Fuel and Fluid Homeostasis During Long-Term Exercise in Healthy Subjects and Type I Diabetic Patients

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OBJECTIVE — This study was designed to examine metabolic and hormonal effects of long-term exercise in healthy subjects and insulin-dependent (type I) diabetic patients.

RESEARCH DESIGN AND METHODS — Two studies were performed. First, 16 healthy males (32 ± 3 yr) were studied during a semitriathlon competition (2 km swimming, 90 km biking, and 21 km running). Second, 9 type I diabetic males (41 ± 2 yr) and 17 healthy matched control subjects were studied during a 75 km cross-country skiing race. Blood samples were taken before and immediately after exercise, and also during the ski race.

RESULTS — During the semitriathlon race, serum insulin, C-peptide, glucagon cortisol, growth hormone ACTH, prolactin, and plasma renin activity increased two- to ninefold, whereas serum testosterone fell. Apart from a fall in magnesium, serum electrolyte concentrations remained unchanged. Before long-term skiing, patients reduced their insulin dose by 30–40%. They were hyperglycemic during the initial part of the race, but near normoglycemic thereafter. There were large interindividual variations in the increments of counterregulatory hormones, whereas serum testosterone and luteinizing hormone fell quite uniformly. Plasma renin activity and aldosterone concentrations rose similarly in diabetic and healthy subjects, whereas the rise in antidiuretic hormone was slightly greater in diabetic patients. During the initial part of the race, serum atrial natriuretic peptide fell in both groups.

CONCLUSIONS — Severalfold increments in hormone concentrations contribute to the maintenance of fuel and fluid homeostasis during long-term exercise. With an appropriate adjustment of insulin dose and diet, also type I diabetic patients can participate in competitive long-term exercise.

There is a burgeoning popularity of endurance exercise, as indicated by the increasing number of various competitions and participants. For example, >10,000 runners participate each year in events such as the London, Boston, New York, or Berlin marathons. In addition, the triathlon—a three-event sport of swimming, biking, and running—is enjoying a tremendous increase in popularity. Races such as the marathon or triathlon probably represent the greatest stress with which humans voluntarily tax their fuel homeostasis (1). In concert with healthy subjects, diabetic patients participate in endurance exercise (2,3). In these patients, extra effort has to be made for the maintenance of adequate fuel homeostasis during endurance exercise because they lack the normal secretion of insulin, a key hormone in the metabolic regulation during exercise (4,5). In this study, we review some of the recent data and present our own results regarding fuel homeostasis during endurance exercise in normal humans and insulin-dependent (type I) diabetic patients.

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CARBOHYDRATE AND FAT UTILIZATION DURING ENDURANCE EXERCISE

— Muscle glycogen is the major source of energy during the first 20–30 min of moderate exercise. The rate of glycogen breakdown is greater, the more intensive the exercise (6). When exercise is prolonged, the proportion of hepatic glucose production as a source of energy is increased. In well-trained athletes, hepatic glucose production increased after 1 h of exercise from a baseline value of 5 mg/kg/h to the maximum of 15 mg/kg/h after 4 h of exercise (7). Thereafter, hepatic glucose production declines, and there is a gradual shift from carbohydrate to fat as a major fuel. Whereas after 60 min of exercise, free fatty acids (FFAs) contribute to 40% of oxidative energy, after 4 h of moderate exercise the contribution of FFAs has risen to 70% (7,8). After 8 h of moderate exercise, lipid oxidation is responsible for 80–85% of oxidative energy in trained individuals, with the rest derived from glucose oxidation (7). In protein turnover, long-term exercise causes an adaptive reduction: after 8 h of muscular work, leucine flux rate attains a plateau at a 20% lower level than in the resting state (7).

Blood glucose remains unchanged or decreases only slightly during the first hour of exercise. Thereafter,

Table 1—*Circulating metabolite, hormone, and electrolyte concentrations at rest and after the Finnish semitriathlon in 16 healthy men*

