Should Amenorrhea Be a Diagnostic Criterion for Anorexia Nervosa?

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ABSTRACT

Objective: The removal of the amenorrhea criterion for anorexia nervosa (AN) is being considered for the fifth edition of The Diagnostic and Statistical Manual (DSM-V). This article presents and discusses the arguments for maintaining as well as those for removing the criterion.

Method: The psychological and biological literatures on the utility of amenorrhea as a distinguishing diagnostic criterion for AN and as an indicator of illness severity are reviewed.

Results: The findings suggest that the majority of differences among patients with AN who do and do not meet the amenorrhea criterion appear largely to reflect nutritional status. Overall, the two groups have few psychological differences. There are mixed findings regarding biological differences between those with AN who do and do not menstruate and the relationship between amenorrhea and bone health among patients with AN.

Discussion: Based on these findings, one option is to describe amenorrhea in DSM-V as a frequent occurrence among individuals with AN that may provide important information about clinical severity, but should not be maintained as a core diagnostic feature. The possibilities of retaining the criterion or eliminating it altogether are discussed.

Keywords: anorexia nervosa; DSM-V; diagnostic criteria; amenorrhea; eating disorder not otherwise specified; menses

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Introduction

The announcement of the upcoming fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V)[1] has prompted the careful consideration of the diagnostic criteria for anorexia nervosa (AN). The amenorrhea criterion has been proposed as a candidate for removal from the current criteria.[2] The DSM-IV-TR specifies the diagnostic criterion for amenorrhea in AN as "the absence of at least three consecutive menstrual cycles (a woman is considered to have amenorrhea if her periods occur only following hormone, e.g., estrogen, administration)" (p 589).[1] This criterion has been the subject of debate for a number of reasons. The criterion is useful because it is clear and objective, serving as an important indicator of physical health status (e.g., alerting clinicians to possible deficits in bone mineral density). The presence of amenorrhea may also reflect important biological abnormalities that provide information about the etiology of the illness and/or might inform the development of biological treatments. In addition, the inclusion of amenorrhea as a diagnostic criterion helps avoid possible misdiagnosis of AN by providing a marker of abnormal physiology that helps distinguish constitutionally thin women who are underweight but menstruating from women with AN.

While these arguments support the inclusion of amenorrhea as a diagnostic criterion, a number of concerns have also been raised. First, many individuals fail to meet the amenorrhea criterion despite exhibiting all other criteria of AN, thereby placing them in the Eating Disorder Not Otherwise Specified (EDNOS) category. Since a primary goal of the DSM is to provide clinicians with guidelines to make diagnoses that can inform treatment decisions, the designation of EDNOS for individuals

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who meet all but the amenorrhea criterion for AN poses a problem because we lack treatment guidelines for the heterogeneous category of EDNOS. In addition, a diagnosis of EDNOS for an underweight woman with AN who continues to menstruate may fail to indicate the severity of the individual's illness. The requirement of the criterion for a diagnosis of AN is also problematic because it cannot be applied to males, to post-menopausal women or to women using hormone replacements such as oral contraceptives. Furthermore, some females with other clinical features of the illness may be too young for a diagnosis of primary amenorrhea and the DSM-IV three-month time frame excludes individuals with a recent onset of the illness who fulfill the other criteria, but who have not ceased menstruating for a sufficient length of time.

Given these concerns, the aims of this article were to review the biological and psychological literatures on (1) the utility of amenorrhea as a distinguishing diagnostic criterion for AN, and (2) the utility of amenorrhea as an indicator of illness severity.

Method

We conducted a literature review to investigate the biological and psychological differences among individuals with AN who were amenorrheic versus those who continued to menstruate. First, we identified articles on menstrual status and AN by searching MEDLINE and PsyInfo computer databases and reviewing the reference sections of the papers that were retrieved from our initial search. Search terms included, but were not limited to: amenorrhea, menstruation, menses, anorexia nervosa, and eating disorder not otherwise specified. Articles were reviewed if biological or psychological comparisons were made between individuals with AN who were menstruating versus those who were not or between individuals with AN versus constitutionally thin women who were menstruating. We also reviewed studies bearing on questions regarding amenorrhea and bone health and resumption of menses among women with AN. The results of the literature review are presented below, and are summarized in Supporting Information Table S1.

Results

Potential Biological Differences Signified by Amenorrhea

It is useful to consider the biological abnormalities associated with the occurrence of amenorrhea in AN. Numerous studies link amenorrhea with reduced body weight and/or percentage of body fat.[3,4] However, while a clear association between reduced body weight and amenorrhea exists, the notion of a required critical percentage of body fat for normal menses has not been supported by empirical evidence.[4] Studies of athletes and individuals with AN have not observed consistent differences in percentage of body fat among those menstruating regularly and those who are amenorrheic. In addition, some women with lower percentages of body fat continue to have normal menses.[4] Furthermore, while amenorrhea often occurs following a reduction in body weight and body fat, it precedes weight loss in approximately 20% of patients with AN[5,6] and can persist after weight gain.[7–9] Amenorrhea can also occur among normal weight women who engage in dietary restraint, who exercise strenuously, or who experience psychological stress.[4] Taken together, these findings suggest that, while reduced weight and/or body fat are associated with amenorrhea for many individuals with AN, other factors also contribute to the development of amenorrhea.

