Effects of Exercise Training on Glucose Homeostasis

The HERITAGE Family Study

NORMAND G. BOULÉ, MA[1]
S. JOHN WEISNAGEL, MD[1,2]
TIMO A. LAKKA, MD, PHD[3,4]
ANGELO TREMBLAY, PHD[1]
RICHARD N. BERGMAN, PHD[5]
TUOMO RANKINEN, PHD[3]
ARTHUR S. LEON, MD[6]
JAMES S. SKINNER, PHD[7]
JACK H. WILMORE, PHD[8]
D.C. RAO, PHD[9]
CLAUDE BOUCHARD, PHD[3]

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% $V\text{O}_{2max}$ for 30 min per session to 75% $V\text{O}_{2max}$ 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% ($P = 0.02$).

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.

Diabetes Care **28:120–126, 2005**

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-

From the [1]Division of Kinesiology, Laval University, Ste-Foy, Québec, Canada; the [2]Diabetes Research Unit, Centre de Recherche sur les Maladies Lipidiques, Laval University, Ste-Foy, Québec, Canada; the [3]Human Genomics Laboratory, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, Louisiana; the [4]Kuopio Research Institute of Exercise Medicine and the Department of Physiology, University of Kuopio, Kuopio, Finland; the [5]Keck School of Medicine, University of Southern California, Los Angeles, California; the [6]Laboratory of Physiological Hygiene and Exercise Science, Division of Kinesiology, University of Minnesota, Minneapolis, Minnesota; the [7]Department of Kinesiology, Indiana University, Bloomington, Indiana; the [8]Department of Health and Kinesiology, Texas A&M University, College Station, Texas; and the [9]Departments of Genetics and Psychiatry, Division of Biostatistics, Washington University School of Medicine, St. Louis, Missouri.

Address correspondence and reprint requests to S. John Weisnagel, MD, FRCPC, Diabetes Research Unit, S-27, Centre Hospitalier Université Laval, Laval University, 2705 Boulevard Laurier Sainte-Foy, Québec, Canada, G1V 4G2. E-mail: john.weisnagel@kin.msp.ulaval.ca.

Received for publication 27 April 2004 and accepted in revised form 21 September 2004.

N.G.B. is currently affiliated with the Faculty of Physical Education and Recreation, University of Alberta, Edmonton, Alberta, Canada.

N.G.B. and S.J.W. contributed equally as first authors to this article.

C.B. has been on advisory panels for Baylor Children's Nutrition Research Center, the Boston Obesity & Nutrition Research Center of the National Institutes of Health, the Institutes for Pharmaceutical Discovery, Mars, Sanofi-Synthelabo, the Cooper Institute for Aerobic Research, and Weight Watchers International; has been on the board of directors for the Pennington Biomedical Research Center; has received consulting fees from the Pennington Biomedical Research Center, the Almond Board of California, and Bristol-Myers Squibb; and has received research/grant support from Bristol-Myers Squibb.

Abbreviations: AIR_g, acute insulin response to glucose; IVGTT, intravenous glucose tolerance test.

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

— 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^2 (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 VO_{2max} for 30 min/day and gradually progressed to the heart rate associated with 75% of their initial VO_{2max} 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 (~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 ($AIR_{glucose}$) 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 $AIR_{glucose}$, 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 (G_{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 (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, K_g, $AIR_{glucose}$, S_i, and D_i values were logarithmically transformed, and G_{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 $AIR_{glucose}$ and D_i analyses because the logarithmically transformed value was >5 SDs from the mean. Other results are presented as means ± SD.

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

	Women			
	Black		White	
Characteristics	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^2)	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_i (10^{-4} min · mU^{-1} · ml^{-1})	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_g (10 min · mU^{-1} · ml^{-1})	1,250 (1,055–1,480)	1,227 (1,032–1,458)	491 (450–536)	480 (440–523)
D_i ($S_i \times AIR_g$)	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_g (min^{-1})	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_g (%/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_{ABF} (mmol · l^{-1} · min^{-1})	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 ($\log_{10}$) 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 O_2 · 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 $AIR_{glucose}$ ($P = 0.04$), 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%, $AIR_{glucose}$ 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 $AIR_{glucose}$ was more than two times higher in blacks compared with whites, but the mean change in $AIR_{glucose}$ was not significantly different between the two races (Table 1). $AIR_{glucose}$ decreased overall ($P = 0.04$). However, in the quartile with the highest glucose tolerance (mean K_g of 2.5% per min), the mean $AIR_{glucose}$ decreased by 14%, while in the quartile with the lowest glucose tolerance (mean K_g of 1.0% per min) $AIR_{glucose}$ 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, $AIR_{glucose}$, 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, $AIR_{glucose}$, 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 $AIR_{glucose}$ (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 $AIR_{glucose}$ 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

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 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 ($P = 0.008$).

