Intravenous Glucose Tolerance Test–Derived Glucose Effectiveness in Strength-Trained Humans

Junzo Fujitani, Yasuki Higaki, Toshiko Kagawa, Makoto Sakamoto, Akira Kiyonaga, Munehiro Shindo, Ataru Taniguchi, Yoshikatu Nakai, Kumpei Tokuyama, and Hiroaki Tanaka

The effect of long-term strenuous resistance training on glucose effectiveness (SG) was examined by comparing 11 strength-trained and 20 sedentary males by a minimal model approach. Lean body mass (LBM) was measured by hydrostatic weighing. The LBM in strength-trained subjects (65.7 ± 3.1 kg) was significantly larger than in sedentary subjects (56.6 ± 1.2 kg, $P < .01$). The glucose disappearance constant ([KG] 3.07% ± 0.45% · min^{-1}) and insulin sensitivity ([SI] 17.5 ± 2.0 × 10^{-5} · min^{-1} · pmol/L^{-1}) in strength-trained subjects were significantly higher than in sedentary subjects (2.06% ± 0.14% · min^{-1} and 10.3 ± 1.2 × 10^{-5} · min^{-1} · pmol/L^{-1}, $P < .05$). SG in strength-trained subjects (0.024 ± 0.003 min^{-1}) was significantly higher than in sedentary subjects (0.018 ± 0.001 min^{-1}, $P < .05$). These results thus suggest that the improved glucose tolerance in strength-trained subjects was due to increased SG and SI.

BENEFICIAL EFFECTS of endurance exercise on glucose tolerance appear to depend on an improvement not only in insulin-mediated glucose uptake but also in non–insulin-mediated glucose uptake. We have shown that the improved glucose tolerance in endurance-trained subjects is due to an increase in glucose effectiveness (SG), as well as insulin sensitivity (SI).[1] SG denotes the effect of glucose per se at basal insulin to enhance net glucose disposal, and it is a component at least as important as insulin itself in the determination of glucose tolerance.[2] A reduction in SG is observed in patients with insulin-dependent and non–insulin-dependent diabetes mellitus,[2] but also in patients with anorexia nervosa[3] and hepatic cirrhosis.[4] Maki and Abraira[5] pointed to a possible role of the skeletal muscle mass as a determinant of SG, and suggested that the decrease in SG in patients with hepatic cirrhosis and anorexia nervosa was attributable to a decrease in skeletal muscle mass.

It is well established that endurance exercise training enhances SI,[6,7] but the effect of resistance exercise training has received less attention. It has recently been reported that 16 weeks of resistance training in older subjects resulted in an increase of SI but not SG.[8] However, the reported mean increase in lean body mass (LBM) of 2.1 kg represents only a 3.7% increase in total muscle mass,[8] and it is still unclear whether an increase in muscle mass due to resistance training enhances SG. In this study, we examined the effect of long-term strenuous resistance exercise training on SG by comparing strength-trained young subjects with sedentary controls.

From the Laboratory of Exercise Physiology, Faculty of Sports and Health Science, Fukuoka University, Fukuoka; Department of Community Health Science, Saga Medical School, Saga; First Department of Internal Medicine, Kansai-Denryoku Hospital, Osaka; Division of the Science of Nursing, College of Medical Technology, Kyoto University, Kyoto; and Laboratory of Biochemistry of Exercise and Nutrition, Institute of Health and Sport Sciences, University of Tsukuba, Ibaraki, Japan.

Submitted October 6, 1997; accepted December 30, 1997.

Supported by the Central Research Institute of Fukuoka University.

Address reprint requests to Hiroaki Tanaka, PhD, Laboratory of Exercise Physiology, Faculty of Sports and Health Science, Fukuoka University, Fukuoka 814-01, Japan.

0026-0495/98/4707-0020$03.00/0

SUBJECTS AND METHODS

Subjects

Eleven strength-trained and 20 sedentary males participated in the study after provision of informed consent. Strength-trained subjects were engaged in weight lifting and/or resistance exercise more than five times per week for at least 1 year. None of the subjects had a family history of diabetes or hypertension. All had a normal response to a 75-g oral glucose tolerance test. The subjects' physical characteristics are listed in Table 1. Body composition was measured by hydrostatic weighing and corrected for residual lung volume.[9] Waist girth was measured at the narrowest part of the torso while the subject was standing, and hip circumference was measured at the level of the greatest gluteal protuberance. All subjects participated in an incremental exercise test on a cycle ergometer. The work load was increased by 20 W every 4 minutes, and maximal oxygen uptake ($\dot{V}O_2max$) was determined by the leveling-off criterion,[10] or greater than 8 mmol/L blood lactate. The exercise test was performed at least 1 week before the intravenous glucose tolerance test (IVGTT). Strength-trained subjects refrained from any type of exercise for 2 days before the IVGTT. On the day before the IVGTT, all subjects were provided with a supper meal containing greater than 140 g carbohydrate, greater than 30 g fat, and greater than 33 g protein.

