Decline in insulin action with age in endurance-trained humans

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Clevenger, Christopher M., Pamela Parker Jones, Hirofumi Tanaka, Douglas R. Seals, and Christopher A. DeSouza. Decline in insulin action with age in endurance-trained humans. J Appl Physiol 93: 2105–2111, 2002.—We tested the hypothesis that regular endurance exercise prevents the age-related decline in insulin action typically observed in healthy, sedentary adults. An index of whole body insulin sensitivity (ISI), obtained from minimal model analysis of insulin and glucose concentrations during a frequently sampled intravenous glucose tolerance test, was determined in 126 healthy adults: 25 young [27 ± 1 (SE) yr; 13 men/12 women] and 43 older [59 ± 1 yr; 20/13]sedentary and 25 young (29 ± 1 yr; 12/13) and 33 older (60 ± 1 yr; 20/13) endurance trained. ISI values were lower in the older vs. young adults in both sedentary (−53%; 3.9 ± 0.3 vs. 7.0 ± 0.7 \times 10^{-4} \text{min}^{-1} \mu \text{U}^{-1} \text{ml}^{-1}; P < 0.01) and endurance-trained (−36%; 7.9 ± 0.6 vs. 12.4 ± 1.0 \times 10^{-4} \text{min}^{-1} \mu \text{U}^{-1} \text{ml}^{-1}; P < 0.01) groups, but the value was 72–102% higher in the trained subjects at either age (P < 0.01). In subgroup analysis of sedentary and endurance-trained adults with similar body fat levels (n = 62), the age-related reduction in ISI persisted only in the endurance-trained subjects (12.9 ± 1.9 vs. 8.7 ± 1.2 \times 10^{-4} \text{min}^{-1} \mu \text{U}^{-1} \text{ml}^{-1}; P < 0.01). The results of the present study suggest that habitual endurance exercise does not prevent the age-associated decline in insulin action. Moreover, the age-related reduction in ISI in endurance-trained adults appears to be independent of adiposity.

Insulin resistance; sedentary; physical activity; glucose metabolism

It is well documented that advancing age is associated with a decline in insulin action (i.e., development of insulin resistance) (10, 11, 15, 37, 41). Studies utilizing either the hyperinsulinemic, euglycemic glucose clamp (11, 15, 37) or minimal model (10, 41) techniques have demonstrated age-related reductions in insulin sensitivity ranging from 30 to 60% in healthy, sedentary men and women.

The decline in insulin action with age is thought to contribute to the high prevalence of impaired glucose tolerance and Type 2 diabetes among the elderly (17, 43). In addition, low insulin sensitivity is associated with increased rates of atherosclerotic vascular disease, in part through related metabolic disorders such as hyperinsulinemia, dyslipidemia, and hypertension. As such, insulin sensitivity represents a major independent factor in the etiology of age-associated coronary and cerebrovascular disease (8, 20, 24, 31).

In contrast to aging, regular aerobic exercise is associated with enhanced insulin sensitivity (26, 36, 39, 40) and a lower incidence of metabolic and cardiovascular diseases (5, 35). Moreover, it has been suggested that age-related declines in insulin sensitivity observed in healthy, sedentary adult humans do not occur in adults who regularly perform endurance exercise (39). However, there has been no direct test of this hypothesis. Absence or attenuation of this decline could contribute to the lower prevalence of age-related metabolic and cardiovascular diseases observed in habitually endurance-trained individuals (35).

Thus the primary purpose of the present investigation was to test the hypothesis that regular endurance exercise prevents the age-related decline in insulin sensitivity observed in healthy, sedentary adults. To address this aim, we employed a cross-sectional model that our laboratory has used successfully in the past to gain insight into issues relating to aging and regular aerobic exercise. Specifically, whole body insulin action was assessed in groups of healthy young and older sedentary and endurance-trained men and women.

