

Exercise-Induced Changes in Insulin Action and Glycogen Metabolism in Elderly Adults

ROBERT H. COKER¹, NICHOLAS P. HAYS¹, RICK H. WILLIAMS¹, AMY D. BROWN¹, SCOTT A. FREELING¹, PATRICK M. KORTEBEIN¹, DENNIS H. SULLIVAN², RAYMOND D. STARLING³, and WILLIAM J. EVANS^{1,2}

¹Nutrition, Metabolism, and Exercise Laboratory, University of Arkansas for Medical Sciences, Little Rock, AR;

²Geriatric Research, Education, and Clinical Center, Central Arkansas Veterans Healthcare System, Little Rock, AR; and ³Pfizer Global Research and Development, New London, CT

ABSTRACT

COKER, R. H., N. P. HAYS, R. H. WILLIAMS, A. D. BROWN, S. A. FREELING, P. M. KORTEBEIN, D. H. SULLIVAN, R. D. STARLING, and W. J. EVANS. Exercise-Induced Changes in Insulin Action and Glycogen Metabolism in Elderly Adults. *Med. Sci. Sports Exerc.*, Vol. 38, No. 3, pp. 433–438, 2006. **Purpose:** Although data suggest that physical activity is associated with decreased insulin resistance, recommendations for exercise training are not specific for age or level of obesity. Therefore, we examined the influence of moderate-intensity (50% of $\dot{V}O_{2max}$) exercise training (MI) versus high-intensity (75% of $\dot{V}O_{2max}$) exercise training (HI) on insulin-stimulated glucose disposal (ISGD) in elderly individuals. **Methods:** Following medical examinations, 21 overweight (body mass index = $29 \pm 1 \text{ kg}\cdot\text{m}^{-2}$) elderly ($74 \pm 1 \text{ yr}$) subjects were randomized to 1) HI, 2) MI, or a 3) nonexercising control group. Subjects enrolled in HI or MI completed a 12-wk exercise training regimen designed to expend $1000 \text{ kcal}\cdot\text{wk}^{-1}$. ISGD was assessed using a hyperinsulinemic, euglycemic clamp pre- and postintervention. ISGD was corrected for hepatic glucose production (glucose R_a) using a constant rate infusion of $[6,6\text{-}^2\text{H}_2]\text{glucose}$ and determined during the last 30 min of the clamp by subtracting glucose R_a from the exogenous glucose infusion rate. Nonoxidative glucose disposal was calculated using indirect calorimetry. Body composition testing was completed using dual energy x-ray absorptiometry. **Results:** ISGD increased by approximately 20% with HI (Δ of $1.4 \pm 0.5 \text{ mg}\cdot\text{kg}^{-1} \text{ FFM}\cdot\text{min}^{-1}$). However, ISGD did not change (Δ of $-0.4 \pm 0.1 \text{ mg}\cdot\text{kg}^{-1} \text{ FFM}\cdot\text{min}^{-1}$) with MI and was not different (Δ of $-0.2 \pm 0.1 \text{ mg}\cdot\text{kg}^{-1} \text{ FFM}\cdot\text{min}^{-1}$) in the control group. Nonoxidative glucose disposal increased with HI (Δ of $1.4 \pm 0.5 \text{ mg}\cdot\text{kg}^{-1} \text{ FFM}\cdot\text{min}^{-1}$), but there was no change in nonoxidative glucose disposal with MI or in the control group. No change in body weight or percentage of body fat was observed in any group. **Conclusion:** In weight-stable subjects, MI resulted in no change in ISGD, and the improvement in ISGD with HI was completely reliant on improvements in nonoxidative glucose disposal. **Key Words:** HYPERINSULINEMIA, GLUCOSE INTOLERANCE, AGING, INSULIN RESISTANCE

Aging is associated with a higher incidence of insulin resistance and type 2 (T2) diabetes, potentially contributing to the development of cardiovascular disease as well as microvascular complications such as neuropathy and blindness (22). As such, T2 diabetes is a major health concern that affects nearly 20% of elderly adults older than 65 yr of age (15).

