Androgen Deficiency: Association With Increased Anxiety and Depression Symptom Severity in Anorexia Nervosa

Karen K. Miller, M.D.; Tamara L. Wexler, M.D., Ph.D.; Alicia M. Zha, B.S.; Elizabeth A. Lawson, M.D.; Erinne M. Meenaghan, N.P.; Madhusmita Misra, M.D.; Anna B. Binstock, B.A.; David B. Herzog, M.D.; and Anne Klibanski, M.D.

Objective: Anorexia nervosa is associated with a high prevalence of psychiatric comorbidities, including anxiety and depression, and with endocrine dysfunction, including relative androgen deficiency compared with healthy young women. Because androgens are known to affect mood and behavior, we hypothesized that low endogenous androgen production in anorexia nervosa would predict anxiety and depression severity.

Method: Serum androgen levels and severity of depression (Hamilton Rating Scale for Depression) and anxiety (Hamilton Rating Scale for Anxiety) were measured in 43 community-dwelling women with DSM-IV–defined anorexia nervosa from May 2004 to July 2006.

Results: Strong inverse associations were observed between both total and free testosterone and anxiety and depression severity, independent of weight. Free testosterone was also inversely associated with 4 eating-disordered thinking and behavior subscales of the Eating Disorder Inventory 2 (EDI-2). Mean free testosterone blood levels were lower in women with clinically significant anxiety and in women with clinically significant depression, compared with those without. In stepwise regression models, free testosterone was an important predictor of anxiety and depression severity. EDI-2 ineffectiveness, perfectionism, interpersonal distress, and social insecurity scores were also inversely associated with androgen levels, independent of weight.

Conclusions: Our data suggest that low androgen levels may contribute to anxiety, depression, and eating-disordered thinking and behavior in women with anorexia nervosa and form the basis for future studies to investigate the effectiveness of androgen replacement therapy.

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Corresponding author and reprints: Karen K. Miller, M.D., Neuroendocrine Unit, Bulfinch 457B, Massachusetts General Hospital, Boston, MA 02114 (e-mail: KKMiller@Partners.org).

Anorexia nervosa is a serious psychiatric disease with a high prevalence of psychiatric comorbidities, including anxiety and depression. Up to 80% of women with anorexia nervosa are affected with major depression, and up to 71% are affected with anxiety disorders.[1–5] Anorexia nervosa is also complicated by a number of endocrine abnormalities, including hypogonadism due to acquired gonadotropin-releasing hormone deficiency and androgen deficiency. In men, androgen deficiency is associated with an increased incidence of depressive illness,[6] and a randomized, placebo-controlled study demonstrated that testosterone therapy results in an improvement in depression in hypogonadal men with selective serotonin reuptake inhibitor (SSRI)-resistant depression.[7] Androgen deficiency has also been shown, primarily in rodents but also in humans, to be associated with increased anxiety.[8–10] We therefore hypothesized that the degree of androgen deficiency would be an important predictor of depression and anxiety severity in women with anorexia nervosa.

METHOD

Setting and Subjects

Women between the ages of 18 and 50 years who met DSM-IV criteria for anorexia nervosa were recruited by advertisements and from health care provider referrals. Women receiving hormone therapy of any kind, including oral contraceptives, were excluded from participation. The study was approved by the institutional review

Table 1. Characteristics of a Sample of Women With Anorexia Nervosa (N = 43)

Characteristic	Mean	SD	Normal Values
Age, y	26.3	6.6	NA
Age at menarche, y	13.1	1.2	10–15
Age at onset of anorexia nervosa, y	19.3	5.9	NA
Duration of anorexia nervosa, mo	84	76	NA
Time since last spontaneous menstrual period, mo	27	36	NA
Education, y	16.1	2.6	NA
% Ideal body weight	77.8	6.1	90–110
Body mass index	17.4	1.4	18.5–24.9
Paffenbarger weekly vigorous exercise, h	5.9	8.3	NA
DXA fat mass	8.7	2.8	NA
DXA % body fat	18.2	4.9	NA
DXA lean body mass	36.9	4.2	NA
Free testosterone, pg/mL	1.6	0.9	1.1–6.3
Total testosterone, ng/dL	23	11	10–55

Abbreviations: DXA = dual-energy x-ray absorptiometry, NA = not applicable.

