Articles

Prospective Evaluation of Risk Factors for Exercise-Induced Hypogonadism in Male Runners

SHAYNE T. SKARDA, MD *and* MARK R. BURGE, MD, *Albuquerque, New Mexico*

Exercise-induced hypogonadotropic hypogonadism is well recognized among female endurance athletes but is less commonly observed in male endurance athletes. We have reported a well-characterized case of severe acquired hypogonadotropic hypogonadism in a male distance runner with osteopenia, stress fracture, and sexual dysfunction. Using this case as an index, we hypothesized that the presence of 1 or more specific risk factors would prospectively identify male endurance athletes with exercise-induced hypogonadotropic hypogonadism. These include a history of stress fracture, sexual dysfunction, or the initiation of endurance exercise before age 18 years. We studied 28 male endurance runners younger than 50 years who ran more than 40 miles per week. Of these runners, 15 had 1 or more of the above risk factors (group 1), and the remaining 13 had none of the putative risk factors (group 2). A group of 10 sedentary control subjects was also studied (group 3). There was no difference between groups 1 and 2 in weekly training mileage. Group 1 was younger than group 2 (32±10 years versus 39±6 years, $P<.05$) and had a lower body mass index (22.4±1.9 kg per m^2 versus 23.9±2.2 kg per m^2, $P<.05$). By bioelectric impedance, preliminary data showed that group 1 had a reduced body fat content (group 1, 14.5%±2.8%; group 2, 16.9%±2.0%; and group 3, 17.5%±4.1%; $P<.05$). Fasting morning concentrations of free testosterone (group 1, 45.3 ± 26.4 pmol/l; group 2, 88.8 ± 24.3 pmol/l; and group 3, 69.1 ±21.5 pmol/l) and luteinizing hormone (group 1, 1.7±0.7 IU per liter; group 2, 2.0±1.1 IU per liter; and group 3, 1.9±0.6 IU per liter) did not differ among the groups ($P>.05$). One subject with primary hypogonadism was identified in group 1. The presence of the aforementioned risk factors does not predict the occurrence of exercise-induced hypogonadotropic hypogonadism among male endurance runners in this pilot study. A larger sample size or more discriminating risk factors (or both) may be necessary to identify this uncommon but potentially debilitating condition.

(Skarda ST, Burge MR. Prospective evaluation of risk factors for exercise-induced hypogonadism in male runners. West J Med 1998; 169:9–12)

Exercise-induced amenorrhea is a well-characterized clinical disorder among female athletes.[1,2] This condition is typified by acquired hypogonadotropic hypogonadism and has been associated with osteopenia and fractures.[1–5] Studies of sex hormone regulation in male athletes are less numerous, although evidence suggests that male endurance athletes have decreased levels of testosterone compared with sedentary controls.[6–11] Although clinically important hypogonadism has been reported rarely among male endurance athletes, most reported cases show normal or slightly decreased concentrations of serum luteinizing hormone (LH) in conjunction with low-normal concentrations of testosterone.[6,11,12] There have been few reports of clinically important hypogonadism in men due to exercise.[6,13–15] In addition, consideration must be given to the possibility of anabolic steroid abuse in all male athletes presenting with hypogonadotropic hypogonadism.[16]

Our group recently published a well-documented case of exercise-associated hypogonadotropic hypogonadism in a 29-year-old male marathon runner who presented with stress fractures of the hip and pelvis, severe osteopenia, and hypogonadotropic hypogonadism.[13] Treatment with clomiphene citrate returned sex hormone levels to the normal range, and the hypogonadal symptoms resolved. Using this observation as an index case for the current study, we hypothesized that exercise-induced hypogonadism in male endurance athletes

From the Division of Endocrinology and Metabolism, Department of Medicine, University of New Mexico School of Medicine, Albuquerque.

Reprint requests to Mark R. Burge, MD, Division of Endocrinology and Metabolism, Department of Medicine, University of New Mexico School of Medicine, Rm 5ACC, Albuquerque, NM 87131.

This research was supported in part by National Institutes of Health National Center for Research Resources grant No. 5M01-RR00997 from the University of New Mexico General Clinical Research Center.

