Resistance Exercise and Growth Hormone Administration in Older Men: Effects on Insulin Sensitivity and Secretion During a Stable-Label Intravenous Glucose Tolerance Test

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To assess the effects of 16 weeks of heavy resistance exercise training (RE) on insulin sensitivity and secretion in healthy older men aged 64 to 75 years (N = 15), stable-label ([6,6,^{2}H$_2$]glucose) intravenous glucose tolerance tests (IVGTTs) were performed before and 7 days after the last bout of exercise. Glucose disappearance rate (R$_d$) and an index of insulin sensitivity (Si*) were derived using the minimal model of labeled glucose disappearance, and insulin secretion parameters were derived from C-peptide and glucose concentrations measured during the IVGTT, using a minimal model of C-peptide secretion and kinetics. Each subject trained at an intensity of 70% to 95% maximum strength 4 d/wk for 16 weeks on Nautilus (DeLand, FL) weight-training equipment. In conjunction with exercise, six men received daily injections of recombinant human growth hormone ([rhGH] 12.5 to 24 μg/kg/d) and the other nine received placebo injections. GH/placebo injections were administered in a double-blind randomized fashion. The RE program was supervised and progressive in nature, consisting of both upper- and lower-body exercises, and significantly increased muscle strength ($P < .05$) with no additional benefit from rhGH except for a tendency toward a greater increase in fat-free mass (FFM) in the RE + GH group ($P = .06$). Peak glucose R$_d$ increased following RE ($P < .01$), and there was a trend for an improved Si* (ie, from 6.79 ± 1.14 to 8.42 ± 0.89 × 10^4 per min/[μU/mL], $P = .06$). Peak glucose R$_d$ and Si* were unchanged in the RE + GH group following treatment. First- and second-phase insulin secretion were not affected by RE or RE + GH. Glucose tolerance, quantified as the glucose disappearance constant (K$_g$) between 10 and 32 minutes of the IVGTT, was unchanged by exercise or hormone treatment. These findings support those of a recent study that used the hyperinsulinemic-euglycemic clamp technique (Miller et al, J Appl Physiol 77:1122-1127, 1994), and suggest that when healthy older men engage in RE, whole-body glucose R$_d$ and Si* are improved, and these beneficial effects are not only due to the acute effects of the last bout of exercise. Additionally, in six subjects who received GH, glucose R$_d$ and Si* were not significantly improved following the RE program. Although this may suggest that GH can diminish improvements in glucose R$_d$ and Si* that result from RE, further study is needed to confirm this observation.
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IT IS KNOWN THAT glucose tolerance deteriorates with advancing age.[1-2] However, much of this reduction in glucose tolerance may not be related to aging per se, but to unfavorable changes in body composition and level of physical activity.[3-5] Regardless, it is well recognized that the development of insulin resistance is an important contributor to the age-associated decline in glucose tolerance.[6]

Typically, older persons have reduced muscle mass and strength, and this can interfere with their ability to lead an independent life-style.[7-9] However, it has recently been determined that heavy resistance exercise training ([RE] ie, weight-lifting) can markedly improve muscle strength and function in this population.[10-11] Far fewer studies have evaluated the effects of increased physical activity in the form of RE on glucose tolerance and insulin sensitivity, although it is well known that insulin sensitivity can be improved in older adults following periods of endurance (ie, brisk walking, jogging, and cycling) exercise training.[12-15]

Age-associated reductions in muscle mass and function

may also be a result of reduced circulating concentrations of growth hormone (GH) and insulin-like growth factor-I (IGF-I).[16] GH replacement therapy has been tested in older adults, and the results suggest that short-term GH administration (1 to 4 weeks) can reduce nitrogen excretion,[17-18] whereas longer-term therapy (6 months) increases lean body mass and reduces body fat.[19] Such changes in body composition have been associated with improved glucose tolerance and insulin sensitivity; however, it is also established that excess GH can induce insulin resistance.[20-21] Whether GH, when given in conjunction with RE, will prevent the possible improvements in insulin sensitivity associated with this type of exercise is not known. Likewise, it is unclear whether the changes in body composition associated with RE can override the diabetogenic effects of GH.

In this study, we evaluated the effects of RE alone or in combination with daily GH replacement therapy on insulin sensitivity and secretion in older men (>65 years). Although there are several ways to assess insulin sensitivity/secretion in vivo,[22] each having a particular advantage, we have used the minimal model of glucose kinetics,[23] which allows simultaneous measurement of insulin sensitivity, insulin secretion, and glucose effectiveness from a single intravenous glucose tolerance test (IVGTT). However, with unlabeled non–steady-state data like the glucose and insulin concentration time courses obtained during an IVGTT, it is difficult to separate out glucose production and disappearance processes. Addition of a glucose tracer allows monitoring of glucose disappearance processes, so we performed IVGTTs with a stable isotope of glucose (6,6,^{2}H$_2$-glucose) to better quantify glucose disappear-

ance[24-25] before and 7 days after RE with and without GH treatment in a group of older men.