Table 2. Mood and Eating Disorder Thinking and Behavior Questionnaire Results in a Sample of Women With Anorexia Nervosa (N = 43)

Measure	Mean	SD	Normal Values
HAM-A	14.8	8.4	≤ 18
HAM-D	16.1	7.3	≤ 12
EDI			
Bulimia	2.5	4.5	0.0–3.0
Body dissatisfaction	14.4	8.6	6.3–18.1
Drive for thinness	12.9	5.8	1.2–9.8
Ineffectiveness	9.2	5.5	0.0–5.4
Perfectionism	8.4	4.8	1.3–11.1
Interpersonal distrust	5.4	4.4	0.0–4.5
Interoceptive awareness	7.6	6.2	0.0–7.1
Maturity fears	5.6	4.3	0.2–5.2
Asceticism	7.5	5.7	0.3–6.5
Impulse regulation	3.4	5.5	0.0–5.4
Social insecurity	8.2	5.0	0.4–6.2
EDEQ			
Binges/mo	5.5	15.0	
Over-exercise/mo	4.4	8.0	
Purges/mo	4.1	11.0	
Laxative use/mo	1.7	5.3	
Diuretic use/mo	1.1	4.6	
Malnutrition/mo	7.9	14.0	

Abbreviations: EDEQ = Eating Disorder Examination Questionnaire, EDI = Eating Disorders Inventory, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating for Depression.

boards of Partners Health Care, Inc., and written informed consent was obtained from all subjects. The study was performed at the Massachusetts General Hospital General Clinical Research Center from May 2004 to July 2006.

Procedures

All data were collected during 1 visit, which included nutritional evaluation by a research bionutritionist. This evaluation included measurement of weight in a gown, height, frame size, and calculation of percent ideal body weight (IBW)[11] and body mass index (BMI). A study investigator conducted interviews with all patients to determine study eligibility, menstrual history, medication use, and illness duration. The 21-item Hamilton Rating Scale for Depression (HAM-D)[12] was administered to investigate depressive symptoms. The Hamilton Rating Scale for Anxiety (HAM-A) 14-item questionnaire[13] was administered to determine severity of anxiety, and the Eating Disorder Inventory 2 (EDI-2)[14] and the Eating Disorder Examination Questionnaire (EDE-Q)[15] were administered to characterize and determine the severity of eating-disordered behavior. Serum was obtained for measurement of testosterone and free testosterone levels, both of which were measured at Esoterix Endocrinology Inc. (Calabasas Hills, Calif.). Total testosterone levels were measured using tandem mass spectroscopy with a sensitivity of 3 ng/dL and an intra-assay coefficient of variation (CV) of 0.72 to 17.30. Percent free testosterone was determined using equilibrium dialysis, with a minimum reportable free fraction of 0.1% and an intra-assay percent CV of 8.8 to 9.4. Esoterix Endocrinology reports a normal range for total testosterone of 10 to 55 ng/dL and a normal range for free testosterone, using these methods, of 1.1 to 6.3 pg/mL for women of reproductive age.

