Exercise Increases Serum Testosterone and Sex Hormone–Binding Globulin Levels in Older Men

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We examined the effects of moderate physical activity on serum luteinizing hormone (LH), sex hormone–binding globulin (SHBG), and testosterone levels in seven sedentary but otherwise healthy men aged 66 to 76 years (mean ± SD, 70 ± 4). Blood samples were obtained at 10-minute intervals for 4 hours before, during, and 4 hours after 60 minutes of cycle ergometry. Blood samples were also obtained every 10 minutes for 9 hours during a separate day to control for normal diurnal variation in serum testosterone levels. Serum testosterone increased 39%, SHBG 19%, total serum protein 13%, and the free testosterone index 23% during exercise ($P < .01$ for all). Testosterone and SHBG levels during the 4-hour sampling period after exercise were similar to values obtained before exercise and on the morning and afternoon of the control day. LH concentrations were unaltered during or after exercise. The change in SHBG levels during exercise correlated positively with the change in testosterone concentrations ($r = .74$, $P = .09$). We conclude that short-term exercise produces a transient elevation in serum testosterone levels in elderly men, which is partly due to an increase in serum SHBG concentrations. The concomitant increase in total protein and the rapid return of total protein and SHBG to baseline values after exercise indicate that hemoconcentration partly contributes to the exercise-associated increase in circulating testosterone levels.

PHYSICAL EXERCISE is known to influence circulating luteinizing hormone (LH) and testosterone levels in men. Prolonged strenuous physical exertion reduces serum LH[1] and testosterone levels,[2-4] apparently by suppressing gonadotropin-releasing hormone secretion.[3] Short-term high-intensity exercise, on the other hand, increases circulating testosterone levels and produces variable effects on LH concentrations.[5] The mechanisms responsible for the increase in serum testosterone levels during short-term exercise are controversial, and may include decreased testosterone clearance,[6] hemoconcentration,[7] and/or increased testosterone production due to stimulation by factors other than LH.[8]

Circulating testosterone concentrations decline as healthy men age.[9-11] Histologic and biochemical studies indicate that testicular dysfunction is a major determinant of the age-related reduction in serum testosterone levels in men.[12-14] Whereas serum testosterone levels decline as men age, LH concentrations are either unchanged[15] or increased slightly,[12,14,16] suggesting that gonadotropin secretion is also modified by the aging process. One hypothesis to explain these findings is that aging increases the sensitivity of gonadotropin secretion to androgen negative-feedback inhibition.[17] We postulated that short-term physical activity would also suppress serum LH and testosterone concentrations in older men. The present study examined this hypothesis by measuring serum LH and testosterone levels before, during, and after an isolated exercise session or during a control period in seven healthy elderly men.

SUBJECTS AND METHODS

Subjects

Seven men aged 66 to 76 years (mean ± SD, 70 ± 4) were recruited by local newspaper advertisement. Their mean body weight and mean body mass index were 80.8 ± 9.9 kg and 26.8 ± 3.6 kg/m^2, respectively. All subjects were white, and none smoked cigarettes, consumed more than two alcoholic beverages daily, or routinely used medications known to affect pituitary-testicular function. Subjects were considered sedentary because they exercised less than once weekly. All men were healthy as determined by medical history, physical examination, resting electrocardiogram, and a graded cycle ergometry test to exhaustion with blood pressure and electrocardiogram monitoring. Subjects provided written informed consent and were paid for their participation. This study was approved by the University of Pittsburgh Institutional Review Board for Biomedical Research.

Study Protocol

Subjects were admitted to the General Clinical Research Center at approximately 7:30 AM on 2 separate days at least 1 week apart. An intravenous catheter was inserted into a forearm or antecubital vein after 30 minutes of seated rest, and the vein was kept patent with normal saline. Blood sampling began 30 minutes after venipuncture. On day 1, blood samples were obtained every 10 minutes for 9 hours. This visit served as an experimental control for normal diurnal variation in testosterone concentrations.[18] During the second day, blood samples were drawn every 10 minutes for 4 hours. Subjects then completed four consecutive bouts of exercise on a model 818E cycle ergometer (Monark, Varberg, Sweden). Each exercise period lasted 15 minutes and was designed to approximate 50%, 60%, 70% and 80% of each subject's predetermined peak heart rate reserve. Subjects rested 5 minutes between exercise bouts. Blood samples were obtained immediately before completion of each exercise period. After the final exercise bout, blood samples were obtained every 10 minutes for an additional 4 hours.

The control and exercise days occurred in random sequence. Subjects were seated during blood sampling and were not permitted to nap or sleep during the protocol. Subjects were instructed to refrain from any strenuous activity for at least 48 hours before both study days, to consume their habitual breakfast before arriving at the Clinical Research Center, and to avoid consuming any caffeinated beverages the morning of each visit. Water was provided ad

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libitum, a light snack was given between 9:30 and 10:30 AM, and lunch was provided between 1:30 and 2:30 PM during both study days.