	At rest	After the race
Glucose (mmol/L)	4.6 ± 0.1	5.6 ± 0.2*
Insulin (pmol/L)	22.2 ± 2.4	31.8 ± 3.6*
C-peptide (nmol/L)	0.37 ± 0.02	0.43 ± 0.05*
Glucagon (ng/L)	314 ± 39	621 ± 62†
Cortisol (nmol/L)	468 ± 20	1039 ± 12‡
Testosterone (nmol/L)	19.6 ± 1.1	13.0 ± 0.9‡
Growth hormone (μg/L)	0.9 ± 0.2	8.6 ± 2.1†
ACTH (ng/L)	30 ± 3	103 ± 63‡
Thyreotropin (mU/L)	2.5 ± 0.2	2.6 ± 0.3
Prolactin (μg/L)	8.5 ± 0.7	21.6 ± 1.3†
Plasma renin activity (ng · L^{-1} · sec^{-1})	1.48 ± 0.28	12.8 ± 2.3†
Na^+ (mmol/L)	143 ± 2	140 ± 2
K^+ (mmol/L)	4.4 ± 0.1	5.0 ± 0.2
Cl^- (mmol/L)	104 ± 2	98 ± 3
Pi (mmol/L)	1.0 ± 0.1	1.4 ± 0.2
Calcium (mmol/L)	2.4 ± 0.2	2.5 ± 0.2
Magnesium (mmol/L)	0.84 ± 0.02	0.72 ± 0.02†
Creatine kinase (U/L)	197 ± 35	868 ± 120‡
Creatinine (μmol/L)	97 ± 3	108 ± 4*
Hb (g/L)	144 ± 2	158 ± 2*
White blood cells (×10^9/L)	4.3 ± 0.3	9.7 ± 0.7†

*$P < 0.05$, †$P < 0.001$, ‡$P < 0.01$.

hepatic glucose production can no longer keep pace with augmented utilization, and blood glucose concentration begins to decline. If no glucose is ingested, long-term exercise may result in hypoglycemia. Blood glucose levels of 2.5 mmol/L with symptoms such as muscular twitching, pallor, and nervous irritability already have been demonstrated in the Boston marathon in 1924 (9). The incidence of hypoglycemia was more recently examined by Felig et al. (10) during long-term exercise. After prolonged (60–150 min) exercise in the fasting state, 35% of the subjects had blood glucose 2.5 mmol/L or below. Yet they continued to exercise for 15–70 min with blood glucose between 1.4 and 2.7 mmol/L.

If glucose (75 g) is ingested before exercise, this raises plasma insulin concentrations at the time exercise begins. Consequently, hyperinsulinemia further enhances glucose utilization by muscle and prevents an adequate rise in hepatic glucose production. As a result, hypoglycemia may ensue both during intensive, short-term exercise (11) or moderate long-term physical work (12). If carbohydrate solutions are taken during exercise, insulin secretion is stimulated less than in the resting state (13). Thus, carbohydrate solutions taken during long-term exercise are effective in maintaining plasma glucose concentrations and improving endurance performance (14).

FUEL HOMEOSTASIS DURING TRIATHLON COMPETITION — The triathlon consists of 3.9 km swimming, 180 km biking, and 42 km running. The time spent for the race varies from 9 to 11 h in top athletes. This heavy competition does not result in hypoglycemia because carbohydrates are ingested by the athletes during the race. In the Hawaii Triathlon, the mean blood glucose concentration after the race (6.5 ± 0.4 mmol/L) was even higher than the fasting glucose level in the same subjects determined on another day (4.3 ± 0.2 mmol/L, $P < 0.001$) (15). The triathlon race caused a marked lipolysis, as indicated by a 3.5-fold rise in serum glycerol concentration from 67 ± 8 to 233 ± 29 μmol/L ($P < 0.005$) and by a threefold rise in serum FFA concentration from 430 ± 70 to 1250 ± 130 μmol/L ($P < 0.005$). In keeping with this, van Rensburg et al. (16) demonstrated in the Johannesburg Triathlon a 18% rise in blood glucose, an 80% increment in lactate, a 2.7-fold rise in serum glycerol, and a 3.8-fold rise in serum FFA concentration in the athletes. Serum electrolyte and hemoglobin levels remained unchanged.

We have recently studied hormone and fuel homeostasis in a Finnish Semitriathlon competition. This race consists of 2 km swimming, 90 km biking, and 21 km running. We studied 16 healthy males with the mean age of 32 ± 3 yr. Ambient temperature during the race was 20°C. The fluid ingested contained 25 g/L glucose (Dexal), and the intake during the competition varied between 2.5 and 3.5 L. Thus, the total carbohydrate intake was between 60 and 90 g. The time the athletes used for the race varied from 4 to 6 h. Postrace blood sample was taken 2–3 min after the end of the competition. The resting sample was taken in the fasting state 2–3 weeks after the race.

