

# Effects of Exercise Training on Glucose Homeostasis

## The HERITAGE Family Study

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**CONCLUSIONS** — Although the effects of structured regular exercise were highly variable, there were improvements in virtually all IVGTT-derived variables. In the absence of substantial weight loss, regular exercise is required for sustained improvements in glucose homeostasis.

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**OBJECTIVE** — To determine the effect of a 20-week endurance training program in healthy, previously sedentary participants on measures derived from an intravenous glucose tolerance test (IVGTT).

**RESEARCH DESIGN AND METHODS** — An IVGTT was performed before and after a standardized training program in 316 women and 280 men (173 blacks and 423 whites). Participants exercised on cycle ergometers 3 days per week for 60 sessions. The exercise intensity was progressively increased from 55%  $VO_{2max}$  for 30 min per session to 75%  $VO_{2max}$  for 50 min per session.

**RESULTS** — Mean insulin sensitivity increased by 10% ( $P < 0.001$ ) following the intervention, but the variability in the changes was high. Men had larger improvements than women ( $P = 0.02$ ). Improvements in fasting insulin were transitory, disappearing 72 h after the last bout of exercise. There were also significant mean increases in the glucose disappearance index (3%,  $P = 0.02$ ) and in glucose effectiveness (11%,  $P < 0.001$ ), measures of glucose tolerance and of the capacity of glucose to mediate its own disposal, respectively. The acute insulin response to glucose, a measure of insulin secretion, increased by 7% in the quartile with the lowest baseline glucose tolerance and decreased by 14% in the quartile with the highest baseline glucose tolerance ( $P < 0.001$ ). The glucose area below fasting levels during the IVGTT was reduced by 7% ( $P = 0.02$ ).

Recent clinical trials and prospective studies have highlighted the importance of physical activity (1–4) or combined physical activity and dietary lifestyle modifications (5–7) in the prevention of type 2 diabetes. Exercise training studies have demonstrated improvements in insulin sensitivity in a variety of groups (8–13). However, the magnitude of the changes in insulin sensitivity has been variable. This variability may be due to the relatively small samples sizes, to the timing of the measurements, to differences in the characteristics of the participants, or to the concomitant changes in adiposity or physical fitness.

Several studies performed in subgroups ranging from type 2 diabetes to trained athletes have suggested that physical training leads to transient improvements in insulin sensitivity or glucose tolerance that return to pretraining levels within a few days (14–16). The time course for the changes in insulin sensitivity has important practical implications in terms of prescribing an optimal exercise frequency. Furthermore, the effects of exercise training on insulin secretion may be important but have not been extensively studied in large populations. In addition, low glucose levels have been shown following weight loss (17,18) and may be associated with an increased feeling of hunger (19,20) and a predisposition to weight regain in humans (21).

Therefore, the purpose of this study was to examine the effects of a 20-week endurance training program on insulin sensitivity, insulin secretion, and other IVGTT-derived variables while consider-

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**Abbreviations:** AIR<sub>g</sub>, acute insulin response to glucose; IVGTT, intravenous glucose tolerance test.

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ing the potentially confounding effects of sex, race, age, and BMI as well as changes in adiposity and physical fitness. In addition, the effects of regular exercise on fasting insulin and glucose concentrations measured 24 and 72 h after the last exercise session were considered.

## RESEARCH DESIGN AND METHODS

**RESEARCH DESIGN AND METHODS**— The HERITAGE Family Study is a multicenter exercise training study, of which the main objective is to assess the role of genetic factors in cardiovascular, metabolic, and hormonal responses to aerobic exercise training in sedentary families. The present analyses included 316 women (109 blacks and 207 whites) and 280 men (64 blacks and 216 whites) for whom complete data from the IVGTT were available. The study protocol has been previously approved by the institutional review boards of the different centers involved in the study (Arizona State University, Indiana University, Laval University, Pennington Biomedical Research Center, University of Minnesota, University of Texas at Austin, Texas A&M, and Washington University). Informed consent was obtained from each subject. A subset of women ( $n = 40$ , age 40–65 years) had not had a menstrual cycle in over 2 years. Details of the aims, experimental design, measurement protocols, and inclusion and exclusion criteria of the HERITAGE Family Study have been described in a previous publication (22). Briefly, inclusion criteria required offspring to be 17 years of age or older and parents to be 65 years old or younger. All participants were required to be sedentary at baseline, which is defined as not engaging in regular vigorous physical activity more than once a week over the previous 6 months. Participants were excluded if they had a BMI  $>40$  kg/m<sup>2</sup> (unless they were able to meet the demands of the exercise tests and exercise training program), systolic and diastolic blood pressure levels  $>159$  mmHg and/or 99 mmHg, respectively, or required lipid-lowering, hypoglycemic, or antihypertensive medication.

