Insulin and Non–Insulin-Dependent Glucose Disposal in Middle-Aged and Young Athletes Versus Sedentary Men

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The purpose of this study was to delineate the respective roles of aging and endurance training on glucose disposal. Thirty-two subjects (16 middle-aged men: 8 cyclists [MAcy], and 8 sedentary men [MAsed] and 16 young men: 8 cyclists [Ycy] and 8 sedentary men [Ysed]) were compared in this study. After overnight fasting, glucose was administered intravenously (0.5 g · kg^{-1}, 30% solution) and insulin-glucose interactions were assessed by measuring indices of insulin sensitivity (SI) and glucose effectiveness (Sg) using Bergman's minimal model. Sg includes basal insulin effectiveness (BIE) and glucose effectiveness at zero insulin (GEZI). Endurance training improved SI and Sg in all subjects, regardless of age ($P < .05$), but an increase in GEZI was found only in young men ($P < .05$). An effect of aging was found in sedentary subjects, who exhibited a lower SI ($P < .05$) when older. However, this effect disappeared with training, in which SI was nearly identical in young and middle-aged subjects. There was a correlation between SI and $\dot{V}O_{2max}$ in middle-aged men ($r = .76$, $P < .01$). These data suggest that the higher glucose uptake in endurance-trained male cyclists was mostly attributable to an increase in non–insulin-dependent glucose uptake in the young men and to an increase in its insulin-dependent component in the middle-aged men.

REGULAR ENDURANCE training results in several adaptations in carbohydrate metabolism, including an improvement in insulin sensitivity.[1-4] However, whole-body insulin action is reduced with increasing age, particularly in skeletal muscle,[5] because of several factors, including changes in body composition and a decrease in GLUT-4 protein level.[6] Older subjects are consequently characterized by a decrease in insulin sensitivity (SI)[7-9] that leads to more frequent glucose intolerance,[10,11] which in turn is enhanced by decreased physical activity[1] and obesity.[12] The mechanism involved is particularly relevant to middle-aged populations because the insulin resistance of aging, which is initiated as early as the third decade of life,[7,13] may be prevented[14,15] or reversed[16] by exercise training. In contrast, it has been suggested that young and aged subjects have similar basal and insulin-stimulated glucose clearance rates in skeletal muscle.[5]

Although several investigators have detailed the beneficial effects of training on glucose uptake,[2-4,16] the combined effect of training and aging on uptake, and more particularly on its non–insulin-dependent component (glucose effectiveness at zero insulin; GEZI), has not yet been specifically investigated. Training increases GLUT-4 protein concentration in human skeletal muscle to a similar extent in young and older men.[3] However, two distinct pathways for moving glucose transporters to the sarcolemma are involved in this process: one is stimulated by insulin, and the other is stimulated by muscular contractions.[17,18] Although training enhances the stimulatory effect of insulin on glucose transporter recruitment, an important part of its effects on glucose disposal is explained by an increase in non–insulin-mediated glucose uptake (NIMGU),[2] a parameter that has been shown to be equivalent to GEZI.[19] However, Kahn et al,[1] showed that endurance training does not alter GEZI in the elderly. We recently showed that endurance training increases GEZI in young subjects.[4] Therefore, we investigated whether aging modifies the effect of endurance training on glucose disposal and, more particularly, GEZI.

SUBJECTS AND METHODS

Subjects

Sixteen male cyclists (8 young [24.7 ± 1.4 years] elite cyclists [Ycy] and 8 middle-aged [51.6 ± 1.2 years] cyclists [MAcy]) and 16 sedentary men (8 young [23.9 ± 0.8 years] men [Ysed] and 8 middle-aged [52.3 ± 1.1 years] men [MAsed]) participated in the study. None had a family history of diabetes or hypertension. Smokers or those currently taking medication for the control of blood pressure and lipid or carbohydrate metabolism were excluded. No subject had electrocardiogram abnormalities at rest or during a maximal ergocycle test. Physical characteristics of all subjects are shown in Table 1. The training program for the middle-aged cyclists was carried out as a group activity and amounted to almost 10 hours of cycling per week. These cyclists had been following this training schedule for the past 10 ± 1.5 (SE) years. The training program for the young elite cyclists was also carried out in a group and amounted to almost 17 hours of training per week. All had followed this training schedule for the past 7 ± 1.2 years. None of the sedentary subjects participated in competitive sports or organized leisure activities. After a complete and accurate verbal description of the procedure and the risks and benefits associated with the study, subjects provided their written consent.