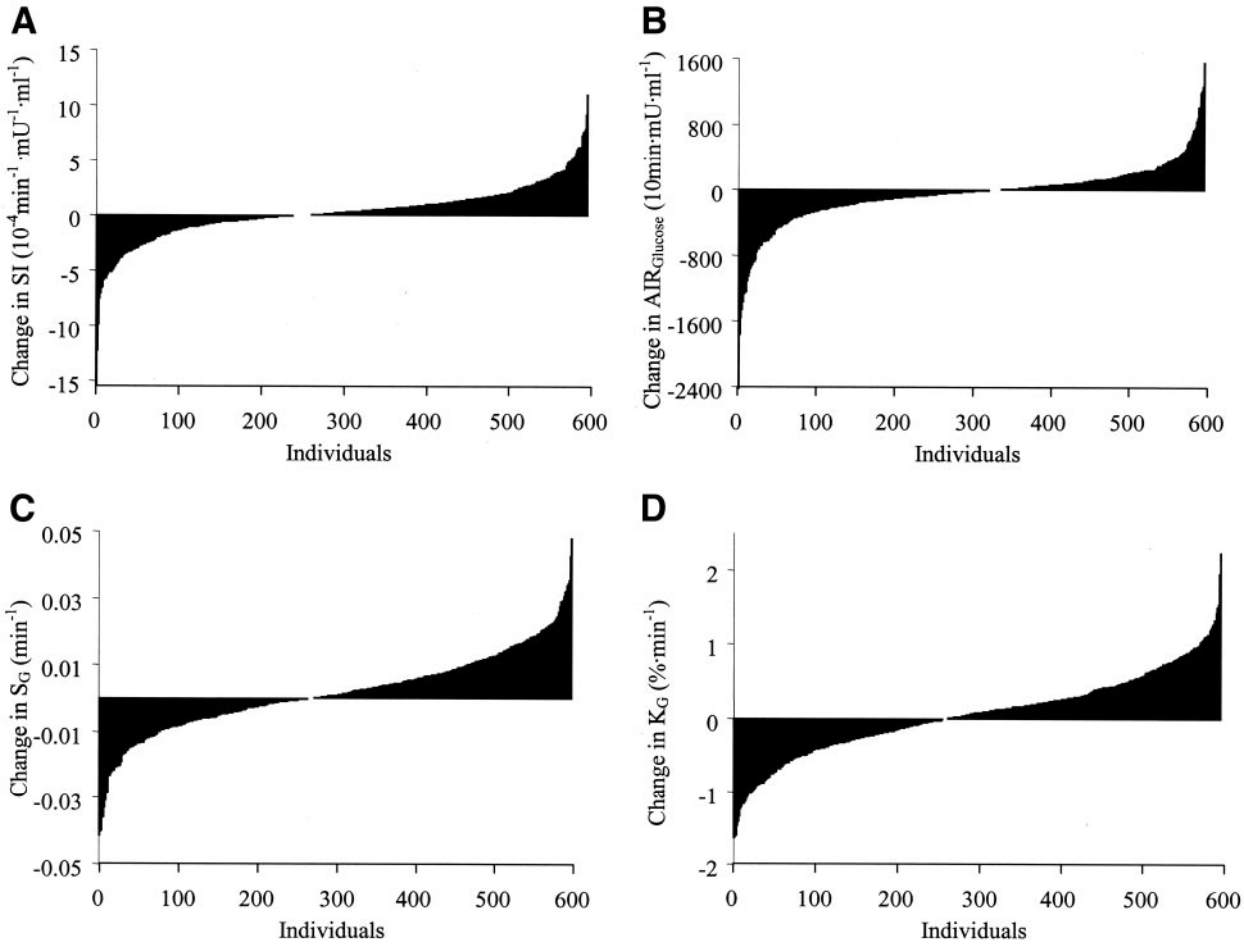

Figure 1— *Individual differences in the changes in insulin sensitivity (S_I), AIR_g, glucose effectiveness (S_g), and glucose disappearance index (K_g). Changes were measured as differences from before to after the 20-week endurance training program. The 596 participants were ranked in ascending order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