SUBJECTS AND METHODS

Subjects

Fifteen healthy, sedentary older men (aged 60 to 75 years) who were of normal weight for height (body mass index, 25.7 ± 0.62 kg/m²) agreed to participate in this study. Before entry, each subject's health status was assessed by medical history, physical examination, treadmill exercise stress test, chest x-ray, and routine blood and urine chemistries. All subjects had a nondiabetic plasma glucose response to a 75-g oral glucose tolerance test. This study was approved by the Human Studies Review Board at Washington University School of Medicine, and each subject signed a consent form after the purpose and procedures were described.

RE Program

All subjects participated in a 16-week supervised progressive RE program consisting of moderate- to high-intensity (75% to 90% maximum strength) low-repetition (four to 10) weight-lifting exercise, completing four sets of each exercise per session and four sessions per week. The weight-training involved all major muscle groups, alternated daily between upper-body (biceps curl, shoulder press, deltoid lift, bench press, latissimus pullover, and arm cross) and lower-body (leg press, knee flexion, and knee extension) exercises, and was performed on Nautilus (DeLand, FL) weight-training equipment.

In conjunction with RE, subjects were randomly assigned to receive daily subcutaneous injections of either placebo (Genentech [South San Francisco, CA] excipient in sterile water, n = 9) or rhGH (Genentech, n = 6) in a double-blind fashion. The first two subjects in the RE + GH group received 18 μg GH/kg/d, but this was reduced to 12.5 μg GH/kg/d for the remaining subjects because of the prevalence of side effects and subject attrition observed at the higher dose.[26-27] Nonetheless, despite the difference in dose, elevations in plasma IGF-I were quantitatively similar (see Table 2 in Yarasheski et al[27]). Injections were given in the afternoon (3 to 6 PM) 7 days/wk.

Muscle Strength Assessment

Before and during the last week of treatment, muscle strength was determined as the maximum number of 4.5-kg plates lifted on each of the Nautilus exercise devices, and as the maximum force (N · m) produced by knee extensor and flexor muscles during maximum isokinetic (60°/s) contraction on a Cybex dynamometer (Ronkonkoma, NY).

Body Composition Assessment

Before and during the last week of RE and injections, at least 12 hours after a single training session/injection, fat mass and fat-free mass (FFM) were determined by hydrodensitometry using previously described methods.[28] Regional fat distribution was assessed with the skinfold method. Seven sites were measured in duplicate by a single investigator: triceps, subscapula, pectoral, suprailiac, umbilicus, midaxillary, and thigh.

IVGTTs and Minimal Modeling

Stable isotopically labeled IVGTTs were performed after an overnight fast. Dietary recall verified that on the day before a study all subjects consumed at least 200 g carbohydrate. Following the weight-training program, a second IVGTT was performed 7 days after the last bout of exercise/injection. Subjects refrained from any strenuous activity (including exercise) during this 7-day period.

On the morning of a test, an intravenous catheter was placed in an antecubital vein of each arm. Through one catheter, a glucose bolus (0.33 g/kg) enriched with [6,6,²H₂]glucose (10% by weight) was administered over 45 seconds. The other catheter was used for blood sampling. Baseline blood samples (5 mL) for determination of glucose, insulin, C-peptide, and [6,6,²H₂]glucose enrichment were obtained at −15 and −5 minutes and immediately before glucose administration (time 0). Thereafter, blood samples were obtained at the following time points: 2, 3, 4, 5, 8, 10, 12, 14, 16, 18, 20, 24, 28, 32, 40, 45, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 210, and 240 minutes. Plasma was separated, and glucose level was determined enzymatically with a glucose analyzer (Beckman Instruments, Fullerton, CA) at bedside. Blood samples for insulin, C-peptide, and [6,6,²H₂]glucose enrichment were kept chilled on ice, centrifuged at 4°C, and stored at −20°C for subsequent analysis.

Samples were analyzed in duplicate by a double-antibody radioimmunoassay method for both insulin[29] and C-peptide.[30] Plasma samples for [6,6,²H₂]glucose enrichment were deproteinized with 300 μL cold acetone. After centrifugation, the supernatant was removed and then evaporated under nitrogen, and the pentaacetate derivative of glucose was formed by addition of 100 μL acetic anhydride:pyridine (1:1). Glucose was separated by gas chromatography at 190°C on a 3% OV 101 packed column, and its ²H enrichment was measured by positive chemical ionization mass spectrometry (Finnigan 3300 quadrupole GC/MS, Sunnyvale, NY) by the use of selective ion monitoring of mass to charge ratios 333 and 331.

Kinetic analysis of the data was achieved by applying the minimal model for glucose disappearance modified for tracer data.[24-25] Whereas the original minimal model proposed by Bergman et al[23] generates an insulin sensitivity index (Si) that describes the effect of insulin to promote glucose disposal and to inhibit hepatic glucose production, addition of a glucose tracer and subsequent modeling of the disappearance of glucose tracer allows the derivation of an insulin sensitivity index (Si*) that describes insulin's effect on glucose disappearance processes only and expresses the fractional glucose disappearance rate (R$_d$) per unit change in insulin (ie, $\times 10^4$ per min/[μU/mL]). The tracer concentration, c(t), is calculated as $[G]Z/(1 + Z)$, where G is the total glucose concentration and Z is the ratio between tracer and natural or tracee glucose. With insulin as the input function, parameter Si* was estimated from the time courses of glucose tracer concentration using a nonlinear least-squares estimation technique.[31] The tracer minimal model also allows estimation of glucose effectiveness, Sg* (min⁻¹), which describes the effect of glucose per se at basal insulin levels to normalize its own concentration through disappearance. Thus, Sg* describes glucose clearance at basal glucose and insulin levels.[25] Finally, the time course of glucose R$_d$ per unit volume during the IVGTT (R$_d$, mg/min/100 mL) was calculated according to the equation $[Sg^* + X^*(t)]c(t)$, where X*(t) represents the time course of peripheral insulin action (expressed in min⁻¹) derived by the model.[24] R$_d$ provides a physiologically meaningful description of the ability of the organism to clear glucose from the accessible pool during an IVGTT.