Statistical Analysis

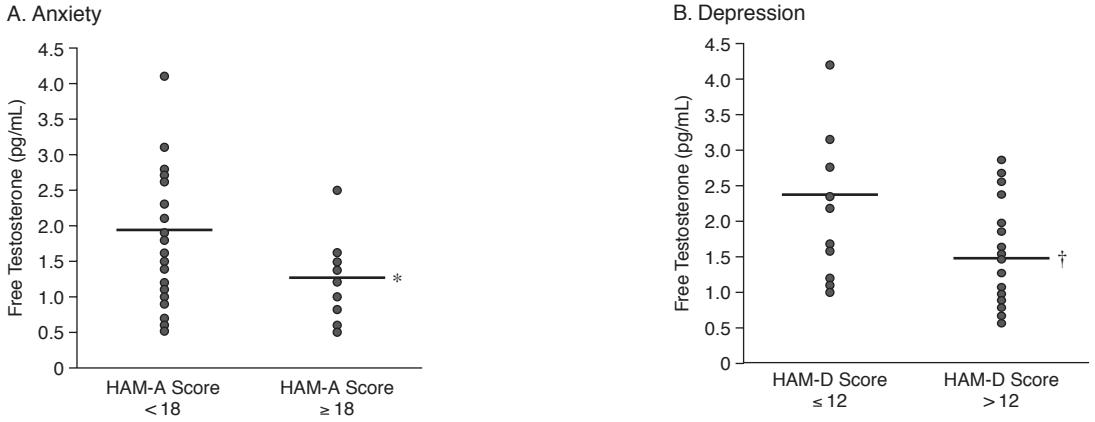
JMP Statistical Discoveries, version V (SAS Institute, Inc.; Cary, N.C.) was used for statistical analysis. All variables were tested for normality by the Shapiro-Wilk test. All variables that were not normally distributed were log transformed. Blood hormone levels and clinical characteristics were compared using analysis of variance. Univariate and stepwise regression analyses were performed to investigate determinants of HAM-A, HAM-D, and EDI-2 scores. Statistical significance was defined as $p \leq .05$. Data are reported as mean ± SD.

RESULTS

Clinical Characteristics

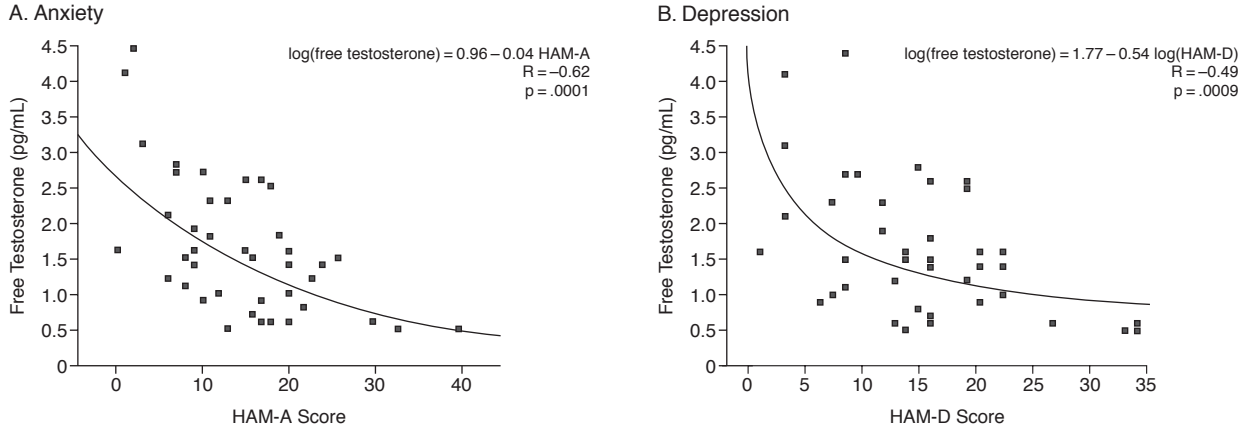
Clinical characteristics are shown in Table 1. Forty-three women with anorexia nervosa were recruited for this study. Mean age was 26.3 ± 6.6 years, mean percent ideal body weight was 77.8 ± 6.1%, and mean number of months since last spontaneous menstrual period was 27 ± 36. Depression, anxiety, and eating-disordered behavior scores are shown in Table 2. Seventy-two percent (N = 31) of subjects were depressed (HAM-D score > 12), and 35% (N = 15) had clinically significant anxiety (HAM-A score ≥ 18). Seventy-two percent (N = 31) reported a prior diagnosis of depression, and 67% (N = 29), of an anxiety disorder. Thirty-five percent (N = 15) were receiving anxiolytic medications, and 47% (N = 20) were receiving antidepressants. Thirty percent (N = 13) were receiving both anxiolytics and antidepressants.