IVGTT

The subjects reported to the laboratory at 8 AM, and an IVGTT was performed in the reclining position at 9 AM as described previously.[1] In brief, baseline samples for glucose and insulin assays were obtained at −20, −10, and −3 minutes. At time 0, glucose (300 mg/kg body weight) was administered intravenously within 2 minutes, and subsequent blood samples were taken at 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 24, 26, 28, 30, 33, 36, 40, 50, 60, 70, 80, 100, 120, 140, 160, and 180 minutes from the contralateral antecubital vein. An additional infusion of insulin (Humalin; Shionogi, Osaka, Japan) was administered (20 mU/kg) via the antecubital vein from 20 to 25 minutes after administration of glucose.

The glucose disappearance constant (KG value) and the area under the insulin curve between 0 and 20 minutes after administration of glucose were calculated as previously described.[1,11] SI and SG were estimated by the minimal model approach.[12-14] In this analysis, fluctuations in circulating glucose levels over time are described by the following differential equations: $dG(t)/dt = -p1[G(t) - Gb] - X(t)G(t)$ and $dX(t)/dt = -p2X(t) + p3[I(t) - Ib]$, where G(t) is the plasma glucose concentration; I(t) is the plasma insulin concentration; Gb and Ib are baseline concentrations; p1, p2, and p3 are model parameters; and X(t) is the time course of peripheral insulin effects in minutes. Parameter p1 represents the effect of glucose per se at basal insulin to enhance net glucose disposal, and is known as SG. SG consists of a

Table 1. Subject Characteristics

Characteristic	Sedentary	Trained
Age (yr)	23 ± 1	20 ± 1
Height (m)	1.73 ± 0.02	1.70 ± 0.02
Weight (kg)	65.8 ± 1.6	73.7 ± 3.6*
WHR	0.84 ± 0.01	0.81 ± 0.01
Body mass index ($kg \cdot m^{-2}$)	22.0 ± 0.5	25.4 ± 0.7†
LBM (kg)	56.6 ± 1.2	65.7 ± 3.1†
Body fat (%)	14.2 ± 1.3	9.0 ± 0.9†
$\dot{V}O_2max$ ($mL \cdot kg^{-1} \cdot min^{-1}$)	43.2 ± 1.5	44.4 ± 2.0

NOTE. Values are the mean ± SE.
*$P < .05$.
†$P < .01$.

non–insulin-dependent component and a basal insulin component. The basal insulin component of SG (BIE) can be calculated as the product of Ib and SI: BIE = Ib × SI. Therefore, the contribution of the non–insulin-dependent component (SG at zero insulin [GEZI]) is the difference between total SG and BIE: GEZI = SG − (Ib × SI).[15] The ratio p3/p2 defines the SI index, which represents the increase in the net glucose disappearance rate, which in turn depends on the increase in insulin above basal. The minimal model program was written in Pascal (Borland International, Scotts Valley, CA) on a Macintosh IIcx computer (Apple Computer, Cupertino, CA) as described previously.[1,11]

Analytical Methods

The glucose oxidase method was used to measure plasma glucose concentrations in triplicate (Glucose B-test; Wako Pure Chemical, Osaka, Japan). The measurement error for glucose was assumed to be "white," with a Gaussian of zero mean and a coefficient of variation of 1.5%. The immunoreactive insulin level was measured in duplicate using a Phadeseph insulin radioimmunoassay kit (Shionogi, Osaka, Japan).

Statistics

The statistical comparison between strength-trained and sedentary subjects was performed by Student's *t* test. Differences were considered statistically significant at *P* less than .05.

RESULTS

Body Composition and $\dot{V}O_2max$

LBM in strength-trained subjects was larger than in sedentary subjects. The percent fat in strength-trained subjects was lower than in sedentary subjects. $\dot{V}O_2max$ was similar between strength-trained and sedentary subjects. The percent body fat and the waist to hip ratio (WHR) were slightly lower in strength-trained subjects than in sedentary subjects, but the difference was not statistically significant (Table 1).

