Serum Levels of Insulin-like Growth Factor-I (IGF-I), and IGF-Binding Proteins-1 and -3 in Middle-Aged and Young Athletes Versus Sedentary Men: Relationship With Glucose Disposal

J. Manetta, J.F. Brun, C. Fedou, L. Maïmoun, C. Prefaut, and J. Mercier

The goal of this study was to characterize the respective effects of aging and endurance training on serum insulin-like growth factor I (IGF-I), as well as IGF-binding proteins (IGFBP)-1 and -3 in relationship with glucose disposal. Thirty-two subjects (16 middle-aged men: 8 cyclists and 8 sedentary men; and 16 young men: 8 cyclists and 8 sedentary men) were compared in this study. Insulin sensitivity (SI) and glucose effectiveness (Sg) were assessed by the minimal model. Endurance training increased SI, Sg, and IGFBP-1 and -3 in both age groups ($P < .05$), but the older group showed a greater increase in SI and IGFBP-1 than the younger group ($P < .05$). IGF-I was increased only in the middle-aged trained men ($P < .05$). An effect of aging was found in the sedentary subjects, who presented lower IGF-I and SI ($P < .05$) when older. This effect disappeared with training since IGF-I and SI were nearly identical in young and middle-aged trained subjects. SI was correlated with IGFBP-1 ($P < .01$). These data suggest that (1) endurance training increases SI, Sg, and IGFBP-1 and -3 in men and, for SI and IGFBP-1, this increase becomes more pronounced with age; (2) endurance training may attenuate the aged-related decline in SI and IGF-I; and (3) IGFBP-1 may protect against the risk of hypoglycemia by counteracting the hypoglycemic effect of IGF-I in such situations of high SI.

IT IS BECOMING widely acknowledged that exercise and endurance training cause substantial adaptations in the somatotropic axis and glucose disposal. Physical activity and a good fitness level improve both the growth hormone/insulin-like growth factor-1 (GH/IGF-I) axis[1,2] and glucose disposal.[3-5] Furthermore, the decline in plasma IGF-I[6-9] and insulin sensitivity (SI)[10-12] that occurs with aging may be related in part to a decline in physical fitness. The anabolic and growth-promoting effects of GH are mediated through the production of IGF-I.[13] However, most IGF-I circulating in blood is bound to IGF-binding proteins (IGFBP), which modify IGF-I bioavailability and bioactivity for action on tissues.[14] IGFBP-1 and IGFBP-3 are the best characterized of the 6 circulating IGFBPs.[15] IGFBP-3 is classically considered to be a reservoir transporting IGFs in the blood stream in a 150-kd complex that also includes the liver-derived acid-labile subunit,[15] and its plasma levels do not fluctuate during a 24-hour period.[16] IGFBP-3 is thus taken to be an integrated index of GH action.[16] IGFBP-1 is a local modulator of IGF-I and is downregulated by insulin, which is its primary regulator.[13]

The effects of exercise and training on IGF-I and IGFBP-1 and -3 remain incompletely understood. The best studied protein of this system is IGF-I, which has repeatedly been found to be increased after both endurance and resistance training.[2,9,17,18,20] However, in the case of insufficient protein and calorie supply, IGF-I was found to decrease after training.[21] Most training protocols have resulted in a higher level of IGFBP-3,[18,19] but this protein also is reduced in situations of increased proteolysis (eg, inflammation, undernutrition, overtraining). On the whole, however, IGFBP-3 is considered to be a marker of physical fitness.[2] Baseline levels of IGFBP-1, which are mostly dependent on nutritional status and insulin levels,[13] are markedly increased after a variety of prolonged exercise training protocols in which glycemia tends to decrease; its physiological role has thus been hypothesized to be a protection against hypoglycemia.[22,23] Some of the discrepancies among studies investigating IGF-I and the IGFBPs are likely to be explained in great part by differences in either subject training level, physical fitness, body composition status, gender, or age.

