Effects of Exercise Training on Glucose Homeostasis

The HERITAGE Family Study

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% \( V_{O2\text{max}} \) for 30 min per session to 75% \( V_{O2\text{max}} \) 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% (\( P = 0.02 \)).

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.
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 VO2max for 30 min/day and gradually progressed to the heart rate associated with 75% of their initial VO2max 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 postraining 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 postraining 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 (~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 (Kg) was used as an index of overall intravenous glucose tolerance. Kg 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 (Si) and glucose effectiveness (SG) were derived from MINMOD analysis (MINMOD Millennium, version 5.18). The acute insulin response to glucose (AIRglucose) 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 (DI), defined as the product of Si and AIRglucose, was used as an overall index of glucose homeostasis and the ability of the β-cell to compensate for insulin resistance. The glucose area below fasting glucose concentration (GABF) 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 (Grafco 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 × 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, Kg, AIRglucose, S1, and D1 values were logarithmically transformed, and GABF 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 AIRglucose and D1 analyses because the logarithmically transformed value was >5 SDs from the mean. Other results are presented as means ± SD.
Exercise training and glucose homeostasis

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

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Black</th>
<th>Women</th>
<th>White</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>109</td>
<td>109</td>
<td>207</td>
</tr>
<tr>
<td>Age (years)</td>
<td>32.9 (30.8–35.0)</td>
<td>27.6 (26.6–28.7)</td>
<td>35.1 (33.1–37.0)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>27.7 (26.6–28.9)</td>
<td>5.2 (5.0–5.3)</td>
<td>4.9 (4.8–4.5)</td>
</tr>
<tr>
<td>Fasting glucose (mmol/l)</td>
<td>5.0 (4.9–5.1)</td>
<td>67.7 (59.7–76.7)</td>
<td>4.9 (4.8–4.5)</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>67.7 (59.7–76.7)</td>
<td>2.3 (2.05–2.69)</td>
<td>3.0 (2.5–3.5)</td>
</tr>
<tr>
<td>S_i (10⁻⁴ min⁻¹·mU⁻¹·ml⁻¹)</td>
<td>1,250 (1,055–1,480)</td>
<td>1,227 (1,032–1,458)</td>
<td>491 (450–536)</td>
</tr>
<tr>
<td>AIRg (10 min·mU⁻¹·ml⁻¹)</td>
<td>2,723 (2,281–3,247)</td>
<td>3,084 (2,578–3,684)</td>
<td>491 (450–536)</td>
</tr>
</tbody>
</table>

Data are means (95% CI). *P < 0.01; †P < 0.05; NS, nonsignificant. All values were logarithmically transformed (log10) before analyses except for G_ABF, which was square root transformed, and age, which was not transformed. S_i, insulin sensitivity; S_g, glucose effectiveness; D_i, disposition index; K_g, glucose disappearance index; G_ABF, 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 O₂·kg⁻¹·min⁻¹ (P < 0.001).

Changes in IVGTT-derived variables
There were significant mean changes between baseline and posttraining IVGTT, including a 10% increase in S_i (P < 0.001), a 3% decrease in AIR_g glucose (P = 0.04), a 7% increase in D_i (P = 0.008), an 11% increase in S_g (P < 0.001), a 3% increase in K_g (P = 0.02), and a 7% decrease in G_ABF (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_i 42%, AIR_g glucose 55%, D_i 44%, S_g 45%, K_g 44%, and G_ABF 54%.

At baseline, the mean S_i 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_i was larger in men than in women (16 vs. 5%, P = 0.02). The mean increase in S_i 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_i (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_i between the 272 premenopausal and 40 postmenopausal women (5 and 3%, respectively, P = 0.82).

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

The mean G_ABF 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_ABF and K_g (r = 0.49, P < 0.001). In addition, there was an inverse association between baseline G_ABF and changes in K_g (r = −0.30, P < 0.001), suggesting that those who had the highest baseline G_ABF (lowest glucose at the end of the IVGTT) had smaller improvements or reductions in glucose tolerance.

Although baseline S_i, S_g, AIR_g glucose, and K_g 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_i, S_g, AIR_g glucose, D_i, K_g, or G_ABF. 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_i and AIR_g glucose (all P > 0.14).

Changes in S_i 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_g glucose 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...
in $S_i$ estimated from the IVGTT. However, fasting insulin had returned to baseline levels after 72 h. Fasting glucose 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 ($P = 0.008$).

### Table 1—Continued

<table>
<thead>
<tr>
<th></th>
<th>Men Pre</th>
<th>Men Post</th>
<th>White Pre</th>
<th>White Post</th>
<th>Time</th>
<th>Time × sex</th>
<th>Time × race</th>
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<tbody>
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<td></td>
<td>216</td>
<td></td>
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<tr>
<td>$S_i$ (95% CI)</td>
<td>33.1 (30.2–36.0)</td>
<td>36.5 (34.5–38.6)</td>
<td>26.6 (25.4–27.8)</td>
<td>26.3 (25.6–26.9)</td>
<td></td>
<td>* NS</td>
<td>NS</td>
</tr>
<tr>
<td>$S_g$ (95% CI)</td>
<td>5.2 (5.1–5.4)</td>
<td>5.3 (5.2–5.5)</td>
<td>5.2 (5.1–5.2)</td>
<td>5.2 (5.1–5.2)</td>
<td></td>
<td>* NS</td>
<td>NS</td>
</tr>
<tr>
<td>$K_g$ (95% CI)</td>
<td>61.9 (52.7–72.8)</td>
<td>61.5 (57.1–66.3)</td>
<td>2.15 (1.78–2.56)</td>
<td>3.29 (2.99–3.62)</td>
<td></td>
<td>* NS</td>
<td>NS</td>
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<tr>
<td>$A_{IR_g}$ (95% CI)</td>
<td>1,046 (837–1,305)</td>
<td>539 (483–601)</td>
<td>2,103 (1,658–2,660)</td>
<td>1,688 (1,501–1,898)</td>
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<tr>
<td>$A_{IR_g}$ (95% CI)</td>
<td>1,018 (0.018–0.021)</td>
<td>0.015 (0.014–0.017)</td>
<td>0.015 (0.017–0.023)</td>
<td>0.015 (0.017–0.023)</td>
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<tr>
<td>$A_{IR_g}$ (95% CI)</td>
<td>1.53 (1.37–1.7)</td>
<td>1.58 (1.41–1.76)</td>
<td>1.43 (1.36–1.5)</td>
<td>1.49 (1.42–1.57)</td>
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<td>$A_{IR_g}$ (95% CI)</td>
<td>48.9 (39.2–59.7)</td>
<td>45.3 (35.3–56.6)</td>
<td>55.5 (50.5–60.7)</td>
<td>51.9 (47.1–56.8)</td>
<td></td>
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**Figure 1**—Individual differences in the changes in insulin sensitivity ($S_i$), $A_{IR_g}$ 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).
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 estimate 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 postraining 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 β-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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