Changes in Insulin Sensitivity, Glucose Effectiveness, and B-Cell Function in Regularly Exercising Subjects

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To determine the relative contributions of changes in glucose effectiveness, B-cell function, and insulin sensitivity to changes in glucose tolerance upon exercise cessation in regularly exercising individuals, we studied seven young subjects who were performing aerobic exercise on a regular schedule. Each subject was studied 12 and 84 hours after the last bout of exercise with an intravenous glucose tolerance test (IVGTT) to quantify insulin sensitivity and glucose effectiveness at zero insulin (GEZI) using the minimal model of glucose kinetics. Additionally, B-cell function was quantified as the acute insulin response to glucose (AIRglucose), and intravenous glucose tolerance as the glucose disappearance constant (K_g). Twelve hours after the last bout of exercise, S_I was 8.47 ± 1.12 × 10^{-5} min^{-1} /pmol/L, as compared with 6.98 ± 1.17 × 10^{-5} min^{-1}/pmol/L 84 hours after exercise (mean ± SE, P = .005). No change was observed in GEZI (0.020 ± 0.004 min^{-1} at 12 hours *v* 0.019 ± 0.002 min^{-1} at 84 hours, P = NS) or AIRglucose (588 ± 213 pmol/L at 12 hours *v* 687 ± 271 pmol/L at 84 hours, P = NS). Thus, the difference in intravenous glucose tolerance observed 12 hours after exercise as compared with 84 hours after the last bout of exercise (K_g, 2.91 ± 0.70 %/min at 12 hours *v* 2.23 ± 0.60 %/min at 84 hours, P < .05) would appear to be entirely related to a difference in S_I and not to differences in glucose effectiveness or B-cell function.

GLUCOSE TOLERANCE is known to deteriorate when exercise is stopped.[1] Since glucose tolerance is dependent on both insulin-independent and insulin-dependent glucose uptake,[2,3] changes in either or both factors could contribute to this change. Additionally, insulin-dependent glucose uptake depends on both insulin sensitivity and B-cell function. Thus, changes in glucose tolerance should be mediated by changes in one or more of insulin-independent glucose uptake, insulin sensitivity, or B-cell function.

The decrease in glucose tolerance upon exercise cessation has been associated with a decrease in insulin sensitivity by investigators who noted an increase in the insulin response to oral or intravenous glucose with unchanged or decreased glucose tolerance,[1,4] or a decrease in the glucose infusion rate during a euglycemic, hyperinsulinemic clamp[5] in humans after a period without exercise. Since insulin-independent glucose uptake is a major factor in glucose tolerance,[3] it is possible that changes in this factor may also contribute to the decrease in glucose tolerance when exercise is stopped. However, neither the glucose tolerance test nor the single-step hyperinsulinemic clamp are able to discern a change in insulin-dependent glucose uptake distinct from a change in insulin-independent glucose uptake. In fact, a decrease in insulin-independent uptake could have been interpreted as a decrease in insulin sensitivity, since total glucose uptake includes the insulin-independent component.

Therefore, to examine the contribution of insulin-independent glucose uptake and B-cell function, as well as insulin sensitivity, to the decrease in glucose tolerance upon exercise cessation, we used the minimal model to measure glucose effectiveness as an index of insulin-independent glucose uptake, insulin sensitivity, B-cell function, and glucose tolerance 12 and 84 hours after the last bout of exercise in individuals who were exercising on a regular basis.

SUBJECTS AND METHODS

Subjects

Seven young, apparently healthy men with no history of major medical illness, taking no medications, and with no first-degree relatives with histories of diabetes mellitus participated in the study. Subjects were between 21 and 30 years of age and had spontaneously participated in regular aerobic exercise for at least 30 minutes per day on four or more occasions per week (Table 1). The study was approved by the Human Subjects Review Committee at the University of Washington, and all subjects gave written informed consent before participation in the study.