ABBREVIATIONS USED IN TEXT
FT = free testosterone
LH = luteinizing hormone

may be identified by the presence of one or more specific risk factors. Specifically, we proposed that male runners with exercise-induced hypogonadism could be prospectively identified by the presence of the following characteristics seen in the index case:

- Intense exercise initiated before the attainment of sexual maturity,
- A history of stress fracture, and either or both
- Sexual dysfunction and
- Decreased libido.

Subjects and Methods

Subjects

Healthy male subjects were recruited by distributing a questionnaire at the 1995 Duke City Marathon, Albuquerque, New Mexico and to a local runners' club and through advertisements in the *University Daily Lobo*, the University of New Mexico, Albuquerque, campus newspaper. Inclusion criteria for runners stipulated that participants run at least 40 miles per week and be younger than 50 years. Of 85 questionnaires returned, 28 runners and 10 sedentary men met inclusion criteria and agreed to participate in the study. The study was approved by the University of New Mexico Human Research Review Committee, and informed consent was obtained from all study participants.

Questionnaire

Subjects completed a one-page questionnaire that quantitated the form, volume, and intensity of exercise. The presence or absence of the following "risk factors" was also ascertained: the initiation of endurance exercise before age 18 years (a surrogate for the attainment of sexual maturity); a previous history of stress fracture; and difficulty attaining erections, diminished sex drive since the initiation of exercise, or both. Fifteen runners in the study reported the presence of at least one of the putative risk factors and were included in group 1. Thirteen runners denied the presence of risk factors and were assigned to group 2. All study subjects denied past or present anabolic steroid abuse.

Ten sedentary control subjects were also studied. Sedentary levels of activity were determined on the basis of self-report using the Physical Activity Assessment Questionnaire.[17] Subjects with activity ratings of B or C (encompassing no regular physical activity or recreational physical activity only) were designated to be sedentary, and these subjects made up group 3.

Study Protocol

All participants reported to the University of New Mexico General Clinical Research Center in the morning following an overnight fast and abstinence from exercise for at least 24 hours for the determination of serum levels of LH, free testosterone (FT), and body composition.

Hormone Analysis

Luteinizing hormone levels were determined using the Coat-A-Count immunoradiometric assay kit (Diagnostic Products Corp, Los Angeles, California), which has a reference range of 1.4 to 11.1 IU per liter, an intra-assay coefficient of variation of 1.6%, and an interassay coefficient of variation of 7.1%. The sensitivity of the LH assay was approximately 0.15 IU per liter. Free testosterone levels were measured using the Coat-A-Count radioimmunoassay kit (Diagnostic Products Corp), which has a reference range of 62.5 pmol/l to 142.3pmol/l, an intra-assay coefficient of variation of 4.3%, an interassay coefficient of variation of 5.5%, and a sensitivity of 0.45 pmol/l.

Body Composition Analysis

Height and weight of subjects were obtained on the day a blood specimen was drawn. Body composition was determined with bioelectric impedance analysis (RJL Systems, Clinton Township, Michigan).[18]

Sample Size

An estimate of the power necessary to demonstrate a difference between groups 1 and 2 in the prevalence of exercise-induced hypogonadism was obtained using the equation for computing sample sizes for comparing two proportions.[19] Assuming a prevalence of exercise-induced hypogonadism of 30% in group 1 and 2% in group 2, 13 subjects were required in each group to demonstrate a significant difference between the groups with a 90% power and an α of .05.

Statistical Analysis

The two-tailed unpaired Student's t test was used to compare continuous variables, such as hormone concentrations. Proportional data, such as the presence or absence of hypogonadotropic hypogonadism, were compared using Fisher's exact test. Data are reported as the mean ± standard deviation, and figures depict the mean ± standard error.

Results

Subject Characteristics

Demographic and physical characteristics of the study subjects are summarized in Table 1. The subjects in group 1 were younger than those in group 2 and had a reduced body mass index compared with those in group 2. In addition, subjects in group 1 had a lower body fat content than those in groups 2 and 3.

