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Endurance Exercise Training Reduces Glucose-Stimulated Insulin Levels in 60- to 70-Year-Old Men and Women

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Background. Aging is frequently associated with development of insulin resistance and deterioration of glucose tolerance. Plasma glucose and insulin concentrations tend to be higher than in young people, even in those older individuals whose glucose tolerance is within the normal range. A sedentary life style could play a role in the development of insulin resistance and hyperinsulinemia with advancing age.

Methods. We evaluated the effect of 9 mo of vigorous endurance exercise training (~80% of maximal heart rate) on the glucose-stimulated insulin response and glucose disposal rate, using the hyperglycemic clamp procedure, in 12 people aged 65 ± 1 yr (mean ± *SE*) with normal glucose tolerance. The post-training hyperglycemic clamps were performed ~ 16 h after a usual exercise session.

Results. $\dot{V}O_2$max increased ~23% in response to the exercise program. The plasma insulin concentration (I) during hyperglycemia (180 mg·dL^{-1}) was significantly lower (mean 36 ± 6 μU·mL^{-1} before vs 26 ± 5 μU·mL^{-1} after; $p < .05$) after the exercise program. Insulin action was improved by the exercise, as the glucose disposal rate (M) during hyperglycemia was unchanged despite the blunted insulin response, resulting in an increase in the M/I ratio from 24 ± 5 to 30 ± 5 ($p < .05$), a value similar to the M/I ratio of 33 ± 4 found in normally active young subjects.

Conclusion. These results provide evidence that regular exercise is effective in reducing hyperinsulinemia and improving insulin action in 65-yr-olds to levels typical of young people.

AGING is often associated with a deterioration in glucose tolerance (1) as a result of development of insulin resistance and/or abnormal function of the pancreatic beta-cell (2). Even in those older people whose glucose tolerance is normal by National Diabetes Data Group (NDDG) standards (3), blood glucose and insulin levels tend to be higher than those of young people following an oral glucose challenge (4–7). The degree to which aging, per se, is responsible for the deterioration in glucose regulation is not clear, as the decline in physical activity and the increase in adiposity that often occur with aging can adversely affect glucose metabolism. In this regard, there is evidence that deterioration of glucose tolerance with aging can be avoided in rats if they are not allowed to become obese (8), and some physically active and/or lean older individuals appear to avoid deterioration in glucose tolerance with aging (9,10).

Considerable evidence indicates that hyperinsulinemia is associated with a cluster of metabolic disorders, including dyslipidemia, atherosclerotic cardiovascular disease, hypertension, non-insulin-dependent diabetes mellitus, and obesity (11–13). Even among people with normal glucose tolerance, Zavaroni et al. (14) found that individuals with hyperinsulinemia had higher blood pressure and fasting plasma triglycerides and lower high-density lipoprotein cholesterol levels than those with normoinsulinemia.

The insulin-lowering effect of endurance exercise training is well documented in young people (15,16) and in master athletes (9,17) who have been training vigorously for many years, but there have been few prospective studies of older men and women (18,19). Although these studies (18,19) showed that exercise training resulted in a reduced plasma insulin response to an oral glucose challenge, the effects of exercise on the insulin response to a controlled glycemic stimulus have not been determined. Therefore, the purpose of the present study was to determine the effect of a program of endurance exercise on the plasma insulin response using the hyperglycemic clamp procedure, in which plasma glucose concentration was held constant, in healthy 60- to 70-yr-old men and women with normal glucose tolerance.

Methods

Subjects. — Twelve subjects (5 men, 7 women) aged 60–70 yr, volunteered for the study. For comparative purposes, data are also presented on young, normally active subjects (7 men, 5 women). Selected physical characteristics are shown in Table 1. The study was approved by the Human Studies Committee of Washington University, and all participants signed an informed consent in accordance with the University guidelines for the protection of human subjects. The young and older subjects were normally active for their respective age groups, but none had participated in regular endurance exercise training (≥ 30 min·d^{-1}, ≥2 d·wk^{-1}) for at least one year prior to the study. The subjects were healthy, as determined by medical history, physical examination, graded exercise test with monitoring of ECG and blood pressure, chest radiograph, and blood and urine chemistries. Three of the older subjects had mild systolic hypertension

