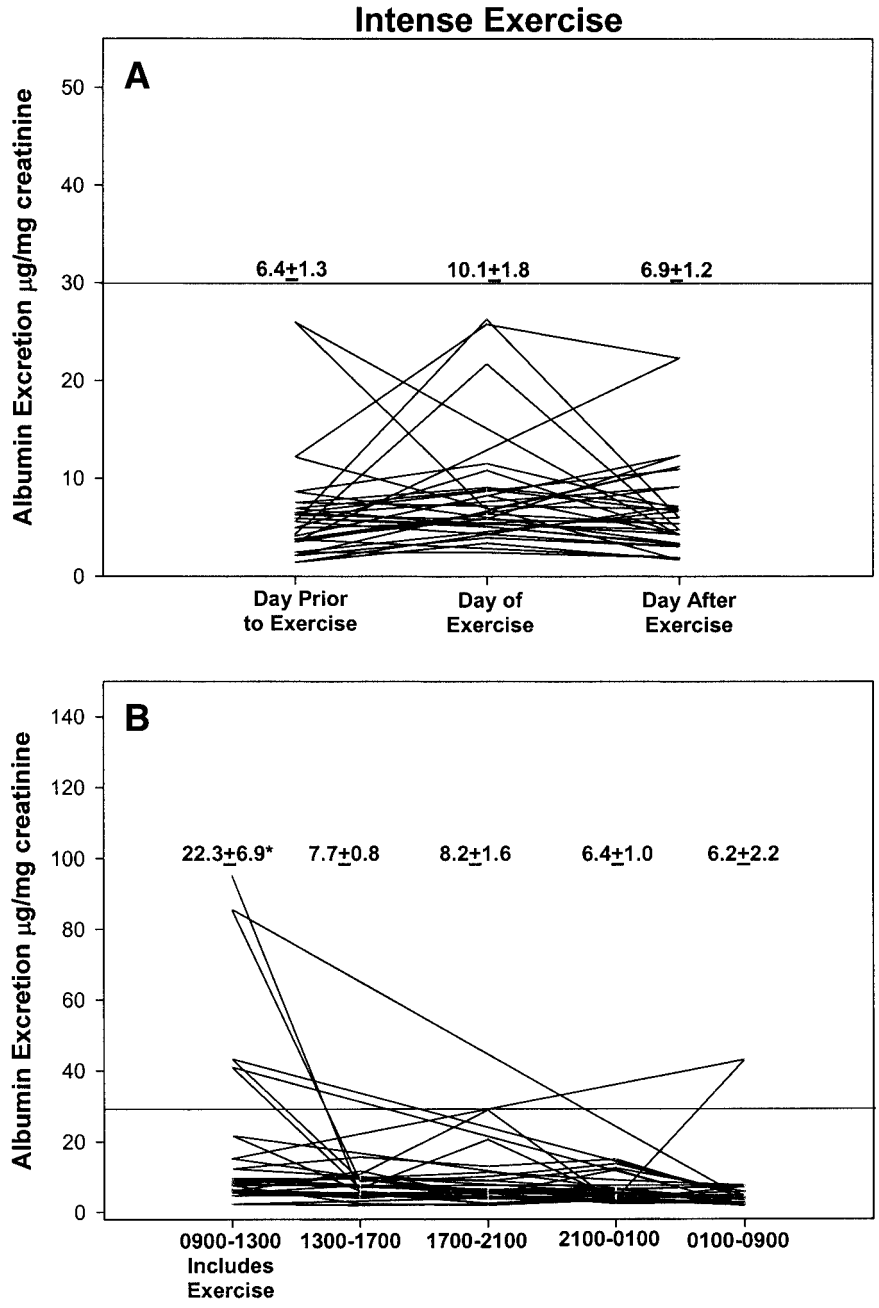

Figure 2—*Effect of intense exercise on urine albumin excretion.* A: *Albumin excretion in micrograms per milligram creatinine on 3 successive days around exercise.* B: *Albumin excretion on timed urine collections throughout the day of exercise. Data for individual subjects are presented with the mean ± SE for the group above each collection point. There was no difference in albumin excretion between days* (P = *0.09). Albumin excretion was higher during the first 4 h compared with the rest of the day. *ANOVA* P = *0.03.*

and Koivisto (5) studied 26 normotensive/normoalbuminuric patients. Half of them received lisinopril and half placebo. Over the 2 years of the study, patients treated with lisinopril had a significant decrease in their albumin excretion rate after exercise. However, the lisinopril group had a level of postexercise albumin excretion that was greater than the placebo group at baseline. Poulsen et al. (19) studied 21 normotensive patients with type 1 diabetes and randomized them to lisinopril versus placebo. This group of patients already had microalbuminuria, with albumin excretion rates of 20–70 µg/min. Lisinopril significantly decreased exercise-induced albumin excretion compared with placebo. The mechanism of benefit may be related to blood pressure or a primary intrarenal effect on glomerular structure or function (19). Similar studies on the effect of pharmacotherapy and exercise-induced albuminuria are not available for ARBs.