Hormone Concentrations

One subject in group 1 exhibited sex hormone concentrations consistent with primary gonadal failure (LH,

TABLE 1.—*Demographic and Baseline Characteristics of Study Participants**

Participants	Age, yr	Weekly Mileage	Body Mass Index, kg/m²	Body Fat, %
Group 1 (n=14)	...32 ± 10†	66.9 ± 29.5	22.4 ± 1.9†	14.4 ± 3.1†‡
Group 2 (n=13)	....39 ± 6	52.7 ± 21.7	23.9 ± 2.2	16.8 ± 2.0
Group 3 (n=10)	....39 ± 10	NA	23.2 ± 4.8	17.5 ± 4.1

NA = not available

*Data are reported as the mean ± standard deviation.
†P<.05 versus group 2.
‡P<.05 versus group 3.

15.9 IU per liter; and FT, 62.1 pmol/l [17.9 pg per ml]) and was excluded from analysis. As shown in Figure 1-A, LH values did not differ significantly among groups 1, 2, and 3. Similarly, there was no statistically significant difference in FT concentrations among the three groups (Figure 1-B).

To further assess the utility of our selected risk factors for predicting hypogonadotropic hypogonadism, we analyzed sex hormone concentrations of the affected runners (group 1) according to the risk factors they possessed: sexual dysfunction only, pubertal initiation of endurance exercise only, or having more than one risk factor. As shown in Figure 2-A and -B, there were no statistically significant differences in LH and FT concentrations among these three risk factor categories.

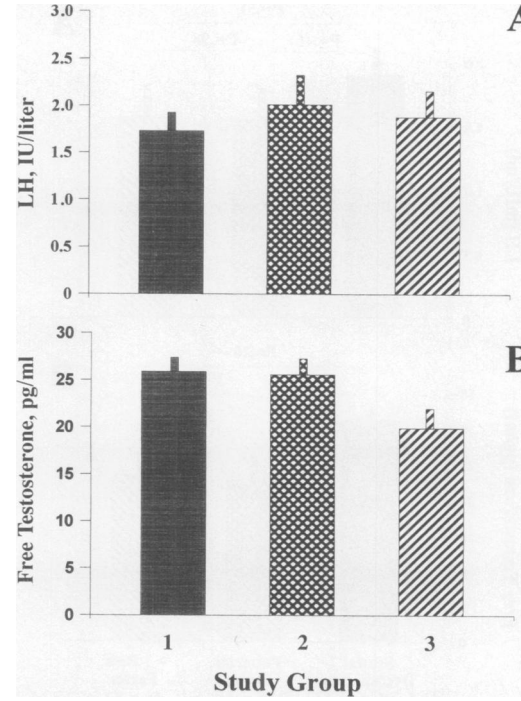

Figure 1.—Serum luteinizing hormone (LH) (A) and free testosterone (FT) (B) concentrations are shown for male endurance athletes with (group 1: LH, 2.8±4.0 IU/liter, and FT, 26.2±7.7 pg/ml) and without (group 2: LH, 2.0±1.1 IU/liter, and FT, 25.6±7.0 pg/ml) prospectively identified risk factors for exercise-induced hypogonadotropic hypogonadism, as well as sedentary control subjects (group 3: LH, 1.9±0.6 IU/liter, and FT, 19.9±16.2 pg/ml).

Discussion

It has been established that athletic amenorrhea is attributable to hypothalamic-pituitary dysfunction.[1,3,4,20] Given the central cause of this disorder, it is rational to expect that a similar disorder occurs in overzealous male athletes. The clinical manifestation of exercise-induced hypogonadism, however, is more readily apparent in women because of the intricate hormonal milieu necessary for normal cyclic menstruation. Men, on the other hand, may tolerate minor disturbances in sex hormone regulation without clinically apparent effects. Accordingly, numerous studies demonstrate that endurance exercise causes slight reductions in testosterone concentrations in men, but reports of clinically important hypogonadism attributable to exercise are uncommon.[6–10,21] Given, however, that this disorder may be associated with sexual dysfunction,[14,16,21] semen abnormalities,[6,8,14] muscle injury,[14] or osteopenia[16,22,23] (or any combination of all of these), identifying and preventing debilitating exercise-induced hypogonadism is desirable. Moreover, the prospective identification of a cohort of affected male athletes would allow the performance of controlled studies to clarify the natural history of the condition and to evaluate possible treatment options. Because exercise-induced hypogonadotropic hypogonadism appears to be rare in men, it is impractical to screen all male endurance athletes for this condition. Therefore, investigative attempts to identify sensitive indicators of the disease are appropriate.