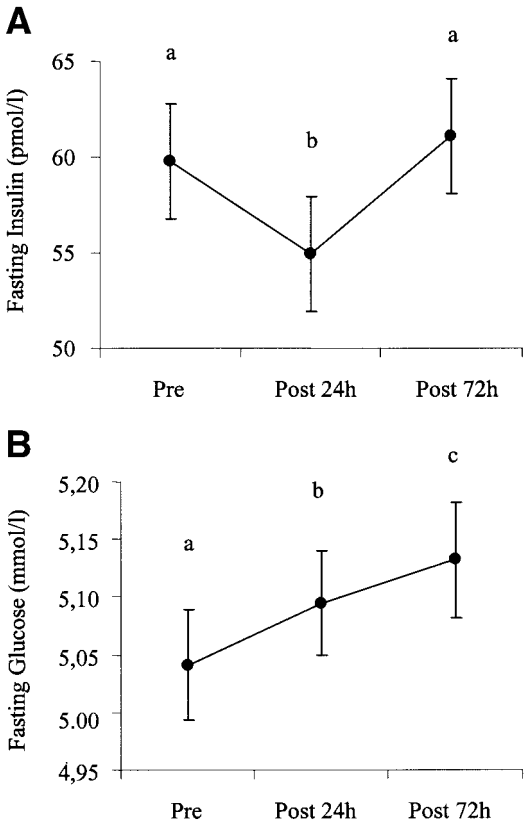

Figure 2— *Fasting insulin and fasting glucose at baseline (Pre), 24 h (Post 24h), and 72 h (Post 72h) following an exercise bout at the end of the 20-week exercise training program in 547 participants. Different letters indicate values that are significantly different from each other ($P < 0.05$). Fasting 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 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 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 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 nonexercise 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.

Acknowledgments— The HERITAGE Family Study is supported by the National Heart, Lung, and Blood Institute through the following grants: HL45670 (to C.B.), HL47323 (to A.S.L.), HL47317 (to D.C.R.), HL47327 (to J.S.S.), and HL47321 (to J.H.W.). A.S.L. was supported by the University of Minnesota Clinical Research Center (M01 RR 00400) and partially by the Henry L. Taylor Professorship in Exercise Science and Health Enhancement. C.B. is partially funded by the George A. Bray Chair in Nutrition. N.G.B is supported by a postgraduate scholarship from National Sciences and Engineering Research Council of Canada. A.T. is partially funded by the Canada Research Chair on Physical Activity, Nutrition, and Energy Balance. T.A.L. is a Research Fellow of the Academy of Finland and was supported by grants from the Academy of Finland, the Yrjo Jahnsson Foundation, and the Maud Kuistila Foundation.

We are grateful to Dr. André Nadeau for the glucose and insulin assays; to Dr. Jacques Gagnon, the HERITAGE Family Study Project Director for several years; and to all who contributed to the study.