Methods

Protocol. The subjects came to the laboratory on two separate occasions for an intravenous glucose tolerance test and a maximal aerobic capacity test. All subjects were asked to refrain from exercise for the 3 days before the glucose tolerance test.

Body composition. Body composition was assessed with a four-terminal impedance plethysmograph Dietosystem Human IM-Scan.[20,21]

Frequently sampled intravenous glucose tolerance test (FSIVGTT). A cannula was placed in the cephalic vein at the level of the cubital fossa for blood sampling at various times, while glucose was administered via the contralateral cephalic vein. Glucose (0.5 g · kg^{-1}, solution at 30%) was slowly injected over 3 minutes. Insulin (0.02 U · kg^{-1} body weight, ie, 1 to 2 units) was injected into the vein contralat-

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Table 1. Baseline Characteristics of Subjects

	Sedentary Subjects		Cyclists	
	Middle-Aged (n = 8)	Young (n = 8)	Middle-Aged (n = 8)	Young (n = 8)
Age (yr)	52.3 ± 1.1	23.9 ± 0.8*	51.6 ± 1.2	24.7 ± 1.4†
Height (cm)	173.3 ± 1.9	179.2 ± 1.6	173.6 ± 1.3	178.4 ± 1.9
Weight (kg)	75.4 ± 2.4	70.9 ± 2.6	72.1 ± 1.1	69.2 ± 2
BMI (kg/m^2)	25.1 ± 0.6	22.1 ± 0.4	23.9 ± 0.3	21.7 ± 0.6&
Fat (%)	22.8 ± 1.5	15.1 ± 2.8	20.3 ± 0.8	12.8 ± 0.5&
$\dot{V}O_{2max}$ (mL/min/kg)	33.3 ± 1.1	47.4 ± 2.2*	50.41 ± 2.3‡	64.1 ± 3.2†§

NOTE. Values are means ± SE.

* Significant difference between young and middle-aged men in sedentary group ($P < .05$).

† Significant difference between young and middle-aged men in trained group ($P < .05$).

‡ Significant difference between trained and sedentary middle-aged men ($P < .05$).

§ Significant difference between trained and sedentary young men ($P < .05$).

eral to the one used for sampling immediately after 19 minutes. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 6, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90, and 180 minutes after glucose injection. Times 1 and 3 minutes were used for determination of the insulin early secretory phase.[22] The other times were necessary for minimal model calculations.[23,24]

Glucose disposal coefficient. The least-square slope of the log of the absolute glucose concentration, between 4 and 19 minutes after the glucose bolus, was used as an index of glucose tolerance ($Kg_{4\text{-}19}$). This Kg value describes glucose disposal by tissue and depends on three factors: insulin release, insulin sensitivity, and glucose effectiveness independent of insulin.

Measurement of insulin sensitivity and glucose effectiveness. Minimal model analysis of FSIVGTT was performed according to the method of Bergman et al[25] using TISPAG software, which uses a nonlinear least-square estimation, from the Department of Physiology, University of Montpellier I.[26,27] This program gave the values of insulin sensitivity (SI) and glucose effectiveness (Sg). SI is an index of the influence of plasma insulin to change glucose's own effect on glucose concentration. Sg is the fractional disappearance rate of glucose, independent of any insulin response. Sg was broken down into its two components[28]: the contribution of hyperglycemia per se to tissue glucose use and the effect of basal insulin on glucose uptake. The basal insulin component of Sg is termed the basal insulin effect (BIE) and can be calculated as the product of basal insulin (Ib) and SI. Thus the contribution of non–insulin-dependent glucose uptake (GEZI) to glucose uptake is the difference between total Sg and BIE: GEZI = Sg − (Ib × SI).

Pretesting exercise. The subject's $\dot{V}O_{2max}$ was measured during 8 to 12 minutes of exercise performed on an electronically braked cycle ergometer (550 ERG; Bosch, Germany). Fractions of oxygen and carbon dioxide in the expired air were measured by a mass spectrometer (Marquette MGA 1100; Blagnac, France). Heart rate was monitored throughout the exercise test. Exercise testing was started with a 3-minute warm-up at 40 W. The workload was increased by steps of 20 W for the sedentary group and 30 W for the trained group every minute until maximal exercise was reached. This was evaluated in terms of maximal heart rate, respiratory exchange ratio (>1.15), and O_2 consumption ($\dot{V}O_2$) stability.

