

Medical Findings in Outpatients With Anorexia Nervosa

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Background: Approximately 0.5% to 1% of college-aged women have anorexia nervosa and most of them live in the community. However, few clinical data exist regarding community-dwelling women with anorexia nervosa. The objective of this study was to determine the prevalences of common medical findings for these women.

Methods: Cross-sectional, community-based study of 214 women with anorexia nervosa as defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*. Participants were recruited through advertisements and community-based referrals to a study investigating skeletal health in outpatients with anorexia nervosa.

Results: The prevalences of medical findings among the 214 participants were as follows: anemia, 38.6%; leukocytopenia, 34.4%; hyponatremia, 19.7%; hypokalemia, 19.7%; bradycardia, 41.3%; hypotension, 16.1%; hypo-

thermia, 22.4%; elevation of alanine aminotransferase concentration, 12.2%; osteopenia, 51.7%; osteoporosis, 34.6%; and primary amenorrhea, 14.8%. Moreover, 30% of the women reported histories of bone fractures. Except for leukocytopenia ($P = .01$), bone loss ($P = .04$), and bradycardia ($P = .01$), the probability of specific medical findings could not be predicted by the degree of undernutrition.

Conclusions: These results demonstrate a high prevalence of medical findings in community-dwelling women with anorexia nervosa. Therefore, women with anorexia nervosa should be carefully followed up with regular physical examinations and laboratory assessments. In addition, low weight, particularly in conjunction with the abnormalities reported, should prompt the consideration of a diagnosis of anorexia nervosa.

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ANOREXIA NERVOSA AFFECTS approximately 0.5% to 1% of college-aged women. The prevalence of this disorder is increasing,¹⁻⁴ and it is associated with a 5.6% mortality rate per decade, 12 times the rate for healthy age-matched women.^{5,6} The increased mortality is in part attributable to a markedly increased rate of suicide among women with anorexia nervosa; yet, many deaths are of unclear etiology in this group and they may be due to medical complications of the disorder.^{5,6} Serious medical complications have been reported, including electrolyte disorders,⁷ severe bone loss,^{8,9} hematologic disorders,¹⁰⁻¹⁵ and cardiac dysfunction.^{16,17} However, there is no comprehensive study reporting medical findings common among community-dwelling women with anorexia nervosa. Because this disorder is a major cause of morbidity and mortality in young women, we investigated the prevalence of medical findings commonly reported in a large community-based group of women with

anorexia nervosa. We also sought to provide normative data to assist physicians in determining whether abnormal laboratory values can reasonably be attributed to the eating disorders themselves or require additional investigation.

METHODS

PARTICIPANTS

Through advertisements and referrals from health care providers we recruited 214 women aged between 17 and 45 years who had anorexia nervosa. Anorexia nervosa, defined by the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)*,¹ was confirmed in all patients. This included intense fear of gaining weight, undue preoccupation with body shape, a weight of 85% of ideal body weight (IBW) or less (as determined by the 1959 Metropolitan Life Tables¹⁸), and a lack of menses for at least 3 months in women not taking estrogens.^{1,18} Women who reported purging were classified as having a "purging" subtype. The study was conducted at the Massachusetts General Hospital and the Massachusetts Institute of Technology after approval by the institutional

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Table 1. Clinical Characteristics of 214 Women With Anorexia Nervosa*

Characteristic	Values
Age, y	25.0 ± 6.4 (17-45)
Percentage of IBW	77 ± 6 (60-85)
Duration of AN, mo	65.9 ± 70.4 (1-336)
Age at onset of AN, y	19.5 ± 5.6 (9-40)
Women who purge, %	24.1
No. of purges/wk†	1.6 ± 15.9 (1-70)
BMI	16.8 ± 1.4 (13.2-20.8)
LBM, kg	34.3 ± 3.9 (24.5-45.5)
Fat mass, kg	8.0 ± 3.3 (2.6-20.3)
Percentage of body fat	17.7 ± 5.9 (6.3-32.4)
LMP, mo	27.1 ± 38.9 (3-300)
Amenorrhea, mo	54.6 ± 61.2 (4-324)
Age at menarche, y	13.6 ± 0.48
Women with primary amenorrhea, %	14.8
Women engaging in vigorous exercise, %	74.6
No. of hours of vigorous exercise/wk †	5.9 ± 4.8 (0.67-23.5)
Women consuming alcohol, %	41.6
No. of drinks/wk‡	2.6 ± 4.1 (0-28.0)
Women who smoke, %	16.4
No. of cigarettes/d†	11.6 ± 9.0 (0.3-40)
Women who incurred fractures, %	30.1