Procedures

Each subject underwent a frequently sampled intravenous glucose tolerance test (IVGTT) on two occasions. The first test was performed approximately 12 hours after the last bout of exercise; this interval was selected to correspond to the typical time interval used in earlier studies. The second study was performed approximately 84 hours after the last bout of exercise to allow dissipation of the acute effect of exercise while minimizing any changes that may occur from detraining. IVGTTs were performed to quantify indices of insulin sensitivity (S_I) and glucose effectiveness at basal insulin (S_G), the acute insulin response to glucose (AIRglucose), and the glucose disappearance constant (K_g). Insulin-independent glucose uptake was computed as glucose effectiveness at zero insulin (GEZI) as detailed later. The subjects were advised to exercise for normal duration and intensity on the evening before the first study, to consume their usual postexercise meal, and not to alter their dietary habits for the duration of the study. No formal aerobic exercise was permitted after this bout of exercise until the end of the study, although other normal daily activities were allowed.

The studies were performed on the metabolic ward of the Seattle Veterans Affairs Medical Center between 7 and 9 AM after an overnight fast. Subjects were supine during the study, and blood samples were obtained through an 18-gauge plastic catheter placed in a forearm vein. This arm was maintained in a heating pad to arterialize venous blood.[6] Infusates were administered through a

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Table 1. Characteristics of Seven Male Subjects

Subject No.	Age (yr)	BMI (kg/m²)	% Maximal HR	Exercise Duration (h/wk)	Exercise Frequency (per wk)	Exercise Type
1	21	19.7	55	5	4	Bicycling
2	25	25.5	69	6	6	Running
3	22	21.0	83	4	4	Swimming
4	22	27.7	91	3	5	Stairmaster®
5	28	24.1	77	12	5	Bicycling
6	29	24.4	81	14	6	Rowing
7	30	22.0	71	5	6	Running

NOTE. % Maximal HR represents the self-reported mean HR during exercise as a percentage of the maximum computed as 220 − age. Exercise duration is also self-reported and measured in hours per week, and exercise frequency as the number of exercise sessions per week.

similar catheter inserted in the contralateral arm. Both catheters were kept patent by a slow infusion of 0.9% saline.

Quantification of S_I, S_g, B-cell Function, and Glucose Tolerance

The IVGTT procedure consisted of collection of three baseline samples for insulin and glucose, followed by injections of glucose 11.4 g/m² over 60 seconds commencing at time 0 and tolbutamide 125 mg/m² at 20 minutes. Tolbutamide was used to improve reliability of parameter identification.[7] Blood samples were collected at 29 time points over the subsequent 180 minutes following glucose administration, and were placed on ice until the plasma was separated and stored at −20°C until assayed for glucose and insulin. Basal glucose and insulin levels were calculated as the average of baseline samples. AIRglucose was determined as the mean of the incremental insulin response at 2, 3, 4, 5, 6, 8, and 10 minutes after administration of glucose. K_g was computed as the slope of the linear least-square regression line to the natural logarithm of the glucose concentration versus time from 10 to 19 minutes after administration of glucose.

Assays

Plasma glucose concentrations were measured in duplicate using a glucose oxidase method (Beckman Instruments, Palo Alto, CA). Plasma insulin level was measured in duplicate using a modification of a double-antibody radioimmunoassay.[8] All samples from the same individual were measured in a single assay. To detect potential catecholamine-induced changes in model parameters,[9] plasma epinephrine and norepinephrine levels were measured using a single-isotope enzymatic method.[10]

Computations and Statistics

S_I and S_g were obtained from IVGTT results by identification of model parameters using a nonlinear least-square technique.[11,12] Since the minimal model provides an estimate of glucose effectiveness at basal insulin levels, this value is influenced by both S_I and basal insulin concentration. To eliminate these dependencies, GEZI was computed by subtracting the glucose disposal mediated by the basal insulin concentration. Thus, GEZI = S_g − Ib · S_I, where Ib is the basal insulin level and S_g and S_I are identified by the minimal model.[13]

An estimate of exercise intensity was computed as 100 × (average heart rate [HR] during exercise)/(maximum HR), where average HR is a self-reported value for each subject for the usual bout of exercise and maximum HR is 220 − age in years.[14] The average HR was obtained from either written exercise logs or from recall based on at least two exercise sessions. Linear regression was used to examine the relationship between exercise intensity and percentage change in S_I.

Unless otherwise stated, paired two-tailed t tests were used for all comparisons. Data are expressed as the mean ± SE.