SUBJECTS AND METHODS

Subjects. One hundred twenty-six healthy men and women, aged 21–35 yr (“young” adults) or 50–80 yr (“older” adults) were studied: 25 young (13 men, 12 women) and 43 older (20 men, 23 women) sedentary individuals and 25 young (12 men, 13 women) and 33 older (20 men, 13 women) endurance-trained runners. The young and older endurance-trained subjects were matched for age-adjusted running performance as described previously by our laboratory (13), ran 52.2 ± 8.3 and 48.5 ± 5.6 km/wk, and had been training for 8 ± 1 and 18 ± 1 yr, respectively. The sedentary subjects had not participated in a regular aerobic exercise program for at

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least 1 yr before the start of the study. All of the older women were at least 2 yr postmenopausal (range = 2–23 yr), and 20 women were taking estrogen-based hormone supplements (12 sedentary individuals and 8 distance runners). The majority (18 of 20) of the users of hormone supplementation were on a oral regimen of conjugated estrogen (Premarin, 0.625–1.0 mg/day) in combination with medroxyprogesterone acetate (Provera, 2.5 mg/day); the remaining women were taking either Premarin or Provera only. We observed no influence of hormone replacement use. Therefore, the data were pooled and presented together. All premenopausal women were eumenorrheic as assessed by self-report of menstrual cycles, not taking oral contraceptives, and studied during the follicular phase of their menstrual cycle.

All subjects were normotensive (blood pressure ≤140/90), were free of overt disease as assessed by medical history questionnaire, and had normal lipid and lipoprotein concentrations all within the normal range (32). The older subjects were further evaluated for clinical evidence of cardiovascular disease with a physical examination and with resting and maximal exercise electrocardiograms. No subjects were on medication other than hormone replacement, and all subjects were nonsmokers. Before participation, all of the subjects had the research study and its potential risks and benefits explained fully before providing written, informed consent according to the guidelines of the University of Colorado at Boulder and the University of Colorado Health Sciences Center in Denver.

**Body composition.** Body mass was measured to the nearest 0.1 kg by using a medical balance beam (Detecto, Webb City, MO). Percent body fat was determined by dual-energy X-ray absorptiometry (model DPX-IQ, Lunar Radiation, Madison, WI) (28). Body mass index (BMI) was calculated as weight (in kg) divided by height (in m) squared. Minimal waist circumference was measured according to previously published guidelines (30).

**Aerobic fitness.** Maximal oxygen consumption (V\(\dot{O}_{2\text{max}}\)) was used as a measure of aerobic fitness and was determined by using an on-line computer-assisted open-circuit spirometry during incremental exercise on a motorized treadmill as previously described (13). A valid V\(\dot{O}_{2\text{max}}\) was accepted when at least three of the following criteria were met: 1) a plateau in oxygen consumption with increasing work rate (<1 ml·kg\(^{-1}\)·min\(^{-1}\) or <100 ml/min), 2) a respiratory exchange ratio at maximal exercise >1.10, 3) achievement of age-predicted maximal heart rate (220−age), and 4) a rating of perceived exertion >18 (Borg scale) (7).

**Frequently sampled intravenous glucose tolerance test.** All studies were performed 24 h after the last bout of exercise in the endurance-trained subjects. To assess whole body insulin action, all subjects underwent an insulin-modified frequently sampled intravenous glucose tolerance test (FSIVGTT) after a 12-h overnight fast as previously described (1, 38). Briefly, intravenous canulas were placed in both antecubital veins; one was for the administration of glucose and insulin, and the other was for venous sampling. Both catheters were kept patent throughout with a slow infusion of saline. After two baseline blood samples (3 ml), a bolus of glucose (300 mg/kg) was injected intravenously over 1 min at time 0 and regular insulin (0.03 U/kg; Humulin-Regular, Eli Lilly, Indianapolis IN) was injected 20 min later. Blood samples were collected at standard time points after glucose infusion for determination of plasma glucose and insulin concentrations. Plasma glucose was determined in duplicate by using a glucose hexokinase method (Gillford 203-S, Oberlin, OH), and insulin was determined by radio-immunoassay (45).