Abbreviations: AN, anorexia nervosa; BMI, body mass index (calculated as weight in kilograms divided by the square of height in meters); IBW, ideal body weight; LBM, lean body mass; LMP, length of time since last menstrual period.

*Values are given as mean ± SD (range) unless otherwise indicated.

†The frequency reported is the mean for all patients who engaged in the activity.

‡Social drinkers who did not specify a number of drinks were assigned zero drinks per week.

Table 2. Medication Use Among 214 Women With Anorexia Nervosa

Medication	% of Women
Estrogen	30.0
Psychiatric medications	53.3
Antidepressant	46.7
Anxiolytic	10.7
Antipsychotic	7.5
Anticonvulsant	5.6
Mood stabilizer (lithium carbonate)	0.5
≥2 Psychiatric medications	15.9
Multivitamin	53.3
Calcium supplements	40.9
Potassium supplements	2.8
Antireflux/gastrointestinal motility medication	4.7

review boards of both institutions. Written informed consent was obtained from all participants.

DESIGN

Participants were recruited through advertisements and community-based referrals for a study investigating skeletal health in outpatients with anorexia nervosa. Nutritional evaluation, including weight (wearing only a gown), height, wrist and frame size, body mass index, and percentage of IBW, was performed by a registered dietician for all participants. A study investiga-

tor conducted interviews with all participants to determine illness duration, medical history, menstrual history, psychiatric comorbidities, purging history, fracture history, medication use, exercise history, use of illicit drugs, and presence of a treatment team. Vigorous exercise and tobacco use were determined using the Paffenbarger Activity Questionnaire.¹⁹

Participants underwent nutritional evaluations that included questions about intake frequency of foods high in calcium, and they were interviewed about medical history and current use of medications, alcohol, and tobacco. Those who had taken estrogen in the past 3 months were excluded from analyses involving number of months since last menstrual period and number of months of amenorrhea. Serum and plasma were obtained for determination of complete blood count and levels of electrolytes, creatinine, alanine aminotransferase, thyrotropin hormone, and albumin.

Bone mineral density readings of the total body and at the anteroposterior lumbar spine (L1-L4), lateral spine, left total hip, femoral neck, and trochanter were done at both sites with dual-energy x-ray absorptiometry (DXA) using Hologic 4500 densitometers (Hologic Inc, Waltham, Mass) and standardized conversion factors. Precision was 0.01 g/cm² for bone mineral density of the lumbar spine,²⁰ 3% for fat mass, and 1.4% for lean body mass.²¹ Data on bone mineral density in subsets of 30 and 130 patients have been published previously.^{8,9}

STATISTICAL ANALYSIS

All statistical analyses were performed using JMP Statistical Discovery Software, version 4 (SAS Institute Inc, Cary, NC). The data were sorted and prevalences determined. Simple distributions were run to calculate mean (SD) values. Differences between the means of subgroups were evaluated by analysis of variance and *t* tests. The relationships between descriptive variables were examined by linear regression analysis. *P* ≤ .05 indicated statistical significance.

RESULTS

CLINICAL CHARACTERISTICS

Clinical characteristics of the study participants are shown in **Table 1**. Half of them had never been hospitalized, and the mean body mass indexes (calculated as weight in kilograms divided by the square of height in meters) of the women who had and who had not been hospitalized were similar (16.6 vs 16.9, *P* = .10). The women who reported purging had a longer mean illness duration compared with those who did not report purging (88.9 vs 57.7 months, *P* = .01). Exercise was performed regularly up to 23.5 hours per week by 75% of the participants (mean time, 5.9 hours). This did not include the women who had been prescribed exercise restrictions (5%), who had sustained injuries preventing them from exercising (2%), and who walked routinely up to 10.5 hours per week (13%). Of all participants, 18% exercised more than 7 hours and 6% exercised more than 14 hours per week.