The metabolite, hormone, and electrolyte concentrations at rest and after the race are shown in Table 1. At the end of the race, plasma glucose, serum insulin, and C-peptide concentrations were higher than in the resting control day. Although immediate postexercise values do not represent steady-state exercise concentrations (17), these findings suggest that the athletes had not suffered hypoglycemia during the race. The avoidance of hypoglycemia is further suggested by unchanged concentrations of TSH (Table 1), because hypoglycemia

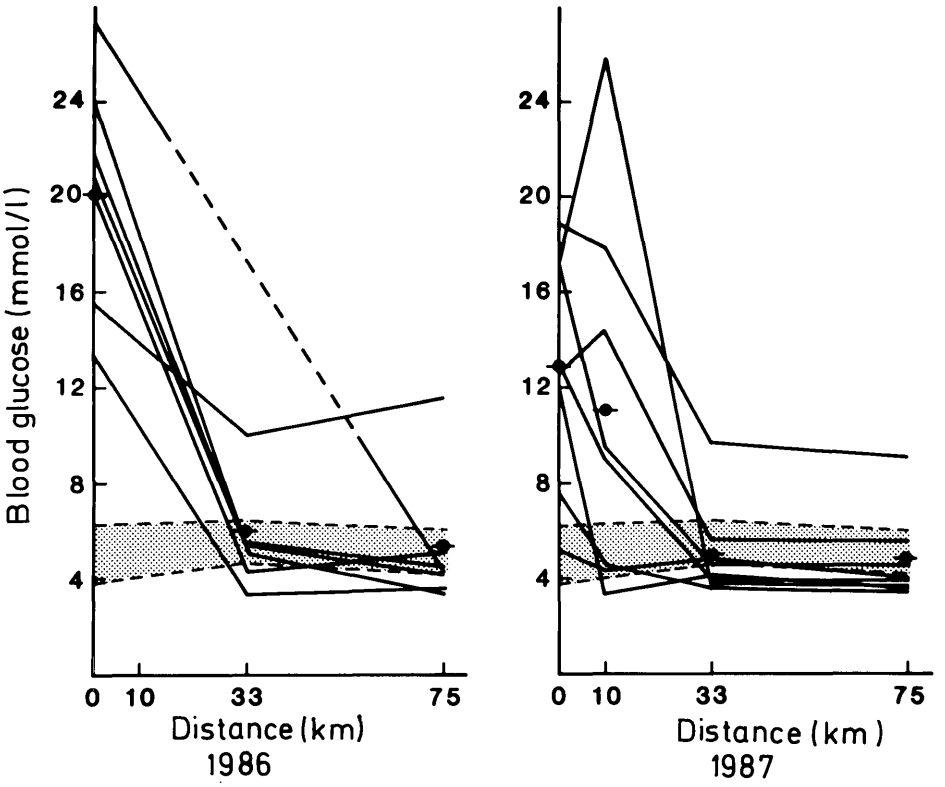

Figure 1—*Changes in plasma glucose concentrations during a 75 km cross-country skiing in healthy subjects (shaded area) and type I diabetic patients (individual curves). From Sane et al. (2). © by Diabetologia.*

can increase TSH secretion (18). Part of the rise in plasma glucose may have occurred postexercise (17). After the end of intensive exercise, plasma catecholamine concentrations are still elevated and maintain augmented glucose production in the face of declining utilization. As a result, plasma glucose concentration rapidly increases, when the rate of glucose production exceeds the rate of utilization (17). Serum growth hormone, prolactin, ACTH, and glucagon concentrations increased, and serum testosterone level fell, as is known to occur during long-term exercise (19). Plasma renin activity increased by 8.7-fold. This is more than previously reported during a marathon run (20). A rise in renin activity is related to a decrease in plasma volume as indicated by a rise in blood hemoglobin concentration (Table 1) and a decrease in renal blood flow, which is also dependent on exercise intensity. In addition, reduced hepatic blood flow during strenuous exercise further increases renin activity by reducing the hepatic clearance of renin. High renin activity is physiologically appropriate because it serves to increase salt and water retention.

In our subjects, serum magnesium concentration decreased and potassium remained unchanged. Under physiological conditions, cells are releasing equal amounts of potassium and magnesium. Different changes in serum potassium and magnesium concentrations reflect the loss of magnesium in the sweat. During prolonged exercise, sweat magnesium concentration markedly increases (21).

