Differences in Endocrine Function With Varying Fitness Capacity in Postpubertal Females Across the Weight Spectrum

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Objective: To relate endocrine and nutritional correlates of fitness in postpubertal physically active females across the normal weight spectrum to identify markers and how these might serve as associations of exercise-related endocrine disruption.

Design: Cross-sectional study analyzed by repeated-measures analysis of variance for frequent blood sampling.

Setting: A general clinical research center.

Subjects: Twenty-two healthy postpubertal female subjects recruited 2 years or more after menarche.

Main Outcome Measures: Maximum oxygen consumption was determined as an index of fitness and daily caloric intake was calculated from a 3-day food diary. During the follicular phase of the cycle, luteinizing hormone was sampled every 10 minutes during a 24-hour period, while follicle-stimulating hormone and cortisol were sampled hourly.

Results: For every 1-unit increase in maximum oxygen consumption, cortisol concentration increased by 2% (P = .005; 95% confidence interval, 1%-3%). However, there was no association between mean gonadotropin concentrations and fitness. Hormone concentrations were not significantly associated with body mass index or percentage of body fat. Higher mean caloric intake from a 3-day summary was inversely related to mean luteinizing hormone concentration, which decreased by 5.5% for every 100-kcal increase (P = .03; 95% confidence interval, 1%-10%). With every 1-year increase in age at menarche, follicle-stimulating hormone concentration decreased by 12% (P = .01; 95% confidence interval, 4%-19%) and cortisol concentration increased by 7% (P = .03; 95% confidence interval, 1%-12%).

Conclusions: In active adolescents, increased cortisol concentration may represent an adaptive change to exercise that may precede gonadotropin changes seen with higher levels of fitness.


Regular exercise can improve cardiovascular fitness and prevent obesity. However, excessive exercise in lean female athletes is associated with a constellation of endocrine aberrations, including declining gonadotropin function, delayed pubertal maturation, and bone loss. These changes have been linked to a negative energy balance in very lean athletes, or insufficient energy intake to meet increased metabolic demands of exercise. What is less clear is how increasingly intense exercise can lead to endocrine aberrations and menstrual irregularities in active young women of normal weight. With the promotion of increased physical activity among girls, a greater understanding of the early signs of excessive exercise would allow young women and their health care providers to modulate the intensity of training to maximize positive impact and prevent the negative consequences of overtraining.

The athlete’s triad is a term that is now widely used to describe the constellation of amenorrhea, disordered eating, and osteoporosis in young female athletes. In this constellation, increased cortisol concentrations have been associated with decreased luteinizing hormone (LH) concentrations. This increased activity of the hypothalamic-pituitary-adrenal axis is believed to represent a response to the stress of inadequate caloric intake, but it is uncertain how increased cortisol concentrations play a role in the development of the athlete’s triad. However, increased cortisol concentrations have been reported in osteopenic ballet dancers, athletes with exercise-induced amenorrhea, and elderly men with an increased risk of fractures. Many athletes have a history of intense physical activity beginning in...
childhood, and there is virtually no information about the early adaptive changes of either the stress or the reproductive axis in adolescence or how this history may be related to active adolescents of normal weight.\textsuperscript{10}

Our objective was to identify whether there were endocrine changes related to the reproductive and the stress axes in young women across the normal weight spectrum with a range of self-reported physical activity in the immediate postpubertal period. We determined maximum oxygen consumption (V\textsubscript{O}2\text{max}) in late-adolescent females with normal body mass index (BMI; calculated as weight in kilograms divided by the square of height in meters) and correlated this measure of cardiovascular fitness to 24-hour profiles of gonadotropins and cortisol concentrations.

**METHODS**

**PATIENTS AND SETTING**

Twenty-two healthy adolescent females, aged 16 to 20 years with BMI between the 10th and 95th percentiles for age,\textsuperscript{12} were enrolled after signing a consent form approved by the institutional review board of the University of Michigan, Ann Arbor. An additional signature was required from one parent or legal guardian of each girl younger than 18 years. The study was conducted in the University of Michigan General Clinical Research Center (GCRC). Potential enrollees were excluded if they had any organic or psychiatric chronic illness, a history of pregnancy, symptoms of cold intolerance, galactorrhea, hirsutism, or a history of recent rapid weight loss or gain within the past year. Enrolled subjects were not taking any medications, birth control, or any other type of hormonal preparation. They were recruited by placement of advertisements in local newspapers and across the campuses of the University of Michigan and Eastern Michigan University, Ypsilanti. The average ±SD age at menarche was 13.1 ± 3.2 years,\textsuperscript{13} with a range of 11 to 16 years,\textsuperscript{14} and all were studied at least 2 years after menarche. Eighteen participants reported a regular menstrual cycle by history, and 4 reported an irregular menstrual cycle with an interval between cycles of more than 38 days.\textsuperscript{15} As it may take 2 years after menarche to establish a regular menstrual cycle, subjects reporting an irregular cycle were not excluded.\textsuperscript{15}