### Exercise training program

The training program was conducted on cycle ergometers (Universal Aerobicycle, Cedar Rapids, IA) interfaced with a Mednet computer system (Universal Gym Mednet, Cedar Rapids, IA) to control the power output of the ergometers so that

constant training heart rates could be maintained. Participants started training at the heart rate associated with 55% of their initial  $\text{VO}_{2\text{max}}$  for 30 min/day and gradually progressed to the heart rate associated with 75% of their initial  $\text{VO}_{2\text{max}}$  for 50 min/day at the end of week 14. They maintained this intensity and duration throughout the remaining 6 weeks. Frequency was maintained at three sessions per week throughout the 20-week training program. A detailed description of the training program can be found elsewhere (23).

### Intravenous glucose tolerance test protocol

The protocol proposed by Walton et al. (24) was followed. The intravenous glucose tolerance test (IVGTT) was performed the morning after an overnight (12 h) fast. The baseline IVGTT was performed before the beginning of the training program, and the posttraining IVGTT was performed on average after 52.3 (SD = 3.9) training sessions. The timing of the posttraining IVGTT was dictated in part by the availability of participants and the menstrual cycle. Women were tested during the follicular phase. Furthermore, the timing of the posttraining IVGTT was selected to allow the test to be performed 1 day following an exercise bout; this was accomplished in 94% of participants. The IVGTT protocol did not include the injection of intravenous insulin or tolbutamide. Details of the IVGTT protocol have been previously published (25).

Fasting plasma insulin and glucose were also obtained 1 and 3 days ( $\sim 72$  h) after the last exercise bout. Plasma insulin was measured by radioimmunoassay after polyethylene glycol separation (26). The intra- and interassay coefficients of variation were 7.7 and 10.3%, respectively. Plasma glucose was enzymatically determined using a reagent kit (Diagnostic Chemicals).

### IVGTT-derived variables

The glucose disappearance index ( $K_g$ ) was used as an index of overall intravenous glucose tolerance.  $K_g$  is an estimate of the disappearance rate (percent/minute) of plasma glucose based on the slope of plasma glucose from 10 through 60 min during the IVGTT (27). The insulin sensitivity index ( $S_i$ ) and glucose effectiveness ( $S_g$ ) were derived from MINMOD analysis (MINMOD Millennium, version

5.18). The acute insulin response to glucose ( $\text{AIR}_{\text{glucose}}$ ) was also derived from the MINMOD program as the integrated area under the curve between minutes 0 and 10 of the IVGTT. The disposition index ( $D_i$ ), defined as the product of  $S_i$  and  $\text{AIR}_{\text{glucose}}$ , was used as an overall index of glucose homeostasis and the ability of the  $\beta$ -cell to compensate for insulin resistance. The glucose area below fasting glucose concentration ( $G_{\text{ABF}}$ ) was calculated by the trapezoid method.

### Cardiorespiratory fitness and anthropometry

Height and body weight were measured to the nearest 0.1 cm and 0.1 kg, respectively, using a balance-beam scale and a stadiometer. Waist circumference was measured to the nearest 0.1 cm using a fiber glass tape (Grafcot Fiberglass Tape; Grahams-Fields, Hauppauge, NY). Progressive maximal exercise tests were conducted on an Ergometrics 800S cycle ergometer from SensorMedics (Yorba Linda, CA) connected to a SensorMedics 2900 metabolic cart. Measurement techniques and changes in cardiorespiratory fitness and body composition have been detailed elsewhere (28,29).

### Statistical methods

All data were analyzed with JMP statistical software (version 3.1.6.2; SAS Institute, Cary, NC). Repeated-measures ANOVA was used to determine the effect of the exercise intervention on IVGTT-derived variables and to consider potential interactions with sex and race. For example, a statistically significant time  $\times$  sex interaction would indicate that men and women responded differently to the training program for a given variable. The associations between variables were determined by Pearson correlations.