Assays

Total testosterone concentrations were measured in hourly serum pools created by combining the 10-minute samples. Testosterone was also assayed in samples obtained during exercise and at similar measurement points during the control day. Total testosterone was determined with a dextran-charcoal radioimmunoassay following extraction of serum with diethyl ether.[13] The antiserum cross-reacts 2.24% with androstenedione and less than 0.01% with cortisol. Sex hormone–binding globulin (SHBG) and total protein levels were determined in three 10-minute samples obtained 1 hour before exercise, in samples obtained at 50%, 60%, and 70% peak effort, and in hourly samples obtained after exercise. SHBG and total protein were also assayed at similar measurement times during the control day. SHBG level was measured with a two-site immunoradiometric assay kit (Diagnostic Systems Laboratory, Webster, TX). The total plasma protein level was measured spectrophotometrically using the Bio-Rad protein assay kit (Richmond, CA). The within-assay coefficient of variation (CV) for SHBG was less than 5%. The free testosterone index, an estimate of biologically available testosterone, was calculated as total testosterone divided by SHBG. LH concentrations were determined in all samples with a Nichols Allegro (San Juan Capistrano, CA) two-site immunoradiometric assay. The intraassay CV for LH at 2.7 mIU/mL was 4.7%, and the interassay CV at 18.6 mIU/mL was 3.4%. Blood samples were allowed to clot at room temperature, and serum was separated and stored at −30°C until analysis. All samples for an individual subject were analyzed in the same immunoassay to eliminate interassay variability.

Statistical Analysis

The data were analyzed with a two-way ANOVA with repeated measures on both factors. When interaction effects were statistically significant, the effect of time for each condition and differences between conditions at each measurement point were statistically tested. A modified Bonferroni procedure was used to adjust for multiple comparisons.[19] Hourly LH values were calculated as the mean of each subject's six 10-minute samples and used in statistical analysis. The data are presented as the mean ± SD unless indicated otherwise.

RESULTS

Mean basal testosterone levels, determined in the first control sample, were 10.7 ± 3.7 nmol/L (range, 7.6 to 17.7). By comparison, morning testosterone levels in 15 young men from our laboratory were 19.6 ± 7.1 nmol/L. Five of seven men in the present study had serum testosterone values less than the range (11.4 to 38.4 nmol/L) in the young men.

Figure 1 indicates that serum testosterone levels increased with increasing exercise intensity, reached a peak increment of 39% at 70% peak effort ($P < .01$), and declined rapidly after exercise. Baseline testosterone values were achieved by 60 minutes after exercise, and remained stable throughout the remainder of the protocol. Testosterone levels during the 4-hour sampling period after exercise were similar to values obtained before exercise and on the afternoon of the control day. Furthermore, visual inspection of the individual response patterns showed that exercise did not reduce testosterone concentrations in any subject.

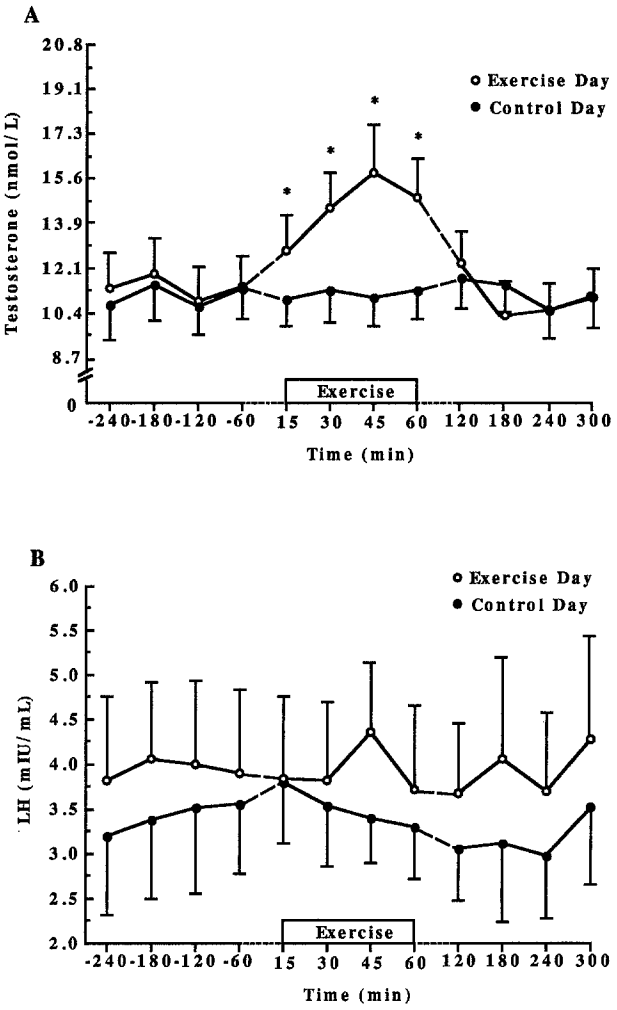

Fig 1. Serum testosterone (A) and LH (B) concentrations before, during, and after 60 minutes of exercise (○) and at similar measurement points during a control day (●). Blood sampling began at approximately 8:30 AM on both study days. *$P < .01$ for the difference from control and preexercise values.