LONG-TERM EXERCISE IN TYPE I DIABETES— Data are scanty regarding endurance exercise in insulin-treated diabetic patients. We are aware of only one controlled study addressing the metabolic and hormonal effects of a 3-h marathon run in these patients (3). The patients were well controlled and took their last insulin injection either 16 or 26 h before the exercise. During exercise, patients had insulin concentrations either normal or slightly above normal. Their blood glucose declined and remained in the normal range. Plasma glucagon, growth hormone, cortisol, epinephrine, and norepinephrine concentrations during exercise were higher in the patients than in the healthy subjects (3). All patients completed the 3-h run without major difficulties.

We examined the metabolic and hormonal changes during a competitive 75 km cross-country skiing in 9 type I diabetic subjects (41 ± 2 yr) and 17 healthy, matched controls. Some of this

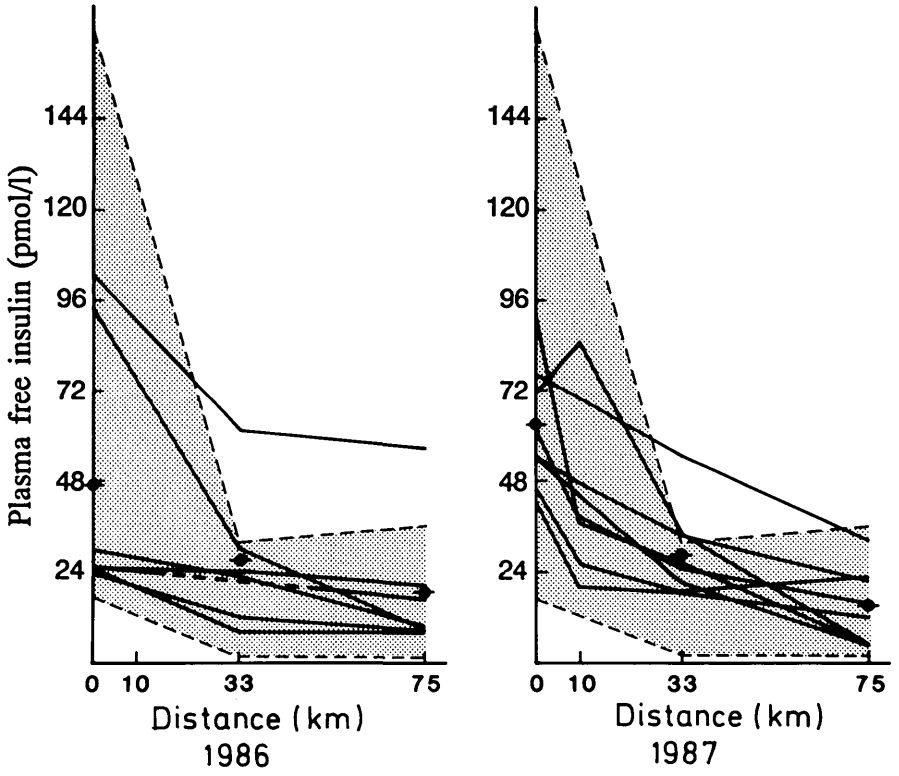

Figure 2—*Changes in plasma-free insulin concentrations in healthy subjects (shaded area) and type I diabetic patients during a 75 km cross-country skiing. From Sane et al. (2). © by Diabetologia.*

data have been published before (2). The average skiing time was 7.5 h for both groups. In the morning, the patients reduced their morning insulin dose by 28% (range 8–47%) and had 65 g carbohydrates and 15 g of protein for breakfast. During the race, the average carbohydrate intake was 36 g/h. During the first 33 km of skiing, plasma glucose (Fig. 1) and insulin (Fig. 2) concentration fell rapidly to normal range. None of the patients had either symptomatic or biochemical hypoglycemia during the race. Exercise was associated with increments in serum growth hormone, cortisol, and glucagon concentrations (Fig. 3), whereas serum testosterone and luteinizing hormone levels declined (Fig. 4). Although the mean hormonal changes were statistically significant, there were large interindividual variations in the hormonal response to exercise. Hormonal response to exercise was not significantly different from that in healthy subjects.