As for glucose kinetics, a model-based approach was used to survey the insulin secretory portrait during the IVGTT. Briefly, insulin secretory parameters, mainly first- and second-phase β-cell sensitivities to glucose, were derived by identifying a model of C-peptide secretion from glucose and C-peptide IVGTT data using a nonlinear least-squares estimation technique.[31] This model requires C-peptide kinetics to be fixed to known values,[32,33] and is based on the packet-storage hypothesis of insulin secretion.[34]

Intravenous glucose tolerance was determined as the glucose disappearance constant (K_g) calculated as the slope of the least-square regression line relating the natural logarithm of the glucose

concentration to time for samples drawn between 10 and 32 minutes of an IVGTT.

Measurement errors for labeled glucose and C-peptide were assumed to be of zero mean, independent, Gaussian, and with experimentally determined variance. In particular, the coefficient of variation for C-peptide was 6%, and that for labeled glucose was 2%.

Statistical Analysis

All data are reported as the mean ± SE. Within-group differences from initial to final testing were evaluated with a paired t test. To assess between-group differences, delta scores (final initial) were computed and compared using an unpaired t test. The level of statistical significance was set at P less than .05.

RESULTS

Body Composition and Muscle Strength

The study groups were of similar age, height, and weight and had comparable estimates of body composition and muscle strength (Table 1). There was a tendency for the RE + GH group to have a higher insulin sensitivity and peak glucose R_d before treatment. Changes in body composition and muscle strength have been reported and discussed in detail in a separate report.[27] In this report, we will only summarize body composition and muscle strength findings for the subgroup of subjects who participated in the IVGTT portion of the study design.

FFM increased and fat mass decreased in both groups (RE and RE + GH), but the increase in FFM tended to be greater for GH recipients ($P = .06$; Table 2). The central to total sum of skinfolds ratio (ie, sum central SF/sum SF, Table 1) was unchanged in both groups; therefore, no significant change in the pattern of fat distribution was observed following exercise or hormone treatment. Similar improvements in upper- and lower-body muscle strength measured on the Nautilus weight-training equipment were noted in both groups. For example, after the RE program, subjects in both the RE and RE + GH groups were able to life five additional 4.5-kg plates on the leg and bench press exercises, respectively ($P < .01$). Isokinetic muscle strength of the knee extensors and flexors was also improved in both groups ($P < .05$; Table 3).

IVGTT and Model-Derived Parameters

Basal glucose, insulin, and C-peptide levels were not affected by RE or RE + GH. Fasting plasma IGF-I,

Table 1. Descriptive Characteristics

Measure	RE	RE + GH
No. of subjects	9	6
Age (yr)	66.3 ± 0.6	66.3 ± 1.8
Height (cm)	173.3 ± 1.3	179.8 ± 1.6
Weight (kg)	80.1 ± 2.6	78.5 ± 1.1
FFM (kg)	56.1 ± 1.3	56.8 ± 1.2
Fat mass (kg)	23.9 ± 1.8	21.8 ± 1.4
Si* (×10^4 per min [μU/mL])	6.8 ± 1.1	10.1 ± 2.5
Peak glucose R_d (mg/100 mL/min)	3.0 ± 0.3	5.2 ± 1.4
Bench press 1 RM	9.5 ± 0.7	10.9 ± 0.6
Leg press 1 RM	13.8 ± 1.9	14.6 ± 1.1

NOTE. Values are the mean ± SE. The 1-RM values for the bench and leg press are the number of 4.5-kg plates lifted.

Abbreviation: 1 RM, 1-repetition maximum.

Table 2. Body Composition

Variable	RE		RE + GH	
	Before	After	Before	After
Weight (kg)	80.1 ± 2.6	80.2 ± 2.6	78.5 ± 1.1	80.5 ± 1.5
Fat mass (kg)	23.9 ± 1.8	22.0 ± 2.0*	21.8 ± 1.4	19.6 ± 1.7*
FFM (kg)	56.1 ± 1.3	58.2 ± 1.7*	56.8 ± 1.2	60.9 ± 0.9*
Sum SF (mm)	136.9 ± 8.8	127.2 ± 9.0*	122.4 ± 8.8	103.5 ± 11.2*
Sum central SF (mm)	63.1 ± 4.3	56.7 ± 4.7*	57.4 ± 5.0	48.4 ± 6.8*

NOTE. Values are the mean ± SE.

Abbreviations: Sum SF, sum of skinfolds from 7 different sites; Sum central SF, sum of umbilicus, suprailiac, and midaxillary skinfolds.