T2 diabetes is preceded by a cascade of events that develops over a period of time, including insulin resistance followed by glucose intolerance and hyperinsulinemia, and may result in insulin deficiency (8,23). The physiological progression of insulin resistance to T2 diabetes results in numerous health-related complications. These include

visual loss, renal failure, amputations, loss of functional independence, and a higher rate of mortality, particularly in the elderly (24). Therefore, the medical, psychological, and financial burdens of these adverse sequelae warrant the determination of age-appropriate interventions to reduce insulin resistance and reduce the risk of T2 diabetes.

The development of insulin resistance is most likely influenced by physical inactivity and increased body fatness and not aging per se (21). Data suggest that regular physical activity (22) and lower adiposity (10) are associated with decreased insulin resistance in older adults. Therefore, strategies aimed at increasing physical activity and decreasing obesity may be the most appropriate method to attenuate insulin resistance in the aging adult. Unfortunately, exercise prescriptions developed specifically for overweight, elderly individuals are not available. We controlled total weekly energy expenditure from aerobic exercise training in both groups ($1000 \text{ kcal}\cdot\text{wk}^{-1}$), and this in turn allowed us to ensure that subjects in moderate-intensity (50% of $\dot{V}O_{2max}$) exercise training (MI) and high-intensity (75% of $\dot{V}O_{2max}$) exercise training (HI) performed the same caloric volume of exercise training. As such, the intensity of the exercise was the main independent variable instead of the energy expenditure. Therefore, we tested the hypothesis that MI and HI

Address for correspondence: Robert H. Coker, Ph.D., Nutrition, Metabolism, and Exercise Laboratory, DWR Institute on Aging, 4301 W. Markham, Slot 806, University of Arkansas for Medical Sciences, Little Rock, AR 72205; E-mail: cokerrobert@uams.edu.

Submitted for publication May 2005.

Accepted for publication August 2005.

0195-9131/06/3803-0433/0

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DOI: 10.1249/01.mss.0000191417.48710.11

exercise would both stimulate efficacious changes in insulin sensitivity.

MATERIALS AND METHODS

Subjects. Men and women aged 65–90 yr were recruited from the central Arkansas area using newspaper advertisements. Subjects who reported being overweight or obese (body mass index (BMI) ≥ 26 and < 37 kg·m⁻²), nonsmoking, sedentary (≤ 2 d·wk⁻¹ of structured physical activity), weight stable (± 5 kg) over the past 6 months, and not consuming medications known to influence glucose metabolism were invited to our laboratory for a comprehensive medical screening. Screening procedures included a medical history, physical examination, routine blood and urine chemistries, oral glucose tolerance test, and a maximal exercise test. Subjects with a plasma glucose concentration of 100–199 mg·dL⁻¹ 2 h following the consumption of a 75-g oral glucose load but who were otherwise healthy, were eligible for study participation. Each subject provided written informed consent prior to screening and study participation, and study procedures were approved by the institutional review board of the University of Arkansas for Medical Sciences and the Central Arkansas Veterans Healthcare System research and development committee.

Experimental protocol. Following completion of the screening visit and eligibility evaluation, subjects were randomly assigned to moderate exercise training (MI; $N = 7$), heavy exercise training (HI; $N = 7$), or a control group (CON; $N = 7$). In order to standardize caloric intake and minimize differences in macronutrient metabolism, each subject was provided a mixed diet (35% fat, 20% protein, 45% carbohydrate) during 4 d of controlled feeding prior to the pre- and postintervention testing periods (9). Subjects were instructed to eat only the food prepared by our metabolic kitchen and to consume them completely. Subjects were advised to maintain their normal dietary habits during the rest of the study.

Subjects who were randomized to one of the exercise training groups were trained 4–5 d·wk⁻¹ for 12 wk at either 50% (MI) or 75% (HI) of their $\dot{V}O_{2\max}$ and caloric expenditure was matched at 1000 kcal·wk⁻¹ for each group. Subjects randomized to the CON group completed only the screening process and the testing periods. All subjects were trained under supervision at the Donald W. Reynolds Institute on Aging using a cycle ergometer (Model 818E, Monarch, Varberg, Sweden) as previously described (9). Nonexercising subjects were instructed to maintain their habitual physical activity.

Body weight and body composition. Body mass, height, and body composition testing was measured pre- and postintervention in association with the clamp procedure. Fat mass and lean tissue mass was measured by dual energy x-ray absorptiometry using a Hologic QDR 2000 densitometer (DXA).