IVGTT

Basal glucose and insulin concentrations were similar in strength-trained and sedentary subjects. Plasma glucose and insulin concentrations during the IVGTT are illustrated in Fig 1. KG was significantly higher in strength-trained subjects versus sedentary subjects. The integrated area of plasma insulin above the basal level during the first 20 minutes of the IVGTT was smaller in strength-trained subjects versus sedentary subjects, but the difference was not statistically significant (Table 2).

Minimal Model Analysis

SI was significantly higher in strength-trained subjects than in sedentary subjects (Table 2). SG in strength-trained subjects was significantly higher than in sedentary subjects. However, the non–insulin-dependent component of SG (GEZI) was similar between strength-trained and sedentary subjects. The insulin-dependent component of SG (BIE) was higher in strength-trained subjects versus sedentary subjects. SG was not found to be significantly associated with LBM ($r = .05, P = .91$) or body fat ($r = -.12, P = .61$).

DISCUSSION

In this study, we used the minimal model approach to assess the effect of resistance training on SG. Strength-trained subjects had a higher SG than sedentary subjects. Our data also

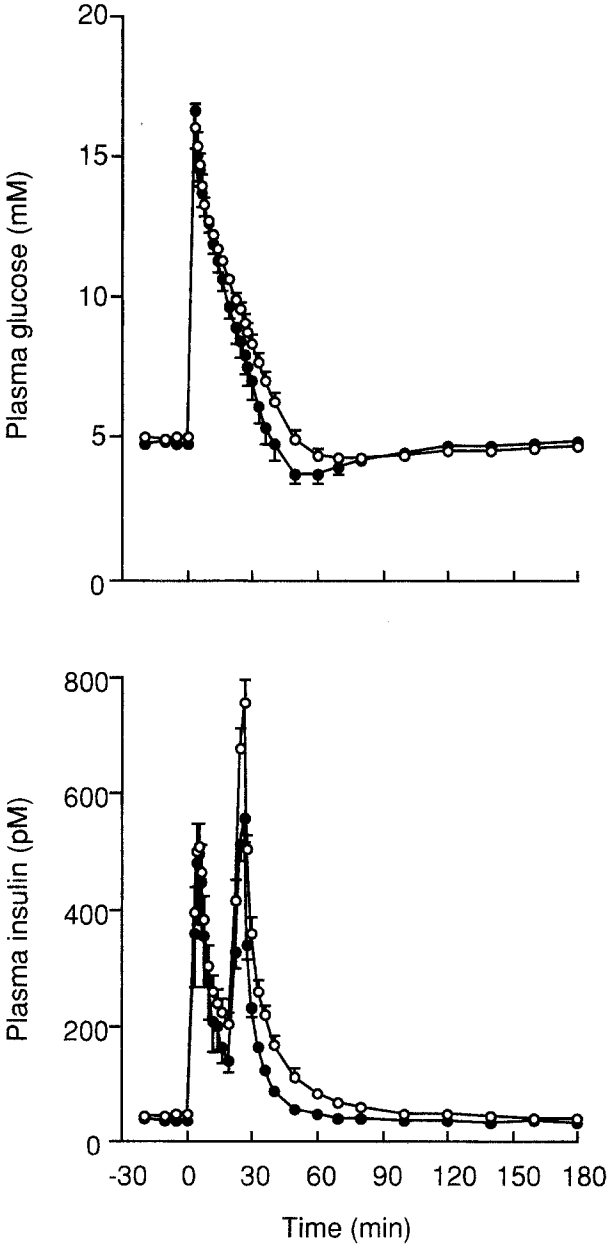

Fig 1. Time course of plasma glucose and insulin during the IVGTT for sedentary (○) and trained (●) subjects. Values are the mean ± SE.

Table 2. Metabolic Parameters

Parameter	Sedentary	Trained
Basal glucose (mmol/L)	5.0 ± 0.1	4.8 ± 0.1
Basal insulin (pmol/L)	45.2 ± 3.2	37.1 ± 3.9
KG (% · min^{-1})	2.06 ± 0.14	3.07 ± 0.45*
Insulin area (pmol/L · min)	4,922 ± 493	4,414 ± 1,042
SG (min^{-1})	0.018 ± 0.001	0.024 ± 0.003*
BIE (min^{-1})	0.004 ± 0.001	0.006 ± 0.001*
GEZI (min^{-1})	0.014 ± 0.001	0.018 ± 0.003
SI ($\times 10^{-5}$ · min^{-1} · $pmol/L^{-1}$)	10.3 ± 1.1	17.5 ± 2.0*

NOTE. Values are the mean ± SE.
*$P < .05$.

confirmed that strength-trained subjects had a higher SI than sedentary subjects.