*$P < .05$, before v after within each group.

measured during the final week of treatment, was increased in the RE + GH group ($P < .05$), while exercise alone did not elevate plasma IGF-I (Table 4). The glucose disappearance constant (K_g) is considered an appropriate descriptor of intravenous glucose tolerance. For the RE group, K_g was 1.4 ± 0.1 %/min before and 1.6 ± 0.1 %/min after training ($P = .17$), while K_g was 1.7 ± 0.3 %/min before and 1.8 ± 0.3 %/min after RE + GH ($P = .50$). These results indicate that the older men had normal intravenous glucose tolerance before intervention and that intravenous glucose tolerance 7 days after treatment was unaffected by RE or RE + GH treatment. However, in comparison to healthy young subjects (n = 7) tested in our laboratory, a reduced level of intravenous glucose tolerance (ie, K_g) was noted in these older men (2.2 ± 0.1 %/min for the young v 1.5 ± 0.2 %/min for the older men, $P < .05$). Young subjects were not part of the overall research design, rather their data is presented here simply as a means for comparison. These young subjects were 22 to 30 years of age, had an average body mass index (kg/m^2) of 23.7, and were of similar body composition and had comparable muscle strength to those previously reported on by our group.[35]

Model predictions for glucose R_d in both the RE and RE + GH groups before and after treatment are presented in Fig 1. Peak glucose R_d was significantly increased following RE, 3.0 ± 0.3 mg/100 mL/min before and 4.0 ± 0.4 mg/100 mL/min after training ($P < .01$). Eight of nine RE subjects had higher peak glucose R_d after treatment. Peak glucose R_d was unchanged following RE + GH treatment. Before treatment, the RE + GH group tended to have a higher peak glucose R_d ($P = .08$).

RE resulted in a 24% increase in Si* from 6.79 ± 1.14 to 8.42 ± 0.89 × 10^4 per min/(μU/mL), and this change

Table 3. Isokinetic Muscle Strength at 60°/s

Exercise	RE		RE + GH	
	Before	After	Before	After
Knee extensors (maximum force, N · m)	142.6 ± 4.7	162.0 ± 7.7*	159.8 ± 4.1	184.0 ± 7.7*
Knee flexors (maximum force, N · m)	102.1 ± 6.2	120.7 ± 6.5*†	121.6 ± 6.1	127.7 ± 6.9*

NOTE. Values are the mean ± SE.

*$P < .05$, before v after within each group.

†Change for RE was greater than that for RE + GH ($P < .05$).

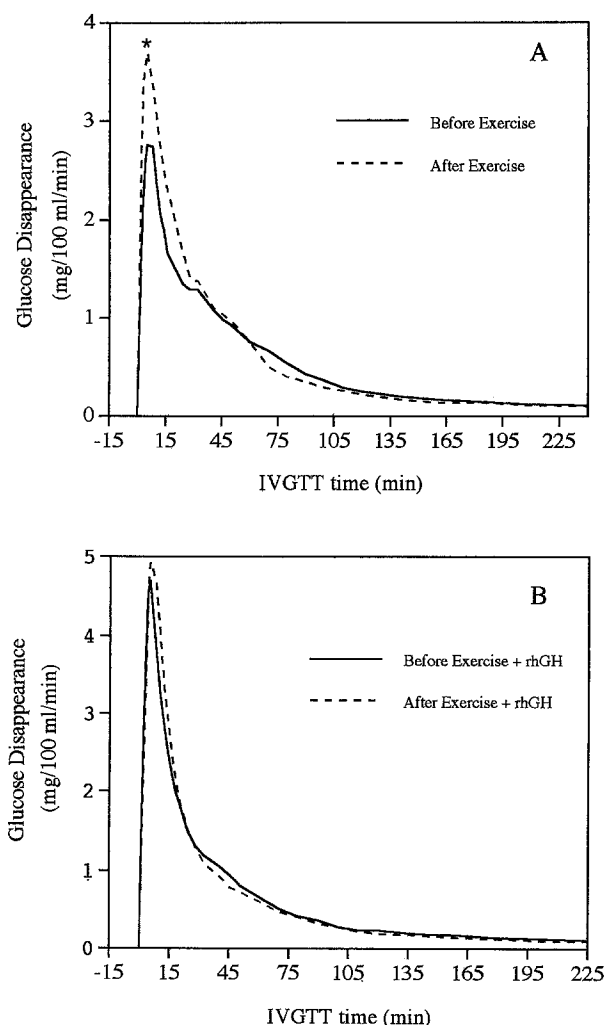**Table 4. Fasting Plasma Glucose, Insulin, C-peptide, and IGF-I**