Insulin sensitivity. Blood samples collected during the hyperinsulinemic, euglycemic clamp were centrifuged

at 1200 force \times g for 20 min at 4°C and plasma was stored at -70°C for future analysis. A 120-min euglycemic-hyperinsulinemic clamp was used to measure insulin-mediated glucose disposal pre- and postintervention. Postintervention clamps were completed 3 d after the last exercise session (in those subjects randomized to one of the exercise groups) in order to minimize acute effects of exercise on insulin sensitivity (19). A primed, continuous infusion (priming dose 18 μ mol·kg⁻¹ FFM·min⁻¹; infusion 0.22 μ mol·kg⁻¹ FFM·min⁻¹) of [6,6-²H₂]glucose (Cambridge Isotope Labs, Andover, MA) was administered for the duration of the clamp to allow measurement of endogenous glucose production. After 120 min of [6,6-²H₂]glucose infusion, a primed continuous infusion (40 mU·m⁻²·min⁻¹) of insulin (Humulin, Eli Lilly, Indianapolis, IN) was administered. Glucose (20% dextrose) was infused using a variable-speed infusion pump (Harvard Apparatus Inc., Holliston, MA) to maintain plasma glucose values at a mean of $\pm 3\%$ of baseline value (mean range 2–5%). A spike of [6,6-²H₂]glucose (800 mg) was added to the exogenously administered glucose in order to maintain a constant plasma glucose isotopic enrichment. Analysis of enrichment of plasma [6,6-²H₂]glucose was performed by gas chromatography/mass spectrometry (GC/MS) (Agilent Technologies, Palo Alto, CA). Plasma deproteinization and purification were completed as described by Tsermg and Kalhan (28). Rates of endogenous glucose production were calculated using a modification of the Steele equation published by Toth et al. (29).

Plasma samples were obtained every 5 min for determination of glucose by the glucose oxidase method (Glucose Analyzer 2, Beckman Coulter Inc., Brea, CA); samples were also drawn every 15–30 min for analyses of plasma insulin and glucose isotope enrichment. Mean glucose disposal (mg·kg⁻¹ FFM·min⁻¹), calculated as glucose infusion plus endogenous glucose production during the final 30 min of the clamp, was used to assess insulin-stimulated glucose disposal (ISGD). Indirect calorimetry (Vmax 29N, SensorMedics Corp., Yorba Linda, CA) was used to measure substrate oxidation during this same time period. Nonoxidative glucose disposal was calculated by subtracting carbohydrate oxidation rates from the sum of exogenous glucose infusion plus endogenous glucose production rates.

Statistical analysis. Repeated-measures ANOVA was used to examine variables associated with anthropometrics, maximal oxygen capacity, and glucose metabolism (ISGD, nonoxidative metabolism, and glucose oxidation). Data are reported as means \pm SEM.

RESULTS

Subjects. We recruited 21 elderly, obese subjects between the ages of 65 and 90 yr with a BMI between 26 and 33 kg·m⁻² (see Table 1 for clinical characteristics). One of the subjects dropped out of the exercise training protocol and did not return for further testing. Following the end of the exercise training, three subjects did not

TABLE 1. Subject characteristics (pre- and postintervention).

	Controls (N = 7)		High Intensity (N = 7)		Moderate Intensity (N = 7)	
	Pre	Post	Pre	Post	Pre	Post
Age (yr)	70 ± 3	—	73 ± 2	—	70 ± 2	—
BMI (kg·m ⁻²)	31 ± 1	31 ± 1	31 ± 1	30 ± 1	29 ± 1	28 ± 1
Body fat (%)	40 ± 3	40 ± 3	39 ± 2	38 ± 2	39 ± 2	39 ± 2
VO _{2max} (L·min ⁻¹)	1.4 ± 0.3	1.2 ± 0.3	1.4 ± 0.3	1.6 ± 0.1*	1.4 ± 0.3	1.6 ± 0.1*
RQ at VO _{2max}	1.1 ± 0.1	1.1 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.2 ± 0.1	1.1 ± 0.1
Maximum watts	110 ± 8	112 ± 8	111 ± 3	143 ± 11*	107 ± 3	155 ± 18*

Values are means ± SEM. There were no significant baseline age differences. There were significant differences in the pre- and postintervention results for VO_{2max} and maximum watts during the bicycle stress test in the high-intensity aerobic exercise and moderate intensity aerobic exercise groups but not the control group.