Laboratory measurements. Samples were analyzed for plasma insulin by radioimmunoassay (kit SB-INSI-5 from the international CIS). The within-assay coefficient of variation (CV) for insulin was determined by repetitive measurements of the same sample and was 6.6%; the between-assay CV was 6.2%. The sensitivity (lowest detectable value) was <1 μU/mL. Plasma glucose was measured with a Beckman glucose analyzer, with CVs of 8.3% (within assay) and 7.9% (between assays).

Statistics

Data are expressed as means ± SE. To detect differences between training status and age groups, a two-way ANOVA was performed. If the ANOVA indicated significant differences, these were located by a pairwise multiple comparison procedure (Student-Newman-Keuls). To detect differences between parameters represented by a single measurement, nonparametric tests for unpaired (Mann-Whitney) and paired (Wilcoxon) data were used as appropriate. Correlations were performed by Pearson analysis. $P < .05$ was considered significant.

RESULTS

Subjects were matched for height, weight, body mass index (BMI), and fat (%) in each category of age (Table 1). $\dot{V}O_{2max}$ was higher in the cyclists than in the sedentary subjects independent of age and was higher in younger than in older subjects (Table 1).

Plasma glucose and insulin concentrations during the FSIVGTT are shown in Fig 1. The basal glucose and insulin levels are presented in Table 2. After glucose administration, the plasma glucose concentration of Ycy subjects was lower than that of Ysed subjects at 4, 6, 8, 10, 15, 19, 20, 22, 24, 30, 41, and 70 minutes ($P < .01$, Fig 1). However, the plasma insulin concentration was lower in Ycy than in Ysed subjects at 30, 41, and 70 minutes ($P < .01$; Fig 1). After glucose administration, the plasma glucose concentration of MAcy was lower than of MAsed subjects at 22, 41, and 70 minutes ($P < .01$, Fig 1). Plasma insulin concentration was lower in MAcy than in MAsed subjects at 3, 4, 6, 8, 10, 15, 41, 70, and 90 minutes ($P < .01$; Fig 1).

Minimal Model Parameters

Effect of Age

Sedentary group. Basal glucose was higher (+21%; $P < .05$; Table 2) in MAsed than in Ysed subjects, SI was lower (−165%; $P < .05$; Fig 2) in MAsed than in Ysed subjects, and BIE was lower (−185%, $P < .05$; Fig 3) in MAsed than in Ysed subjects.

Trained group. Basal insulin was lower (−31%; $P < .05$; Table 2) in MAcy than in Ycy subjects. No difference in minimal model parameters was found between MAcy and Ycy subjects.

Effect of Training

Young subjects. SI was higher in Ycy than in Ysed subjects (+100%; $P < .05$; Fig 2), and Sg and GEZI were higher (+83% and +82%, respectively; $P < .05$; Fig 3) in Ycy than in Ysed subjects.

Middle-aged subjects. Basal insulin and glucose levels were lower (−40% and −15%, respectively; $P < .05$; Table 2) in MAcy than in MAsed subjects. The insulin peak was higher (+33%; $P < .05$; Table 2) and BIE was higher (+500%, $P < .05$; Fig 3) in MAcy than in MAsed subjects. SI and Kg were