MEDICATION USE

Medication use at the time of the study is shown in **Table 2**. Seventy-four percent of the women had histories of estrogen use and 30% were taking estrogen at the time of the visit (there was no difference in percentage of IBW [*P* = .25],

body mass index [$P=.35$], or percentage of body fat [$P=.73$] between those who were and those who were not currently taking estrogen); 53% reported current use of at least 1 psychiatric medication and 16% of at least 2 psychiatric medications; and 73% reported having used antidepressants and 47% reported current use.

HEALTH CARE

Of all participants, 96% reported having primary care physicians, 75% reported current treatment by psychotherapists (including psychiatrists, psychologists, and social workers), and 52% reported current treatment by nutritionists.

VITAL SIGNS

Vital signs are shown in **Table 3**. Of the 214 participants, 43% had heart rates below normal (<60 beats per minute), 17% had heart rates of less than 50 beats per minute, and 1% had heart rates less than 40 beats per minute; 15% had systolic blood pressures less than 90 mm Hg and 2% had diastolic blood pressures less than 50 mm Hg; and 22% had hypothermia, as defined by temperature below 36°C. Participants with bradycardia had a lower mean percentage of IBW than those whose heart rates were at least 60 beats per minute (75.4% vs 77.8%, $P=.01$). Correlations of vital signs with body composition, duration of illness, and exercise are shown in **Table 4**.

LABORATORY VALUES

Laboratory values are shown in **Figure 1**. One woman had a hematocrit value as low as 25.1% (normal range, 36%-46%), and 39% of the women had anemia as indicated by a hematocrit below normal; however, 94% of the women with anemia had normal mean corpuscular volumes. The percentage of IBW was not lower in women with anemia than in those without anemia (75.7% vs 76.3%, $P=.56$). The lowest value for the women's white blood cell counts was 2300/ μ L (normal range, 4500-13 000/ μ L) and it was below normal in 34% of the women, whereas 5% had thrombocytopenia with platelet counts as low as 114 000/ μ L (normal range, 150 000-350 000/ μ L).

The lowest value for plasma sodium was 122 mEq/L (normal range, 135-145 mEq/L) and 7% of participants had hyponatremia. One participant reported a history of seizures secondary to hyponatremia and none had hypernatremia. The lowest value for plasma potassium was 1.9 mEq/L (normal range, 3.4-4.8 mEq/L) and 20% of participants had hypokalemia, including the 6 women who reported taking potassium supplements. Of the participants with low potassium levels, 48% reported that they regularly purged, whereas the remainder (52%) denied purging. In the setting of a one-time study visit, however, we could not confirm these reports, and a previous large study in an outpatient treatment program has reported the absence of hypokalemia in nonpurgers.¹² Mean plasma potassium level was lower for the women who reported purging than for those who did not (3.5 vs 3.7 mEq/L, $P=.02$). A history of dysrhythmia was reported by 2% of the women and, in most cases, hypokalemia was noted as the prob-

Table 3. Vital Signs of Women With Anorexia Nervosa

Sign	Mean \pm SD (Range)
Heart rate, beats/min	61.6 \pm 12.7 (36-100)
Blood pressure, mm Hg	
Systolic	100.1 \pm 11.9 (74-138)
Diastolic	63.5 \pm 8.7 (41-90)
Temperature, °C	36.6 \pm 0.5 (35.0-37.6)

able cause. Serum calcium levels were low in 6% of participants; serum alanine aminotransferase levels were elevated in 12%, with a range of 31 to 161 U/L (normal range, 7-30 U/L); and serum albumin levels were elevated in 18%, possibly reflecting hypovolemia. Only 2 participants had low thyrotropin levels, 1 of whom was taking levothyroxine sodium.