Morning basal LH levels, determined by averaging each subject's first six control samples, were 3.2 ± 2.2 mIU/mL (range, 2.30 to 7.99). The range of morning values in 15 young men in our laboratory was 1.3 to 9.0 mIU/mL. Figure 1 shows that mean LH values increased slightly but not significantly during exercise. Mean LH levels during the 4-hour sampling period after exericse were similar to values obtained before exercise and on the afternoon of the control day.

Figure 2 indicates that SHBG levels also increased with exercise, achieved a peak increment of 19% at 50% peak effort ($P < .01$), and declined rapidly after exercise. SHBG concentrations did not change during the control day. Total protein levels also increased by 13% at 50% effort ($P < .01$; Fig 2) and returned to baseline levels shortly after exercise. Total protein levels were unchanged during the control period. The change in total testosterone during exercise

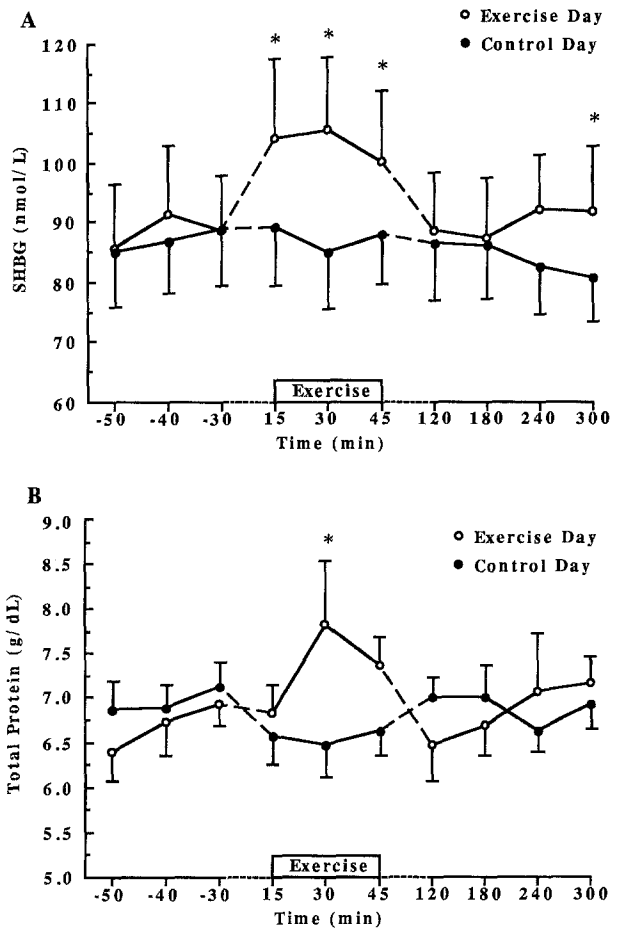

Fig 2. SHBG (A) and total protein (B) concentrations before, during, and after exercise (○) and at similar measurement points during a control day (●). Blood sampling began at approximately 8:30 AM on both study days. *$P < .01$ for the difference from control and preexercise values.

was highly positively correlated with the change in SHBG ($r = .74, P = .09$). The free testosterone index (testosterone/SHBG) increased by 23% at 70% effort from 0.138 ± 0.039 to 0.170 ± 0.036 ($P < .01$), but was unchanged on the control day. The free testosterone index after exercise did not differ from values obtained before exercise and on the afternoon of the control day.

DISCUSSION

The present study examined the effects of moderate physical activity on serum LH and testosterone levels in older men. Blood samples were obtained before, during, and after an isolated exercise session, and at similar times on a separate day to control for normal diurnal variation in circulating testosterone levels.[18] Because the gonadotropin-suppressive action of testosterone appears to increase as men age,[17] we postulated that moderate exercise might also suppress LH levels in older men. The present results did not substantiate this hypothesis. Instead, serum testosterone levels increased with increasing exercise intensity and returned to baseline values soon after exercise, whereas circulating LH was unchanged during and for 4 hours after exercise.