In conclusion, we have demonstrated that postexercise albumin excretion under conditions of moderate and intense exercise does not exceed abnormal levels in normotensive/normoalbuminuric patients with type 1 diabetes not on anti–angiotensin II therapy. These results should reassure practitioners regarding the use of spot urine studies after usual levels of exercise in such patients.

Acknowledgments— This study was supported through funding from the University of Nebraska Medical Center's Research Support Fund and the Clinical Research Center.

The authors acknowledge the assistance of Maxine McElligott, RD, CDE, in the nutritional counseling of patients before exercise.

This work was presented in part at the 2002 ADA Scientific Sessions, San Francisco, California, June 2002.

References

1. American Diabetes Association: Diabetic nephropathy (Position Statement). *Diabetes Care* 26 (Suppl. 1):S94–S102, 2003
2. Vittinghus E, Mogensen C: Graded exercise and protein excretion in diabetic man and the effect of insulin treatment. *Kidney Int* 21:725–729, 1982
3. Feldt-Rasmussen B, Baker L, Deckert T: Exercise as a provocative test in early renal disease in type 1 (insulin-dependent) diabetes: albuminuria, systemic and renal haemodynamic responses. *Diabetologia* 28:389–396, 1985
4. Parving H, Hommel E, Smidt U: Protection of kidney function and decrease in albuminuria by captopril in insulin dependent diabetics with nephropathy. *BMJ* 297:1086–1091, 1988
5. Tuominenet J, Ebeling P, Koivisto V: Long-term lisinopril therapy reduces exercise-induced albuminuria in normoalbuminuric normotensive IDDM patients. *Diabetes Care* 21:1345–1348, 1998
6. The EUCLID Study Group: Randomized placebo-controlled trial of lisinopril in normotensive patients with insulin-dependent diabetes and normoalbuminuria or microalbuminuria. *Lancet* 349:1787–1792, 1997
7. Brenner B, Cooper M, Zeeuw DD, Keane W, Mitch W, Parving H, Remuzzi G,

Snapinn S, Zhang Z, Shanifar S: Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 345:861–869, 2001
8. Lewis E, Hunsicker L, Clarke W, Berl T, Pohl M, Lewis J, Ritz E, Atkins R, Rohde R, Raz I: Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 345:851–860, 2001
9. Parving H, Lehnert H, Brochner-Mortensen J, Gomis R, Andersen S, Arner P: The effect of irbesartan on the development of diabetic nephropathy in patients with type 2 diabetes. *N Engl J Med* 345: 870–878, 2001
10. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus (Position Statement). *Diabetes Care* 26 (Suppl. 1):S5–S20, 2003
11. Hill J, Timmis A: Exercise tolerance testing. *BMJ* 424:1084–1087, 2002
12. Swain D, Leutholtz B: Heart rate reserve is equivalent to %VO2 reserve, not to %VO2max. *Med Sci Sports Exerc* 29:410–414, 1997
13. Swain D, Leutholtz B, King M, Haas L, Branch J: Relationship between % heart rate reserve and %VO2 reserve in treadmill exercise. *Med Sci Sports Exerc* 30:318–321, 1998
14. Camp SV: Pharmacologic factors in exercise and exercise testing. In *Resource Manual for Guidelines for Exercise Testing and Prescription*. 2nd ed. Durstine J, King A, Painter P, Roitman J, Zwiren L, Kenney W, Eds. Philadelphia, Lea and Febiger, 1993, p. 197–215
15. American Diabetes Association: Evidence-based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications (Position Statement). *Diabetes Care* 26 (Suppl. 1):S51–S61, 2003
16. Mogensen C: Nephropathy: early. In *Handbook of Exercise in Diabetes*. 2nd ed. Ruderman N, Devlin J, Schneider S, Kriska A, Eds. Alexandria, VA, American Diabetes Association, 2002, p. 433–449
17. Mogensen C, Vittinghus E, Solling K: Abnormal albumin excretion after two provocative renal tests in diabetes: physical exercise and lysine injection. *Kidney Int* 16:385–393, 1979
18. Christensen C: Abnormal albuminuria and blood pressure rise in incipient diabetic nephropathy induced by exercise. *Kidney Int* 25:819–823, 1984
19. Poulsen P, Ebbehoj E, Mogensen C: Lisinopril reduces albuminuria during exercise in low-grade microalbuminuric type 1 diabetic patients: a double blind randomized study. *J Intern Med* 249:433–440, 2001