Figure 1. Mean Free Testosterone Levels Are Lower in Women With Anorexia Nervosa and Anxiety (HAM-A score ≥ 18) Than Without Anxiety (A) and With Depression (HAM-D score > 12) Than Without Depression (B)[a]



[a]Horizontal lines indicate mean values.
*p < .004.
†p < .007.
Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

Figure 2. Free Testosterone Levels Are Inversely Associated With Anxiety and Depression Severity



Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

Twenty-one patients (49%) were receiving no psychotropic medications. Eight patients (19%) reported no history of an anxiety or depressive disorder diagnosis and were not taking psychotropic medications of any kind.

Association of Hypoandrogenemia With Psychological Endpoints

Mean free testosterone levels were lower in subjects who had clinically significant depression (HAM-D score > 12) compared with those who did not (1.4 ± 0.7 vs. 2.3 ± 1.2 pg/mL, p = .007) and in subjects who had clinically significant anxiety (HAM-A score ≥ 18) compared with those who did not (1.1 ± 0.9 vs. 1.9 ± 0.9 pg/mL, p = .004) (Figure 1). These differences remained significant after controlling for percent IBW, age, and months since last menstrual period. There were strong inverse associations between psychological endpoints—anxiety and depression scores (Figure 2), EDI-2 ineffectiveness, perfectionism, interpersonal distress, and social insecurity subscales (Figure 3)—and androgen levels, both free testosterone and total testosterone (significantly associated with anxiety and depression scores only) (Table 3). These associations remained significant after controlling for variables that were also associated or tended to be associated with androgen levels or psychological endpoint scores, including percent IBW (vs. free testosterone, R = 0.28, p = .068), number of months since last spontaneous menstrual period (vs. free testosterone, R = –0.53, p = .001; vs. total testosterone, R = –0.32, p = .072; vs. HAM-A score, R = 0.40, p = .020; vs. HAM-D score,

Figure 3. Free Testosterone Levels Are Inversely Associated With Eating Disorder Inventory Subscale Scores