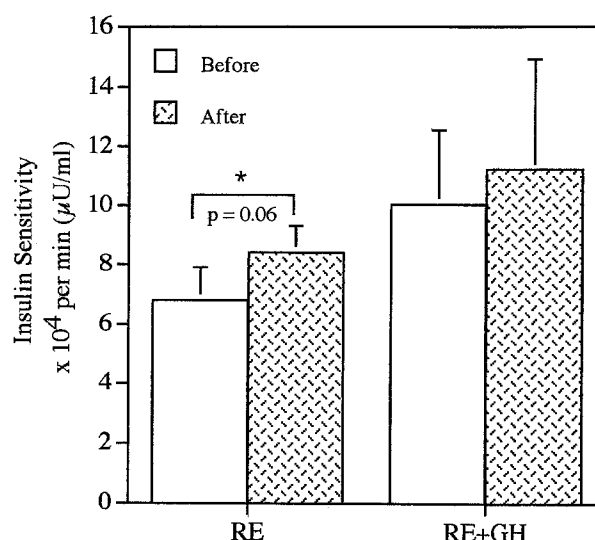| Parameter	RE		RE + GH	
	Before	After	Before	After
Glucose (mg/dL)	95 ± 3.2	99 ± 2.4	104 ± 2.8	99 ± 2.4
Insulin (μU/mL)	6.5 ± 0.9	6.8 ± 0.8	5.3 ± 0.4	4.9 ± 0.5
C-peptide (pmol/L)	492.0 ± 55.9	514.6 ± 47.4	494.3 ± 47.0	425.7 ± 31.3
IGF-I (ng/mL)†	124.6 ± 10.3	117.4 ± 6.5	104.1 ± 27.9	238.3 ± 39.0*

NOTE. Values are the mean ± SE.

*$P < .05$, before v after.

†Measurement was made during final week of treatment, all others were made before IVGTT.

approached statistical significance ($P = .06$; Fig 2). Following RE + GH treatment, Si* was only slightly greater, $10.06 ± 2.52$ before and $11.23 ± 3.67 × 10^4$ per min/(μU/mL) after treatment. The initial difference in Si* between groups was not statistically significant ($P = .21$). Si* was

Fig 2. Insulin sensitivity index (Si*) before and after 16 weeks of RE. In conjunction with RE, 6 men received daily injections of GH while the remaining 9 received a placebo injection. Posttraining measurement of Si* was performed 7 days after the last bout of exercise. Although the pretreatment Si* value tended to be greater for RE + GH, this difference did not reach statistical significance. Values are the mean ± SE.

$13.91 ± 2.66 × 10^4$ per min/(μU/mL) in the group of young subjects mentioned earlier, significantly greater ($P < .05$) than Si* values for the older men in this study. Neither RE nor RE + GH changed the glucose effectiveness parameter, Sg*. For the RE group, Sg* was $0.0056 ± 0.0004$ before and $0.0058 ± 0.0002$ min^{-1} after treatment, whereas Sg* was $0.0055 ± 0.0004$ before and $0.0052 ± 0.0003$ min^{-1} after the RE + GH treatment. The mean of the fractional standard deviations (precision of parameter estimate) for parameter estimates Si* and Sg* was 4.2% and 2.8%, respectively, and was in close agreement with those published by Avogaro et al.[24]

Insulin secretory parameters are presented in Table 5. First-phase (φ1) and second-phase (φ2) pancreatic sensitivity to glucose were not affected by RE or RE + GH. For example, φ1 was $99.4 ± 45$ before and decreased slightly to $88.4 ± 34.2$ (10^{-9}) after treatment in the RE group. φ1 was $110.6 ± 34.9$ before and $112.1 ± 64.8$ (10^{-9}) after RE + GH treatment. φ2 was, respectively, for the RE group $10.6 ± 3.1$ and $9.5 ± 3.9$ (min^{-1} × 10^{-9}) and for RE + GH $9.7 ± 3.2$ and $8.5 ± 1.8$ (min^{-1} × 10^{-9}). The disposition index (Si* × φ2) was not significantly affected by either treatment.

Fig 1. Glucose R$_d$ during an IVGTT before and after 16 weeks of either RE alone (n = 9, A) or RE + GH (n = 6, B). Peak glucose R$_d$ was higher (*$P < .01$) after RE, but was unchanged following RE + GH.

DISCUSSION

Whereas previous investigations have shown that endurance exercise (ie, brisk walking, jogging, and cycling)

Table 5. Insulin Secretion Parameters

Parameter	RE		RE + GH	
	Before	After	Before	After
φ1 (10^{-9})	99.4 ± 45.0	88.4 ± 34.2	110.6 ± 34.9	112.0 ± 64.8
φ2 (min^{-1} × 10^{-9})	10.6 ± 3.1	9.5 ± 3.9	9.7 ± 3.2	8.5 ± 1.8

NOTE. Values are the mean ± SE.

Abbreviations: φ1, glucose sensitivity of first-phase insulin secretion; φ2, glucose sensitivity of second-phase insulin secretion.

training can diminish the insulin resistance associated with advancing age,[12-15] it was the purpose of this study to determine if heavy RE (weight-lifting) would improve insulin sensitivity in older adults. We found that RE: (1) increased upper- and lower-body muscle strength, (2) increased FFM, and (3) increased peak glucose R_d and Si* during an IVGTT, effects that were evident 7 days after the last bout of exercise. Interestingly, when GH, a potential muscle anabolic hormone, was given in conjunction with RE, the effect on peak glucose R_d and Si* appeared to be lost. In addition, GH administration did not potentiate the strength gains associated with RE.[27]