Glucose and insulin data from the FSIVGTT were subsequently analyzed using the minimal model method of Bergman to determine the insulin sensitivity index (ISI) (1), a measure of whole body insulin action. Calculation of ISI was made from a least squares fitting of the temporal pattern of glucose and insulin throughout the FSIVGTT (1). The acute insulin response to glucose (AIR\(G\)) was calculated as the mean increment in plasma insulin above baseline from 2 to 10 min after the intravenous administration of glucose (21)

The disposition index (DI), an estimate of β-cell response to the prevailing degree of insulin action, was determined as the product of ISI and AIR\(G\) (4, 23).

**Statistical analysis.** The influence of age, gender, and training status on all variables were determined by a multifactor analysis of variance (age × gender × training status). When indicated by a significant F-value, specific mean comparisons were performed to identify significant group differences. Linear and stepwise regression analyses were performed to determine relations between the ISI and variables of interest. All data are expressed as means ± SE. Statistical significance was set at P < 0.05.

**RESULTS**

**Age-related differences in the sedentary and endurance-trained subjects.** Table 1 presents selected physical and metabolic characteristics of the subjects. There were no age-related differences in body mass in either the men or women. Percent body fat, BMI, and waist circumference were higher (P < 0.05) and V\(\dot{O}_{2\text{max}}\) and fat-free mass were lower in the older subjects compared with their respective young controls. Fasting plasma glucose concentrations were higher (P < 0.05) with age, although within the normal range, in both the sedentary and endurance-trained groups. There was no effect of age on fasting plasma insulin concentrations in either the sedentary or endurance-trained subjects. However, the endurance-trained subjects demonstrated lower (P < 0.01) plasma insulin concentrations than their sedentary peers.

**Age-related differences in ISI in the sedentary and endurance-trained subjects.** There was no main effect of gender on ISI, AIR\(G\), or DI (Table 2); therefore, the data were pooled and presented together. ISI values were 44 and 36% lower in the older vs. young sedentary (3.9 ± 0.3 vs. 7.0 ± 0.7 × 10\(^{-6}\)·min\(^{-1}\)·pmol\(^{-1}\)·l\(^{-1}\); P < 0.01) and endurance-trained (7.9 ± 0.6 vs. 12.4 ± 1.0 × 10\(^{-6}\)·min\(^{-1}\)·pmol\(^{-1}\)·l\(^{-1}\); P < 0.01) subjects, respectively (Fig. 1). However, the endurance-trained subjects demonstrated markedly higher (72–102%) ISI values than their sedentary age-matched peers (P < 0.01). Moreover, ISI of the older endurance-trained group was similar to that of the sedentary young group. There were no significant age-related differences in AIR\(G\) in either the sedentary (278.6 ± 32.9 vs. 255.4 ± 34.6 pmol/l) or endurance-trained (131.5 ± 17.5 vs. 113.3 ± 14.5 pmol/l) subjects. AIR\(G\), however, was lower (P < 0.01) in the endurance-trained subjects compared with their age-matched endurance counterparts. DI values were lower (P < 0.05) in the older sedentary (862.5 ± 67.9 vs. 1,437.0 ± 133.4 10\(^{-5}\)·min\(^{-1}\)) and endurance-trained (872.6 ± 84.4 vs. 1,291.0 ± 161.6 10\(^{-5}\)·min\(^{-1}\)) subjects compared with their young
counterparts. There was no main effect of training status on DI.

Age-related differences in ISI in sedentary and endurance-trained subjects with similar whole body adiposity. Because body composition, particularly adiposity, is one of the strongest predictors of insulin sensitivity in both men and women, we sought to determine the influence of adiposity on ISI. First, univariate correlations performed on the pooled population revealed that ISI was inversely related (all P < 0.01) to body mass (r = −0.32), percent body fat (r = −0.60), BMI (r = −0.49), and waist circumference (r = −0.48). In light of these relations, subgroups (n = 62) of young and older sedentary and endurance-trained subjects with similar levels of body fatness were then compared. There was no main effect of gender in the subgroup analysis, so the data were pooled and presented together (Table 3). In the subgroup of sedentary subjects with similar percent body fat, there was no significant difference in ISI in the older compared with the young subjects (4.4 ± 0.7 vs. 5.7 ± 1.0 \times 10^{-4} \text{pmol}^{-1} \text{min}^{-1} \cdot \text{ml}^{-1}; P = 0.13). However, in the endurance-trained subgroup, ISI remained 33% lower (P < 0.01) in the older vs. young subjects (8.7 ± 1.2 vs. 12.9 ± 1.9 \times 10^{-4} \text{min}^{-1} \cdot \text{pmol}^{-1} \cdot \text{ml}^{-1}; P < 0.01) (Fig. 2).