Table 1. Subject Characteristics

	Older		
	Sedentary	Trained	Young
Men			
n	5		7
Age (yr)	65 ± 1		25 ± 1
Height (cm)	178.3 ± 1.8		180.0 ± 1.5
Weight (kg)	85.2 ± 7.6	83.4 ± 8.4*	76.2 ± 2.6
Body fat (%)	26.7 ± 2.4†	25.5 ± 3.2*†	16.2 ± 1.5
Waist girth (cm)	99.0 ± 6.5	97.5 ± 6.8	
$\dot{V}O_2$max (mL·min^{-1}·kg^{-1})	28.2 ± 2.0†	35.8 ± 3.9*†	49.0 ± 1.4
Women			
n	7		5
Age (yr)	65 ± 1		24 ± 1
Height (cm)	162.9 ± 2.5		167.1 ± 3.7
Weight (kg)	60.6 ± 3.3	59.6 ± 3.3*	65.6 ± 4.5
Body fat (%)	37.2 ± 1.4†	36.6 ± 2.3*†	29.7 ± 4.8
Waist girth (cm)	81.4 ± 3.2	79.9 ± 2.9	
$\dot{V}O_2$max (mL·min^{-1}·kg^{-1})	21.7 ± 0.4†	26.5 ± 0.8*†	37.1 ± 1.9

Note. Values are means ± *SE*.
*Older trained vs sedentary, $p < .05$; †older vs young, $p < .05$.

(140 to 160 mm Hg) at rest. Subjects were not on medications other than Premarin (1 woman) and aspirin (1 man, self-prescribed). All participants had a normal response to a 75-g oral glucose tolerance test (GTT) by NDDG criteria (3) (Figure 1). Diet was monitored for 3 days prior to the GTT to ensure an intake of at least 150 g of carbohydrate per day.

Exercise testing. — As part of the initial screening, all of the older subjects performed a graded treadmill exercise test using the Bruce protocol. Subsequently, subjects performed a second treadmill test for the determination of maximal oxygen uptake ($\dot{V}O_2$max) using a constant speed (2–4 mph), incremental grade (1.5–2.5% every 2 min) protocol. The walking speed selected was that which elicited 60 to 70% of maximal heart rate (HR) during a 5- to 10-min warm-up on the treadmill set at zero incline. At least two of the following criteria had to be satisfied for assurance that $\dot{V}O_2$max had been attained: plateau in $\dot{V}O_2$, HR within 10 beats·min^{-1} of age-predicted maximal HR, and respiratory exchange ratio >1.10. Inspired gas volumes were measured using a dry gas meter (Parkinson-Cowan CD-4), and O_2 and CO_2 concentrations were measured with Applied Electrochemistry S-3A O_2 and Beckman LB-2 CO_2 analyzers. Heart rate was monitored using a 12-lead electrocardiograph.

Body composition and diet evaluations. — Body density was determined by hydrostatic weighing (20). Residual lung volume was measured by nitrogen dilution (21), and percent body fat was estimated using the equation of Brožek et al. (22). In the older subjects, the waist circumference, which is an index of visceral adipose tissue (23), was measured as described previously (20).

The subjects completed 7-day food records before and after the exercise training program. A dietician instructed participants on how to record food intake and conducted individual interviews to determine accuracy of the portions that were recorded. Food records were evaluated using the Datadiet Nutrient Analysis program (IPC Datadiet, Camarillo, CA). Subjects were instructed not to reduce their food intake or alter the composition of their diet during the course of the study. Although they were not specifically instructed to maintain body weight throughout the study, they were not discouraged from eating more if their appetite increased in response to the exercise training.

Training. — The supervised endurance training program consisted primarily of walking and running on an indoor track or treadmill and was supplemented with stationary cycling and rowing. The subjects trained approximately 45 min·d^{-1} (not including warm-up or cool-down), 4 d·wk^{-1} for 9 months. Exercise was initially prescribed at an intensity of 60 to 70% of maximal heart rate (HRmax). The exercise intensity was gradually increased so that during the final 3 months, all subjects were exercising at 80 to 85% of HRmax. $\dot{V}O_2$max was measured as described previously at 3-month intervals to provide information for adjusting the training intensity.