* *P* < 0.05. There were no differences in pre- and postintervention results for BMI, percentage of body fat or RQ at VO_{2max} in any group.

return for the $\dot{V}O_{2max}$ testing (two subjects in the MI group and one subject in the HI group).

Anthropometrics. All groups were similar at baseline with respect to body weight (kg), BMI (kg·m⁻²), and percentage of fat. Sex distribution between groups was also well matched (i.e., four women and three men in all three groups). There was no significant change in body weight or BMI, and percentage of fat did not change from pre- to postintervention in MI, HI, or CON (Table 1). In other words, exercise training (1000 kcal·wk⁻¹) without any dietary manipulation did not result in weight loss or a change in percentage of fat, regardless of exercise intensity.

Maximal exercise capacity. Baseline $\dot{V}O_{2max}$ was not significantly different between MI, HI, or CON at baseline. However, there was a significant increase in $\dot{V}O_{2max}$ in MI and HI from pre- to postintervention (*P* < 0.05). No significant change in $\dot{V}O_{2max}$ was noted in CON (Table 1).

Glucose metabolism. All groups had similar results for HbA1c values and the 2-h plasma glucose from the oral glucose tolerance test (Table 2). There were no significant differences in ISGD between MI, HI, or CON at baseline. There was an increase in ISGD (5.0 ± 0.6 to 6.4 ± 0.5 mg·kg⁻¹ FFM·min⁻¹) in the HI group (*P* < 0.05) (Fig. 1). However, there was no significant increase in ISGD (5.4 ± 0.7 to 5.0 ± 0.6 mg·kg⁻¹ FFM·min⁻¹) in the MI group. ISGD did not change (5.7 ± 0.8 to 5.5 ± 0.9 mg·kg⁻¹ FFM·min⁻¹) from pre- to postintervention in the CON group. Notably, nonoxidative glucose disposal increased to a similar extent (4.6 ± 0.6 to 6.0 ± 0.8 mg·kg⁻¹ FFM·min⁻¹) in the HI group. However, there was no change in nonoxidative glucose disposal in the MI (4.8 ±

TABLE 2. Baseline blood chemistries.

	Controls (N = 7)	High Intensity (N = 7)	Moderate Intensity (N = 7)
Fasting plasma glucose	103 ± 4	101 ± 3	102 ± 4
2-h OGTT plasma glucose (mg·dL ⁻¹)	157 ± 9	163 ± 9	157 ± 9
HbA1c (%)	5.8 ± 0.2	5.7 ± 0.2	5.4 ± 0.2

Values are means ± SEM for 21 subjects. There were no significant baseline differences.

OGTT, oral glucose tolerance test.

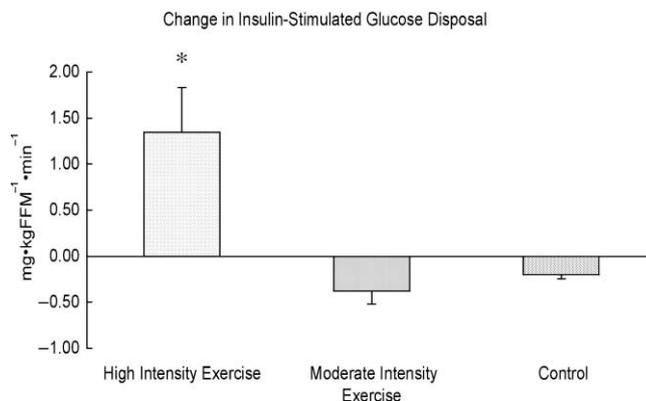


FIGURE 1—Change in insulin-stimulated glucose disposal from baseline in high-intensity aerobic exercise, moderate-intensity aerobic exercise, and sedentary control groups from baseline. Values are means ± SEM for 21 subjects. * Denotes a significant training effect; *P* < 0.05.