Fasting insulin, fasting glucose,  $K_g$ ,  $\text{AIR}_{\text{glucose}}$ ,  $S_i$ , and  $D_i$  values were logarithmically transformed, and  $G_{\text{ABF}}$  was square root transformed to normalize their distributions before analysis. However, mean values and 95% CIs for the mean were untransformed (inverse logarithm or squared) before being presented throughout the report. One participant was excluded from the  $\text{AIR}_{\text{glucose}}$  and  $D_i$  analyses because the logarithmically transformed value was  $>5$  SDs from the mean. Other results are presented as means  $\pm$  SD.

Table 1—Change in measures of glucose homeostasis derived from an IVGTT

Characteristics	Women			
	Black		White	
	Pre	Post	Pre	Post
n	109	109	207	207
Age (years)	32.9 (30.8–35.0)	—	35.1 (33.1–37.0)	—
BMI (kg/m <sup>2</sup> )	27.7 (26.6–28.9)	27.6 (26.6–28.7)	24.7 (24.1–25.4)	24.7 (24.1–25.3)
Fasting glucose (mmol/l)	5.0 (4.9–5.1)	5.2 (5.0–5.3)	4.9 (4.8–4.5)	5.0 (4.9–5.0)
Fasting insulin (pmol/l)	67.7 (59.7–76.7)	61.7 (55.5–68.7)	54.4 (51.1–57.8)	50.4 (47.2–53.9)
S <sub>i</sub> (10 <sup>-4</sup> min · mU <sup>-1</sup> · ml <sup>-1</sup> )	2.35 (2.05–2.69)	2.68 (2.37–3.01)	4.08 (3.75–4.42)	4.15 (3.83–4.49)
AIR <sub>g</sub> (10 min · mU <sup>-1</sup> · ml <sup>-1</sup> )	1,250 (1,055–1,480)	1,227 (1,032–1,458)	491 (450–536)	480 (440–523)
D <sub>i</sub> (S <sub>i</sub> × AIR <sub>g</sub> )	2,723 (2,281–3,247)	3,084 (2,578–3,684)	1,931 (1,754–2,125)	1,920 (1,745–2,111)
S <sub>g</sub> (min <sup>-1</sup> )	0.021 (0.018–0.023)	0.023 (0.021–0.026)	0.017 (0.016–0.018)	0.018 (0.017–0.019)
K <sub>g</sub> (%/min)	1.81 (1.68–1.94)	1.92 (1.79–2.06)	1.62 (1.55–1.69)	1.62 (1.55–1.70)
G <sub>ABF</sub> (mmol · l <sup>-1</sup> · min <sup>-1</sup> )	64.5 (56.2–73.4)	67.8 (58.8–77.4)	57.0 (51.9–62.4)	49.1 (44.4–54)

Data are means (95% CI). \*P < 0.01; †P < 0.05; NS, nonsignificant. All values were logarithmically transformed (log<sub>10</sub>) before analyses except for G<sub>ABF</sub>, which was square root transformed, and age, which was not transformed. S<sub>i</sub>, insulin sensitivity; S<sub>g</sub>, glucose effectiveness; D<sub>i</sub>, disposition index; K<sub>g</sub>, glucose disappearance index; G<sub>ABF</sub>, glucose area below fasting levels. There was no time × sex × race interaction.

## RESULTS

### Participant characteristics

The mean age and BMI of the participants are described in Table 1. Following the 20-week exercise training program, mean body weight decreased by 0.3 ± 2.3 kg (P = 0.007) and mean waist circumference decreased by 1.0 ± 3.0 cm (P < 0.001). Maximal oxygen consumption increased from 31.7 ± 8.9 to 37.2 ± 9.6 ml O<sub>2</sub> · kg<sup>-1</sup> · min<sup>-1</sup> (P < 0.001).

### Changes in IVGTT-derived variables

There were significant mean changes between baseline and posttraining IVGTT, including a 10% increase in S<sub>i</sub> (P < 0.001), a 3% decrease in AIR<sub>glucose</sub> (P = 0.04), a 7% increase in D<sub>i</sub> (P = 0.008), an 11% increase in S<sub>g</sub> (P < 0.001), a 3% increase in K<sub>g</sub> (P = 0.02), and a 7% decrease in G<sub>ABF</sub> (P = 0.02) (Table 1). The changes in these indexes of glucose homeostasis varied greatly among participants (Fig. 1). The proportion of participants who had no change or a decrease in IVGTT parameters was as follows: S<sub>i</sub> 42%, AIR<sub>glucose</sub> 55%, D<sub>i</sub> 44%, S<sub>g</sub> 45%, K<sub>g</sub> 44%, and G<sub>ABF</sub> 54%.