Hyperglycemic clamp. — Subjects consumed at least 250 g of carbohydrate per day for the 3 days prior to the clamp procedure. Hyperglycemic clamps were performed in the morning, after an overnight fast, according to the procedures described by DeFronzo et al. (24); post-training clamps were performed ~16 hours after a typical exercise session. The subjects voided, were weighed, then remained supine throughout the procedure. A polyethylene catheter was inserted into an antecubital vein for glucose infusion (20% dextrose). A second catheter was positioned in retrograde fashion in a dorsal hand vein, and the hand was warmed in a heated box (~70°C) for sampling of arterialized blood.

Three baseline blood samples were drawn at 5-min intervals for the determination of plasma glucose and insulin concentrations. Plasma glucose concentration was then raised to 180 mg·dL^{-1} within 15 min using a primed infusion, and was maintained at that level for 165 min using a variable speed infusion pump (Harvard Apparatus, Millis, MA). Plasma glucose concentration was measured at 2-min intervals for the first 10 min of the clamp and at 5-min intervals

for the subsequent 165 min with an automated glucose analyzer (Beckman Instruments, Fullerton, CA). Blood samples for determination of plasma insulin concentration were drawn at 2-min intervals for the first 10 min and at 15-min intervals for the remainder of the clamp. Blood samples were placed in chilled tubes containing Trasylol (aprotinin, FBA Pharmaceuticals, New York) and EDTA, centrifuged, and stored at −20°C for subsequent insulin analysis using a double antibody radioimmunoassay (25). Insulin assays were performed at the Diabetes Research and Training Center at the Washington University School of Medicine.

Calculations and statistics. — Areas under the early-phase (0 to 10 min) and late-phase (15 to 180 min) insulin curves were determined by the trapezoidal model. Glucose disposal rate was calculated for each 30-min interval. The effect of training on the insulin response during the hyperglycemic clamp was analyzed using a two-way analysis of variance, with training status and time as within-subject factors. Changes in the dependent variables in response to training were examined with paired *t*-tests. Differences among young and older subjects were determined with independent *t*-tests. All data are expressed as the mean ± *SE*. The acceptable level for statistical significance was $p < .05$.

RESULTS

Training. — Subjects exercised an average of 45 ± 1 min·d^{-1}, 4.2 ± 0.1 d·wk^{-1}, at 82 ± 1% of maximal HR over the 9 months. In all subjects, $\dot{V}O_2$max increased 23%, from 24.0 to 29.6 mL·min^{-1}·kg^{-1} ($p < .05$). There were modest, but significant, reductions in body weight and percent body fat in response to exercise training (Table 1). Mean changes in waist circumference were not statistically significant. There was a tendency for food intake to be higher after training (2241 ± 188 kcal·d^{-1} before vs 2488 ± 175 kcal·d^{-1} after, $p = .08$), but the proportion of energy from protein (17 ± 1% vs 17 ± 1%), fat (36 ± 2% vs 34 ± 2%), carbohydrate (45 ± 2% vs 47 ± 2%), and alcohol (2 ± 1% vs 2 ± 1%) did not change significantly.

Oral glucose tolerance. — Although the older subjects had normal glucose tolerance by NDDG standards, the areas under the glucose and insulin curves before training were significantly higher than those of the young people (Figure 1; $p < .01$). The exercise training resulted in a significantly lower insulin, but not glucose, response ($p < .05$). The post-training insulin area was not significantly different from that of the young subjects.

Hyperglycemic clamp: plasma glucose. — Fasting plasma glucose levels were significantly lower after exercise training (105 ± 2 mg·dL^{-1} before vs 100 ± 2 mg·dL^{-1} after). The level of hyperglycemia maintained during the clamp procedure was similar before and after exercise training (Table 2). The rate of glucose disposal during hyperglycemia was not changed as a result of exercise training (Table 2) and was significantly slower than in young people.