These proteins are assumed to play a role in glucoregulatory adaptation to exercise. A recent study showed that low plasma IGF-I concentrations are predictive of a decline in whole body glucose uptake in older people.[24] This process is particularly relevant for the middle-aged, since the insulin resistance of aging is initiated as early as the third decade of life.[10,11] IGF-I and IGFBP-1 may be involved in glucose homeostasis since alterations in IGF-I availability have been shown to modulate its insulin-like effects.[22,25] Moreover, IGFBP-1 is the sole binding protein that has been unequivocally demonstrated to modulate the hypoglycemic activity of IGF-I.[26] Injection of human IGFBP-1 into rodents increases blood glucose levels,[25] whereas in transgenic mice overexpressing IGFBP-1, it results in impaired glucose tolerance with normal insulin sensitivity (SI).[27]

Finally, the age-related declines in anabolic hormone status[24] and glucose disposal[4,5] may both be attenuated by exercise, although the extent to which training counteracts these metabolic effects of aging has been incompletely elucidated. In particular, the combined effects of training and aging on IGF-I, IGFBP-1, and IGFBP-3 are unknown. The relationships of these mechanisms with the changes in glucose disposal (SI, glucose effectiveness [Sg]) induced by both aging and training are also quite unclear. We therefore investigated whether aging

From the Metabolic Unit, Service Central de Physiologie Clinique, Centre d'Exploration et de Réadaptation des Anomalies Métaboliques et Musculaires (CERAMM); and the Service de Médecine Nucléaire; Hôpital Lapeyronie, Montpellier, France.

Submitted July 17, 2002; accepted February 23, 2003.

Supported by Novo Nordisk France.

Address reprint requests to J. Manetta, PhD, Service Central de Physiologie Clinique (CERAMM), CHU Lapeyronie, 371 avenue du Doyen Gaston Giraud, 34295 Montpellier Cedex 5, France.

0026-0495/03/5207-0008$30.00/0

doi:10.1016/S0026-0495(03)00096-9

Table 1. Baseline Characteristics for Cyclists and Sedentary Subjects

	Sedentary Subjects		Cyclists	
	Middle-Aged (n = 8)	Young (n = 8)	Middle-Aged (n = 8)	Young (n = 8)
Age (yr)	52.1 ± 1.1	23.7 ± 0.7‡	51.8 ± 1.2	24.5 ± 1.68
Height (cm)	173.1 ± 1.4	178.8 ± 1.5	173.7 ± 1.2	178.3 ± 1.9
Weight (kg)	75.2 ± 2.4	70.8 ± 2.6	72.7 ± 1.1	69.3 ± 2.1
BMI (kg/m^2)	25.09 ± 0.6	22.1 ± 0.4	24.09 ± 0.5	21.8 ± 0.8§
Fat (%)	22.4 ± 1.5	15.1 ± 2.7	20.4 ± 0.7	12.7 ± 0.5§
Vo_{2max} (mL/min/kg)	33.1 ± 1.2	47.3 ± 2.2‡	50.5 ± 2.3†	64.9 ± 3.1*§

NOTE. Values are means ± SE.

*Significant difference between trained *v* sedentary in young group, $P < .05$.

†Significant difference between trained *v* sedentary in middle-aged group, $P < .05$.

‡Significant difference between young *v* middle-aged in sedentary group, $P < .05$.

§Significant difference between young *v* middle-aged in trained group, $P < .05$.

modifies the effect of endurance training on IGF-I, IGFBP-1, and IGFBP-3 levels in connection with glucose homeostasis.

SUBJECTS AND METHODS

Subjects

Sixteen male cyclists (8 young [24.7 ± 1.4 years] cyclists [Ycy] and 8 middle-aged [51.6 ± 1.2 years] cyclists [MAcy]) and 16 sedentary males (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 using medication for the control of blood pressure or lipid or carbohydrate metabolism were excluded. No subject exhibited 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 12 hours of cycling per week. These cyclists had been following this training schedule for the past 11 ± 1.4 (SE) years. The training program for the young cyclists was also carried out in a group and amounted to almost 16 hours of training per week. All had followed this training schedule for the past 7 ± 1.2 (SE) years. None of the sedentary subjects participated in competitive sports or organized leisure time activities. Prior to study enrollment, a brief interview was conducted to ascertain that all subjects had approximately the same dietary habits. After a complete and accurate verbal description of the procedure, risks, and benefits associated with the study, subjects provided their written consent.

Methods

Protocol. The subjects came to the laboratory on 2 separate occasions for a maximal aerobic capacity test and an intravenous glucose tolerance test. All subjects were requested to refrain from exercise for 3 days before the glucose tolerance test. The subjects were asked to fast overnight before the intravenous glucose tolerance test until their arrival in our hospital unit at 8 AM+ so that the different tests of the protocol could be performed at the same time of day.