Earlier, it was reported that heavy RE did not improve oral glucose tolerance in young,[36] middle-aged,[37] or older[38] adults with normal glucose tolerance. In agreement with this, we found that intravenous glucose tolerance (K_g) was unchanged following RE. However, in these earlier studies, RE did significantly reduce the plasma insulin response to an oral glucose challenge, an effect consistent with the tendency for improved Si* in the present investigation. Maintenance of glucose tolerance in an older population (albeit inferior to that of young controls) with a higher degree of insulin sensitivity is clearly a beneficial adaptation to RE, since hyperinsulinemia and insulin resistance have been associated with dyslipidemia, type II diabetes, hypertension, and atherosclerosis.[39]

We performed the posttraining IVGTT 7 days after the last training session to avoid any acute effects of exercise,[13,40] but in doing so, we may have allowed adequate time for some of the effects of training to dissipate. For example, other studies have reported that if endurance-trained athletes do not exercise for 7 to 14 days, both glucose tolerance and insulin sensitivity deteriorate significantly.[41-43] Although peak glucose R_d remained elevated 7 days postexercise in the RE group, there was only a trend for an elevated Si* (Figs 1 and 2). Whether this represents a reversal of the RE effects or a lack of statistical power due to a small sample size is unclear. However, a sustained effect from RE may have been possible because it involved all large upper- and lower-body muscle groups, and because it produced significant reductions in body fat (including reductions from central regions) and equivalent increments in FFM. It should be noted that in the studies mentioned earlier, the time course for loss of improved insulin action with detraining was determined in younger, leaner, or more fit subjects than those presently studied. One or all of these factors may have an effect on the loss of improved insulin action during periods without exercise. Further research should be performed to separate out acute and chronic effects of exercise training on insulin sensitivity in various subgroups of the population (young, old, diabetic, etc.) stratified by fitness level and body composition.

Using the hyperinsulinemic-euglycemic clamp technique, Miller et al[44] have recently reported improved insulin sensitivity in middle-aged and older adults following 12 weeks of RE. The final measurement of insulin sensitivity in their study was made 22 to 24 hours after the last RE session. Thus, it is likely that improvements in insulin sensitivity and glucose R_d were attributable to alterations in skeletal muscle glucose metabolism (possibly increased glycogen synthase activity and improved glucose transporter activity) that occurred as a result of an acute bout of exercise. Nonetheless, taken together, our study and the study by Miller et al[44] suggest that RE can induce both acute and sustained positive effects on insulin sensitivity and glucose R_d in older adults (ie, a true exercise training effect).

Data from cross-sectional studies on young adults suggest that RE influences insulin sensitivity and possibly glucose tolerance by increasing the amount of FFM.[45,46] In particular, RE increases the skeletal muscle component of FFM, the primary target for insulin-mediated glucose disappearance. Furthermore, in previously sedentary young adults, Miller et al[36] were able to show a positive relationship between a reduction in total area under the insulin curve during an oral glucose tolerance test and an increase in FFM achieved as the result of a 12-week RE program. Accordingly, it may be hypothesized that part of the reduction in insulin sensitivity with aging is the result of a reduction in FFM, and reversal of FFM wasting would lead to improvements in insulin sensitivity. Although a tendency for improved Si* was noted in the present investigation, there was no relationship between Si* or peak glucose R_d and an increase in FFM. In addition, we found no significant relationship between Si* and FFM when discrete values obtained both before and after training were correlated. Our data and the recent data of Miller et al[44] suggest that in older adults, a RE-induced change in FFM is not the sole determinant of improvements in insulin sensitivity and glucose R_d.

Although GH may have significant protein anabolic actions, especially when administered to older persons with low serum IGF-I levels,[19] moderate elevations in circulating GH for several hours have been shown to impair both stimulation of peripheral glucose uptake and insulin suppression of endogenous glucose production.[20-21] This potential side effect of GH could limit its use in an older population, since these individuals already exhibit reduced levels of glucose tolerance and insulin sensitivity. On the other hand, long-term treatment with GH may induce significant reductions in body fat and consequently lead to an overall improvement in insulin sensitivity. When we combined GH treatment and daily RE, no improvement in peak glucose R_d or Si* was observed (Figs 1 and 2). Moreover, reductions in body fat were no greater for the RE + GH treatment than for RE alone (Table 2). Thus, in six subjects studied, it appears that the diabetogenic properties of GH may have counteracted the beneficial effects of RE and prevented the improvement in peak glucose R_d and Si* that are normally achieved with RE alone. Alternatively, it could be argued that the RE + GH group had little room for improvement, since initially the group mean value for Si*, although not statistically significant, was 60% higher than that observed for the RE group. Regardless, it is interesting that the data presented here are consistent with the results of an earlier study by our group, which showed that in young subjects a combined GH and RE treatment was not associated with reductions in the area under the glucose and insulin curves obtained during an oral glucose tolerance test performed

within 15 hours of the previous exercise session/GH injection.[35] Given that a combined GH and RE treatment in older adults does not improve muscle mass or function to any greater degree than RE alone[27] and that there are potential harmful side effects, including development of glucose intolerance and mild insulin resistance associated with GH administration, RE without GH supplementation appears to be the preferred treatment for reversing the insulin resistance and decrements in muscle strength and function associated with aging. Still, the results of this investigation are limited to the GH-dosing regimen used, and we cannot exclude the possibility that more physiologic or pulsatile replacement of GH may have resulted in a more positive outcome. Additionally, given the small sample size and given that the RE + GH group had initially high levels of glucose disappearance and insulin sensitivity, further study into the combined effects of exercise training and rhGH administration on glucose tolerance and insulin sensitivity in older adults is warranted.