RESULTS

The study group consisted of young men between 21 and 30 years of age whose exercise program varied in intensity from 55% of maximum HR for 5 hours per week to 81% of maximum HR for 14 hours per week (Table 1). The median interval between the last bout of exercise and the start of the IVGTT was 12 hours (range, 10 to 18). The mean body mass index was 23.5 kg/m², with a range of 19.7 to 27.7.

S_I was 8.47 ± 1.12 × 10^{-5} min^{-1}/pmol/L when measured 12 hours after the last bout of exercise, and decreased to 6.98 ± 1.17 × 10^{-5} min^{-1}/pmol/L 84 hours after the last exercise bout (P = .005). AIRglucose, a measure of B-cell function, was not different 12 and 84 hours postexercise (588 ± 213 pmol/L at 12 hours and 687 ± 271 pmol/L at 84 hours, P = NS). Insulin-independent glucose uptake quantified as GEZI was also not different, being 0.020 ± 0.004 min^{-1} 12 hours after the last bout of exercise and 0.019 ± 0.002 min^{-1} at 84 hours after the last bout of exercise (P = NS). K_g was 2.91 ± 0.70 %/min 12 hours following the exercise bout, and decreased to 2.23 ± 0.60 %/min 84 hours following exercise (P < .05). Individual results for each subject are shown for S_I (Fig 1A), GEZI (Fig 1B), AIRglucose (Fig 1C), and intravenous glucose tolerance (Fig 2). Fasting glucose, insulin, and catecholamine levels did not change (Table 2). A significant relationship between percent maximum HR and percentage difference in S_I could be demonstrated (r = .79, P < .05), suggesting that exercise intensity was a determinant of the change in S_I.

DISCUSSION

Our study has shown that intravenous glucose tolerance is lower when measured 84 hours after exercise as compared with 12 hours postexercise in regularly exercising men. This change appears to be due to a change in S_I

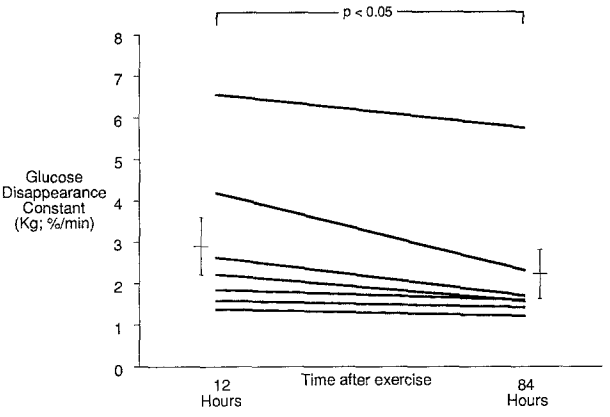

Fig 1. Individual measurements of S_I (A), GEZI (B), and AIRglucose (C) in 7 subjects studied 12 and 84 hours after a bout of exercise. Results are the mean ± SE. The effect of time since the last bout of exercise was significant (P = .005) for S_I but not for the other two measurements.