At baseline, the mean S<sub>i</sub> was ~61% higher in whites compared with blacks (P < 0.001) and 12% higher in women compared with men (P = 0.03). A significant time × sex interaction indicated that the mean increase in S<sub>i</sub> was larger in men than in women (16 vs. 5%, P = 0.02). The mean increase in S<sub>i</sub> was larger in blacks than in whites, but the time × race

interaction was not statistically significant (16 vs. 8%, P = 0.15). Normal weight subjects at baseline tended to have a smaller mean increase in S<sub>i</sub> (6%) compared with the overweight (14%) and obese (15%) participants, but the difference was not statistically significant (P = 0.33). There were no significant differences in changes in S<sub>i</sub> between the 272 premenopausal and 40 postmenopausal women (5 and 3%, respectively, P = 0.82).

The baseline mean AIR<sub>glucose</sub> was more than two times higher in blacks compared with whites, but the mean change in AIR<sub>glucose</sub> was not significantly different between the two races (Table 1). AIR<sub>glucose</sub> decreased overall (P = 0.04). However, in the quartile with the highest glucose tolerance (mean K<sub>g</sub> of 2.5% per min), the mean AIR<sub>glucose</sub> decreased by 14%, while in the quartile with the lowest glucose tolerance (mean K<sub>g</sub> of 1.0% per min) AIR<sub>glucose</sub> increased by 7% (P < 0.001 among all four quartiles while considering potential interactions with the sex and race of participants).

The mean G<sub>ABF</sub> decreased by 7% (P = 0.02), indicating that following the exercise program, glucose values were not as low at the end of the IVGTT. Before the exercise intervention, there was a positive association between G<sub>ABF</sub> and K<sub>g</sub> (r = 0.49, P < 0.001). In addition, there was an inverse association between baseline G<sub>ABF</sub> and changes in K<sub>g</sub> (r = -0.30, P < 0.001), suggesting that those who had the highest baseline G<sub>ABF</sub> (lowest glucose at

the end of the IVGTT) had smaller improvements or reductions in glucose tolerance.

Although baseline S<sub>i</sub>, S<sub>g</sub>, AIR<sub>glucose</sub>, and K<sub>g</sub> decreased with increasing age (r = -0.11, -0.13, -0.24, and -0.33, respectively, all P < 0.01), there were no associations between age and training-induced changes in S<sub>i</sub>, S<sub>g</sub>, AIR<sub>glucose</sub>, D<sub>i</sub>, K<sub>g</sub>, or G<sub>ABF</sub>. The exercise program characteristics (duration, intensity, and total volume) and the number of exercise sessions performed preceding the second IVGTT explained <1% of the variance of the changes in S<sub>i</sub> and AIR<sub>glucose</sub> (all P > 0.14).

Changes in S<sub>i</sub> were not associated with changes in body weight, waist circumference, physical fitness, and plasma LDL and HDL cholesterol or triglycerides. On the other hand, there was a positive association between changes in AIR<sub>glucose</sub> and changes in body weight (r = 0.13, P = 0.002), waist circumference (r = 0.10, P = 0.02), plasma triglycerides (r = 0.10, P = 0.02), and total cholesterol (r = 0.09, P = 0.03). These findings suggest that the participants who had greater amounts of weight loss had a greater reduction in insulin secretion despite not having larger changes in insulin sensitivity.