Because the prerace plasma glucose concentration was very high (20.3 ± 1.8 mmol/L), patients were restudied during the race the following year. In the restudy, they were instructed to reduce insulin dose more (by 38%, range 25–52%), have less carbohydrates (38 g), and have more protein (30 g) for breakfast than the previous year. Consequently, they were less hyperglycemic (12.9 ± 1.6 mmol/L) before the race than the previous year (Figs. 1 and 2). During skiing, they maintained near normoglycemia as they did the year before.

Because some diabetic patients have hypoglycemic symptoms postexercise, we determined insulin sensitivity in four patients on the day after the race. As determined with insulin clamp technique, the rate of insulin-mediated glucose disposal was increased in each of the four patients postexercise (2). Previously, Devlin et al. (22) reported increased insulin sensitivity in non-insulin-

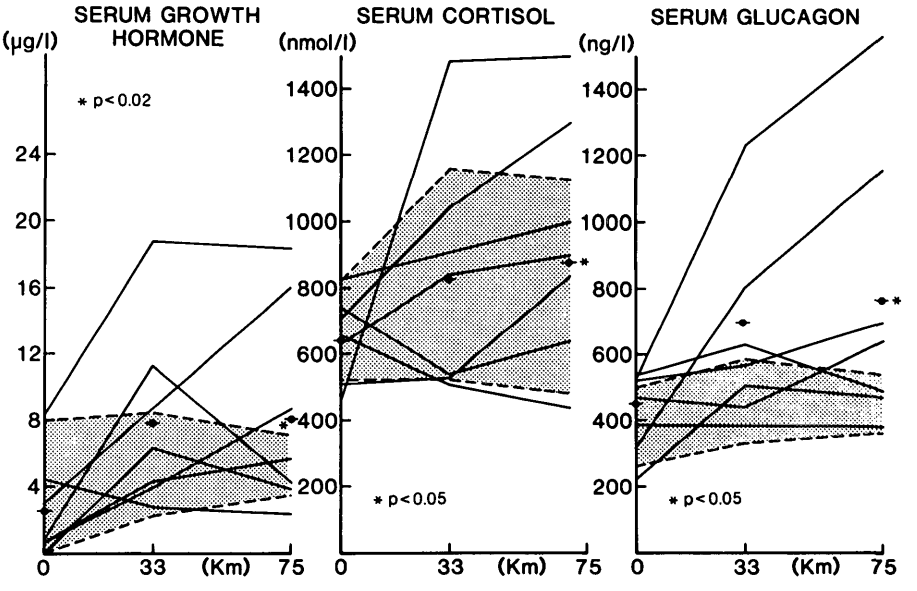

Figure 3—*Changes in serum growth hormone, cortisol, and glucagon concentrations in healthy subjects (shaded area) and type I diabetic subjects (individual curves) during a 75 km cross-country skiing race. Determinations were made in the race of 1986.*

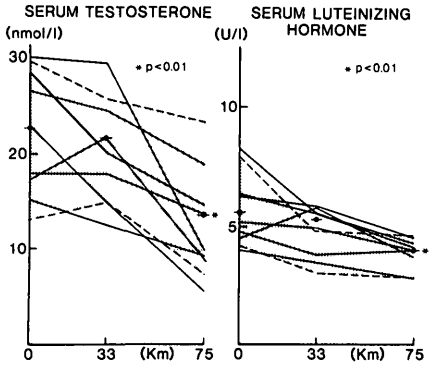

Figure 4—*Serum testosterone and luteinizing hormone concentrations in healthy subjects (shaded area) and type I diabetic patients (individual curves) during a 75 km cross-country skiing race.*

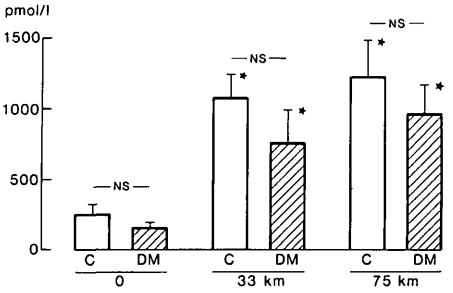

Figure 6—*Serum aldosterone concentrations before, after 33 km, and after 75 km skiing race in healthy controls (C) and type I diabetic patients (DM). NS, not significant. *P < 0.05 vs. baseline.*