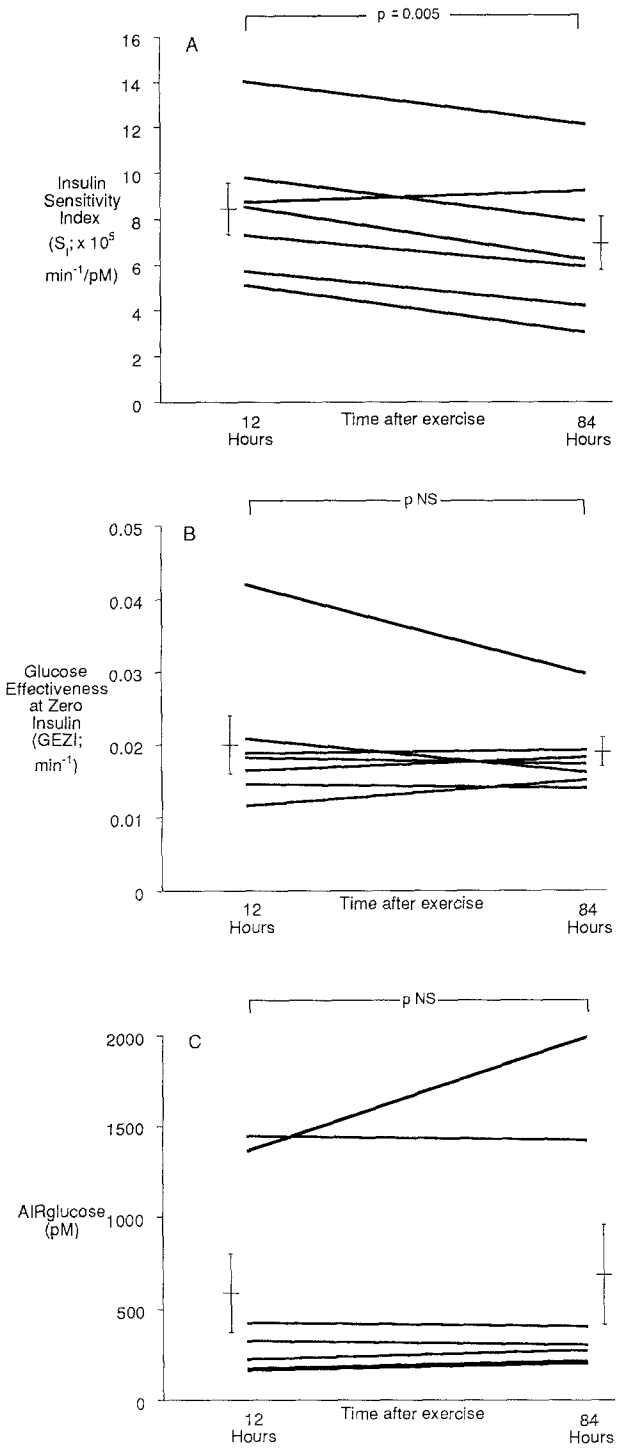

Fig 2. Individual measurements of K_g in 7 subjects studied 12 and 84 hours after a bout of exercise. Results are the mean ± SE. The effect of time since the last bout of exercise was significant ($P < .05$).

without a contribution from changes in glucose effectiveness or B-cell function, since GEZI and AIRglucose were similar at 12 and 84 hours after exercise. We observed this change in S_I in six of seven subjects, with the one exception being the subject who had the lowest exercise intensity. The 5.3% increase in S_I at 84 hours observed in this individual is well within the 16.9% coefficient of variation for this measurement.[15] Since we found that the change in S_I was related to the intensity of exercise, it seems possible that the exercise intensity in this individual was so low that the day-to-day variability in S_I may have masked any effect of exercise cessation.

In view of the increased insulin-independent glucose uptake observed by other investigators during exercise in humans[16] and immediately after exercise in rats,[17,18] we believe that glucose effectiveness was probably increased immediately postexercise in our subjects, but had dissipated 12 hours after exercise at the time of our initial study. In support of this, studies in rats show that insulin-independent glucose uptake quickly dissipates postexercise, and this decrease appears to be related to repletion of glycogen stores.[17,19] It seems possible that the same relationship between insulin-independent glucose uptake and the state of glycogen stores is present in humans. Thus, although we have not measured muscle glycogen content, based on previous reports of the time course of glycogen repletion, we believe that the lack of a difference in GEZI when measured 12 hours postexercise as compared with 84 hours may be related to similar muscle glycogen stores at 12 and 84 hours postexercise.[20-23]

There are other potential explanations for the lack of change in GEZI that we observed. First, it is possible that regular exercise causes an improvement in GEZI that persists without change during the period between the 12- and 84-hour study, as suggested by Tokuyama et al.[24] They studied a highly trained group at 16 hours and 1 week after a bout of exercise and a sedentary group in a nonexercising state. Although a major difference in GEZI and S_I as compared with values in sedentary subjects was found, no significant change in glucose tolerance was noted between studies performed 16 hours and 1 week after a bout of exercise in the trained group. Additionally, no changes were measured in GEZI, S_I, or B-cell function, the factors that influence glucose tolerance. A comparison of several parameters suggests that the study group used by Tokuyama et al was not equivalent to the study group we examined. First, the mean S_I in exercise-trained subjects was 24.3 × 10^{-5} min^{-1}/pmol/L, which is greater than three times the value of 6.98 × 10^{-5} min^{-1}/pmol/L that we observed. Also, intravenous glucose tolerance quantified as K_g in trained subjects was 3.60%/min, as compared with 2.23%/min in our subjects. Thus, it appears that the study populations were different, and that highly trained individuals with extremely high S_I, GEZI, and glucose tolerance fail to show