Body composition. Body composition was assessed with a 4-terminal impedance plethysmograph (Dietosystem Human IM-Scan, Milan, Italy).[28]

Frequently sampled intravenous glucose tolerance test (FSIVGTT) and blood samples. 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 units/kg^{-1} body weight, ie, 1 to 2 units) was injected into the vein contralateral to the one used for sampling, immediately after 19 minutes. Blood samples were drawn twice before the glucose bolus and at 1, 3, 4, 8, 10, 15, 19, 20, 22, 30, 41, 70, 90, and 180 minutes following glucose injection. Other basal blood samples were pooled for determination of basal plasma concentration of IGF-I, IGFBP-1, and IGFBP-3.

Measurement of SI and Sg. Minimal model analysis of FSIVGTT was according to Bergman et al[29] with TISPAG software from the Department of Physiology, University of Montpellier I,[30] which uses a nonlinear least square estimation. This program gave the values of SI and 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.

Incremental maximal exercise test. The subject's Vo_{2max} was measured during 8 to 12 minutes of exercise on an electronically braked cycle ergometer (550 ERG, Bosch, Berlin, Germany). Fractions of oxygen and carbon dioxide in the expired air were measured by a mass spectrometer (Marquette MGA 1100, St Quentin, France). The calibration of the mass spectrometer was checked before each test with standard calibration gases. A 3-L syringe was used to calibrate the volume turbine using flow rates similar to subject ventilation. Heart rate was monitored throughout the exercise test. Exercise testing 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 (RER) values (>1.15) and O_2 consumption (Vo_2) stability.

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

Serum somatomedin C/IGF-I was assayed with the kit from Medegenix (Brussels, Belgium). This is a double-antibody disequilibrium assay which includes an ethanol acid extraction procedure from serum samples. After the extraction procedure, radioimmunoassay (RIA) is performed employing the addition of sample and rabbit anti–IGF-I, followed by a 2-hour incubation at 2 to 8°C. Iodine 125 IGF-I is then added, followed by a second incubation for 20 hours at 2 to 8°C. Pre-precipitated carrier, the second antibody, and polyethylene glycol are added in a single step. The assay is centrifuged after the second 2-hour antibody incubation at 2 to 8°C. The detection limit is 2 nmol/L. This assay does not cross-react (<1%) with IGF-2, human GH, fibroblast growth factor (FGF), or platelet-derived growth factor (PDGF).

Table 2. Insulin Sensitivity and Glucose Effectiveness for 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)	5.1 ± 0.1	4.37 ± 0.2‡	4.59 ± 0.1†	4.21 ± 0.1
Basal insulin (μU/mL)	10.6 ± 0.8	9.68 ± 1.3	6.48 ± 0.6†	8.3 ± 0.4§
Sg (% · min^{-1})	2.5 ± 0.2	2.7 ± 0.2	3.9 ± 0.6†	4.9 ± 0.4*
SI [× 10^{-4} (μU/mL · min^{-1})]	3.1 ± 0.6	7.9 ± 2.1‡	15.8 ± 2.2†	16.1 ± 2.1*

NOTE. Values are means ± SE.

*Significant difference between trained vs sedentary in young group, $P < .05$.

†Significant difference between trained *v* sedentary in middle-aged group, $P < .05$.

‡Significant difference between young *v* middle-aged in sedentary group, $P < .05$.

§Significant difference between young *v* middle-aged in trained group, $P < .05$.

Within-assay CVs range between 9.1% and 10.1%; between-assay CVs range between 10.3% and15.2%.

Serum IGFBP-1 was assayed with the DSL ACTIVE IGFBP-1 coated-tube immunoradiometric assay kit (Diagnostic System Laboratories, Webster, TX). This is a 2-site immunoradiometric assay (IRMA) in which the analyte to be measured is "sandwiched" between 2 antibodies. The first antibody is immobilized on the inside wall of the tubes. The other antibody is radiolabeled for detection. The analyte present in patient samples, standards, and controls is bound by both of the antibodies to form a sandwich complex. Unbound materials are removed by decanting and washing the tubes. The detection limit is 0.01 ng/mL. Within-assay CVs range between 3.4% and 6%; between-assay CVs range between 1% and 3.5%. No cross-reactivity with IGFBP-2, -3, or -4 has been detected.