0.7 to 4.6 ± 0.6 mg·kg⁻¹ FFM·min⁻¹) or CON (5.1 ± 0.8 to 4.7 ± 0.9 mg·kg⁻¹ FFM·min⁻¹) groups (Fig. 2).

DISCUSSION

The results of this study demonstrated that in the absence of weight loss, HI but not MI facilitates an improvement in ISGD in obese, elderly subjects. In addition, the improvements in ISGD were entirely reliant on an increase in non-oxidative glucose metabolism, conceivably due to greater muscle glycogen utilization during high-intensity aerobic exercise training. Therefore, the results of this study demonstrate that while HI improves ISGD, the influence of training is likely transient due to a greater rate of muscle glycogen synthesis compared to MI and that 1000 kcal·wk⁻¹ of aerobic exercise training, independent of exercise intensity, does not result in weight or fat loss. Interventions that include additional caloric expenditure through exercise training and/or caloric restriction through dietary modification are more likely to cause weight loss, a potentially powerful variable in the treatment of insulin resistance.

Several cross-sectional studies have demonstrated enhanced peripheral insulin action in healthy, trained

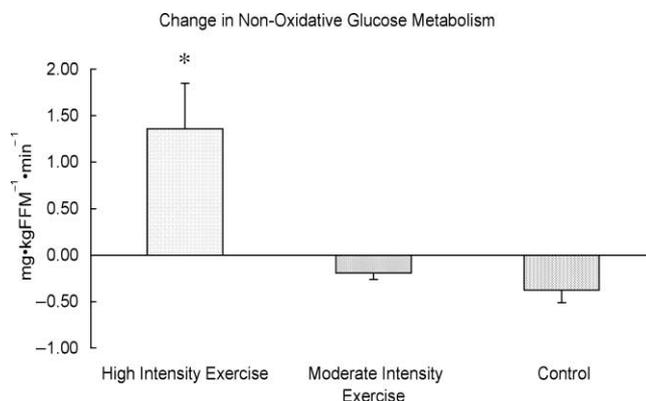


FIGURE 2—Change in nonoxidative glucose metabolism from baseline in high-intensity aerobic exercise, moderate-intensity aerobic exercise, and sedentary control groups from baseline. Values are means ± SEM for 21 subjects. * Denotes a significant training effect; *P* < 0.05.

individuals compared to sedentary individuals using the hyperinsulinemic, euglycemic clamp technique (5,16,20). In addition, longitudinal studies have demonstrated the effectiveness of aerobic exercise training in the treatment of insulin resistance associated with obesity and metabolic syndrome (3,4,12). In healthy and obese individuals and persons with T2 diabetes, aerobic exercise training results in improvements in insulin action as measured by the euglycemic, hyperinsulinemic clamp technique (4,5). Since many studies have reported efficacious improvements in insulin sensitivity through exercise training in middle-aged populations (4,16,20), it may be possible that reduced muscle mass and altered muscle morphology dampen exercise training-induced changes in glucose metabolism (18).

Our studies are relatively unique in that the influence of exercise training on insulin action has received little attention in the elderly population. Recent work from Evans et al. (7) found an approximately 30% increase in ISGD in octogenarians using a high-intensity aerobic exercise training protocol (an average of 2.5 exercise sessions weekly at 83% of $\dot{V}O_{2max}$) despite a relatively minimal improvement in $\dot{V}O_{2max}$. It is important to mention that the total caloric expenditure per week in these studies is very similar to that in our exercise paradigm. The key difference between the results of Evans et al. and our results was that their 1-yr training program initiated a significant change in body weight. As a result, the separate effect of weight loss on insulin action may have influenced their results. As far as other shorter term studies, earlier work in elderly subjects (69 ± 2 yr old) has also described a 13% improvement in ISGD with a 12-wk high-intensity aerobic exercise training regimen (85% HR_{max}) (27). Unfortunately, pre- and postintervention glucose oxidation and nonoxidative metabolism was not described in either of these studies. Based on the results of our investigation, high-intensity aerobic exercise training-induced improvements in ISGD are most likely facilitated through enhanced nonoxidative glucose metabolism.