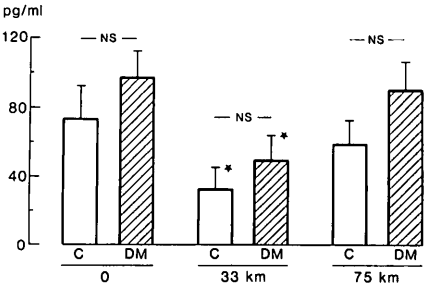

Figure 8—*Serum atrial natriuretic peptide concentrations before, after 33 km, and after 75 km skiing race in healthy controls (C) and type I diabetic patients (DM). NS, not significant. *P < 0.05 vs. baseline.*

dependent diabetic patients after a single bout of exercise on the previous day. The increased glucose uptake was caused by augmented nonoxidative glucose disposal. This probably reflects increased glucose storage as glycogen after exhaustive, glycogen-depleting exercise.

As previously reported for short-term exercise in healthy humans (19,23), we observed a significant increase in plasma renin activity (Fig. 5), serum aldosterone (Fig. 6), and antidiuretic hormone concentrations (Fig. 7). The two-fold increase in renin activity in healthy subjects during 75 km skiing was less than the 8.7-fold rise observed in semi-triathlon competition (Table 1). The lower rise during skiing may be caused by less volume depletion by sweating, because the ambient temperature during the ski race was −20°C, in contrast to 20°C on the day of triathlon. The rise in plasma renin activity and serum aldosterone concentration was similar in diabetic and control subjects, whereas serum antidiuretic hormone concentration rose slightly more in diabetic patients (Fig. 7). The greater increment in antidiuretic hormone in diabetic patients may be caused by their initial hyperglycemia and glucosuria, which may have reduced plasma volume more than in control subjects.

Several studies have demonstrated an increase in serum atrial natriuretic peptide (ANP) concentration after a short-term exercise (24–28). These observations have been made either in healthy subjects or in patients with congestive heart failure. Regarding the long-term exercise, Lijnen and coworkers (29) observed a 2.5-fold increase of ANP in healthy runners after a marathon. In contrast to previous data, in our subjects ANP fell during the initial 33 km skiing and returned back to the baseline values postexercise (Fig. 8). The decline was similar in both healthy and diabetic skiers. A decrease of ANP during long-term exercise is physiologically appropriate for several reasons. First, ANP increases the glomerular filtration rate and the sodium filtration fraction. Thus, a rise in ANP could increase volume depletion during long-term exercise. Second, ANP reduces cardiac output. Third, ANP inhibits renin release and aldosterone response to angiotensin. Thus, a reduction in ANP concentration maintains plasma volume and adequate cardiac output during long-term exercise. Whether the postexercise recovery of ANP represents a rise that occurred immediately after the end of the exercise, or whether that is related to an extremely long-term exercise, is not possible to conclude from this study.

Taken together, hormonal changes for the maintenance of fluid ho-

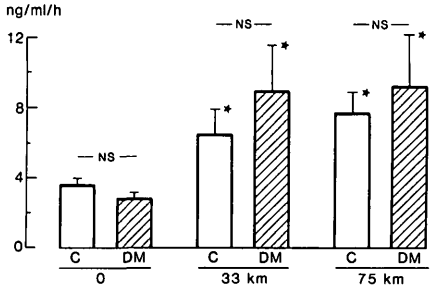

Figure 5—*Plasma renin activity in healthy controls (C) and type I diabetic patients (DM) before, after 33 km, and after 75 km skiing race. *P < 0.05 vs. baseline.*

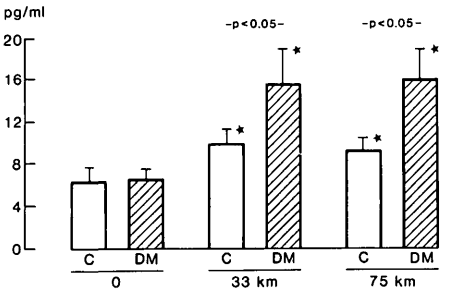

Figure 7—*Serum antidiuretic hormone concentrations before, after 33 km, and after 75 km skiing race in healthy controls (C) and type I diabetic patients (DM). *P < 0.05 vs. baseline.*

meostasis during long-term exercise are in type I diabetic patients similar to those seen in healthy humans. This, and the maintenance of near normoglycemia during competitive exercise of several hours, indicate that insulin-treated diabetic patients are able to participate in exhaustive endurance exercise.

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