Endurance exercise training results not only in enhanced insulin sensitivity, but also in a reduction in insulin secretion,[43] and this may be the result of single or multiple exercise-induced alterations within the β cell.[47,48] Interestingly, with aging, the β cell does not seem to lose its capacity to respond to exercise, since a reduction in insulin secretion following exercise training of older persons has been reported.[14] We found no exercise effect on first- or second-phase insulin secretion, but a tendency for an improved Si*. In the earlier studies, endurance exercise training improved insulin sensitivity and reduced insulin secretion, whereas RE was the mode of activity in this investigation. It is possible that RE affects primarily glucose disappearance processes in skeletal muscle rather than altering glucose disappearance and β-cell function in a reciprocal fashion. On the other hand, exercise-induced alterations in β-cell function may be shorter-lived than exercise effects on skeletal muscle glucose disappearance, and after 7 days without exercise, any positive alteration in β-cell function may have already been lost. Additional studies focusing on RE-induced alterations in β-cell function and the time course for reversal of change in both insulin sensitivity and secretion parameters are required before we have a more complete understanding of the glucoregulatory effects of this form of exercise.

In summary, RE improved FFM and muscle strength in men aged 64 to 75 years, and therefore may be particularly useful in reversing the functional limitations in this population that are due to muscle weakness. An additional benefit of this form of physical activity was an improved glucose R_d and a strong tendency toward improved insulin sensitivity during an IVGTT performed 7 days after the last exercise session. Thus, RE is an effective intervention strategy for reversing the muscle weakness and insulin resistance associated with aging.

ACKNOWLEDGMENT

REFERENCES

1. Chen M, Bergman RN, Pacini G, et al: Pathogenesis of age-related glucose intolerance in man: Insulin resistance and decreased β-cell function. J Clin Endocrinol Metab 60:13-20, 1985

2. Reaven GM, Chen N, Hollenbeck C, et al: Effect of age on glucose tolerance and glucose uptake in healthy individuals. J Am Geriatr Soc 37:735-740, 1989

3. Kohrt WM, Kirwan JP, Staten MA, et al: Insulin resistance in aging is related to abdominal obesity. Diabetes 42:273-281, 1993

4. Pacini G, Valerio A, Beccaro F, et al: Insulin sensitivity and beta-cell responsivity are not decreased in elderly subjects with normal OGTT. J Am Geriatr Soc 36:317-323, 1988

5. Zavaroni I, Dall'Aglio E, Bruschi F, et al: Effect of age and environmental factors on glucose tolerance and insulin secretion in a worker population. J Am Geriatr Soc 34:271-275, 1986

6. Defronzo R: Glucose intolerance and aging. Evidence for tissue insensitivity to insulin. Diabetes 28:1095-1101, 1979

7. Bemben MG, Massey BH, Bemben DA, et al: Isometric muscle force production as a function of age in healthy 20- to 74-yr-old men. Med Sci Sports Exerc 23:1302-1310, 1991

8. Frontera WR, Hughes VA, Lutz KJ, et al: A cross-sectional study of muscle strength and mass in 45- to 78-yr-old men and women. J Appl Physiol 71:644-650, 1991

9. Jette AM, Branch LG: The Framingham Disability Study. II. Physical disability among the aging. Am J Public Health 71:1211-1216, 1981

10. Frontera WR, Meredith CN, O'Reilly KP, et al: Strength conditioning in older men: Skeletal muscle hypertrophy and improved function. J Appl Physiol 64:1038-1044, 1988

11. Fiatarone MA, Marks EC, Ryan ND, et al: High intensity strength training in nonagenarians: Effects on skeletal muscle. JAMA 263:3029-3034, 1990

12. Seals DS, Hagberg JM, Hurley BF, et al: Effects of endurance training on glucose tolerance and plasma lipid levels in older men and women. JAMA 252:645-649, 1984

13. Tonino R: Effect of physical training on the insulin resistance of aging. Am J Physiol 256:E352-E356, 1989

14. Kahn SE, Larson VG, Beard JC, et al: Effect of exercise on insulin action, glucose tolerance, and insulin secretion in aging. Am J Physiol 258:E937-E943, 1990

15. Kirwan JP, Kohrt WM, Wojta DM, et al: Endurance exercise training reduces glucose-stimulated insulin levels in 60- to 70-year-old men and women. J Gerontol 48:M84-M90, 1993

16. Rudman D, Kutner MH, Rogers CM, et al: Impaired growth hormone secretion in the adult population: Relation to age and adiposity. J Clin Invest 67:1361-1369, 1981

17. Marcus R, Butterfield G, Holloway L, et al: Effects of short term administration of recombinant human growth hormone to elderly people. J Clin Endocrinol Metab 70:519-527, 1990

18. Zachwieja JJ, Bier DM, Yarasheski KE: Growth hormone administration in older adults: Effects on albumin synthesis. Am J Physiol 266:E840-E844, 1994