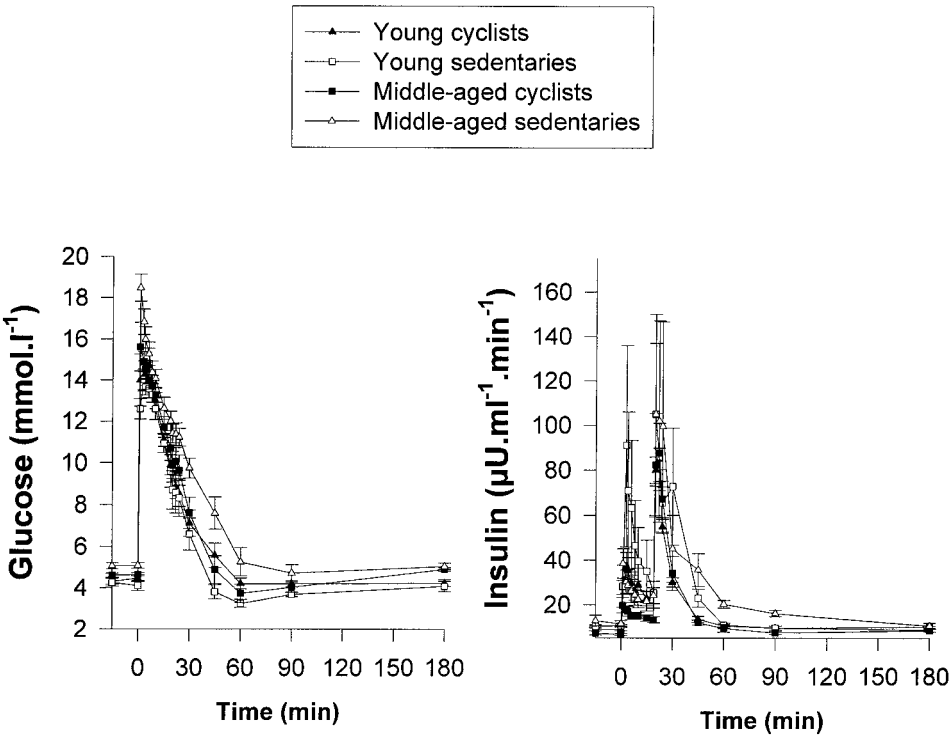

Fig 1. Glucose and insulin levels through FSIVGTT in middle-aged and young sedentary men and in middle-aged and young trained cyclists. Values are means ± SE.

higher (+500% and +31%, respectively; $P < .05$; Fig 2) and Sg was higher (+43%; $P < .05$; Fig 3) in MAcy than in MAsed subjects.

Relationship Between SI and Fitness Level

When we considered all middle-aged subjects together, we found a positive correlation between SI and $\dot{V}O_{2max}$ ($r = .76$; $P < .01$; n = 16).

DISCUSSION

The purpose of this study was to characterize the effect of an interaction between aging and endurance training on glucose disposal and, more particularly, GEZI. The data clearly show that endurance training improved SI and Sg in both middle-aged and young men. GEZI was increased by endurance training only in young men, as was also observed in a recent longitudinal study.[4] The effect of age was distinctly pronounced in the sedentary population, with a decrease in SI in the older subjects, whereas in the trained population, this parameter was identical in the two age groups. In addition, we find a correlation between SI and $\dot{V}O_{2max}$ in middle-aged men.

Two methodological aspects of our study require some comments. First, training intensity and duration were scheduled to be almost the same in both groups. They underwent almost all of the training program together, simultaneously, in the same club, in the same climatic conditions, on the same roads. On the

Table 2. Minimal Model Analysis of FSIVGTT in Cyclists and Sedentary Subjects

	Sedentary Subjects		Cyclists	
	Middle-Aged (n = 8)	Young (n = 8)	Middle-Aged (n = 8)	Young (n = 8)
Basal glucose (mmol/L)	5.03 ± 0.1	4.37 ± 0.2*	4.59 ± 0.1†	4.21 ± 0.1
Basal insulin (µU/mL)	10.5 ± 0.8	9.71 ± 1.3	6.42 ± 0.5†	8.35 ± 0.4‡
Insulin peak (µU/mL)	68.8 ± 11.4	80.14 ± 12.5	46.92 ± 9.5†	67.5 ± 7.5
Kg (% · min^{-1})	1.92 ± 0.2	1.98 ± 0.3	2.6 ± 0.4†	2.87 ± 0.4
Sg (% · min^{-1})	2.77 ± 0.2	2.75 ± 0.3	4.03 ± 0.5†	4.93 ± 0.4§
SI ($\times 10^{-4}$ µU/mL · min^{-1})	3.02 ± 0.6	7.96 ± 2.1*	15.7 ± 2.2†	16.06 ± 2§
BIE (% · min^{-1})	0.29 ± 0.1	0.83 ± 0.4*	1.48 ± 0.4†	1.42 ± 0.1
GEZI (% · min^{-1})	2.48 ± 0.2	1.92 ± 0.3	2.55 ± 0.4	3.51 ± 0.7§

NOTE. Values are means ± SE.

* Significant difference between young and middle-aged men in sedentary group ($P < .05$).

† Significant difference between trained and sedentary middle-aged men ($P < .05$).

‡ Significant difference between young and middle-aged men in trained group ($P < .05$).

§ Significant difference between trained and sedentary young men ($P < .05$).