DISCUSSION

The primary new finding of the present study is that the age-related decline in insulin action typically observed in healthy, sedentary adults also is evident in adults who perform regular endurance exercise. In addition, whereas the age-associated decline in ISI was abolished in the sedentary adults after accounting for adiposity, the diminution in ISI with age in the endurance-trained adults was independent of this factor. To the best of our knowledge, this is the first study to demonstrate lower insulin action with age in endurance-trained adults. However, it is noteworthy that,

Table 1. Selected physical and metabolic characteristics of the sedentary and endurance-trained subjects

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<td>13</td>
<td>20</td>
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<tr>
<td>Age, yr</td>
<td>27±1</td>
<td>58±2*</td>
<td>28±1</td>
<td>62±2*</td>
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<tr>
<td>Body mass, kg</td>
<td>83.5±4.4</td>
<td>87.6±3.7</td>
<td>73.8±2.0†</td>
<td>74.5±1.7†</td>
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<td>Body fat, %</td>
<td>20.3±12.4</td>
<td>28.6±1.2*</td>
<td>11.8±0.9†</td>
<td>19.1±11.3†</td>
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<td>Waist, cm</td>
<td>86.7±3.8</td>
<td>100.5±2.5*</td>
<td>79.1±1.0†</td>
<td>86.5±1.0†</td>
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<td>BMI, kg/m²</td>
<td>23.6±0.7</td>
<td>27.9±1.0*</td>
<td>23.1±0.5</td>
<td>23.9±0.5*</td>
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<tr>
<td>Fat-free mass, kg</td>
<td>66.5±3.1</td>
<td>62.6±1.9*</td>
<td>65.1±1.6</td>
<td>60.0±1.1*</td>
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<tr>
<td>VO₂max, ml·kg⁻¹·min⁻¹</td>
<td>42.5±2.0</td>
<td>30.0±1.2*</td>
<td>59.5±2.0†</td>
<td>43.4±1.9†</td>
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<td>Glucose, mmol/l</td>
<td>4.8±0.1</td>
<td>5.8±0.1*</td>
<td>4.8±0.2</td>
<td>5.2±0.1*</td>
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<tr>
<td>Insulin, pmol/l</td>
<td>32.0±4.5</td>
<td>60.6±8.3*</td>
<td>25.5±1.1</td>
<td>26.7±2.6*</td>
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Women

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<td>n</td>
<td>12</td>
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<tr>
<td>Age, yr</td>
<td>28±1</td>
<td>59±1*</td>
</tr>
<tr>
<td>Body mass, kg</td>
<td>62.1±3.6</td>
<td>69.5±1.8</td>
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<tr>
<td>Body fat, %</td>
<td>27.5±2.4</td>
<td>40.3±1.0*</td>
</tr>
<tr>
<td>Waist, cm</td>
<td>74.8±2.4</td>
<td>85.7±1.9*</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>22.5±1.2</td>
<td>26.1±0.7*</td>
</tr>
<tr>
<td>Fat-free mass, kg</td>
<td>44.4±1.5</td>
<td>41.3±0.8*</td>
</tr>
<tr>
<td>Glucose, mmol/l</td>
<td>4.9±0.1</td>
<td>5.3±0.1*</td>
</tr>
<tr>
<td>Insulin, pmol/l</td>
<td>41.0±5.2</td>
<td>38.6±2.7</td>
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Values are means ± SE; n, no. of subjects. BMI, body mass index; VO₂max, maximal oxygen consumption. *P < 0.05 vs. young same exercise status. †P < 0.05 vs. age-matched sedentary.