Despite previous validation studies,[16,17] several reports[18-20] have noted that the minimal model systematically overestimates SG. Caumo et al[18] have suggested that the use of a monocompartmental model to describe glucose kinetics may be responsible for inaccuracies in the estimation of model parameters. Recently, the significance of the assumed single-compartment glucose distribution embedded in the minimal model for the estimation of SG was examined by Ni et al.[21] The theoretical evaluation revealed that the minimal model–derived SG is not equal to but correlates well with the actual glucose effectiveness. It is therefore suggested that the minimal model–derived SG is dependable index of in vivo glucose effectiveness. Finegood and Tzur[19] have suggested that the degree of overestimation also depends on the insulin concentration. However, it is unlikely that the enhanced SG in the trained subjects would be explained by the slightly decreased insulin level, since it has been reported that the lower the insulin level, the smaller the overestimation of SG. Taken together, the higher SG observed in the trained athletes suggests that an improved glucose tolerance in strength-trained subjects may be due to an increase in glucose effectiveness.

Although several studies have demonstrated the effect of resistance training on insulin sensitivity,[8,22-24] there is only one study that assessed the effect of resistance training on glucose effectiveness.[8] In the study, 16 weeks of heavy resistance exercise training was performed in healthy older men aged 64 to 75 years, and an IVGTT with stable isotope–labeled glucose was performed 7 days after the last bout of exercise. The ability of insulin to stimulate peripheral glucose uptake (SI*) showed a tendency to increase after the training ($P = .06$), but the ability of glucose itself to enhance glucose disposal (SG*) did not change with the training. Since a time course of labeled glucose was analyzed in the study, a distinction between the IVGTT and labeled IVGTT must be kept in mind to reconcile our results with their report. While glucose effectiveness (SG) denotes the effect of glucose per se to enhance peripheral glucose uptake and to suppress hepatic glucose output, tracer minimal model–derived glucose effectiveness (SG*) denotes the effect of glucose to enhance glucose uptake alone. Therefore, one possible explanation for the apparently contradictory results is that resistance exercise selectively enhances the effect of glucose to suppress hepatic glucose output. Alternatively, the effect of resistance training on SG did not last more than 1 week, since IVGTTs were performed 2 days after the last bout of exercise in the young strength-trained subjects of our cross-sectional study. Furthermore, a difference in the intensity of training or aging itself may have impacted the effect of resistance training on SG.

The role of LBM as a determinant of glucose effectiveness has been suggested by Maki and Abraira[5] from several lines of evidence. Chronic undernutrition may be responsible, in part, for the depression of SG in anorexia nervosa[3] and hepatic cirrhosis.[4] Cirrhotic patients also demonstrated a significantly reduced 24-hour urinary creatine excretion normalized to height, and the decrease in SG was strongly correlated with the creatine excretion to height ratio, suggesting that reduced skeletal muscle mass may be responsible for the depression of SG in hepatic cirrhosis. Consistently, an increase in LBM due to resistance training was accompanied by an increase in glucose effectiveness in the present study, although contradictory results[8] exist, as already discussed. However, the increase in SG was not greater in strength-trained subjects versus endurance-trained subjects with normal LBM. SG estimated 16 hours and 1 week after the endurance training bout was 0.028 ± 0.003 and 0.030 ± 0.004 min^{-1}, respectively.[1] Furthermore, the variation in SG values among control subjects was not correlated with LBM, at least in our 29 subjects ($R^2 = .001$, $P = .91$; Y. Higaki, J. Fujitani, T. Kagawa, et al, unpublished data, September 1997). Taken together, factors other than skeletal muscle mass and LBM exist as a major determinant of SG in the general population and athletes.

We have shown that SG in endurance-trained subjects with a lower percentage of body fat (10.3% ± 0.8%) was higher than in sedentary subjects.[1] In this study, the percent body fat in strength-trained subjects (9.0% ± 0.9%) was also lower than in sedentary subjects. Therefore, reduced body fat might reflect an improvement of SG, as well as SI. However, there is no significant correlation between SG and body fat. Further, Clausen et al[25] observed in 380 young healthy caucasians that glucose effectiveness was not significantly associated with any measure of body fat. These results suggest that low body fat may not be a determinant of glucose effectiveness.