Hyperglycemic clamp: plasma insulin. — There was a significant reduction in fasting plasma insulin concentration

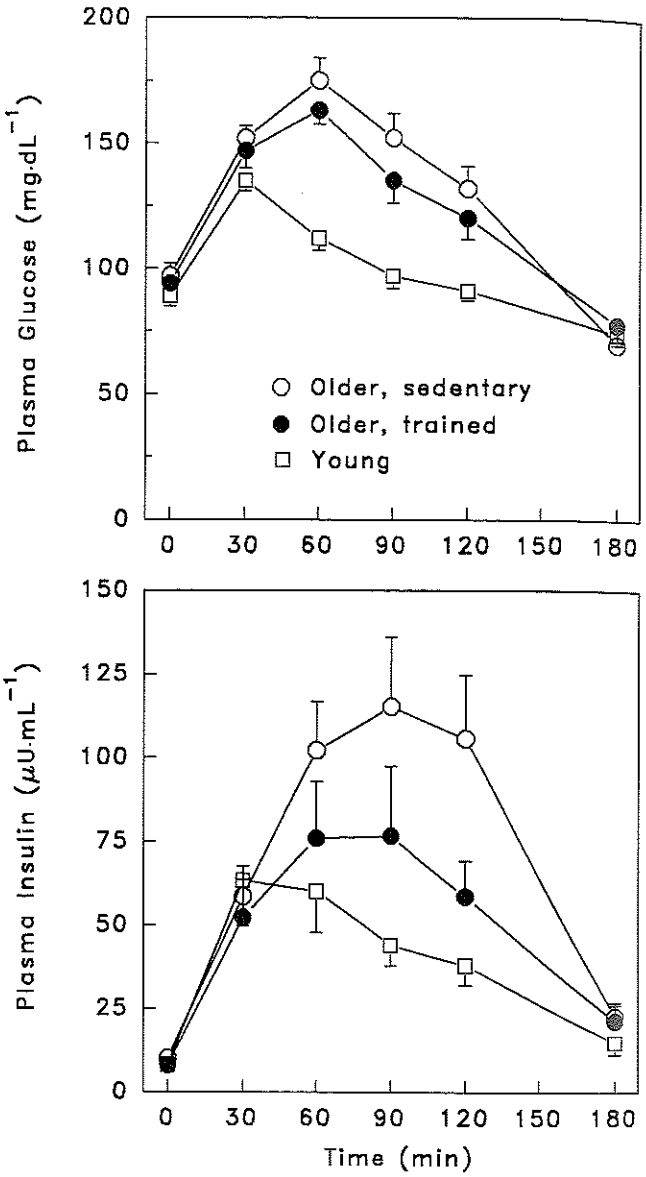

Figure 1. Plasma glucose (top panel) and insulin (bottom panel) concentrations during an oral glucose tolerance test of older people before and after endurance exercise training and of young people.

in response to exercise training, from 7.4 ± 1.5 to 5.5 ± 0.8 μU·mL^{-1}. In the trained state, fasting insulin levels were similar to those of young sedentary subjects (6.2 ± 0.6 μU·mL^{-1}).

During the hyperglycemic clamp procedure, glucose infusion resulted in a typical biphasic insulin response. In the early phase (0–10 min) of hyperglycemia, the peak insulin level was attained at 4 minutes both before and after exercise training. The average insulin concentration during the early phase was not significantly different in the sedentary and trained conditions (20 ± 3 vs 17 ± 2, respectively; $p = .06$). Neither of these insulin responses was significantly different from that of the young subjects (19 ± 2 μU·mL^{-1}).

The plasma insulin concentration increased throughout the late phase (15–180 min) of hyperglycemia (Figure 2).