Table 2. ISI, AIRG, and DI values in the male and female subjects in the overall study population

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<td>Young</td>
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<td>ISI, \times 10^{-5}·min⁻¹·pmol⁻¹·l⁻¹</td>
<td>6.7±0.7</td>
<td>3.6±0.4*</td>
<td>12.2±1.2</td>
<td>8.1±0.9*</td>
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<td>AIRG, pmol/l</td>
<td>270.0±39.7</td>
<td>316.5±58.4</td>
<td>116.1±25.5†</td>
<td>151.5±27.5†</td>
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<td>DI, \times 10^{-5}·min⁻¹</td>
<td>1,536.6±149.2</td>
<td>840.3±115.1*</td>
<td>1,386.5±310.8</td>
<td>963.1±123.5*</td>
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Women

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<tr>
<td>ISI, \times 10^{-5}·min⁻¹·pmol⁻¹·l⁻¹</td>
<td>7.4±1.3</td>
<td>4.1±0.3*</td>
</tr>
<tr>
<td>AIRG, pmol/l</td>
<td>238.1±60.8</td>
<td>245.7±34.5</td>
</tr>
<tr>
<td>DI, \times 10^{-5}·min⁻¹</td>
<td>1,319.3±234.8</td>
<td>881.8±80.4*</td>
</tr>
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</table>

Values are means ± SE. ISI, insulin sensitivity index; AIRG, acute insulin response to glucose; DI, disposition index. *P < 0.05 vs. young same gender. †P < 0.05 vs. age-matched sedentary.

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Despite this decline, ISI was higher at any age in endurance-trained compared with sedentary adults.

Deterioration of insulin action is considered to be a common characteristic of sedentary aging. In fact, our finding of a 53% reduction in insulin action in healthy older compared with young adults is consistent with previous observations (15, 27, 33, 37, 41). Importantly, the results of the present study extend these data by showing that insulin action declines with age in regularly exercising humans. Specifically, we observed a significant main effect of age on ISI in the endurance-trained groups. Indeed, ISI was 36% lower in the older compared with young endurance-trained adults.

There are two important limitations of our study that should be emphasized. First and foremost, because of the cross-sectional design of our study we cannot rule out the inherent possibility that genetic or constitutional factors may have influenced our findings. Although the levels of insulin sensitivity reported herein are consistent with previous studies involving both sedentary (1, 9) and physically active (22) populations, and the higher ISI values associated with regular physical activity in the present study are similar to those reported in response to endurance exercise training in older men (21, 22), our results should be viewed within the context and constraints of the study design. Second, the residual effects of the last bout of exercise on insulin sensitivity has been reported to persist for 40–72 h (25, 44). In the present study, ISI was determined ~20 h after the last bout of exercise in the endurance-trained groups. Because these adults exercise most days of the week, we reasoned that the 20-h postexercise condition used in the present study represents their normal biological state (habitually endurance-trained). However, the influence of the last bout of exercise on ISI cannot be discounted and the reader should interpret the data presented accordingly.

Our results contradict the results of an earlier cross-sectional study on the same topic (39). Seals et al. (39) reported no age-associated increase in the plasma insulin responses to an oral glucose challenge in middle-aged and older endurance-trained athletes compared with young athletes. On the basis of these findings, the authors suggested that the decline in insulin sensitivity with age may be prevented in adults who perform regular vigorous exercise. Plasma insulin response to an oral glucose challenge, however, is at best a crude marker of insulin action (1, 2). Although the oral glucose tolerance test (OGTT) is clinically important for the diagnosis of impaired glucose tolerance and diabetes, it is difficult to tease out the contribution of insulin sensitivity, glucose effectiveness, and β-cell responsiveness to the observed response (3). Indeed, it has been suggested that only 37% of the variance in plasma insulin responses to an OGTT can be attributed to differences in insulin action (29). On the basis of the use of a more sensitive assessment of whole body insulin action (3), the results of the present study provide new insight on the influence of regular aerobic exercise on the age-associated decline in insulin sensitivity in adult humans. We are aware of no other studies examining the influence of age and habitual aerobic-endurance exercise on insulin action in adult male and female humans.