Participants whose laboratory results were outside normal limits did not have a lower mean percentage of IBW than those whose laboratory results were within normal limits, except for white blood cell count (women with leukopenia weighed a mean 74.2% of their IBW and women with normal WBCs weighed a mean 77.1% of their IBW [$P=.01$]). However, women who weighed less than 75% of their IBW had lower levels of plasma sodium (140 vs 141 mEq/L, $P=.02$) and total serum calcium (8.9 vs 9.3 mg/dL [2.23 vs 2.33 mmol/L], $P=.05$) and higher mean corpuscular volumes (91.8 vs 89.1 g/L, $P=.004$) and mean corpuscular hemoglobin (31.3 vs 30.4 pg per red blood cell, $P=.01$) than women who weighed at least 75% of their IBW. Correlations of laboratory results with body composition, duration of illness, and level of exercise are shown in Table 4.

MENSTRUAL FUNCTION

The mean time since the last menstrual period was 27.1 months (range, 3-300 months [Table 1]), and mean age at menarche was 13.6 years for the study participants. Of these 214 women with anorexia nervosa, 69% had menarche later than the mean age for white girls in the United States, 12.88 years,²² and 15% had "delayed menarche," defined as more than 2 SDs later than the normal mean (ie, later than 15.28 years). This subset included all the women who had primary amenorrhea, defined as menarche occurring in girls older than 16 years. The women who had primary amenorrhea developed anorexia nervosa at a younger mean age than those with secondary amenorrhea (17.6 \pm 6.6 years vs 19.9 \pm 5.4 years, $P=.05$).

SKELETAL HEALTH

Fifty-two percent of these women with anorexia nervosa had osteopenia, defined as a T score between -1 and -2.5 SD from the mean value for healthy young women; 34% had osteoporosis, defined as T score of less than -2.5 (**Figure 2**); and only 13.8% had normal bone density at all sites. Bone mineral density correlated most strongly with lean body mass but also with percentage of IBW, duration of illness (number of years since diagnosis of anorexia nervosa), and number of hours per week of vigorous exercise

Table 4. Correlations of Medical Findings With Clinical Characteristics

Characteristic	% IBW		LBM		% Body Fat		Duration of AN		Vigorous Exercise	
	R	P Value	R	P Value	R	P Value	R	P Value	R	P Value
HR	0.22	.005	-0.08	.39	0.28	.002	0.16	.06	-0.17	.03
Systolic BP	0.22	.005	0.13	.17	0.14	.14	0.09	.29	-0.00	.97
Temperature	0.15	.21	-0.14	.42	0.44	.01	-0.04	.81	-0.26	.03
HCT	0.04	.63	-0.03	.77	0.1	.27	0.14	.11	-0.00	.98
WBC count	0.07	.37	0.00	.97	0.01	.93	0.10	.25	-0.12	.14
Platelet count	-0.08	.37	-0.19	.05	-0.12	.22	0.33	<.001	-0.01	.89
Potassium	0.10	.19	0.28	.002	-0.19	.04	-0.1	.26	0.06	.43
Sodium	0.16	.05	0.13	.14	0.28	.002	-0.25	.004	0.15	.07
ALT	0.02	.91	-0.11	.44	-0.01	.95	0.21	.22	0.09	.53
AP spine BMD	0.25	.006	0.45	<.001	-0.12	.27	-0.20	.07	0.22	.01
Lateral spine BMD	0.27	.005	0.36	.001	-0.01	.96	-0.09	.45	0.26	.007
Total hip BMD	0.29	.002	0.60	<.001	-0.05	.67	-0.34	.002	0.37	<.001
Total body BMD	0.05	.64	0.43	<.001	-0.34	.002	-0.21	.11	0.34	.002

Abbreviations: ALT, alanine aminotransferase; AN, anorexia nervosa; AP, anteroposterior; BMD, bone mineral density; BP, blood pressure; HCT, hematocrit; HR, heart rate; IBW, ideal body weight; LBM, lean body mass; WBC, white blood cell.