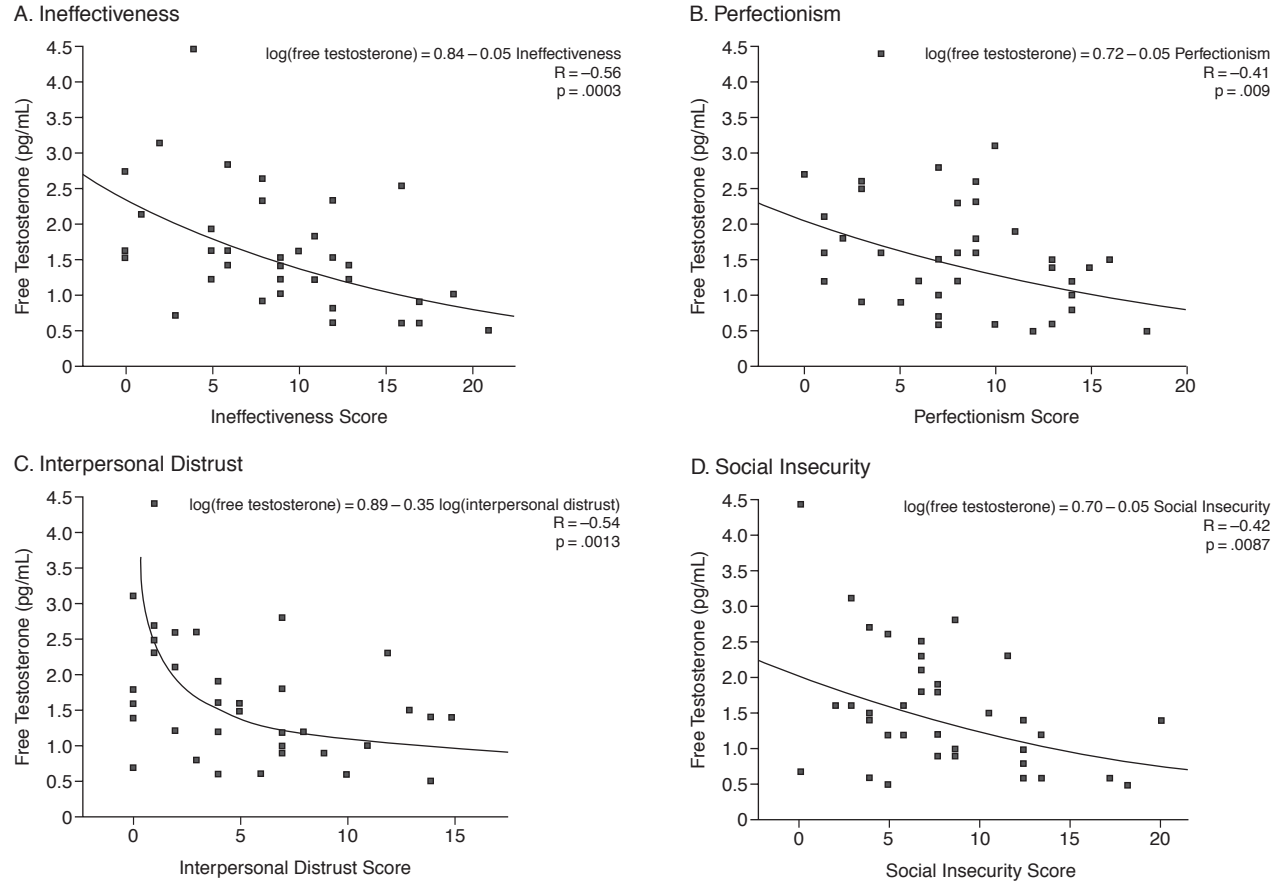


Table 3. Linear Regression: Androgen Levels and Psychological Endpoints

	Free Testosterone		Total Testosterone	
Psychological Endpoint	R	p	R	p
HAM-A	–0.62	.0001	–0.49	.001
HAM-D	–0.49	.0009	–0.38	.014
EDI				
Ineffectiveness	–0.56	.0003	–0.31	.061
Perfectionism	–0.41	.009	–0.13	NS
Interpersonal distrust	–0.54	.001	–0.34	.058
Social insecurity	–0.42	.009	–0.13	NS

Abbreviations: EDI = Eating Disorders Inventory, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating for Depression, NS = nonsignificant.

R = 0.43, p = .010; vs. EDI-2 ineffectiveness score, R = 0.49, p = .006; vs. EDI-2 perfectionism score, R = 0.45, p = .010; vs. EDI-2 interpersonal distress score, R = 0.37, p = .067; vs. EDI-2 social insecurity score, R = 0.48, p = .006), and age (vs. HAM-A score, R = 0.31, p = .038; vs. EDI-2 interpersonal distress score, R = 0.35, p = .049; vs. EDI-2 social insecurity score, R = 0.31, p = .052), except for the association between HAM-D and free testosterone, which was no longer significant after controlling for percent ideal body weight. Stepwise regression models were constructed to determine the predictors of HAM-A, HAM-D, EDI-2 ineffectiveness, EDI-2 perfectionism, EDI-2 interpersonal distress, and EDI-2 social insecurity scores. The variables entered into the model were age, percent IBW, number of months since last menstrual period, and free testosterone. Free testosterone was an important determinant of all psychological variables tested, accounting for between 19.5% and 37.4% of the variability (Table 4).