As a screen for potential nonmaturational causes of menstrual cycle disruption, thyrotropin and prolactin were measured and identified as being normal in all subjects, and free androgen index was determined. Pregnancy was excluded by measurement of serum human chorionic gonadotropin.

**LABORATORY INVESTIGATIONS**

There was a performance-based as well as an interview-based measure of fitness. To quantify individual levels of fitness, maximum aerobic capacity (V\textsubscript{O}2\text{max}) was determined by a treadmill test according to the Bruce protocol.\textsuperscript{16} In addition, each subject was asked the number of days per week during which she exercised for at least 1 hour of continuous aerobic exercise (reported daily exercise [RDE]); this activity self-report provided a more qualitative assessment of the participant’s perception of her own level of exercise. Because strenuous exercise can alter cortisol secretion, no hormonal samples were collected on the day of the treadmill test.

All subjects were asked at enrollment whether they were dieting and then whether they were hoping to lose some weight. Only 1 subject, with a BMI of 31.8, reported occasional dieting in the hope of losing 2.25 kg. No other subject reported dieting, although an additional 4 participants wished they weighed less. A 3-day prospective diary that had been mailed before the admission was collected to further characterize the diet. To obtain an estimation of daily average caloric intake (ACI), collection of the prospective 3-day food diary was followed by an interview with the GCRC dietary staff. Nutrient calculations were performed with the Nutrition Data System for Research software, version 4.03, developed by the Nutrition Coordinating Center, University of Minnesota, Minneapolis, Food and Nutrient Database 31, released November 2000.\textsuperscript{17} The participants were not asked to change their dietary habits, and while in the GCRC, they were fed a self-selected diet from the hospital menu with standard meal times.

All participants were admitted to the GCRC in the follicular phase between days 0 and 8 of the menstrual cycle, or at random for the enrollees with an irregular cycle. No blood was drawn during the day of the treadmill test, which was on average scheduled within 2 weeks (mean ±SD, 13.4 ± 9.1 days) from the admission. Serum progesterone level was determined to confirm the follicular phase status at the time of admission (mean ±SD, 0.5 ± 0.3 ng/mL [1.5 ± 1.1 nmol/L]). In 19 participants, including all of those with irregular menses, testosterone and sex hormone–binding globulin were measured for the calculation of the free androgen index, which was within the normal range (mean ±SD, 2.6 ± 2.1).\textsuperscript{18}

The admission to the GCRC took place on the night before the study to allow the participants to acclimate to their surroundings. Because the hormones of interest have a diurnal pattern, blood was repeatedly sampled throughout a 24-hour period. Gonadotropins were measured as an index of the reproductive-axis activity and cortisol as an index of the stress-axis activity. By 7 AM an intravenous catheter was inserted in the forearm, and blood was sampled every 10 minutes for 24 hours for LH to account for diurnal variability and pulsatility.\textsuperscript{19} Follicle-stimulating hormone (FSH) and cortisol were measured hourly.

Plasma LH, FSH, and cortisol were measured by means of a chemiluminescent enzyme immunometric assay for use with an automated analyzer (Immulite; Diagnostic Product Corp, Los Angeles, Calif). Assay sensitivity was 0.7 mIU/mL for LH, 0.1 mIU/mL for FSH, and 0.2 pg/dL [5.32 nmol/L] for cortisol. The intra-assay and interassay coefficients of variation were, respectively, 4.0% and 8.0% for LH, 4.0% and 4.3% for FSH, and 5.0% and 7.5% for cortisol. In our hands and considering all time points, LH range was 1.0 to 18.0 mIU/mL; FSH, 1.6 to 7.6 mIU/mL; and cortisol, 1.0 to 14 µg/dL (27.59-386.26 nmol/L).