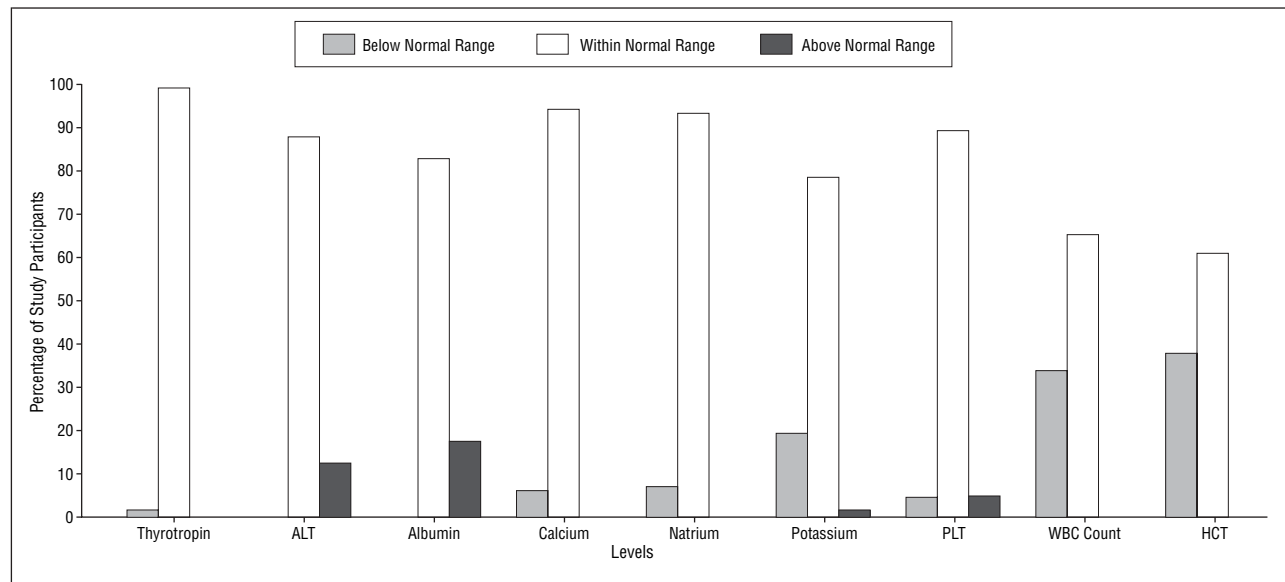


Figure 1. Percentage of study participants with anorexia nervosa who had laboratory results below, above, and within the normal range. ALT indicates alanine aminotransferase; HCT, hematocrit; PLT, platelet; THS, thyroid stimulating hormone; and WBC, white blood cell.

(Table 4). Thirty percent of the women reported histories of bone fractures and 36% had histories of multiple fractures. In 42% of cases the fractures were atraumatic, ie, stress fractures or fractures resulting from a minor injury that would not be expected normally to result in a fracture.

COMMENT

Anorexia nervosa is a serious psychiatric disease with severe medical complications, including a mortality rate of 5.6% per decade of illness, 12 times that expected for age and sex.^{5,6} In our study of 214 women with anorexia nervosa living in the community, we demonstrate a high prevalence of medical findings, ie, 39% for anemia, 20% for hypokalemia, 34% for leukocytopenia, 7% for hyponatremia, 12% for alanine aminotransferase elevation, 15% for primary amenorrhea, 52% for osteopenia, and 35% for osteo-

porosis. Bradycardia was observed in 43%, hypotension in 16%, and hypothermia in 22% of the women studied. Of note, half of all participants had never been hospitalized.

Our findings demonstrate a high prevalence of hematologic abnormalities in women with anorexia nervosa. Anemia occurred in 39%, thrombocytopenia in 5%, and leukocytopenia in 34% of our study participants. Hematologic suppression can be severe, as we observed an hematocrit value as low as 25.1%, platelet counts as low as 114000/mL, and white blood cell counts as low as 2300/ μ L. Previously studies have reported lower rates of anemia¹⁴ and similar rates of leukocytopenia (34%),^{11,14} but these were studies of hospitalized patients rather than persons living in the community, and there were fewer of these patients than there were in our study. However, the clinical significance of the anemia, leukocytopenia, and thrombocytopenia that our study detected is unknown.