The mechanisms underlying the age-associated decline in insulin sensitivity are not completely un-
stood. Because a number of factors can influence the metabolic actions of insulin, it has been suggested that the age-associated decline in insulin sensitivity is not solely due to aging per se but rather to other concomitants of aging, particularly increasing whole body adiposity (6, 14), body fat distribution (16, 27), and physical inactivity (18, 42). Kohrt et al. (27) have reported that age-related insulin resistance is more closely associated with abdominal adiposity than with age. Using the hyperinsulinemic euglycemic clamp procedure to quantify insulin action in groups of young and older adults, the authors noted that waist circumference accounted for >40% of the variance in insulin action, whereas age accounted for <20% of the total variance and, importantly, <2% of the variance when adjusted for waist circumference. Similar findings involving relations between age, BMI, and insulin sensitivity have been reported by the European Group for the Study of Insulin Resistance in 1,146 healthy Caucasian men and women (14).

In the present study, we observed no age-related decline in insulin action in our subgroup of sedentary subjects with similar levels of body fatness. These findings support the postulate that reductions in insulin sensitivity with age in sedentary humans are dependent on age-associated increases in adiposity (14, 27). However, this does not appear to be the case in endurance-trained adults. A novel finding of the present study is that, in contrast to sedentary aging, the decline in insulin action with age in endurance-trained adults appears to be independent of adiposity. When we compared subgroups of young and older runners with similar body fat levels the magnitude of the age-related difference in ISI was similar to that observed in the whole groups (33 vs. 36%). These findings suggest that the age-associated decline in ISI in sedentary and endurance-trained subjects does not share a common etiology.

Given the present study design, we can only speculate on potential mechanisms responsible for the age-related decline in ISI in the endurance-trained adults. One possibility is a reduction in exercise training intensity with age. For example, our laboratory (13) and others (34) have shown that in habitually endurance-trained adults absolute training intensity (running velocity) decreases with advancing age as a consequence of reduced exercise capacity. Thus age-associated reductions in exercise training intensity may result in a training stimulus insufficient to maintain the high levels of muscle insulin sensitivity (the main determinant of whole body insulin action) established at a young age. It is also possible that regular aerobic exercise does not affect the age-related decline in GLUT-4 protein concentration observed in sedentary adults (19). Future studies are needed to determine the mechanisms responsible for the decline in insulin sensitivity with age in endurance-trained adults.

To our knowledge, this is the first study to demonstrate an age-related decline in DI in both sedentary and endurance-trained adults. DI was ~35% lower in the older compared with young adults regardless of training status. In accordance with the hyperbolic relationship between insulin secretion and insulin sensitivity advocated by Elbein et al. (12) and Kahn et al. (23), this finding suggests that the ability of the β-cell to compensate for the degree of insulin sensitivity declines with age and is unaffected by habitual physical activity. Indeed, we observed no age-related increase in AIRG values in either the sedentary or endurance-trained subjects, indicating that β-cell insulin secretion was not modified in response to reduced insulin action in either group. DI has been shown to be lower in other populations with reduced insulin sensitivity (12).

In light of the present findings that ISI declines with age even in adult humans who exercise vigorously, it is clinically important to emphasize the following. First, ISI was much greater at any age in regularly exercising adults. Second, the main effect of exercise status on ISI was twice as strong as age. Thus, although habitual endurance exercise does not appear to prevent the age-related decline in ISI in adult humans, the endurance-trained adults demonstrated greater insulin at any age compared with their sedentary peers. This likely contributes to the lower incidence of metabolic and cardiovascular diseases observed in adults who exercise regularly (35).
In conclusion, the results of the present study suggest that habitual endurance exercise does not prevent the age-associated decline in insulin action. As in sedentary adults, we observed a significant reduction in ISI in the young vs. older endurance-trained adults. However, in contrast to sedentary adults, the reduction in insulin sensitivity with age in endurance-trained adults appears to be independent of whole body adiposity.

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