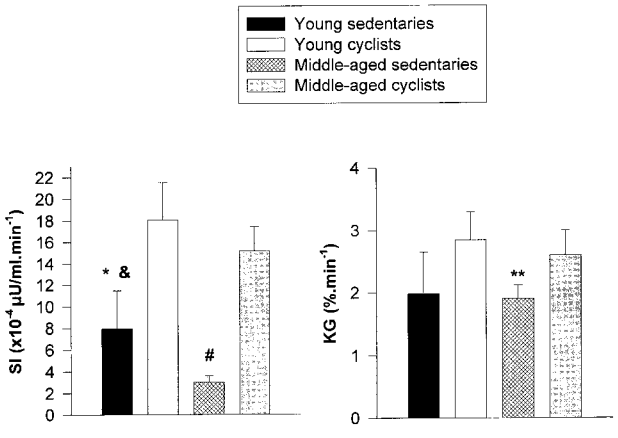

Fig 2. Comparison of SI and Kg in middle-aged and young men. * *P* < .05, Ysed *v* Ycy; # *P* < .05, MAsed *v* MAcy; & *P* < .05, Ysed *v* MAsed; ** *P* < .05, Ycy *v* MAcy.

whole, it could be considered that they all performed on the average an equivalent amount of training (15 h/wk). On the other hand, because this study is cross-sectional in nature, an influence of the previous status of subjects (including possibly genetic influences) cannot be ruled out. On the whole, however, this study allows to describe the combined effects of training and aging on glucose disposal parameters.

Although it is well known that exercise training increases SI,[1-4] the present study shows that training improves SI more markedly in middle-aged men than in young men (500% *v* 100%). We can explain this finding by a lower SI in MAsed than in Ysed subjects (3 ± 0.62 *v* 8.98 ± 3.52 [$\times 10^{-4}$ μU/mL · min^{-1}]). Inversely, training increased Sg more markedly in young men than in middle-aged men (83% *v* 43%). Our data contrast with those of a study[1] on the effect of physical training on Sg in healthy aged men that found no improvement of Sg after training. A possible explanation for the difference between their observations and our findings is that their population was older than ours (68 *v* 52 years). It could be hypothesized that aging itself affects the potential of physical training to enhance Sg.[2]

We showed that the glucose tolerance index (Kg) was higher in MAcy than in MAsed subjects. This finding is in contrast with that of others,[1] who concluded that endurance training in the elderly does not change glucose tolerance, despite improvement in SI. This difference in results may be explained by a difference in age (their subjects were older) or in training status (ie, intensity and duration). Although aerobic exercise is generally acknowledged to be effective for improving SI, little attention has been paid to the kind of training that yields the best results, and therefore optimal exercise programs have not been defined. Differences in training intensity and duration, for example, would certainly be sufficient to modify glucose disposal, especially with endurance sports such as cycling. On the other hand, after prolonged extreme running exercise, Kg is reduced,[29] suggesting the importance of refraining from exercise before the glucose tolerance test. In addition, the present data suggest that Kg is increased by training only in middle-aged subjects. This indicates a direct effect of fitness level on glucose tolerance in the middle-aged population but not in the young population. In agreement with this, we found a significant positive association between $\dot{V}O_{2max}$ and SI when we considered all middle-aged subjects together. Another study[6] has previously shown this relationship, but in a broader age range than ours (18 to 80 years *v* 52 years). It is well known that regular exercise training improves $\dot{V}O_{2max}$ and insulin action in skeletal muscle,[3,5] and thus our findings presumably reflect this common association with physical activity in middle-aged men. Consistent with previous studies,[7-9] our data show that aging decreases SI and BIE in sedentary individuals, while training results in high values of these parameters, which are quite the same in young and middle-aged subjects. In contrast, B-cell response, as assessed by both basal and peak insulin levels, appears to be modified by training mostly in middle-aged subjects, although there are only minimal differences in young subjects. Such data should be interpreted with caution because the B-cell response is likely to be influenced by both SI itself[30-32] and aging.[33] Accordingly, insulin levels in our middle-aged subjects are likely to reflect both the homeostatic feedback loop between SI and insulin secretion[31] and the diminished B-cell function associated with aging.[19] However, SI and BIE were completely preserved in the middle-aged trained subjects, a finding that suggests that the age at which training takes place may be a critical factor for an optimal effect on insulin action. If this is so, middle age in men is a beneficial period for exercise (cycling) training to counteract the decrease in insulin sensitivity associated with aging. Interestingly, the decrement in insulin action has been attributed to an increase in body fat and a decrease in physical activity.[33] Therefore, fat mass[12] is involved in this glucose intolerance. Because body composition can affect SI,[34] the decrease in fat mass after training may contribute to the improvement in SI.[1] To control for this pa-