In conclusion, we have shown that resistance training induces an increase in muscle mass and results in an enhancement of SG and SI.

ACKNOWLEDGMENT

We are grateful to Shionogi Biomedical Laboratory, Osaka, Japan, for assistance in this study.

REFERENCES

1. Tokuyama K, Higaki Y, Fujitani J, et al: Intravenous glucose tolerance test–derived glucose effectiveness in physically trained humans. Am J Physiol 265:E298-E303, 1993

2. Best JD, Kahn SE, Ader M, et al: Role of glucose effectiveness in the determination of glucose tolerance. Diabetes Care 19:1018-1030, 1996

3. Fukushima M, Nakai Y, Taniguchi A, et al: Insulin sensitivity, insulin secretion and glucose effectiveness in anorexia nervosa: A minimal model analysis. Metabolism 42:1164-1168, 1993

4. Marchesini G, Pacini G, Bianchi G, et al: Glucose disposal, β-cell secretion, and hepatic insulin extraction in cirrhosis: A minimal model assessment. Gastroenterology 99:1715-1722, 1990

5. Maki KC, Abraira C: Correspondence. Metabolism 43:529-530, 1994 (letter)

6. Koivisto VA, Yki-Jarvinen H, DeFronzo RA: Physical training and insulin sensitivity. Diabetes Metab Rev 1:445-481, 1986

7. Mikines KJ, Sonne B, Farrell PA, et al: Effect of physical exercise on sensitivity and responsiveness to insulin in humans. Am J Physiol 254:E248-E259, 1988

8. Zachwieja JJ, Toffolo G, Cobelli C, et al: Resistance exercise and growth hormone administration in older men: Effects on insulin sensitivity and secretion during a stable-label intravenous glucose tolerance test. Metabolism 45:254-260, 1996

9. Goldman RF, Buskirk ER: A method for underwater weighing and the determination of body density, in Brozek J, Hershel A (eds): Techniques for Measuring Body Composition. Washington, DC, National Research Council, 1961, pp 78-89

10. Astrand PO, Rodahl K: Textbook of Work Physiology (ed 3). New York, NY, McGraw-Hill, 1988

11. Taniguchi A, Nakai Y, Doi K, et al: Insulin sensitivity, insulin secretion, and glucose effectiveness in obese subjects: A minimal model analysis. Metabolism 44:1397-1400, 1995

12. Bergman RN: Toward physiological understanding of glucose tolerance. Minimal-model approach. Diabetes 38:1512-1527, 1989

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

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

15. Kahn SE, Klaff LJ, Schwartz MW, et al: Treatment with somatostatin analog decreases pancreatic β-cell and whole body sensitivity to glucose. J Clin Endocrinol Metab 71:994-1002, 1990

16. Ader M, Pacini G, Yang YJ, et al: Importance of glucose per se to intravenous glucose tolerance. Comparison of the minimal-model prediction with direct measurements. Diabetes 34:1092-1103, 1985

17. Ward GM, Weber KM, Walter IM, et al: A modified minimal model analysis of insulin sensitivity and glucose mediated glucose disposal in insulin-dependent diabetes. Metabolism 40:4-9, 1991

18. Caumo A, Vicini P, Cobelli C: Is the minimal model too minimal? Diabetologia 39:997-1000, 1996

19. Finegood DT, Tzur D: Reduced glucose effectiveness associated with reduced insulin release: An artifact of the minimal-model method. Am J Physiol 271:E485-E495, 1996

20. Quon MJ, Cochran C, Taylor SI, et al: Non–insulin-mediated glucose disappearance in subjects with IDDM. Discordance between experimental results and minimal model analysis. Diabetes 43:890-896, 1994

21. Ni T-C, Ader M, Bergman R: Reassessment of glucose effectiveness and insulin sensitivity from minimal model analysis. A theoretical evaluation of the single-compartment glucose distribution assumption. Diabetes 46:1813-1821, 1997

22. Hersey WC III, Graves JE, Pollock ML, et al: Endurance exercise training improves body composition and plasma insulin responses in 70- to 79-year-old men and women. Metabolism 43:847-854, 1994

23. 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

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

25. Clausen JO, Borch-Johnsen K, Ibsen H, et al: Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy caucasians. J Clin Invest 98:1195-1209, 1996