Table 2. Hyperglycemic Clamp Data

	Time	Older		Young
		Sedentary	Trained	
Glucose	15′–180′	179 ± 1	180 ± 2	178 ± 2
(mg·dL^{-1})	150′–180′	179 ± 1	180 ± 1	179 ± 1
CV (%)	15′–180′	3.4 ± 0.7	3.2 ± 0.7	3.2 ± 0.2
	150′–180′	2.0 ± 0.4	3.0 ± 1.4	2.3 ± 0.2
Insulin	15′–180′	33.7 ± 6.8	26.0 ± 5.5*	31.3 ± 8.7
(μU·mL^{-1})	150′–180′	42.0 ± 9.6	30.8 ± 6.6*	41.2 ± 8.5
GDR	15′–180′	5.2 ± 0.3†	5.4 ± 0.2†	8.2 ± 0.6
(mg·kg FFM^{-1}·min^{-1})	150′–180′	6.4 ± 0.5†	7.0 ± 0.5†	12.1 ± 1.1

Notes. Values are means ± *SE*. CV, coefficient of variation for plasma glucose; GDR, glucose disposal rate; FFM, fat-free mass.
*Older trained vs sedentary, $p < .05$; †older vs young, $p < .05$.

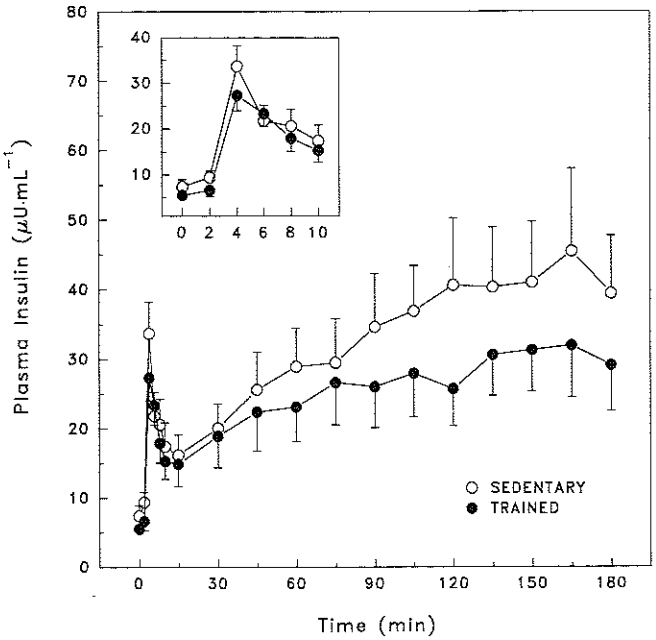

Figure 2. Plasma insulin concentrations of older people before and after endurance exercise training during a 3-hr hyperglycemic clamp. The inset figure is a magnification of the first 10 minutes of the hyperglycemic clamp.

The average plasma insulin concentration during the late phase of the clamp was 23% lower when the subjects were exercising regularly (34 ± 7 vs 26 ±6 μU·mL^{-1}; $p < .05$). Both before and after training, the average late-phase insulin concentration of the older subjects was not significantly different from that of the young subjects (31 ± 9 μU·mL^{-1}).

The ratio between the glucose disposal rate (M) and the prevailing plasma insulin concentration (I) during the last 30 minutes of hyperglycemia was used as a rough index of insulin action. The M/I ratio was significantly increased in the older subjects after the exercise program (23.7 ± 4.5 vs 30.0 ± 4.4) and was similar to the M/I ratio of young subjects (33.0 ± 3.0). It should be noted that M/I ratios do not always reflect insulin action, as the relationship between M and I is not linear across a wide range of insulin concentrations or when there is an acute change in insulin concentration. However, we believe the M/I ratios in this study can be used as an index of insulin action for the following reasons. First, the insulin concentrations attained during the clamp were in the linear region of a typical dose-response curve for insulin-stimulated glucose disposal, and second, the M/I ratio was calculated from data obtained during the final 30 minutes of the clamp, when both plasma insulin concentration and glucose disposal rate were relatively stable.

Effect of weight loss. — Regression analyses were performed to determine if changes in body composition (weight, fat mass, waist circumference) in response to training were associated with changes in the insulin response to hyperglycemia or to the rate of glucose disposal during the hyperglycemic clamp. Changes in body composition were not predictive of changes in the insulin response ($r = .04$, $r = .05$, and $r = .01$ for weight, fat mass, and waist girth, respectively). However, the individual changes in glucose disposal rate were significantly associated with changes in body weight ($r = -.71$, $p < .01$) and waist circumference ($r = -.68$, $p < .01$; Figure 3), but not fat mass ($r = -.54$, $p = .07$).