Previous studies of sex hormone regulation in male athletes have not attempted to identify specific patient attributes that might predict the presence of acquired hypogonadotropic hypogonadism. This study evaluated the utility of specific, prospectively determined risk factors in identifying a subset of male endurance athletes who may be at high risk for the development of exercise-induced hypogonadism. No difference in sex hormone concentrations was observed among runners possessing at least one of the proposed risk factors and those who denied having them. This may reflect that the presence of risk factors alone is insufficient to identify cases of hypogonadotropic hypogonadism or that our assumptions of disease prevalence are incorrect, and a larger study population is necessary to demonstrate a difference.

A limitation of this study is the single-point measurement of hormone levels. Other studies have detected abnormal LH pulse frequency and amplitude in both men and women with normal mean LH, FT, and estradiol levels.[20,24] In addition, our exclusion of the person with evidence of primary gonadal failure by an elevated LH level may be inappropriate. Although exercise-

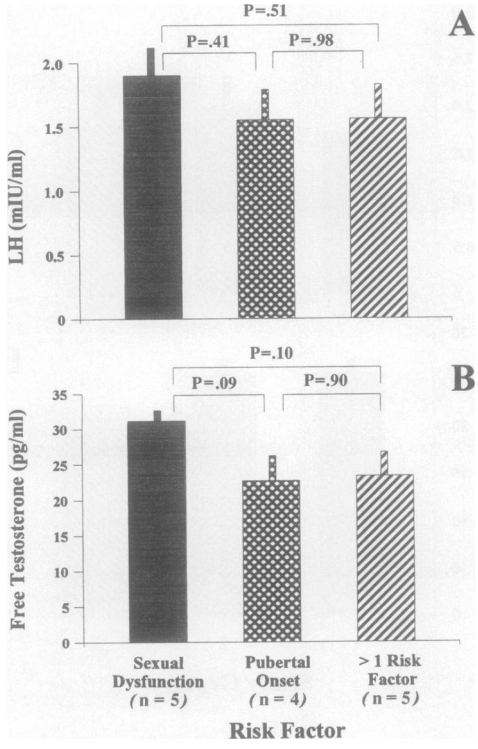

Figure 2.—Serum luteinizing hormone (LH) (A) and free testosterone (FT) (B) concentrations are shown according to risk factor among male endurance athletes having ≥1 putative risk factors for exercise-induced hypogonadotropic hypogonadism (group 1). The shaded bars denote sexual dysfunction (LH, 1.9±0.7 IU/liter, and FT, 31.1±2.6 pg/ml), the cross-hatched bars denote the start of endurance exercise before age 18 years (LH, 1.8±0.2 IU/liter, and FT, 25.7±9.0 pg/ml), and striped bars denote the presence of >1 risk factor, as described in the text (LH, 1.6±0.9 IU/liter, and FT, 23.3±8.4 pg/ml).

induced hypogonadotropic hypogonadism appears to be a centrally mediated condition, there are rare reports of elevated LH levels associated with decreased testosterone levels in male athletes.[24,25] The mechanism of this occurrence remains unclear, however.

The differences in LH and FT levels in the affected group of runners reporting only sexual dysfunction compared with other risk factors approach statistical significance (Figure 2). This implies that sexual dysfunction may be a less sensitive predictor of low testosterone levels in male runners than the other risk factors. That a true difference was not shown may represent a type II error that could possibly be remedied with a larger sample size.

Further study of the pathogenesis and prevalence of exercise-induced hypogonadotropic hypogonadism among male endurance athletes is clearly required. Research designed to sensitively identify affected athletes is a logical approach that may eventually advance our understanding of the condition. Considerations for future study design include a larger study population, an increased training mileage requirement, and the possible exclusion of sexual dysfunction alone as a risk factor. Finally, the utility of semen quality should be investigated as an additional factor for the possible identification of men debilitated by endurance exercise.