References

1. Pan XR, Li GW, Hu YH, Wang JX, Yang WY, An ZX, Hu ZX, Lin J, Xiao JZ, Cao HB, Liu PA, Jiang XG, Jiang YY, Wang JP, Zheng H, Zhang H, Bennett PH, Howard BV: Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. *Diabetes Care* 20:537–544, 1997
2. Helmrich SP, Ragland DR, Leung RW, Paffenbarger RS Jr: Physical activity and reduced occurrence of non-insulin-dependent diabetes mellitus. *N Engl J Med* 325:147–152, 1991
3. Manson JE, Rimm EB, Stampfer MJ, Colditz GA, Willett WC, Krolewski AS, Rosner B, Hennekens CH, Speizer FE: Physical activity and incidence of non-insulin-dependent diabetes mellitus in women. *Lancet* 338:774–778, 1991
4. Manson JE, Nathan DM, Krolewski AS, Stampfer MJ, Willett WC, Hennekens CH: A prospective study of exercise and incidence of diabetes among US male physicians. *JAMA* 268:63–67, 1992
5. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
6. Tuomilehto J, Lindstrom J, Eriksson JG, Valle TT, Hamalainen H, Ilanne-Parikka P, Keinanen-Kiukaanniemi S, Laakso M, Louheranta A, Rastas M, Salminen V, Uusitupa M: Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med* 344:1343–1350, 2001
7. Eriksson KF, Lindgarde F: Prevention of type 2 (non-insulin-dependent) diabetes mellitus by diet and physical exercise: the 6-year Malmo feasibility study. *Diabetologia* 34:891–898, 1991
8. DeFronzo RA, Sherwin RS, Kraemer N: Effect of physical training on insulin action in obesity. *Diabetes* 36:1379–1385, 1987
9. Cox JH, Cortright RN, Dohm GL, Houmard JA: Effect of aging on response to exercise training in humans: skeletal muscle GLUT-4 and insulin sensitivity. *J Appl Physiol* 86:2019–2025, 1999
10. Perseghin G, Price TB, Petersen KF, Roden M, Cline GW, Gerow K, Rothman DL, Shulman GI: Increased glucose transport-phosphorylation and muscle glycogen synthesis after exercise training in insulin-resistant subjects. *N Engl J Med* 335:1357–1362, 1996
11. Tonino RP: Effect of physical training on the insulin resistance of aging. *Am J Physiol* 256:E352–E356, 1989
12. Hughes VA, Fiatarone MA, Fielding RA, Kahn BB, Ferrara CM, Shepherd P, Fisher EC, Wolfe RR, Elahi D, Evans WJ: Exercise increases muscle GLUT-4 levels and insulin action in subjects with impaired glucose tolerance. *Am J Physiol* 264:E855–E862, 1993
13. Dela F, Larsen JJ, Mikines KJ, Ploug T, Peterson LN, Gablo H: Insulin-stimulated muscle glucose clearance in patients with NIDDM: effects of one-legged physical training. *Diabetes* 44:1010–1020, 1995
14. Burstein R, Polychronakos C, Toews CJ, MacDougall JD, Guyda HJ, Posner BI: Acute reversal of the enhanced insulin action in trained athletes: association with insulin receptor changes. *Diabetes* 34: 756–760, 1985
15. Schneider SH, Amorosa LF, Khachadurian AK, Ruderman NB: Studies on the mechanism of improved glucose control during regular exercise in type 2 (non-insulin-dependent) diabetes. *Diabetologia* 26:355–360, 1984
16. Heath GW, Gavin JR 3rd, Hinderliter JM, Hagberg JM, Bloomfield SA, Holloszy JO: Effects of exercise and lack of exercise on glucose tolerance and insulin sensitivity. *J Appl Physiol* 55:512–517, 1983
17. Marsoobian V, Grosvenor M, Jacob M, Ipp E: Very-low-energy diets alter the counterregulatory response to falling plasma glucose concentrations. *Am J Clin Nutr* 61:373–378, 1995
18. Tremblay A, Doucet E, Imbeault P, Mauriege P, Despres JP, Richard D: Metabolic fitness in active reduced-obese individuals. *Obes Res* 7:556–563, 1999
19. Campfield LA, Smith FJ, Rosenbaum M, Hirsch J: Human eating: evidence for a physiological basis using a modified paradigm. *Neurosci Biobehav Rev* 20:133–137, 1996
20. Melanson KJ, Westerterp-Plantenga MS,