DISCUSSION

The purpose of this study was to determine the effect of vigorous endurance exercise training on the response of plasma insulin to glucose stimulation in healthy 60- to 70-yr-old men and women with normal glucose tolerance using the hyperglycemic clamp procedure. The advantage of this procedure is that the stimulus to the β-cell is controlled, allowing the independent assessment of the effects of exercise on the plasma insulin response to glucose. We found that plasma insulin concentrations were lower by an average of 13% ($p = .06$) and 23% ($p < .05$) during the early (0 to 10 min) and late (15 to 180 min) phases of hyperglycemia after the subjects had been exercising. Although it might be argued that the conditions during the hyperglycemic clamp (i.e., sustained hyperglycemia) are not physiological, we believe that these improvements are reflective of physiological conditions, as the insulin response to an oral glucose challenge was also reduced by ~30%. These results extend the findings of Seals et al. (18) and Kahn et al. (19), who found reduced insulin responses to an oral GTT (18,19) and lower acute insulin responses to an intravenous bolus of glucose and to intravenous injections of arginine at different glucose concentrations (19) in older people after an exercise training program.

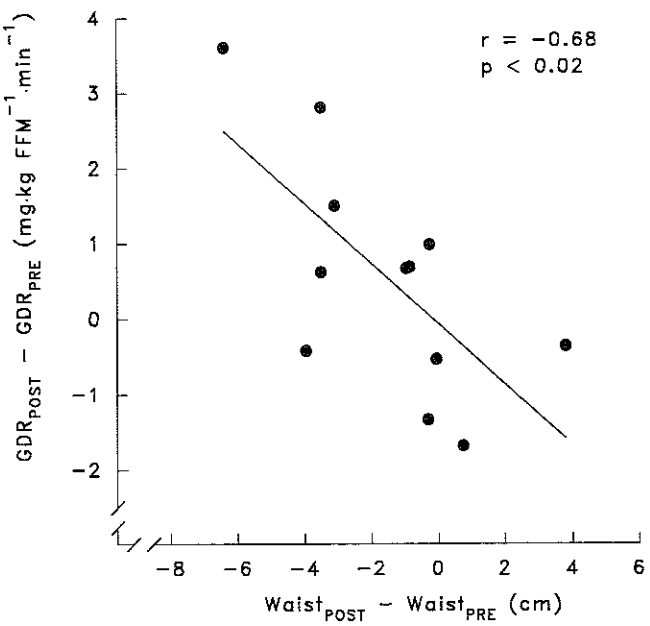

Figure 3. Training-induced changes in glucose disposal rate during a hyperglycemic clamp as a function of changes in waist circumference in 12 older men and women.

It could reasonably be argued that the blunted insulin response to glucose and the accompanying increase in insulin action were acute effects of the last bout of exercise rather than long-term adaptations to exercise training. However, this is not a useful distinction. If sedentary individuals try to perform a bout of exercise sufficiently vigorous to influence insulin secretion and insulin sensitivity, they usually develop sufficient muscle damage to result in insulin resistance and an unchanged or increased insulin response (26–28). Thus, it may be necessary to be trained to perform exercise sufficiently prolonged and vigorous to result in a blunted insulin response and increased insulin sensitivity. Furthermore, it appears that the only adaptation to exercise training with a major impact on insulin sensitivity and insulin secretion that can be considered "long term" is the change in body composition, i.e., the decrease in body fat content (29,30). The other adaptations appear to have a short half-life and are lost rapidly (15,31–35). Thus, the effects of exercise on insulin action and insulin secretion are largely short-term responses to sufficiently vigorous exercise that are made possible by prior exercise training.