19. Rudman D, Feller AG, Nagraj HS, et al: Effects of human growth hormone in men over 60 years old. N Engl J Med 323:1-6, 1990

20. Fowelin J, Attvall S, von Schenck H, et al: Characterization of the insulin-antagonistic effect of growth hormone in man. Diabetologia 34:500-506, 1991

21. Bak JF, Moller N, Schmitz O: Effects of growth hormone on

fuel utilization and muscle glycogen synthase activity in normal humans. Am J Physiol 260:E736-E742, 1991

22. Bergman RN, Finegood DT, Ader M: Assessment of insulin sensitivity in vivo. Endocr Rev 6:45-86, 1985

23. Bergman RN, Ider YZ, Bowden CR, et al: Quantitative estimation of insulin sensitivity. Am J Physiol 236:E667-E677, 1979

24. Avogaro A, Bristow JD, Bier DM, et al: Stable-label intravenous glucose tolerance test minimal model. Diabetes 38:1048-1055, 1989

25. Cobelli C, Pacini G, Toffolo G, et al: Estimation of insulin sensitivity and glucose clearance from minimal model: New insights from labeled IVGTT. Am J Physiol 250:E591-E598, 1986

26. Yarasheski KE, Zachwieja JJ: Growth hormone therapy for the elderly: Fountain of youth? JAMA 270:1694, 1993 (letter)

27. Yarasheski KE, Zachwieja JJ, Campbell JA, et al: Effect of growth hormone and resistance exercise on muscle growth and function in older men. Am J Physiol 268:E268-E276, 1995

28. Kohrt WM, Obert KA, Holloszy JO: Exercise training improves fat distribution patterns in 60- to 70-year-old men and women. J Gerontol 47:M99-M105, 1992

29. Hales C, Randle PJ: Immunoassay of insulin with insulin antibody precipitate. Biochem J 88:137-146, 1963

30. Kuzuya H, Blix PM, Horwitz DL, et al: Determination of free and total insulin and C-peptide in insulin treated diabetics. Diabetes 26:22-29, 1977

31. Carson ER, Cobelli C, Finkelstein L: The mathematical modeling of endocrine-metabolic systems, in Model Formulation, Identification and Validation. New York, NY, Wiley, 1983

32. Van Cauter E, Mestrez F, Sturis I, et al: Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 41:368-377, 1992

33. Toffolo G, De Grandi F, Cobelli C: Estimation of beta cell sensitivity from IVGTT C-peptide data. Knowledge of the kinetics avoids errors in modeling the secretion. Diabetes 44:845-854, 1995

34. Grodsky GM: A threshold distribution hypothesis for packet storage of insulin and its mathematical modeling. J Clin Invest 51:2047-2059, 1972

35. Yarasheski KE, Campbell JA, Smith K, et al: Effect of growth hormone and resistance exercise on muscle growth in young men. Am J Physiol 262:E261-E267, 1992

36. Miller WJ, Sherman WM, Ivy JL: Effect of strength training on glucose tolerance and post-glucose insulin response. Med Sci Sports Exerc 16:539-543, 1984

37. Hurley BF, Hagberg JM, Goldberg AP, et al: Resistive training can reduce coronary risk factors without altering Vo₂max or percent body fat. Med Sci Sports Exerc 20:150-154, 1988

38. Craig BW, Everhart J, Brown R: The influence of high-resistance training on glucose tolerance in young and elderly subjects. Mech Ageing Dev 49:147-157, 1989

39. Defronzo RA, Ferrannini E: Insulin resistance. A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia, and atherosclerotic cardiovascular disease. Diabetes Care 14:173-194, 1991

40. Heath GW, Gavin JR III, Hinderliter JM, et al: Effect of exercise and lack of exercise on glucose tolerance and insulin sensitivity. J Appl Physiol 55:512-517, 1983

41. Rogers MA, King DS, Hagberg JS, et al: Effect of 10 days of physical inactivity on glucose tolerance in master athletes. J Appl Physiol 68:1833-1837, 1990

42. Oshida Y, Yamanouchi K, Hayamizu S, et al: Effects of training and training cessation on insulin action. Int J Sports Med 12:484-486, 1991

43. King DS, Dalsky GP, Clutter WE, et al: Effects of lack of exercise on insulin secretion and action in trained subjects. Am J Physiol 254:E537-E542, 1988

44. Miller JP, Pratley RE, Goldberg AP, et al: Strength training increases insulin action in healthy 50- to 65-yr-old men. J Appl Physiol 77:1122-1127, 1994

45. Yki-Järvinen H, Koivisto VA: Effects of body composition on insulin sensitivity. Diabetes 32:965-969, 1983

46. Szczypaczewska M, Nazar K, Kaciuba-Uscilko H: Glucose tolerance and insulin response to glucose load in body builders. Int J Sports Med 10:34-37, 1989

47. Koranyi LI, Bourey RA, Slentz CA, et al: Coordinate reduction of rat pancreatic islet glucokinase and proinsulin mRNA by exercise training. Diabetes 40:401-404, 1991

48. Shima K, Hirota M, Sato M, et al: Effect of exercise training on insulin and glucagon release from perfused rat pancreas. Horm Metab Res 19:395-399, 1987