Saris WH, Smith FJ, Campfield LA: Blood glucose patterns and appetite in time-blinded humans: carbohydrate versus fat. *Am J Physiol* 277:R337–R345, 1999
21. Boulé NG, Doucet E, Richard D, Tremblay A: Weight loss increases the risk of hypoglycemia in obese adults (Abstract). *Int J Obes* 25:P119, 2001
22. Bouchard C, Leon AS, Rao DC, Skinner JS, Wilmore JH, Gagnon J: The HERITAGE family study: aims, design, and measurement protocol. *Med Sci Sports Exerc* 27:721–729, 1995
23. Skinner JS, Wilmore KM, Krasnoff JB, Jaskolski A, Jaskolska A, Gagnon J, Province MA, Leon AS, Rao DC, Wilmore JH, Bouchard C: Adaptation to a standardized training program and changes in fitness in a large, heterogeneous population: the HERITAGE Family Study. *Med Sci Sports Exerc* 32:157–161, 2000
24. Walton C, Godsland IF, Proudler AJ, Felton C, Wynn V: Evaluation of four mathematical models of glucose and insulin dynamics with analysis of effects of age and obesity. *Am J Physiol* 262:E755–E762, 1992
25. An P, Hong Y, Weisnagel SJ, Rice T, Rankinen T, Leon AS, Skinner JS, Wilmore JH, Chagnon YC, Bergman RN, Bouchard C, Rao DC: Genomic scan of glucose and insulin metabolism phenotypes: the HERITAGE Family Study. *Metabolism* 52:246–253, 2003
26. Desbuquois B, Aurbach GD: Use of polyethylene glycol to separate free and antibody-bound peptide hormones in radioimmunoassays. *J Clin Endocrinol Metab* 37:732–738, 1971
27. Araujo-Vilar D, Garcia-Estevez DA, Cabezas-Cerrato J: Both a reduced acute insulin response to glucose and lower glucose effectiveness are responsible for the worsening of intravenous glucose tolerance in healthy subjects independently of the degree of obesity. *Metabolism* 47:313–320, 1998
28. Wilmore JH, Despres JP, Stanforth PR, Mandel S, Rice T, Gagnon J, Leon AS, Rao D, Skinner JS, Bouchard C: Alterations in body weight and composition consequent to 20 wk of endurance training: the HERITAGE Family Study. *Am J Clin Nutr* 70: 346–352, 1999
29. Bouchard C, An P, Rice T, Skinner JS, Wilmore JH, Gagnon J, Perusse L, Leon AS, Rao DC: Familial aggregation of VO2max response to exercise training: results from the HERITAGE Family Study. *J Appl Physiol* 87:1003–1008, 1999
30. Holloszy JO, Schultz J, Kusnierkiewicz J, Hagberg JM, Ehsani AA: Effects of exercise on glucose tolerance and insulin resistance: brief review and some preliminary results. *Acta Med Scand Suppl* 711: 55–65, 1986
31. Trovati M, Carta Q, Cavalot F, Vitali S, Banaudi C, Lucchina PG, Fiocchi F, Emanuelli G, Lenti G: Influence of physical training on blood glucose control, glucose tolerance, insulin secretion, and insulin action in non-insulin-dependent diabetic patients. *Diabetes Care* 7:416–420, 1984
32. Segal KR, Edano A, Abalos A, Albu J, Blando L, Tomas MB, Pi-Sunyer FX: Effect of exercise training on insulin sensitivity and glucose metabolism in lean, obese, and diabetic men. *J Appl Physiol* 71:2402–2411, 1991
33. Beard JC, Bergman RN, Ward WK, Porte D Jr: The insulin sensitivity index in nondiabetic man: correlation between clamp-derived and IVGTT-derived values. *Diabetes* 35:362–369, 1986
34. Pacini G, Tonolo G, Sambataro M, Maioli M, Ciccarese M, Brocco E, Avogaro A, Nosadini R: Insulin sensitivity and glucose effectiveness: minimal model analysis of regular and insulin-modified FSIGT. *Am J Physiol* 274:E592–E599, 1998
35. Lakka TA, Rankinen T, Weisnagel SJ, Chagnon YC, Rice T, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bouchard C: A quantitative trait locus on 7q31 for the changes in plasma insulin in response to exercise training: the HERITAGE Family Study. *Diabetes* 52:1583–1587, 2003
36. Lakka TA, Rankinen T, Weisnagel SJ, Chagnon YC, Lakka HM, Ukkola O, Boule N, Rice T, Leon AS, Skinner JS, Wilmore JH, Rao DC, Bergman R, Bouchard C: Leptin and leptin receptor gene polymorphisms and changes in glucose homeostasis in response to regular exercise in nondiabetic individuals: the HERITAGE Family Study. *Diabetes* 53:1603–1608, 2004
37. Pratley RE, Weyer C: The role of impaired early insulin secretion in the pathogenesis of type II diabetes mellitus. *Diabetologia* 44:929–945, 2001