**STATISTICAL ANALYSIS**

The LH sampling resulted in 145 time points of observation during a period of 24 hours, which were divided into four 6-hour intervals as follows: time 1, 11 PM to 4:50 AM; time 2, 5 AM to 10:50 AM; time 3, 11 AM to 4:50 PM; and time 4, 5 PM to 10:50 PM. Measurements of FSH and cortisol resulted in 25 points of observation during 24 hours, which were divided into four 6-hour intervals. Mean concentrations of FSH and cortisol for each interval were also calculated. The mean concentration for each time interval was then calculated and referred to as a block mean. Each block mean was log transformed before analysis to adjust the left skewness of the data. Pearson correlations between V\textsubscript{O}2\text{max}, RDE, and ACI with age at menarche were calculated.

Since there were multiple time blocks per participant, repeated-measures analysis of variance was used to determine the effects of time and the association of the major variables with LH, FSH, and cortisol.
The outcome variables were LH, FSH, and cortisol concentrations. The results are reported as mean±SD. The primary variables were RDE, VO₂max, and BMI. Secondary covariates included age at menarche and daily ACI. A Tukey adjustment was used when the means of different periods were compared.

The average VO₂max for healthy female subjects in a comparable age group is 40 mg/kg per minute and the 24-hour mean cortisol concentration in comparable groups is 7.25±1.5 μg/dL (200.03±41.38 nmol/L). A sample size greater than 18 subjects was necessary to detect a 15% increase in mean 24-hour cortisol with 80% power.

**RESULTS**

**PATTERNS AND MEASURES OF ACTIVITY**

Table 1 describes the demographic characteristics and Table 2 lists the activity patterns of the participants at the time of enrollment and in earlier years. The mean age was 18.6±1.0 years. Sixteen of 22 subjects had been or were still enrolled in organized sports in high school. A few subjects were enrolled in 1 main sport (jogging, aerobics, field hockey, volleyball, soccer), while most practiced an active lifestyle with no definite prominence of 1 or 2 sports. Activities cited included in-line skating, skiing, diving, daily biking, resistance training, gymnastics, and exercise videotapes. The range of menarche was 11 to 16 years. Reports of irregular menses in 4 subjects appeared linked to exercise and/or slower pubertal maturation. Three were running track in high school and had a later age at menarche, and the fourth one had menarche at age 13 years but was exercising daily as an aerobics instructor on campus. The ACI was 2050.2±421.8 kcal/d, within the expected requirements for moderately active adolescent girls.

All 3 hormones had a diurnal pattern, as shown in Table 3. Both LH and FSH reached their lowest levels at time 1, while cortisol’s nadir was at time 1 with a peak at time 2. The values and diurnal patterns were within the expected range for age for all of the participants.

Mean VO₂max was 42.1±1.44 mg/kg per minute, comparable with published norms for this sex and age group, as nonobese girls aged 16 to 18 years have an average VO₂max of 40.1 mL/kg per minute. Self-reported days of exercise or RDE correlated with VO₂max measures (Pearson correlation coefficient, 0.52; P = .01).

**HORMONAL RELATIONSHIPS WITH MEASURES OF FITNESS AND NUTRITION**

**Cortisol**

Both RDE and VO₂max had a positive relationship with 24-hour average cortisol concentrations. However, when both measures of physical activity were simultaneously included in a regression model, RDE was no longer statistically significant, indicating that VO₂max was a better measure of the fitness-cortisol relationship: with a 1-unit increase in VO₂max, cortisol concentration increased by 2% (P = .005; 95% confidence interval, 1%-3%). Figure 1 shows the positive relationship between VO₂max and mean cortisol concentration. Three representative cortisol profiles are shown in Figure 2.

The BMI, percentage of body fat, and ACI did not significantly affect mean cortisol concentration (P = .93, .14, and .53, respectively).

**Gonadotropins**

The RDE showed no association with LH (P = .28) or FSH (P = .42) for any time block. Likewise, VO₂max had no relationship with LH (P = .51) or FSH (P = .35) concentrations.

Neither LH nor FSH concentrations were significantly associated with BMI (P = .34 and .74, respectively). Percentage of body fat was not associated with LH and FSH concentrations (P = .67 and .51); however, there was an inverse relationship between estimated daily ACI and LH concentrations, which decreased by 5.5% with every 100-kcal increase in ACI (P = .03; 95% confidence interval, 1%-10%), as shown in Figure 3.

**AGE AT MENARCHE**

The 4 subjects with irregular menses at the time of the study had higher than the average age at menarche (13-16 years), and all were engaged in organized sports in high school.