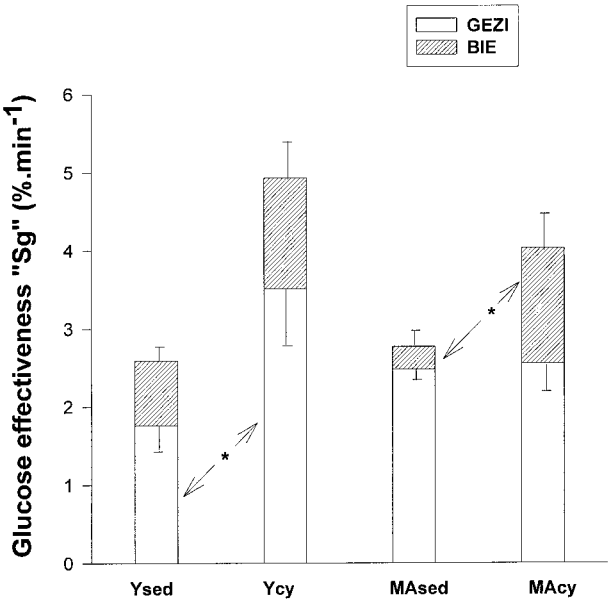

Fig 3. Comparison of Sg and its two components, BIE and GEZI, in middle-aged and young men. Sg were higher in Ycy than in Ysed and in MAcy than MAsed (*P* < .05). BIE and GEZI are different, * *P* < .05.

rameter, we matched subjects of each age group for percentage of fat. As shown on Table 1, there was no significant difference in fatness in middle-aged subjects and only a minimal difference (2%) in young subjects. Literature on the influence of fatness on SI[35-37] clearly does not support the assumption that so little difference in fatness could induce a twofold or threefold increase in SI. Thus, the higher SI in our trained groups is not likely to be explained by differences in fat mass.

An important part of this study was the measurement of the non–insulin-dependent glucose uptake, GEZI, which is closely related to NIMGU.[28] Although the literature abounds with reports on insulin-mediated glucose uptake in physically trained subjects (see above), there are few studies on the effect of training on NIMGU. These studies have shown that GEZI increases after a single submaximal exercise bout[27] and after exercise training,[2,4] which is in accordance with our data in the young population. However, training did not change GEZI values in our middle-aged population. Because the effect of training on SI was markedly greater in middle-aged men in than in young men (see above), a possible explanation is that the effect of training on the NIMGU is reduced in middle-aged men but improved in young men. However, a physiological upper boundary to the effect of training on SI and Sg has recently been evidenced in young cyclists.[4] Therefore, it seems the two patterns of glucose uptake (insulin-dependent and non–insulin-dependent)[17,18] are modified differently according to age. In support of this conclusion, we were able to show that training increased BIE in middle-aged subjects but not in young subjects. On the other hand, we suggested in a previous study[4] that modifications in GEZI after training in young cyclists may reflect this non–insulin-mediated mobilization of glucose transporters. This finding is not confirmed in our middle-aged men. In support of this, Cox et al[3] recently reported that older human muscle retains the ability to rapidly increase muscle GLUT-4 with endurance training. This could imply a decreased effect of non–insulin-dependent glucose transporter recruitment[16] on glucose disposal in middle-aged men.

The results of the present study indicate that aging does not modify GEZI in the middle-aged population. Because GEZI is a measurement of NIMGU,[28] this finding appears to differ from the result reported in a previous study,[38] which found that NIMGU decreased in sedentary older men. The difference may be related to the fact that Sg is calculated from glucose disappearance that occurs over a broad range of glucose concentrations after a single bolus injection of glucose, whereas NIMGU is measured during a continuous glucose infusion.[28] Thus, the difference in results may be attributable to different methodologies.

In summary, the results of this study show that endurance training improved SI and Sg in men independent of age, whereas the parameter GEZI was increased in young men. Although the effect of age was distinctly pronounced in a sedentary population, with a decrease in SI, this parameter was identical in the two trained populations. We found a correlation between SI and Sg and $\dot{V}O_{2max}$ in the middle-aged men, however, reflecting the insulin resistance associated with a decrease in physical activity in an aging population. The better glucose uptake in male endurance-trained cyclists, compared with that in age-matched sedentary men, was caused by an increase in non–insulin-dependent glucose uptake in the young cyclists and an increase in its insulin-dependent component in the middle-aged cyclists. Both effects are likely to have similar consequences, so that endurance cycling can effectively enhance whole glucose disposal independent of age.

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