### Acute versus chronic effects of exercise training

As shown in Fig. 2, fasting insulin was decreased by 8% (P < 0.001) 24 h after an exercise bout. This decrease was quite similar to the mean 10% increase

Table 1—Continued

Men				Time	Time × sex	Time × race
Black		White		P	P	P
Pre	Post	Pre	Post			
64	64	216	216	—	—	—
33.1 (30.2–36.0)	—	36.5 (34.5–38.6)	—	—	—	—
26.6 (25.4–27.8)	26.4 (25.3–27.7)	26.3 (25.6–26.9)	26.1 (25.5–26.7)	*	NS	NS
5.2 (5.1–5.4)	5.3 (5.2–5.5)	5.2 (5.1–5.2)	5.2 (5.1–5.2)	*	NS	*
61.9 (52.7–72.8)	57.7 (49.7–66.9)	61.5 (57.1–66.3)	56.2 (52.2–60.6)	*	NS	NS
2.15 (1.78–2.56)	2.60 (2.16–3.11)	3.29 (2.99–3.62)	3.80 (3.48–4.14)	*	†	NS
1,046 (837–1,305)	964 (774–1,198)	539 (483–601)	521 (472–575)	†	NS	NS
2,103 (1,658–2,660)	2,287 (1,763–2,957)	1,688 (1,501–1,898)	1,894 (1,696–2,114)	*	NS	NS
0.018 (0.015–0.021)	0.020 (0.017–0.023)	0.015 (0.014–0.017)	0.018 (0.016–0.019)	*	NS	NS
1.53 (1.37–1.7)	1.58 (1.41–1.76)	1.43 (1.36–1.5)	1.49 (1.42–1.57)	†	NS	NS
48.9 (39.2–59.7)	45.3 (35.3–56.6)	55.5 (50.5–60.7)	51.9 (47.1–56.8)	†	NS	NS

in  $S_i$  estimated from the IVGTT. However, fasting insulin had returned to baseline levels after 72 h. Fasting glu-

cose slightly increased 24 and 72 h after the previous exercise bout. There was a significant time × race interaction that

suggested a larger increase in fasting glucose in blacks compared with whites ( $P = 0.008$ ).

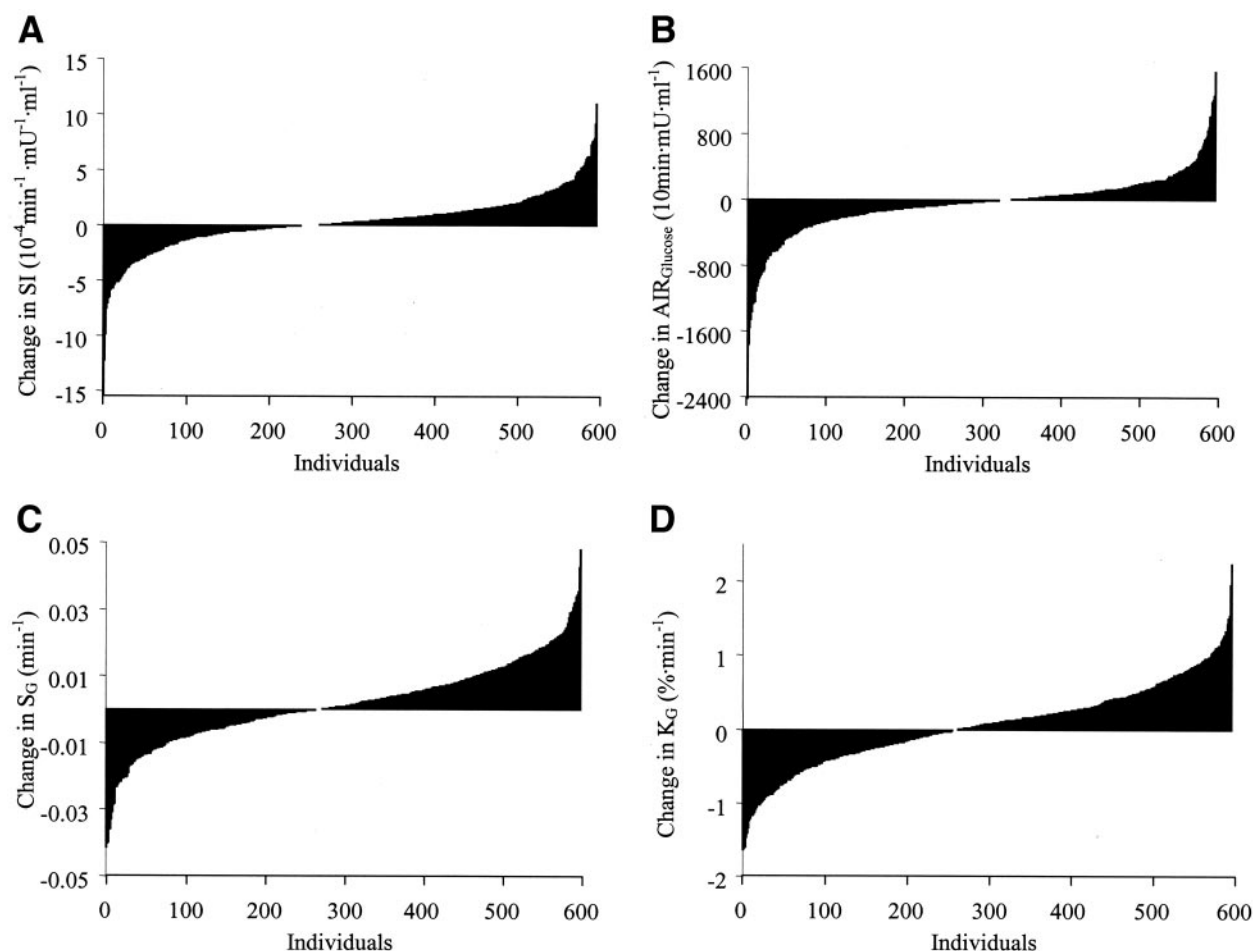
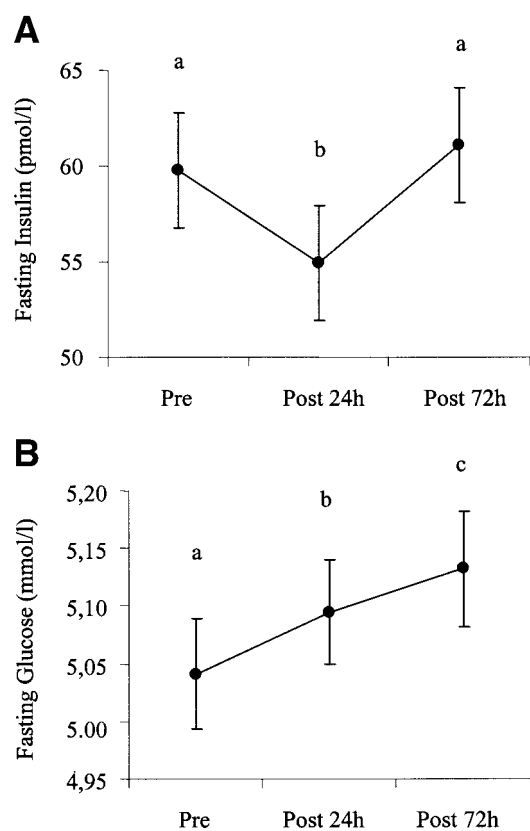