Serum IGFBP-3 was assayed with the DSL IGFBP-3 RIA kit (Diagnostic System Laboratories). This is a classical RIA with competition between a radioactive and a nonradioactive antigen for a fixed number of antibody-binding sites. The separation of free and bound antigen is achieved using a double-antibody system. The detection limit is 0.01 ng/mL. Within-assay CVs range between 5.3% and 6.7%; between-assay CVs range between 4.2% and 8%. No cross-reactivity with IGFBP-1, -2, and -4 has been detected.

Statistics

Data are expressed as means ± SE. To detect differences between training status and age groups, a 2-way analysis of variance (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 independently of age and it was higher in the younger than in the older subjects (Table 1).

Effect of Age

Sedentary group. Basal glucose was higher (+17 %, $P < .05$; Table 2) in MAsed than in Ysed, and SI was lower (−154 %, $P < .05$; Table 2) in MAsed than in Ysed. Basal IGF-I was lower (−31%, $P < .05$; Fig 1) in MAsed than in Ysed.

Trained group. Basal insulin was lower (−28%, $P < .05$; Table 2) in MAcy than in Ycy. No difference in the minimal model parameters was found between MAcy and Ycy. Basal IGFBP-1 was higher (+26%, $P < .05$; Fig 1) in MAcy than in Ycy.

Effect of Training

Young subjects. SI and Sg were higher (+205 % and 81%, respectively, $P < .05$; Table 2) in Ycy than in Ysed. Basal

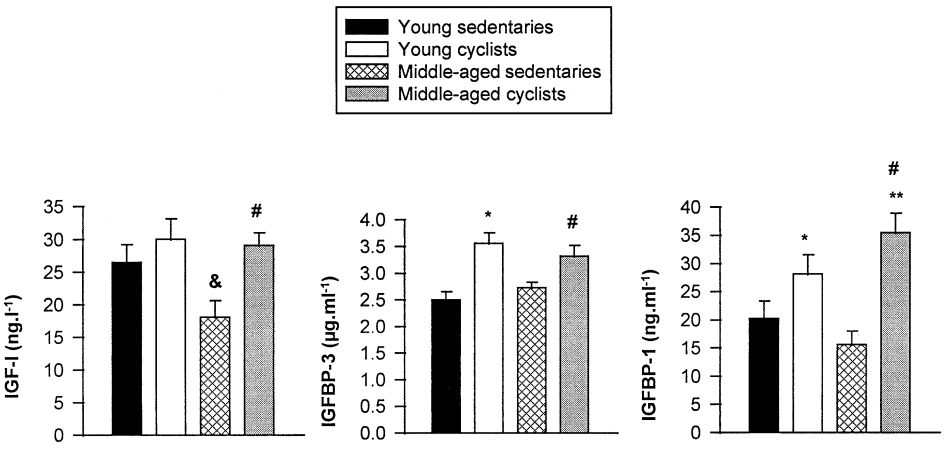

Fig 1. Comparison of IGF-I, IGFBP-1, and IGFBP-3 levels in middle-aged (sedentary [MAsed] and cyclists [MAcy]) and in young (sedentary [Ysed] and cyclists [Ycy]) men. *$P < .05$, Ysed *v* Ycy. #$P < .05$, MAsed *v* MAcy. &$P < .05$, Ysed *v* MAsed. **$P < .05$, Ycy *v* MAcy.

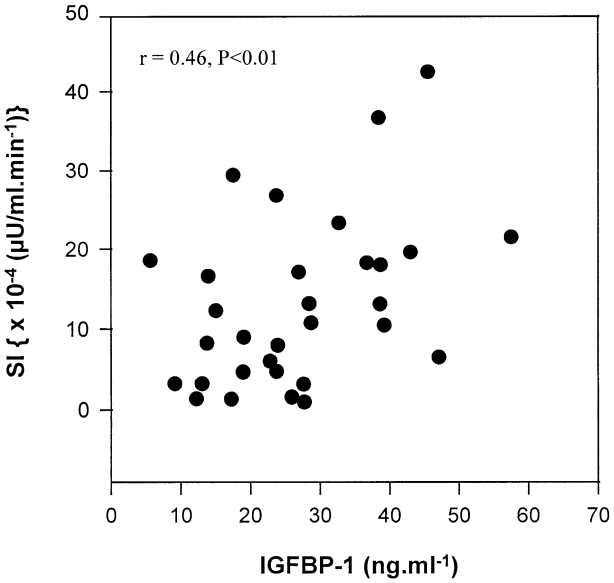

Fig 2. Relationship between SI and IGFBP-1 in all subjects together (N = 32).