Subjects with later age at menarche did not have higher VO₂max values (P = .97, r = 0.01). Age at menarche was not related to RDE (Pearson correlation coefficient, 0.27; P = .26), nor was it associated with BMI (Pearson correlation coefficient, 0.22; P = .33) or ACI (Pearson correlation coefficient, 0.03; P = .89).

Age at menarche was positively related to mean cortisol concentrations, as shown in Figure 4. For cortisol, a 1-year increase in age at menarche was related to a 7% increase in cortisol concentration (P = .03; 95% confidence interval, 1%-12%). Age at menarche was also inversely related to mean 24-hour FSH concentrations but not to mean LH concentrations (P = .24). A 1-year increase in age at menarche was related to a 12% decrease in mean FSH (P = .01; 95% confidence interval, 4%-19%) (Figure 5).

**COMMENT**

The focus of this study was endocrine changes in late-adolescent female subjects who were not exercising at a
competitive level. We recruited postpubertal subjects across the weight spectrum with fitness levels in the normal range, and within this nonathletic range, we found that cortisol level is linked to \( V \cdot O_2 \text{max} \). Previous reports have described increased cortisol concentrations in competitive athletes with a preserved but magnified circadian excursion or, in extreme cases, a loss of circadian pattern. In the participants in this study, hourly cortisol sampling showed a well-preserved day-night variation. Although increased cortisol concentrations and decreased gonadotropin concentrations coexist in competitive athletes, little is known about early adaptive changes of both stress and reproductive axes associated with moderate exercise. The average \( V \cdot O_2 \text{max} \) in our participants was not in the competitive range and was at the threshold used for the classification of sedentary young women. Endurance-trained young women reach \( V \cdot O_2 \text{max} \) levels that are markedly higher. Our study suggests that increased cortisol concentrations may represent an adaptive response to exercise that is evident before gonadotropins are decreased.

Table 2. Individualized Characteristics and Exercise Patterns

<table>
<thead>
<tr>
<th>Subject</th>
<th>Ethnic Group</th>
<th>BMI</th>
<th>Body Fat</th>
<th>( V \cdot O_2 \text{max}, \text{mL/kg per min} )</th>
<th>Entry in Sports</th>
<th>AM, y</th>
<th>Exercise at Entry</th>
<th>Exercise Pattern</th>
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Table 3. LH, FSH, and Cortisol Levels for Each Time*

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<th>Maximum</th>
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<table>
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<table>
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<td>0.33</td>
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<td>8.82</td>
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Abbreviations: A, Asian; AA, African American; AM, age at menarche; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); HS, high school; MS, middle school; NA, not applicable; NR, none reported; RDE, reported days of exercise; \( V \cdot O_2 \text{max} \), maximum oxygen consumption; W, white.

*Includes in-line skating, snowboarding, diving, biking, resistance training, jogging, skiing, exercise videotapes, and gymnasium.

Figure 1. Relationship between maximum oxygen consumption (\( V \cdot O_2 \text{max} \)) and 24-hour mean cortisol concentration. CI indicates confidence interval. To convert cortisol to nanomoles per liter, multiply by 27.59.

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direct effect on daily cortisol secretion or whether the effect is mediated via a chronic state of relative energy deficit \(^{23,27}\) needs further study. Alternatively, hypercortisolism could also represent a normal maturation pattern.

Because of the potential link between exercise-related endocrine disruption and caloric intake, \(^2\) we collected information from a prospective 3-day food diary in the participants. None of the participating subjects reported active dieting, although some expressed the wish that they were thinner. There was no association between cortisol and caloric intake.

Longitudinal studies should determine whether an increase in cortisol concentrations is a precursor to the development of other endocrine and skeletal disruptions associated with intense and sustained long-term exercise. The greatest challenge of the athlete's triad is that there are no exercise or metabolic predictors of the severity of the endocrine disturbances and the osteoporosis that may ensue. It has been postulated that subclini-
ocal hypercortisolism in athletes may play a role in the subsequent development of osteoporosis.\textsuperscript{9} If cortisol increases early and for a longer period in the cascade of events leading to hypothalamic amenorrhea\textsuperscript{28} and osteoporosis,\textsuperscript{10,11} it could play a more central role in the development of the athlete’s triad. In our study, the participants were well nourished, as their BMI and caloric intake suggest.\textsuperscript{21} Proper nutrition may offset the catabolic effect of cortisol and perhaps delay its potential harmful effects on the menstrual cycle and bone health.