Figure 1— Individual differences in the changes in insulin sensitivity ( $S_i$ ),  $AIR_g$ , glucose effectiveness ( $S_g$ ), and glucose disappearance index ( $K_g$ ). Changes were measured as differences from before to after the 20-week endurance training program. The 596 participants were ranked in ascending order (negative values represent decreases in IVGTT-derived variables).



**Figure 2**— Fasting insulin and fasting glucose at baseline (Pre), 24 h (Post 24h), and 72 h (Post 72h) following an exercise bout at the end of the 20-week exercise training program in 547 participants. Different letters indicate values that are significantly different from each other ( $P < 0.05$ ). Fasting insulin and fasting glucose were logarithmically transformed before the repeated-measures ANOVA. Data are presented as untransformed (inverse logarithm) means and 95% CIs for the mean.

**CONCLUSIONS**— The principal finding of this study was that structured regular exercise leads, on average, to beneficial effects on insulin sensitivity and many other IVGTT-derived measures. However, the magnitude of the changes was highly variable. Regardless of race, men had larger improvements in insulin sensitivity than women, and participants with the lowest glucose tolerance had an increase in insulin secretion. While several previous studies have focused on the effects of exercise training on indexes of glucose homeostasis in small groups, the present study is by far the largest of its kind. Given the variability among participants, it is clear that large studies are important.

Prior studies have generally suggested improvements in insulin sensitivity following exercise training programs ranging from ~10 to 65% (8–13). Small sample sizes may explain, in part, the variability in results among these studies. The average 10% improvement in insulin sensitivity observed in the present study is at the lower end of these values. One potential explanation for this observation could be that some of these previous reports were based on samples with a higher

prevalence of participants with initially low levels of insulin sensitivity. Indeed, earlier studies have suggested larger improvements in glucose tolerance and insulin sensitivity in patients with type 2 diabetes (30,31). In addition to studying participants with type 2 diabetes, these studies had small sample sizes (five participants per study) and prescribed larger exercise volumes (30,31). On the other hand, a previous study demonstrated similar relative improvements in glucose disposal in normal and insulin resistant subjects (10). Our results are consistent with others, (9,32), suggesting that changes in insulin sensitivity are not associated with the initial body mass or age of participants.