REFERENCES

1. Keizer H, Rogol A. Physical exercise and menstrual cycle alterations: what are the mechanisms? Sports Med 1990; 10:218–235

2. Yen S. Female hypogonadotropic hypogonadism. Endocrinol Metab Clin North Am 1993; 22:29–58

3. Fisher E, Nelson M, Frontera W, Turksoy R, Evans W. Bone mineral content and levels of gonadotropins and estrogens in amenorrheic running women. J Clin Endocrinol Metab 1986; 62:1232–1236

4. Baker E, Mathur R, Kirk R, Williamson H. Female runners and secondary amenorrhea: correlation with age, parity, mileage, and plasma hormonal and sex-hormone-binding globulin concentrations. Fertil Steril 1981; 36:183–187

5. Lindberg J, Fears W, Hunt M, Powell M, Boll D, Wade C. Exercise-induced amenorrhea and bone mineral density. Ann Intern Med 1984; 101:647–648

6. Ayers JW, Komesu Y, Romani T, Ansbacher R. Anthropomorphic, hormonal, and psychologic correlates of semen quality in endurance-trained male athletes. Fertil Steril 1985; 43:917–921

7. Wheeler G, Wall S, Belcastro A, Cumming D. Reduced serum testosterone and prolactin levels in male distance runners. JAMA 1984; 252:514–516

8. Arce JC, De Souza MJ, Pescatello LS, Luciano AA. Subclinical alterations in hormone and semen profile in athletes. Fertil Steril 1993; 59:398–404

9. Wheeler G, Singh W, Pierce D, Epling W, Cumming D. Endurance training decreases serum testosterone levels in men without change in luteinizing hormone pulsatile release. J Clin Endocrinol Metab 1991; 72:422–425

10. Smith R, Rutherford O. Spine and total body bone mineral density and serum testosterone in male athletes. Eur J Appl Physiol 1993; 67:330–334

11. Duclos M, Corcuff J, Rashedi M, Fougere V, Manier G. Does functional alteration of the gonadotropic axis occur in endurance trained athletes during and after exercise? Eur J Appl Physiol 1996; 73:427–433

12. Cumming D, Wheeler G, McColl E. The effects of exercise on reproductive function in men. Sports Med 1989; 7:1–17

13. Burge MR, Lanzi RA, Skarda ST, Eaton RP. Idiopathic hypogonadotropic hypogonadism in a male runner is reversed by clomiphene citrate. Fertil Steril 1997; 67:783–785

14. Naessens G, DeSlypere J, Dijs H, Driessens M. Hypogonadism as a cause of recurrent muscle injury in a high level soccer player. Int J Sports Med 1995; 16:413–417

15. Strauss R, Lanese R, Malarkey W. Decreased testosterone and libido with severe weight loss. Phys Sports Med 1993; 21:64–71

16. Bickelman C, Ferries L, Eaton RP. Impotence related to anabolic steroid use in a body builder—Response to clomiphene citrate. West J Med 1995; 162:158–160

17. Blair SN. Measurement of physical activity. In: Brownell KD, Fairburn CG, eds. Eating Disorders and obesity: a comprehensive handbook. New York (NY): Guilford Press; 1995:111–116

18. Lukaski HC, Bolonchuk WW, Hall CB, Siders WA. Validation of tetrapolar bioelectrical impedance method to assess human body composition. J Appl Physiol 1986; 60:1327–1332

19. Dawson-Saunders B, Trapp R. Basic and clinical biostatistics. 1st ed. Norwalk (Conn): Appleton & Lange; 1990

20. MacConnie SE, Barkan A, Lampman RM, Schork MA, Beitins IZ. Decreased hypothalamic gonadotropin-releasing hormone secretion in male marathon runners. N Engl J Med 1986; 315:411–417

21. Celani M, Grandi M. The pituitary-testicular axis in nonprofessional soccer players. Exp Clin Endocrinol 1989; 94:244–252

22. Griffith R, Dressendorfer R, Fullbright C, Wade C. Testicular function during exhaustive endurance training. Physician Sports Med 1990; 18:54–64

23. Bilanin J, Blanchard M, Russek-Cohen E. Lower vertebral bone density in male long distance runners. Sci Sports Exerc 1989; 21:66–70

24. Veldhuis JD, Evans WS, Demers LM, Thorner MO, Wakat D, Rogol AD. Altered neuroendocrine regulation of gonadotropin secretion in women distance runners. J Clin Endocrinol Metab 1985; 61:557–563

25. Hackney A, Sinning W, Bruot B. Reproductive hormonal profiles of endurance-trained and untrained males. Med Sci Sports Exerc 1988; 20:60–65