IGFBP-1 and IGFBP-3 were higher (+38 % and +17 %, respectively, $P < .05$; Fig 1) in Ycy than in Ysed.

Middle-aged subjects. Basal insulin and glucose were lower (−39 % and −10%, respectively, $P < .05$; Table 2) in MAcy than in MAsed. SI and Sg were higher (+510 % and +56 %, respectively, $P < .05$; Table 2) in MAcy than in MAsed. Basal IGF-I, IGFBP-1, and IGFBP-3 were higher (+61%, +127%, and 21%, respectively, $P < .05$; Fig 1) in MAcy than in MAsed.

However, the increase in SI and IGFBP-1 was higher in older than younger subjects (+250% and +330%, respectively, $P < .05$; Table 2 and Fig 1).

Relationships Between Glucose Disposal, GH/IGF-I Axis, and Fitness Level

When we considered all subjects together (n = 32), we found a positive correlation between SI and IGFBP-1 ($r = 0.46$, $P < .01$; Fig 2) and a negative correlation between fasting insulin and IGFBP-1 ($r = -0.6$, $P < .001$). In addition, Vo_{2max} was positively correlated with IGFBP-3 ($r = 0.49$, $P < .01$).

DISCUSSION

In the present study, we delineated the effect of an interaction between aging and endurance training on IGF-I and its binding proteins IGFBP-1 and -3 in relationship with glucose disposal. The main results of this cross-sectional investigation were that endurance training increased IGFBP-1 and IGFBP-3 in both middle-aged and young men in association with an improvement in SI and Sg. However, the increase in SI and IGFBP-1 was higher in the older subjects. IGF-I was increased by endurance training in the middle-aged men but not in the young subjects, in accordance with a recent study.[17] The effect of age was quite pronounced in the sedentary population, with a decrease in IGF-I in the older subjects in association with impaired SI, whereas in the trained population, these parameters were identical in the 2 age groups. Further, when we considered all subjects together, we found a positive correlation between SI and IGFBP-1 and between Vo_{2max} and IGFBP-3, and a negative correlation between fasting insulin and IGFBP-1.

Endurance training increased IGFBP-1 and IGFBP-3 independently of age. Although this finding agrees with the reports of others who investigated in a young population,[19,31] our data contrast with those of a study[9] that found no improvement in IGFBP-1 and -3 after training in healthy aged men. A possible explanation for this difference is that their population was older (66 *v* 52 years); in fact, aging itself may affect the potential of physical training to enhance IGFBP-1 and IGFBP-3. Another explanation is a difference in training status (ie, intensity and duration), particularly when it concerns comparison with an aged population. For example, 2 weeks of endurance training at moderate intensity did not increase IGFBP-3 in an aged sedentary population,[9] whereas specific intense training in elite athletes performed over several months increased this binding protein.[17,19] In the latter case, the positive effects on the IGF system could be supported by an increased gene expression of these proteins in skeletal muscular tissue after long periods of training, as previously demonstrated for IGF-I from an animal study.[32]

Although aerobic exercise is generally acknowledged to be effective for increasing GH and IGF-I levels, little attention has been paid to the kind of training that yields the best results and, therefore, optimal exercise programs have not been defined. Greater intensity and duration during training, for example, would be sufficient to improve somatotropic activity, especially with endurance sports such as cycling. However, circulating IGF-I and its binding proteins seem to affect previously trained and untrained individuals differently during prolonged physical training, with more extensive increases in the untrained subjects.[33] Moreover, if training is intense and the expenditure of energy exceeds energy intake, this calorie restriction can cause IGF-I to decrease in the circulation.[21] In addition, Poehlman et al[9] showed that the increased fasting level of IGF-I by endurance training was more pronounced in older men than women. This last finding explains in part why the secretion activity of the GH/IGF-I axis was not enhanced after exercise and/or training in studies with exclusively female populations or with non-inclusion of women.[21,34]

Our athletes were well-nourished men who belonged to the same cycling club. Training intensity and duration were almost the same in the 2 groups (an average of 14 hours per week), and because the study design ensured that no subject fasted for more than 12 hours, we do not believe that an altered energy balance could have modulated IGF-I under the present experimental conditions. Our study was cross-sectional, however, and the role of genetics is important in determining hormonal responses. A recent study[35] that investigated elderly twins showed that approximately 60% of IGF-I levels are genetically determined. To limit this impact and control for all possible confounding factors, we carefully matched our subjects in terms of body composition, age, weight, height, gender, nutritional status, and pattern of physical activity. Our results are thus very likely a reflection of the effect of endurance training.