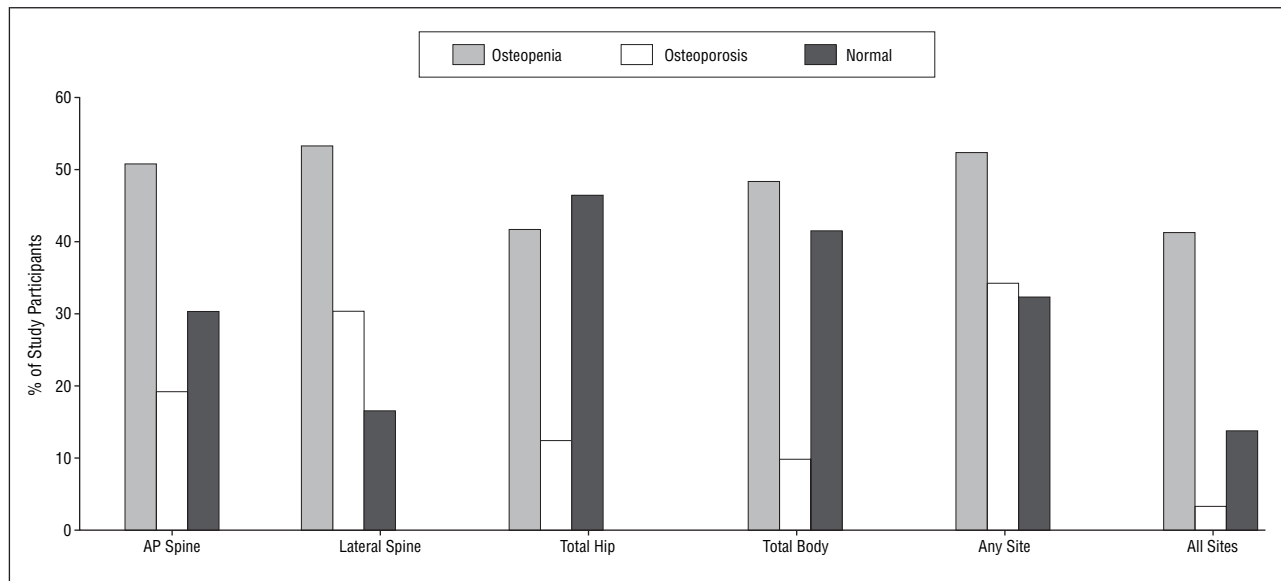


Figure 2. Percentage of study participants with anorexia nervosa who had normal bone density, osteopenia, and osteoporosis. A T score less than -1.0 defines osteopenia and a T score less than -2.5 defines osteoporosis. AP indicates anteroposterior.

The rate of electrolyte abnormalities in this large community-dwelling group of women with anorexia nervosa was surprisingly high. We found a 20% prevalence of hypokalemia, which is higher than previously reported, and more than half of our study participants with hypokalemia reported no history of purging. This contrasts with a large study by Greenfeld et al⁷ of women with anorexia nervosa attending an outpatient eating disorders program. These authors found that only 4.6% of their study patients had hypokalemia—therefore, a rare occurrence in individuals who did not report purging.⁷ The discrepancy between our data and those of Greenfeld et al regarding the association of purging and hypokalemia may reflect discomfort in revealing purging behaviors in the setting of a one-time study visit. Therefore, we recommend pursuing the possibility of purging behaviors in all patients with hypokalemia. However, based on our data we cannot rule out the possibility that hypokalemia may occur in low-weight patients who do not purge. Therefore, because hypokalemia can precipitate potentially fatal cardiac arrhythmias, we also recommend measurement of potassium levels in all patients with anorexia nervosa, even in patients who report no history of purging.

We report that sodium levels were reduced in 7% of our participants. We did not measure urine sodium levels and therefore are unable to determine the mechanism of hyponatremia in these women. Of note, 1 woman had a history of seizures secondary to hyponatremia. Therefore, it is important to measure sodium levels in patients with anorexia nervosa. Similarly, in underweight women with hyponatremia, the diagnosis of anorexia nervosa should be considered.