The high variability in the present study may be due, in part, to the IVGTT protocol. Previous studies have suggested that the use of a modified IVGTT protocol, which includes the injection of intravenous insulin or tolbutamide 20 min after the glucose injection, could improve the precision of the estimates of insulin sensitivity and glucose effectiveness (33,34). The absence of a nonexercise control group in the HERITAGE Family Study makes it difficult to precisely esti-

mate the magnitude of the effect of regular exercise on insulin sensitivity. However, this study was not designed to get an accurate estimate of the effect size of regular exercise on risk factors for cardiovascular disease and type 2 diabetes but rather to understand the heterogeneity in the responses to exercise training. Food intake was not standardized in this study, but participants were asked not to make dietary changes. Monitoring dietary practices at baseline, midprogram, and posttraining indicated that no significant changes in diet took place. As shown by previous reports based on the same cohort (25,35,36), genetic factors also contributed to the heterogeneity in the changes in measures of glucose homeostasis in response to regular exercise.

Twenty-four hours after an exercise bout, the mean improvements in  $S_i$  paralleled those in fasting insulin. However, the improvements in fasting insulin were no longer present 72 h after the last exercise period. This finding is consistent with previous studies conducted in both athletes and individuals with type 2 diabetes, which suggested that improvements in insulin sensitivity and glucose tolerance were short lived and in large part return to baseline levels 60–72 h after the last exercise session (14–16). Taken together, these results support the importance of the frequency component of an exercise program if sustained improvements in insulin sensitivity are to be achieved and are consistent with the fact that changes in  $S_i$  were not associated with changes in body mass or physical fitness. On the other hand, there was a small but significant association between changes in acute insulin secretion and changes in body mass or waist circumference, potentially suggesting that changes in secretion may not be due only to the acute effect of the previous exercise bout.

Only taking into account the changes in insulin sensitivity may underestimate the benefits of regular exercise for the prevention of type 2 diabetes. The amount of insulin secreted must be proportional to the level of insulin resistance in order to maintain normal glucose homeostasis (37). A closer look at the changes in insulin secretion revealed an interesting association. In the quartile with the highest baseline glucose tolerance, insulin secretion was reduced following regular exercise. This is an indication that lower amounts of insulin secretion were re-

quired to normalize glycemia and probably reflects reduction of the load on the pancreatic  $\beta$ -cells. In contrast, the quartile with the lowest glucose tolerance registered an increase in insulin secretion following regular exercise. This increase in insulin secretion as well as the overall 11% increase in glucose effectiveness, which reflects the capacity of glucose to mediate its own disposal, may have contributed to the improvement in glucose tolerance.

A novel finding of the present study was that exercise training not only increased intravenous glucose tolerance, thereby protecting against postprandial hyperglycemia, but also protected against low blood glucose levels at the end of the IVGTT. According to the glucostatic theory of food intake, transient declines in blood glucose may precede the feeling of hunger and the initiation of food seeking behaviors in humans and animals (19,20). Low glucose levels at the end of an oral glucose tolerance test have been reported following weight loss (17,18). The present results suggest that adding exercise to other weight loss interventions could improve glucose tolerance while diminishing the risk of low glucose values.

In conclusion, the absence of a non-exercise control group in the present study makes it difficult to obtain a precise estimate of the effect of structured regular exercise on the results on IVGTT-derived variables. However, although the effects of structured regular exercise were highly variable, there were improvements in virtually all IVGTT-derived variables. These improvements resulted in a better control of both high and low glucose levels and better overall glucose homeostasis. Men had larger improvements in insulin sensitivity than women, and participants with the lowest glucose tolerance showed an increase in insulin secretion following exercise training. Fasting insulin values suggest that the improvements in insulin sensitivity observed 24 h following an exercise session were transient, as they had disappeared after 72 h. Therefore, in the absence of substantial weight loss, regular exercise is required for sustained improvements in glucose homeostasis.

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