The increase in IGF-I through exercise training was seen only in the middle-aged subjects. This agrees with previous studies[9,17,18] and suggests that physical activity may reverse the age-related decline in this hormone.[9] In this case, the exercise-induced increase in IGF-I would stimulate protein synthesis in muscle[36] and thus correct the loss of lean body mass observed in aged subjects.[8] On the other hand, few data on IGFBP-3 are available in the current literature, especially in older subjects. IGFBP-3 is considered to be an integrated index of GH secretion[16] and, although we did not measure plasma GH, the training-related increase in both IGFBP-3 and IGF-I in our middle-aged subjects indicates increased GH and IGF-I secretion. In fact, it appears likely that endurance training amplified the secretory activity of the GH/IGF-I axis in these men. This suggests that the age-associated decline in somatotropic system activity[7] may be attenuated by endurance training. A recent study that investigated older marathon runners compared with age-matched sedentary controls[37] did not support this hypothesis, but it should be noted that there was a significant difference in BMI between the 2 groups and the low body fat percentage in their runners may have modified the GH/IGF-I response.[38] In the present study, we matched subjects of each age group for fat percentage to control for this parameter. As seen in Table 1, there was no significant difference in the middle-aged subjects and only a minimal one (2%) in the young subjects. The higher somatotropic response in our trained groups is therefore not likely to be explained by differences in fat mass. Moreover, since $V_{O_{2max}}$ is in relationship with the IGF-I response,[10] the lack of physical fitness data in their report[37] limited the interpretation of their result. We showed a relationship between IGFBP-3 and $V_{O_{2max}}$, which confirms that the level of physical activity is an important modulator of the GH/IGF-I axis[1] and that IGFBP-3 is a marker of physical fitness.[2] However, lower levels of IGF-I in aging men are more strongly related to the decline in maximal aerobic power than to an increase in adiposity.[8] In the present study, we did not find a negative relationship between IGF-I and $V_{O_{2max}}$.

Consistent with previous studies,[5,8,9] our data showed that aging decreased IGF-I and SI in sedentary individuals. On the other hand, training resulted in high values of IGF-I, which in fact were quite the same in the young and middle-aged cyclists. Given that IGF-I and SI were both completely preserved in our older trained subjects, it thus appears that middle-age in men is a beneficial period for exercise training (ie, cycling) to counteract the decrease in SI and GH/IGF-I responses associated with aging.

Because aging has been demonstrated to impair both glucose disposal[5,10,11] and this axis,[6,7] we investigated SI and Sg in relationship with the GH/IGF-I axis. In agreement with several studies,[3-5] we showed that training improved SI and Sg. Interestingly, it has been shown both this study and a previous one of other group[39] that endurance training decreased fasting insulin concentration and increased IGFBP-1. Although noted in both groups, the increase in SI and IGFBP-1 was higher in the older than in the younger men. Hopkins et al[22] proposed that IGFBP-1 directs circulating IGFs to skeletal muscle, in which IGF-I receptors are abundant and IGFs could facilitate glucose uptake into muscle. In agreement with this, IGFBP-1 is also thought to be an insulin counter-regulator, blocking "free" insulin-like activity during hypoglycemia.[23] In addition, a direct effect of IGF-I on SI and specifically on glycogen storage in skeletal muscle tissue has been evidenced.[40] The higher glucose uptake in middle-aged trained men, due to an increase in the insulin-dependent component rather than non–insulin-dependent glucose uptake,[5] might therefore be controlled by the IGFBP-1 level. If this is so, the effect of IGFBP-1 on glucose metabolism by counteracting the hypoglycemic effect of both insulin[23,27] and IGF-I[26] would be more pronounced in our well-trained middle-aged population, who showed the higher IGFBP-1 level. In addition, we found a negative relationship between fasting insulin level and IGFBP-1 and a positive relationship between SI and IGFBP-1. This last correlation has been interpreted as reflecting a homeostatic loop aimed at preventing hypoglycemia in subjects whose SI is high and in whom IGF-I may result in hypoglycemia.[2] These results indicate a role for IGFBP-1 in regulating glucose disposal and, more particularly, insulin action.

On the whole, the observation of higher concomitant increases in SI and IGFBP-1 through endurance training in middle-aged men suggests an physiological role for IGFBP-1 in the regulation of glucose metabolism in this age population. However, this requires further investigation.