Although the positive influence of exercise training on insulin action has been reported in numerous investigations (3–5,12,16,20), differences in the degree of improvement or lack thereof might be attributed to a variety of factors, including the intensity of the exercise. For example, high-intensity aerobic exercise training relies on muscle glycogen metabolism to a greater degree than moderate-intensity aerobic exercise training (26), and reduced muscle glycogen content is associated with enhanced ISGD (25). In addition, studies in humans have demonstrated that muscle glycogen utilization is strongly correlated with ISGD (30). Interestingly, results from Hughes et al. (13) demonstrated that a high-intensity aerobic exercise training program when combined with a high-carbohydrate diet resulted in no change in ISGD in weight-stable volunteers. Combined with a high-carbohydrate diet, high-intensity aerobic exercise training also doubled muscle glycogen stores, potentially limiting nonoxidative glucose disposal. In

middle-aged, insulin-resistant T2 diabetes patients, glycogen synthase activity and GLUT4 protein were increased with 8 wk of high-intensity aerobic exercise training, and these changes were associated with a significant increase in ISGD (4), and this occurred without an improvement in phosphatidylinositol-3 kinase (PI-3 kinase). Although the studies performed by Houmard et al. (11) suggested that a high-intensity aerobic exercise training-induced improvement in insulin sensitivity was associated with enhanced activation of PI-3 kinase, their studies were performed in lean, healthy adults. The results of studies by Christ-Roberts et al. (4) performed in insulin-resistant, obese subjects did not suggest a training-induced influence on insulin signaling *per se*. Hughes et al. (14) conducted a study similar to our investigation. In their studies, they recruited older men and women with impaired glucose tolerance and examined the influence of moderate- and high-intensity exercise on the rate of ISGD. Their results reported a 10% increase in ISGD regardless of the exercise intensity. However, it must be noted that moderate-intensity aerobic exercise was defined as 50% of maximal heart reserve, and this would have resulted in subjects training at a greater percentage of $\dot{V}O_{2max}$ since exercise intensity was defined by maximal $\dot{V}O_2$ in the present study. The interpretation of the previous studies are also complicated by similar exercise duration in both groups and lack of randomization. In the present study, caloric expenditure was similar in HI and MI, subjects were randomized to groups and consumed a regular mixed diet, and non-oxidative glucose disposal accounted for all the improvement in ISGD.

Our study was designed to assess the influence of exercise intensity on improvements in insulin sensitivity in elderly, obese adults, independent of caloric expenditure. Although the HI training-induced improvement in ISGD and nonoxidative glucose metabolism seem to reflect the influence of muscle glycogen content on insulin sensitivity, our studies are limited by the fact that we did not measure muscle glycogen content, GLUT 4, or glycogen synthase. We do know that two different mechanisms are primarily responsible for the exercise-induced increase in nonoxidative glucose metabolism. The first mechanism is based on the contention that exercise training facilitates an increase in insulin-induced activation of glycogen synthase. The second mechanism promotes increased glycogen synthase activity due to glycogen depletion. It is also known that glycogen synthase activity is closely associated with glycogen concentration, and glycogen synthase activity will remain elevated as long as the glycogen content is low (31). Our measurement of ISGD 72 h after the last exercise bout minimizes the acute influence of exercise training and allows us to study the specific influence of moderate- versus high-intensity aerobic exercise training regimens (25). In addition, our controlled diet prior to the pre- and postintervention measurement of ISGD negates the acute influence of dietary intake that may have complicated the interpretation of previous studies (2). Last, measurement of insulin

sensitivity via the hyperinsulinemic, euglycemic clamp technique provides a direct value for insulin action instead of a derived (intravenous glucose tolerance test) or estimated (oral glucose tolerance test) measurement of insulin action (1).

In summary, our studies provide further evidence that the intensity, duration, and frequency of aerobic exercise training play critical roles in the efficacious treatment of insulin resistance. In obese, elderly adults, HI facilitated an improvement in ISGD that was entirely reliant on non-oxidative glucose metabolism. On the contrary, MI training did not initiate any change in ISGD, nonoxidative glucose metabolism or glucose oxidation. It is extremely important to mention that the recent Surgeon General's Report on Physical Activity and Health recommends 30 min of moderate-intensity aerobic exercise training on most days of the week for health promotion and disease prevention (31). While this amount of activity will certainly provide

health benefits, overweight individuals at an increased risk of diabetes and cardiovascular complications may require more aggressive therapeutic regimens that include dietary modifications, increased duration of physical activity, and/or weight loss. Neither HI or MI ($1000 \text{ kcal}\cdot\text{wk}^{-1}$) resulted in weight loss or a change in the percentage of fat. Therefore, exercise training programs in the elderly that do not result in weight or fat loss may only improve insulin action through short-term improvements in glycogen metabolism. As such, exercise training programs should be modified to facilitate weight loss through additional caloric expenditure or include dietary manipulation to treat insulin resistance in obese, elderly adults.