Although the older subjects had normal glucose tolerance prior to training, their glucose and insulin responses during the GTT were greater than those of young people (Figure 1). The rate of glucose disposal during the hyperglycemic clamp was also significantly lower in the older subjects, even though their plasma insulin concentrations were similar to those of the young subjects. Both of these findings indicate a state of mild insulin resistance, which is not uncommon among sedentary, older people (4–7). Insulin action improved in response to exercise training, as evidenced by the finding that the rate of glucose disposal during hyperglycemia was unchanged despite a significantly lower insulin concentration (Table 2). Following the exercise program, the insulin action of the older people was comparable to that of the young active subjects, as reflected by the M/I ratios. However, the improvement in insulin action was counterbalanced by the reduction in insulin levels, as evidenced by no improvement in either oral or intravenous glucose tolerance.

The reciprocal relationship between insulin secretion and insulin action in the sedentary and trained states and the absence of a training effect on glucose tolerance have been noted by others. Seals et al. (18) found a 23% reduction in insulin area but no change in oral glucose tolerance in older people with normal glucose tolerance after 12 months of endurance training. Kahn et al. (19), who determined the responses to intravenous and oral glucose tolerance tests and the acute glucose-potentiated insulin responses to intravenous arginine, also found that exercise training resulted in a reduction in insulin response and an enhancement of insulin action in older people, but that glucose tolerance was not changed. This was true both in subjects who had normal and abnormal glucose tolerance. Kahn et al. (19) speculated that there may be a set point for glucose tolerance that declines with age. They further suggested that the set point is sensitive to diet, but not exercise, since raising the carbohydrate content of the diet has been shown to improve glucose tolerance (36). The potential benefits of exercise training cannot be dismissed, however, as the glucose tolerance of some master athletes who stopped training for 10 days was similar to that of young, lean, sedentary men (17). Rogers et al. (17) suggested that the protective effect of habitual exercise training against the deterioration of glucose tolerance with aging may be mediated by prevention of increased fat deposition, particularly in the intra-abdominal region. In this regard, the waist-to-hip circumference ratio (WHR) (37) and computerized tomography measures of intra-abdominal and chest fat areas (38) have been shown to be stronger predictors of glucose tolerance than age among men aged 41 to 76 years. In the present study, training-induced changes in the insulin response to hyperglycemia were not associated with changes in body composition. However, those subjects who had the largest reductions in body weight and waist circumference tended to have the greatest increases in the rate of glucose disposal during the hyperglycemic clamp (Figure 3).

There is growing evidence that accumulation of adipose tissue in intra-abdominal regions is associated with aberrations in glucose and insulin metabolism, although the underlying mechanisms are not clear (39,40). Adipose tissue in those visceral regions drained by the portal circulation is highly sensitive to lipolytic stimuli, and it has been suggested that this may lead to an increased exposure of the liver to free fatty acids (FFA) (41). An increase in portal FFA appears to reduce hepatic insulin clearance (42), thereby contributing to hyperinsulinemia and insulin resistance. An increase in hepatic FFA oxidation stimulates gluconeogenesis, leading to hyperglycemia (43). Since aging is associated with increasing intra-abdominal fat accumulation (44), it is possible that complete normalization of glucose tolerance in older men and women is contingent upon the reduction of this fat mass. Clearly, the potential interactions of exercise and fat distribution on the glucose tolerance of the aging warrant further investigation.

Although glucose tolerance was not improved as a result of exercise training, the blunted insulin response to glucose and the enhanced insulin action must be considered favorable adaptations. There is accumulating evidence implicating hyperinsulinemia and insulin resistance as the common links in a syndrome of metabolic disorders that includes dyslipidemia, atherosclerosis, hypertension, and non-insulin-dependent diabetes (11–13). Our data indicate that endurance exercise training was effective in reducing both fasted and glucose-stimulated peripheral insulin concentrations of older men and women to levels that are typical of young people. There was also an increase in insulin action in response to exercise training, as evidenced by the finding that the rate of glucose disposal during hyperglycemia was unchanged despite a significantly lower insulin concentration. Our data suggest, therefore, that regular endurance exercise training has the potential to reduce the risk of developing the metabolic disorders associated with age-related hyperinsulinemia and insulin resistance.

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