In summary, our results show that endurance training improved glucose disposal (ie, SI and Sg) and increased serum levels of IGFBP-1 and -3 in men independently of age, whereas IGF-I was increased only in middle-aged men. Although the effect of age was quite pronounced in the sedentary population, with decreases in SI and IGF-I, these parameters were identical in the 2 trained populations. Thus, endurance training may attenuate the age-related decline in both the GH/IGF-I axis and insulin sensitivity. Higher IGFBP-1 levels due to training seem to be involved in glucoregulation in relationship with insulin sensitivity and may provide protection against hypoglycemia. This phenomenon seems to be more pronounced in middle-aged trained men.

ACKNOWLEDGMENT

The authors wish to thank the laboratory of Professor C. Sultan and Dr S. Lumbroso (Service d'Endocrinologie de la Reproduction, CHU Lapeyronie) for the radioimmunoassays.

REFERENCES

1. Cuneo RC, Wallace JD: Growth hormone, insulin-like growth factors and sport. Endocrinol Metab 1:3-13, 1994

2. Manetta J, Brun JF, Maïmoun L, et al: Effect of training on the growth hormone-IGF-I axis during exercise in middle-aged men: Relationship with glucose homeostasis. Am J Physiol 283:929-936, 2002

3. Manetta J, Brun JF, Mercier J, Prefaut C: The effects of exercise training intensification on glucose disposal in elite cyclists. Int J Sports Med 21:338-343, 2000

4. Tokuyama K, Higaki Y, Fujitani J, et al: Intravenous glucose tolerance test-derived glucose effectiveness in physically trained humans. Am J Physiol 265:E298-E3033, 1993

5. Manetta J, Brun JF, Callis A, et al: Non-insulin-dependent glu-

cose disposal in middle-aged and young athletes versus sedentary men. Metabolism 50:349-354, 2001

6. Kelly PJ, Eisman JA, Stuart MC, et al: Somatomedin-C, physical fitness, and bone density. J Clin Endocrinol Metab 70:718-723, 1990

7. Pavlov EP, Harman SM, Merriam GR, et al: Responses of growth hormone (GH) and somatomedin-C to GH-releasing hormone in healthy aging men. J Clin Endocrinol Metab 62:595-600, 1986

8. Poehlman ET, Copeland KC: Influence of physical activity on insulin-like growth factor-1 in healthy younger and older men. J Clin Endocrinol Metab 71:1468-1473, 1990

9. Poehlman ET, Rosen CJ, Copeland KC: Influence of endurance training on insulin-like growth factor-I in older individuals. Metabolism 43:1401-1405, 1994

10. Davidson MB: The effect of aging on carbohydrate metabolism: A review of the English literature and a practical approach to the diagnosis of diabetes mellitus in the elderly. Metabolism 28:687-705, 1979

11. Defronzo RA: Glucose intolerance in aging. Evidence for tissue insensitivity to insulin. Diabetes 28:1095-1101, 1979

12. Houmard JA, Weidner MD, Dolan PL, et al: Skeletal muscle GLUT-4 protein concentration and aging in humans. Diabetes 44:555-560, 1995

13. Van Wyck JJ: Somatomedins: Biologic actions and physiologic control mechanisms, in Li CH (ed): Growth Factors, vol 12, Hormonal Proteins and Peptides. New York, NY, Academic Press, 1984, pp 81-125

14. Rutamen EM, Pekonen F, Mäkinen T: Soluble 34K binding protein inhibits the binding of insulin-like growth factor I to its cell receptors in human secretory phase endometrium: Evidence for autocrine/paracrine regulation of growth factor action. J Clin Endocrinol Metab 66:266-272, 1998

15. Nyomba BLG, Berard L, Murphy LJ: Free insulin-like growth factor I (IGF-I) in healthy subjects: Relationship with IGF-binding proteins and insulin sensitivity. J Clin Endocrinol Metab 82:2177-2181, 1997

16. Blum WF, Albertsson-Wikland K, Rosberg S, et al: Serum levels of insulin-like growth factor I (IGF-I) and IGF binding protein 3 reflect spontaneous growth hormone secretion. J Clin Endocrinol Metab 76:1610-1616, 1993

17. Koziris LP, Hickson RC, Chatterton RT, et al: Serum levels of total and free IGF-I and IGFBP-3 are increased and maintained in long-term training. J Appl Physiol 86:1436-1442, 1999