In a subset analysis of the 21 patients (49%) not receiving any psychotropic medications, the inverse associations between free testosterone levels and both depression (R = –0.44, p = .045) and anxiety (R = –0.57, p = .007) scores remained strong. Inverse associations between free testosterone and the following EDI-2 subscales also remained strong and significant: EDI-2 ineffectiveness (R = –0.48, p = .043), EDI-2 interpersonal distress (R = –0.83, p = .0005), and EDI-2 social insecurity (R = –0.55, p = .018); there was a trend toward an inverse association between free testosterone levels and the EDI-2 perfectionism subscale (R = –0.46, p = .057) in the subset.

Table 4. Stepwise Regression Model Results[a]

Psychological Endpoint	Predictor	Variability Explained by Model (%)	Cumulative Variability Explained by Model (%)
HAM-A	Free testosterone	36.4	36.4
	% Ideal body weight	7.0	43.4
HAM-D	Free testosterone	19.5	19.5
	Months since last menstrual period	5.6	25.1
EDI ineffectiveness	Free testosterone	37.4	37.4
	Months since last menstrual period	5.2	42.6
EDI perfectionism	Free testosterone	25.7	25.7
	Months since last menstrual period	5.2	30.9
EDI interpersonal distrust	Free testosterone	33.3	33.3
	% Ideal body weight	5.8	39.1
EDI social insecurity	Free testosterone	23.2	23.2
	Months since last menstrual period	7.2	30.4

[a]The following variables were entered into the models: percentage of ideal body weight, months since last menstrual period, age, and free testosterone.
Abbreviations: EDI = Eating Disorders Inventory, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D = Hamilton Rating Scale for Depression.

DISCUSSION

Our data suggest that androgen deficiency is associated with comorbid anxiety and/or depressive symptomatology in women with anorexia nervosa. Importantly, the associations that we observed between androgen levels and severity of both depression and anxiety symptoms were independent of weight, age, and the length of time ill with anorexia nervosa. Moreover, women with clinically significant depressive or anxiety symptoms had mean testosterone and free testosterone levels far lower than women without these comorbid diseases. In a small, randomized, placebo-controlled pilot study in another group of women with anorexia nervosa, we previously demonstrated similar inverse associations between free testosterone levels and severity of depressive symptoms, as measured by the Beck Depression Inventory. Furthermore, we observed a decrease in mean depressive symptom severity in depressed women with anorexia nervosa after receiving testosterone replacement versus placebo for 3 weeks.[16] However, to our knowledge, these are the first data that suggest that low androgen levels are associated with anxiety symptom severity and disordered eating thinking or behaviors. It is unknown whether testosterone replacement would ameliorate anxiety, improve eating disorder symptoms, or result in a sustained improvement in depressive symptoms. Further studies in this area are merited.

Published data have demonstrated anxiolytic properties of testosterone administration in both female and male rodents. These include studies in which investigators injected testosterone, dihydrotestosterone (DHT), or 3α-diol into ovariectomized female rats, with a resultant decrease in anxiety symptoms.[17] Similar results with testosterone, DHT, and 3α-diol have been demonstrated in gonadectomized[18] male rats, with reversal of increased anxiety observed after castration.[8–10] Because nonaromatizable androgens were effective in reducing anxiety, the anxiolytic effect of testosterone cannot be solely attributed to estradiol, systemically or locally, at brain receptors. In addition, in a study of male mice, 5α-dihydrotestosterone was more anxiolytic than estradiol benzoate. In this same study, picrotoxin and bicuculline, noncompetitive and competitive antagonists of GABA(A) receptors, respectively, blocked the anxiolytic effects of testosterone.[19] This led the authors to posit that the anxiolytic effects of testosterone were mediated by GABA(A) receptors. There are few human studies investigating the effects of androgens on anxiety. However, 2 randomized, placebo-controlled studies in healthy women have been conducted, in which 1 dose of sublingual testosterone, 0.5 mg, was administered. In these studies, testosterone decreased fear potentiation of the startle reflex and decreased the emotional response to fear.[20,21] The authors concluded from their data that testosterone attenuates the emotional response to fear but not the conscious appreciation of anxiety. No androgen levels were measured in the study subjects. Therefore, it is unknown whether a sustained course of physiologic-dose androgen therapy might reduce anxiety severity in women.