Because of the known effect of exercise on age at menarche when intense training begins before the onset of puberty,\textsuperscript{10,29} we recruited only subjects with a normal age at menarche and studied them at least 2 years later. Bearing in mind that participants were in the immediate postpubertal period, we did not exclude subjects with some menstrual irregularity, as long as they were not older than 16 years at the time at menarche. Historically, the age of 16 years has been used as the limit of normalcy for the onset of menses in the presence of normal growth and development.\textsuperscript{30} The normal range for the onset of puberty in girls has been the subject of a recent debate,\textsuperscript{31} yet, because of the scarcity of studies in late-adolescent girls, a clear definition of the timing for the completion of normal pubertal maturation has remained elusive. Larger longitudinal studies are needed to determine whether girls with menarche between 14 and 16 years of age represent a subgroup that might be more vulnerable to hormonal disruptions associated with exercise or nutrition. From the latest analysis of the National Health and Nutrition Examination Survey data by Chumlea et al,\textsuperscript{14} 80% of all US girls menstruate between 11 and 14 years of age, but the sample size was too small at the later ages to provide a precise estimate of the 97th percentile. In our study, the average age at menarche was 13 years, within the normal range for the population of the United States,\textsuperscript{31} and girls who had a later age at menarche had higher cortisol concentrations. The association between the regular practice of sports at a young age and delayed menarche has been reported before.\textsuperscript{29} Whether the history of exercise had an impact on the age at menarche was not addressed by our study.

There were no significant trends with LH, which drives the pubertal process.\textsuperscript{32} Twenty-four–hour LH and FSH patterns were also consistent with adequate reproductive-axis functioning.\textsuperscript{19} Lower FSH concentrations were present in girls with a later age at menarche, and this would be consistent with a slower pace of maturation of the reproductive axis. Indeed, FSH is the first gonadotropin to increase in girls as they enter puberty. Marshall et al\textsuperscript{33} have shown that gonadotropin-releasing hormone treatment of young women with hypothalamic amenorrhea duplicated the initial increase in FSH concentration before an increase in LH concentration could be elicited. The lower FSH concentration in the girls with a later age at menarche suggests that these girls’ reproductive axis was less mature. Whether this relatively “immature gonadotropin state” renders them more vulnerable to increases in cortisol concentration and/or the metabolic demands of exercise needs further study. Several reports have highlighted exercise-
induced endocrine disruptions in older women at the start of the third decade of life, but the window of opportunity for prevention is likely to be present at an earlier age. Little is known about the athlete’s triad in adolescent girls, and the immediate postpubertal period may yield very important insights on the onset of exercise-induced endocrine aberrations.

The finding of lower gonadotropin concentrations associated with higher caloric intake in this study is counterintuitive and requires further study. There was an inverse relationship between daily caloric intake and LH concentrations. We propose that this finding could be consistent with a compensatory increase of caloric intake to meet higher caloric demands associated with increased physical activity and lower gonadotropin concentrations. However, there was no association between LH concentration and VO2max. A possible mechanism whereby lower caloric intake would be linked to higher gonadotropin concentrations could be mediated via leptin, an adipocyte-derived hormone that plays a role in weight homeostasis as well as gonadotropin regulation.

Both VO2max and RDE were positively associated with higher cortisol concentrations, but only VO2max retained its significance when both were analyzed together. Although the average RDE was 5 days a week, the individual descriptions of the participants show that the range of V·O2max was 40.1±6.1 mL/kg per minute. In this study, the fit individuals achieved. The range of V·O2max was in the expected range for age and sex. Ahmad et al reported normative data from nonobese white children; of 20 girls aged 16 to 18 years, the average ± SE VO2max was 25.26. Ahmad et al16 reported normative data from nonobese white children; of 20 girls aged 16 to 18 years, the average ± SE VO2max was 40.1 ± 6.1 mL/kg per minute. In this study, the fitness results are quite comparable, although we recruited subjects who were active or interested in a study on fitness, accounting for the higher average and narrower range for VO2max.

We conclude that increased cortisol concentration associated with exercise may represent an adaptive metabolic adjustment to exercise without the decrease in gonadotropin concentrations that would be associated with more intense or sustained training.

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What This Study Adds

In healthy and moderately active postpubertal late-adolescent females across the weight spectrum, increased VO2max is associated with increased cortisol concentrations. Increased cortisol concentrations may represent an early adaptive change to exercise that may precede gonadotropin changes seen with higher levels of fitness.

REFERENCES


Announcement