Table 2. Fasting Plasma Parameters in Seven Subjects 12 and 84 Hours After a Bout of Exercise

Parameter	12 Hours After Exercise	84 Hours After Exercise
Glucose (mmol/L)	4.94 ± 0.10	4.94 ± 0.08
Insulin (pmol/L)	68 ± 22	57 ± 11
Norepinephrine (pg/mL)	177 ± 18	190 ± 27
Epinephrine (pg/mL)	46 ± 6	48 ± 9

NOTE. Data are the mean ± SE. No comparisons were statistically significant.

postexercise changes of glucose tolerance and the factors important to glucose disposal.

A second possible explanation for the lack of change in GEZI between 12 and 84 hours postexercise is that a change in GEZI was indeed present but measurement inaccuracy prevented detection of this change. One subject had a 41% higher value for GEZI at 12 hours as compared with 84 hours. Since reproducibility of GEZI is 18.3%,[15] this individual may have had a true decrease in GEZI at 84 hours postexercise due to other unexplained factors. The remaining six subjects showed a change in GEZI of +29%, +5%, +4%, −8%, −8%, and −21%, consistent with no change or a small change in GEZI and random measurement error. To quantify the minimum detectable change in GEZI in the current study, we determined the reproducibility of the GEZI measurement from the 12- and 84-hour pairs of GEZI values as 12.9%. Monte Carlo simulation was then used to determine the minimum detectible change in GEZI as 14% with 80% confidence, that is, there is a 20% chance that a 14% or greater true change in GEZI was present but not detected in this study. Therefore, any change in GEZI, if present, is likely to be small.

A third potential explanation is that dietary alterations associated with cessation of exercise could have masked a change in GEZI. We do not believe this is a factor, since we asked the participants not to alter their intake or nutrient balance and since we and others have previously shown that dietary changes do not alter this parameter,[25,26] although Swinburn et al[27] noted a small change in glucose effectiveness with a large change in dietary fat content. Finally, differences in catecholamine levels associated with cessation of exercise or with increased familiarity with the IVGTT protocol on the second study day could potentially influence the metabolic parameters.[9] However, no significant change was noted in fasting catecholamine levels.

Since the comparison study was performed 84 hours after the last bout of exercise, one might suggest that the observed changes are due to detraining. However, the detraining effect should have been small based on the findings from two lines of investigation. First, several investigators have determined that the decrease in training over time as measured by maximal O_2 consumption is less than 1% per day.[1,28,29] This change is much less than the decrease of 7% per day in S_I that we documented over the 3 days that separated our two studies. In addition, a study reported by Hickson and Rosenkoetter[30] showed that subjects were able to maintain their trained state when the frequency of exercise was decreased from 6 to 2 days per week, the latter being similar to the 3-day interval between studies in the present protocol. Thus, although a small amount of detraining may have occurred, this seems unlikely to be the major cause of the changes we observed, and most likely we are observing the effect of the last bout of exercise.

Although other investigators have found a relationship between degree of training measured by maximal O_2 consumption and S_I, to our knowledge the present study is the first to show a significant correlation between exercise intensity and the acute change in S_I upon exercise cessation in humans. This significant relationship was observed, even though the measure of exercise intensity was based on a self-reported HR during exercise and an age-determined maximum HR. The method we used would be expected to increase the variance in the data,[31] thus making it more difficult to achieve statistical significance. Since we found a relationship with this less precise method, we would expect an improvement in the strength of the relationship if we had computed the HR reserve from individual resting and maximum HRs and monitored HRs during exercise.

In conclusion, we have shown that cessation of exercise is associated with a decrease in intravenous glucose tolerance in regularly exercising subjects. This decrease is apparently related to a reduction in S_I with no change in GEZI or B-cell function.

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