There are more published data linking depressive than anxiety symptoms with hypoandrogenemia, particularly in men. Cross-sectional studies have demonstrated associations between severity of depressive symptoms and testosterone levels in men. These include a study of over 4000 Vietnam veterans, which demonstrated an increased rate of depression in men with below-average testosterone levels.[22] Another study, in 278 men 45 years and older, demonstrated a 2-year incidence of diagnosed depressive illness of 21.7% in hypogonadal men compared with 7.1% in men with normal testosterone levels, for an unadjusted odds ratio for depression of 3.5 (95% CI = 1.3 to 9.4).[6] In addition, testosterone administration has been demonstrated to improve depression severity in men with

hypogonadism, including men with SSRI-resistant depression, studied in a randomized, placebo-controlled protocol.[7]

There are many fewer data in women. Previously, we demonstrated an improvement in depression scores, as measured by the Beck Depression Inventory, in a small number of women with anorexia nervosa and comorbid depression after a 3-week course of testosterone replacement compared with placebo administration.[16] Likewise, we performed a 12-month randomized, placebo-controlled trial in 51 women with androgen deficiency due to hypopituitarism and observed an improvement in depression symptom severity in those who received low-dose testosterone replacement therapy compared with those who received placebo for 12 months.[23] Other groups have shown improvements in depression and anxiety scores in women in response to therapy with low-dose testosterone[24] or dehydroepiandrosterone (DHEA), a prehormone that is converted in the body to both androgens and estrogens.[25–28] Our data provide a strong rationale for pursuing additional studies to determine whether chronic low-dose testosterone replacement therapy would be effective to improve anxiety and depressive symptoms in women with anorexia nervosa.

Limitations of this study include its cross-sectional design, which cannot determine causality. There is also some overlap between HAM-A and HAM-D questions. In addition, some of the HAM-A and HAM-D questions, although designed to determine severity of anxiety and depression symptomatology, respectively, utilize variables such as amenorrhea and weight loss, the etiology of which is likely the anorexia nervosa itself, and therefore may overestimate the severity of the psychological symptoms in this population.

There are no effective psychopharmacologic treatments for anorexia nervosa and few effective behavioral therapies. Our data demonstrate inverse relationships between androgen levels and several EDI-2 subscales, specifically ineffectiveness, perfectionism, interpersonal distress, and social insecurity. There are no published studies investigating whether androgen replacement would be helpful in the treatment of eating-disordered behavior in conjunction with established or empirically based therapies for anorexia nervosa. Our data form the basis for future studies to investigate this question. Future studies should also utilize structured clinical interviews to better characterize specific depressive and anxiety phenomenology. This would enhance our understanding of the impact of androgen deficiency and replacement on these conditions.

In summary, our data suggest that low androgen levels are associated with anxiety, depression, and eating-disordered thinking and behavior in women with anorexia nervosa. These are the first data to demonstrate an association of low androgens with increased anxiety severity and eating-disordered thinking and behavior, and they confirm our previous report of an inverse relationship of androgen levels with depression severity in this population. These data form the basis for future studies investigating the effectiveness of androgen replacement therapy for anxiety, depression, and/or eating-disordered thinking and behavior in women with anorexia nervosa.

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