We found that a high percentage of our study participants had bradycardia (41%) and hypotension (16%). Serious cardiac abnormalities have been reported in hospitalized persons with anorexia nervosa.^{10,11,15} These include dysrhythmias, some of which may be secondary to hypokalemia.^{16,23} Two percent of our participants had histories of dysrhythmias, and low potassium levels were

reported as a likely cause in most cases. A reversible cardiomyopathy due to chronic ipecac use has also been reported,²⁴ although none of our participants reported experiencing this complication. Therefore, screening and monitoring patients with anorexia nervosa for cardiac risk factors and dysfunction is important. This should include asking patients whether they purge or have histories of hypokalemia and/or ipecac use. Monitoring vital signs and performing electrocardiograms and serial measurements of plasma potassium are also important.

In our study, women with a longer duration of anorexia nervosa were more likely to exhibit purging behaviors than those with a shorter duration of the condition. Eddy et al²⁵ reported that duration of anorexia nervosa is a significant risk factor for the development of purging symptoms. This is important, as purging may increase the risk of hypokalemia and subsequent cardiac dysrhythmias, and self-induced vomiting increases the risk of additional complications, including Mallory-Weiss tears, esophagitis, and dentin erosion.

An elevation of serum alanine aminotransferase was observed in 12% of our participants, a much higher prevalence than in healthy young patients,²⁶ and 1 reading was 5.4 times the upper limit of normal. These findings are similar to the 6.5% prevalence of elevated alanine aminotransferase levels observed in a study of outpatients with anorexia nervosa by Mickley et al.²⁸ Malnutrition²⁸ and refeeding¹⁵ are possible causes of such abnormalities in anorexia nervosa, but we were not able to determine the etiology of alanine aminotransferase abnormalities in our participants. Importantly, in the study by Mickley et al,²⁸ a number of patients were found to have causes other than low weight for the elevated liver enzymes, including alcoholism, acetaminophen overdose, use of other hepatotoxic medications, and common bile duct stones. Therefore, persistent elevation of transaminases should prompt an evaluation for other possible causes.²⁷

Of note, thyrotropin stimulating hormone levels were normal in all but 2 participants. Our data suggest that

abnormal thyrotropin levels in patients with anorexia nervosa should not be attributed to the eating disorder itself.

In this study, 52% of participants had osteopenia and 34% had osteoporosis at least 1 skeletal site, and these findings are similar to those published in our report on a subset of these women.⁸ Moreover, fewer than 15% of participants had normal bone density at all skeletal sites tested and 30% reported histories of fractures. This is markedly higher than the rates for healthy young women,²⁹ as previously reported by Rigotti et al,³⁰ who observed a non-spinal fracture rate 7 times higher than normal in women with anorexia nervosa. The prevalence of bone loss and fractures observed in our community-dwelling group of young women with anorexia nervosa suggests that skeletal health is particularly at risk. Estrogen use is not effective in reversing bone loss in anorexia nervosa,^{31,32} and weight recovery is associated with increases in bone density, though often not to normal.³³ Although there are no known Food and Drug Administration–approved therapies for bone loss in anorexia nervosa, bone density evaluations may be useful to demonstrate the detrimental effects of anorexia nervosa and to counsel patients regarding fracture risk.

We report a high prevalence of metabolic, hematologic, hemodynamic, and skeletal abnormal findings in a large group of community-dwelling women with anorexia nervosa. Medical findings associated with anorexia nervosa have primarily been reported for small numbers of hospitalized patients. A limitation of our study was that patients were recruited through advertisements and community-based referrals for a study investigating skeletal health in individuals with anorexia nervosa, and therefore may not reflect a representative cross-section of persons with anorexia nervosa. Moreover, the clinical significance of many of these laboratory abnormalities has not been established. Nevertheless, these findings suggest that a medical evaluation of all women with anorexia nervosa is important and should proceed in concert with psychiatric evaluation and treatment. Of importance, the finding of such otherwise unexplained abnormalities in underweight women should lead to the consideration of the diagnosis of anorexia nervosa.

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