Supported by NIH grants KO1 DK 64716-01 (R.H.C.), RO1 AG 19346-01 (W.J.E.), and F32 AG 21374 (N.P.H.), and AHA grant SDA 0335172N (R.H.C.). We also acknowledge the support of the University of Arkansas for Medical Sciences General Clinical Research Center funded through grant M01 RR14288.

REFERENCES

1. BEST, J. D., F. P. ALFORD, I. K. MARTIN, R. G. PESTELL, and G. M. WARD. Practical application of methods for in vivo assessment of insulin secretion and action. *Horm. Metab. Res. Suppl.* 24:60–66, 1990.
2. BISSCHOP, P. H., J. DEMETZ, M. T. ACKERMANS, et al. Dietary fat content alters insulin-mediated glucose metabolism in healthy men. *Am. J. Clin. Nutr.* 73:554–559, 2001.
3. BOULE, N. G., S. J. WEISNAGEL, T. A. LAKKA, et al. Effects of exercise training on glucose homeostasis (The HERITAGE Family Study). *Diabetes Care* 28:120–126, 2005.
4. CHRIST-ROBERTS, C. Y., T. PRATIPANAWATR, R. BERRIA, R. BELFORT, S. KASHYAP, and L. J. MANDARINO. Exercise training increases glycogen synthase activity and GLUT 4 expression but not insulin signaling in overweight nondiabetic and type 2 diabetic subjects. *Metabolism* 53:1233–1242, 2004.
5. DELA, F., K. J. MIKINES, M. V. LINSTOW, N. H. SECHER, and H. GALBO. Effect of training on insulin-mediated glucose uptake in human skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.* 263:E1134–E1143, 1992.
6. DELA, F., J. J. LARSEN, K. J. MIKINES, T. PLOUG, L. N. PETERSEN, and H. GALBO. Insulin-stimulated glucose clearance in patients with NIDDM. *Diabetes* 44:1010–1020, 1995.
7. EVANS, E. M., S. B. RACETTE, L. R. PETERSON, D. T. VILLAREAL, J. S. GREIWE, and J. O. HOLLOSZY. Aerobic power and insulin action improve in response to endurance exercise training in healthy 77–87 year olds. *J. Appl. Physiol.* 98:40–45, 2005.
8. GALLOWAY, M. T., and P. JOKL. Aging successfully: the importance of physical activity in maintaining health and function. *J. Am. Acad. Orthop. Surg.* 8:37–44, 2000.
9. HAYS, N. P., R. D., STARLING, X. LIU, et al. Effects of an ad libitum, low-fat, high-carbohydrate diet on body weight, body composition, and fat distribution in older men and women: a randomized controlled trial. *Arch. Intern. Med.* 164:210–217, 2004.
10. HEATH, G., J. GAVIN, J. HINDERLITER, J. M. HAGBERG, S. A. BLOOMFIELD, and J. O. HOLLOSZY. Effects of exercise and lack of exercise on glucose tolerance and insulin sensitivity. *J. Appl. Physiol.* 55:512–517, 1983.
11. HOUMARD, J., C. D. SHAW, M. S. HICKEY, and C. J. TANNER. Effect of short-term exercise training on insulin-stimulated PI 3 kinase activity in human skeletal muscle. *Am. J. Physiol. Endocrinol. Metab.* 277:E1055–E1060, 1999.
12. HOUMARD, J. A., C. J. TANNER, C. A. SLENTZ, B. D. DUSCHA, J. S. McCARTNEY, and W. E. KRAUS. Effect of the volume and intensity of exercise training on insulin sensitivity. *J. Appl. Physiol.* 93:101–106, 2003.
13. HUGHES, V. A., M. A. FIATARONE, R. A. FIELDING, C. M. FERRARA, D. ELAHI, and W. J. EVANS. Long term effects of a high-carbohydrate diet and exercise on insulin action in older subjects with impaired glucose tolerance. *Am. J. Clin. Nutr.* 62:426–433, 1995.
14. HUGHES, V. A., M. A. FIATARONE, R. A. FIELDING, et al. Exercise increases GLUT 4 and insulin action in subjects with impaired glucose tolerance. *Am. J. Physiol. Endocrinol. Metab.* 264:E855–E862, 1993.
15. IRWIN, M. L., E. J. MAYER-DAVIS, C. L. ADDY, et al. Moderate-intensity physical activity and fasting insulin levels in women. *Diabetes Care* 23:449–454, 2000.
16. KING, D. S., G. P. DALSKY, W. E. CLUTTER, et al. Effects of lack of exercise on insulin secretion and action in trained subjects. *Am. J. Physiol. Endocrinol. Metab.* 254:E537–E542, 1988.
17. KAHN, S. E., V. G. LARSON, J. C. BEARD, et al. Effect of exercise on insulin action, glucose tolerance, and insulin secretion. *Am. J. Physiol. Endocrinol. Metab.* 258:E937–E943, 1990.
18. KORHT, W. M., and J. O. HOLLOSZY. Loss of skeletal muscle mass with aging; effect on glucose tolerance. *J. Gerontol. A Biol. Sci. Med. Sci.* 50:68–72, 1995.
19. MIKINES, K. J., B. SONNE, P. A. FARRELL, B. TRONIER, and H. GALBO. Effect of physical exercise on sensitivity and responsiveness to insulin in man. *Am. J. Physiol. Endocrinol. Metab.* 254:E248–E259, 1988.
20. MIKINES, K. J., B. SONNE, B. TRONIER, and H. GALBO. Effects of acute exercise and detraining on insulin action in trained men. *J. Appl. Physiol.* 66:704–711, 1989.
21. MORLEY, J. E. An overview of diabetes mellitus in older persons. *Clin. Geriatr. Med.* 15:211–224, 1999.
22. MULLER, D. C., D. ELAHI, J. D. TOBIN, and R. ANDRES. The effect of age on insulin resistance and secretion: a review. *Semin. Nephrol.* 16:289–298, 1996.
23. OSTROW, A. C., and D. A. DZEWLITOWSKI. Older adults' perception of physical activity participation based on age-role and sex-role appropriateness. *Res. Q. Exerc. Sport* 57:167–169, 1986.