18. Roelen CAM, Devries WR, Koppeschaar HPF, et al: Plasma insulin-like growth factor-I and high affinity growth hormone-binding protein levels increase after two weeks of strenuous physical training. Int J Sports Med 18:238-241, 1997

19. Manetta J, Brun JF, Fedou C, et al: Effects of intensive training on insulin-like growth factor (IGF)-I and IGF binding proteins-1 and -3 in competitive cyclists: Relationships with glucose disposal. J Sports Sci 21:147-154, 2003

20. Borst SE, De Hoyos DV, Garzarelle L, et al: Effect of resistance training on insuli-like growth factor-I and IGF binding protein. Med Sci Sports Exerc 33:643-653, 2001

21. Jahreis PJ, Kauf E, Fröhner G, et al: Influence of intensive exercise on insulin-like growth factor 1, thyroid and steroid hormones in females gymnasts. Growth Regul 1:95-99, 1991

22. Hopkins NJ, Jakeman PM, Hughes SC, et al: Changes in circulating insulin-like growth factor-binding protein-1 (IGFBP-1) during prolonged exercise: effect of carbohydrate feeding. J Clin Endocrinol Metab 79:1887-1890, 1994

23. Baxter RC: Insulin-like growth factor binding proteins in the human circulation: A review. Horm Res 42:140-144, 1994

24. Corpas E, Harman SM, Blackman MR: Human growth hormone and human aging. Endocrinol Rev 14:20-39, 1993

25. Lewitt MS, Denyer GS, Cooney GJ, Baxter RC: Insulin-like growth factor-binding protein-1 modulates blood glucose levels. Endocrinology 129:2254-2256, 1991

26. Birsmar K., Hall K: Clinical applications of IGFBP-1 and its regulation. Growth Regul 3:98-100, 1993

27. Rakumar K, Dheen ST, Murphy LJ: Hyperglycemia and impaired glucose tolerance in IGF binding protein-1 transgenic mice. Am J Physiol 270:E565-E571, 1996

28. Lukaski HC, Johnson PE, Bolonchuch WW, Lykken V: Assessment of fat-free mass using bioelectrical impedance measurements of the human body. Am J Clin Nutr 41:810-817, 1995

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

30. Brun JF, Guintrand-Hugret R, Boegner R, et al: Influence of short submaximal exercise on parameters of glucose assimilation analyzed with the minimal model. Metabolism 44:833-840, 1995

31. Nguyen UN, Mougin F, Simon-Rigaud ML, et al: Influence of exercise duration on insulin-like growth factor and its binding proteins in athletes. Eur J Appl Physiol 78:533-537, 1998

32. Zanconato S, Moromisato DY, Moromisato MY, et al: Effect of training and growth hormone suppression on insulin-like growth factor I mRNA in young rats. J Appl Physiol 76:2204-2209, 1994

33. Rosendal L, Langberg H, Flyvbjerg A, et al: Physical capacity influences the response of insulin-like growth factor and its binding proteins to training. J Appl Physiol 93:1669-1675, 2002

34. Vitiello MV, Wilkinson CW, Merriam GR, et al: Successful 6-month endurance training does not alter insulin-like growth factor-I in heathly older men and women. J Gerontol 52:149-154, 1997

35. Hall K, Hilding A, Thoren M: Determinants of circulating insulin-like growth factor-I. J Endocrinol Invest 22:48-57, 1999

36. Adams GR, Haddad F: The relationships among IGF-I, DNA content and protein accumulation during muscle hypertrophy. J Appl Physiol 81:2509-2516, 1996

37. Deuschle M, Blum WF, Frystyk J, et al: Endurance training and its effect upon the activity of GH-IGFs system in elderly. Int J Sports Med 19:250-254, 1998

38. Copeland KC, Coletti RB, Devlin JT, et al: The relationship between insulin-like growth factor-1, adiposity and aging. Metabolism 39:584-587, 1990

39. Hellenius ML, Brisman KE, Berglund BH, et al: Effects on glucose tolerance, insulin secretion, insulin-like growth factor I and its binding protein, IGFBP-1, in a randomized controlled diet and exercise study in healthy, middle-aged men. J Intern Med 238:121-130, 1995

40. Hussain MA, Smith O, Christiansen JS, et al: IGF-I alters skeletal muscle substrate metabolism and blunts recovery from insulin-induced hypoglycemia. Am J Physiol 270:545-551, 1996