The influence of aging on the endocrine response to exercise is not well defined. In one study, the absolute decrease in testosterone levels in older athletes completing a triathlon lasting 11.2 to 16.3 hours was similar to that observed in young athletes who required 9.3 to 11.7 hours to complete the event.[20] In that study, absolute increases in adrenocorticotropin, cortisol, thyrotropin, and thyroxine were similar in young and older athletes, but increases in growth hormone and prolactin were smaller in the older men. A second study compared the acute response of testosterone and growth hormone to resistance exercise in young and elderly subjects.[21] Growth hormone levels increased to a lesser extent in elderly men than in young men, whereas testosterone concentrations were unchanged in both study groups.

The mechanism responsible for the increase in serum testosterone levels during short-term exercise is controversial, and may be due to increased testosterone production, decreased testosterone clearance, and/or hemoconcentration.[5] Our results for LH indicate that the increase in testosterone levels is not due to increased LH production. This conclusion is supported by the results of previous studies in young men that demonstrated that LH levels during exercise either increased simultaneously with testosterone concentrations[8,22] or were unchanged.[23,24] A simultaneous increase is not consistent with the usual lag in LH-stimulated testosterone production. Although plasma growth hormone,[20] vasopressin,[25] adrenocorticotropin,[26] cortisol,[26] and prolactin[27] levels increase with exercise, these hormones are not known to substantially increase testosterone production. In fact, a recent study found a slight augmentation of the exercise-induced increase in plasma testosterone levels when growth hormone secretion was suppressed by octreotide.[28] An increase in catecholamine levels during exercise is also well documented.[29] Some investigators have suggested that catecholamines stimulate testosterone production during exertion,[30] since β-receptor blockade with propranolol inhibits the testosterone response to exercise[30] and since isoproterenol added to Leydig cell cultures[31] or infused into the spermatic artery in rats[32] increases testosterone synthesis. We did not examine this possibility in the present study.

SHBG is a glycoprotein that binds testosterone with high affinity.[33] Approximately half the circulating testosterone in men is bound to SHBG,[34] and SHBG retards hepatic clearance of testosterone.[35] Previous studies have reported no change in SHBG levels following prolonged intensive exercise,[20,36] but we are unaware of any studies that examined SHBG concentrations during exercise. SHBG concentrations increased 19% and total testosterone levels increased 39% during exercise in the present study. The change in SHBG levels during exercise correlated positively with the change in serum testosterone concentrations, and the temporal relationship between changes in SHBG and testosterone was striking. Therefore, increased SHBG appears to explain some of the increase in testosterone levels during exercise.

Experiments in monkeys suggest that SHBG is cleared slowly from the vascular compartment.[37] Consequently, increased SHBG production is an unlikely explanation for the abrupt increase in SHBG levels during exercise. Total protein concentrations increased by 13% during exercise, but did not change during the control period. This observation is consistent with the 10% to 15% decrease in plasma volume reported by others during cycle ergometry exercise.[38] The reduction in plasma volume during exercise is caused by a redistribution of body fluids from the intravascular to the extravascular space, and this fluid shift results in hemoconcentration.[38] The magnitude of the total protein increase in the present study approximates the 19% increase in SHBG, suggesting that hemoconcentration was a major determinant of the increase in SHBG with exercise. Although the route of metabolism of SHBG is not well defined, decreases in hepatic blood flow may also have contributed to the increase in SHBG during exercise. The increase in SHBG, in turn, may have retarded hepatic clearance of testosterone during exercise and thereby increased circulating testosterone levels.

Calculation of the free testosterone index indicates that the increase in SHBG does not completely explain the increase in circulating testosterone levels. Since the liver is the major site of testosterone clearance[35] and since hepatic blood flow decreases during exercise,[39] reduced testosterone clearance most likely contributed to our results as well. One previous study examined tritium-labeled testosterone metabolism at rest and during 60 minutes of cycle ergometry in four young men. The 29% increase in testosterone levels during exercise in that study was associated with a 28% decrease in testosterone clearance. Testosterone production was unaltered, suggesting that decreased hepatic clearance was largely responsible for the increase in testosterone during exercise.

What is the significance of the acute increase in free testosterone and SHBG levels with exercise? Androgen receptors are present in skeletal[40] and cardiac[41] muscle and regulate the expression of the muscle proteins actin[42] and myosin heavy chain.[43] Long-term exertion may enhance the responsiveness of muscle to androgenic hormones by increasing androgen receptor concentration.[44-46] Androgens may also acutely affect muscle characteristics without altering cellular protein production, since testosterone injection into the bulbocavernosus muscle of orchidectomized rats produces electromyographic bursts within minutes.[47] Furthermore, since specific membrane binding sites for SHBG have been described in several androgen-responsive tissues,[48,49] it is possible that SHBG directly mediates the rapid nongenomic effects of androgens on muscle cells. Consequently, rapid elevations in free testosterone and SHBG during exercise could acutely affect muscle performance and ultimately contribute to the adaptive response to long-term physical activity.

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