24. REAVEN, G. M. Pathophysiology of insulin resistance in human disease. *Physiol. Rev.* 75:476–486, 1995.
25. RICHTER, E. A., W. DERAVE, and J. F. P. WOJTASZEWSKI. Glucose, exercise and insulin: emerging concepts. *J. Physiol.* 535:313–322, 2001.
26. ROMJN, J. A., E. F. COYLE, L. S. SIDOSSIS, A. GASTALDELLI, J. F. HOROWITZ, and E. ENDERT. Regulation of endogenous fat and carbohydrate metabolism in relation to exercise intensity and duration. *Am. J. Physiol. Endocrinol. Metab.* 265:E380–E391, 1993.
27. Surgeon General's report on physical activity and health. From the Centers for Disease Control and Prevention. *JAMA* 276:522, 1996.
28. TONINO, R. P. Effect of physical training on the insulin resistance of aging. *Am. J. Physiol. Endocrinol. Metab.* 256:E352–E356, 1989.
29. TOTH, M. J., C. K. SITES, W. T. CEFALU, D. E. MATTHEWS, and E. T. POEHLMAN. Determinants of insulin-stimulated glucose disposal in middle-aged, pre-menopausal woman. *Am. J. Physiol. Endocrinol. Metab.* E113–E121, 2001.
30. TSENG, K. Y., and S. C. KALHAN. Calculation of substrate turnover rate in stable isotope tracer studies. *Am. J. Physiol. Endocrinol. Metab.* 245:E308–E311, 1983.
31. WOJTASZEWSKI, J. F., B. F. HANSEN, B. KIENS, and E. A. RICHTER. Insulin signaling in human skeletal muscle: time course and effect of exercise. *Diabetes* 43:1775–1781, 1997.