The relationship between amenorrhea and energy deficits is informed by considering the role of leptin, a protein released by fat cells that contributes to the regulation of energy intake and expenditure and body weight. In general, low leptin levels have been observed in individuals with AN compared to controls and compared to constitutionally thin menstruating women who had comparable BMIs, but did not have eating disorders. In addition, leptin levels increase in response to weight-restoration among women with AN.[4,10] However, those women who remain amenorrheic following nutritional rehabilitation have lower leptin levels than those who experience a return of menses. In a study comparing constitutionally thin women and women with AN, those with AN also had significantly lower median serum insulin-like growth factor I (IGF-1) levels and lower caloric intake, yet BMI and fat mass were comparable between the groups. This suggests that weight and/or body fat may not fully explain the reduced levels of both IGF-1 and leptin, but the decreased caloric intake among women with AN does point to a difference in nutritional status between the groups.[10] Luteinizing hormone (LH) levels were also significantly lower in women with AN and best distinguished them from constitutionally thin menstruating women suggesting that the presence of amenorrhea may denote important biological differences between individuals with AN and those without the illness.[10]

A study by Germain et al.[11] also compared women with AN (n = 12) to constitutionally thin

women (n = 10) and normal controls (n = 7). Again, women with AN reported lower caloric intake compared to constitutionally thin women and normal controls, and constitutionally thin women had significantly higher levels of Peptide YY (PYY) and lower levels of glucagon-like peptide 1 (GLP-1) when compared to patients with AN. Ghrelin was higher among AN women while leptin levels were significantly lower. Similarly, another small study of seven constitutionally thin women, seven normal controls, and six patients with restricting subtype AN (AN-R)[12] found that AN patients consumed a significantly smaller percentage of lipids and had significantly less fat mass percentage though the groups had comparable total energy expenditure. Women with AN also had significantly lower free thyroid hormone T3, IGF-1 and leptin when compared with normal controls and constitutionally thin women. The results from these comparisons highlight the utility of the amenorrhea criterion as a biological marker of abnormalities that are not captured by weight alone; however, these studies did not make comparisons between women with AN who met all of the other diagnostic criteria except for amenorrhea and constitutionally thin women.

Other biological studies have linked functional hypothalamic amenorrhea to deficiencies in pulsatile gonadotropin releasing hormone (GnRH) secretion,[13] estrogen,[14] leptin,[15,16] insulin-like growth factor-1 (IGF-1)[17] and prolactin levels as well as increased secretion of cortisol, ACTH, CRH[18,19] and endogenous opioids[20] or nocturnal melatonin secretion.[21] It has also been hypothesized that amenorrhea is related to neurotransmitter abnormalities such as increased dopamine activity.[22,23] Therefore, it is possible that important biological differences exist between individuals with AN who are menstruating compared with those who are not. If the presence of amenorrhea reflects biological differences central to understanding the etiology of the illness and/or developing treatments, then it may be a useful diagnostic criterion. However, if it reflects biological differences that are important, but secondary to the development and/or maintenance of AN, it might merit a description in the DSM, but not be a core diagnostic feature.

Clinical Features and Amenorrhea

While few studies have examined biological differences between women with AN who menstruate and those who do not, there is a growing literature evaluating clinical differences between individuals who do and do not meet the amenorrhea criterion. Garfinkel et al.[24] sought to examine differences in a range of clinical measures among individuals with AN in a community-based study. They assessed 24 women meeting full criteria for AN and 44 meeting all criteria except for amenorrhea. The groups did not differ significantly in age of onset, maximum and minimum weight, percent weight loss or bulimic behaviors. While the menstruating group had higher rates of co-morbidity and history of family problems, these differences were not statistically significant. Cachelin and Maher.[25] also failed to uncover statistically significant differences in socio-economic status, years in treatment, age of onset, subtype, body-size overestimation, body distortion, body dissatisfaction, eating concerns, sense of ineffectiveness, external locus of control, depression and general psychopathology between 40 amenorrheic and 12 menstruating women with AN. The non-amenorrheic group was significantly older, weighed significantly more and reported more family control and less family active-recreational orientation, though the analyses were not controlled for a large number of multiple comparisons. In addition, the very small sample size of menstruating patients suggests these results should be interpreted with caution.

A comparison of 16 women with a BMI of less than 17.5 kg/m^2 who had amenorrhea and seven without revealed that those with amenorrhea were more likely to exercise, scored lower on novelty seeking, were less likely to smoke and had lower pulse rates and systolic blood pressure.[26] In addition, percentage body fat, serum T4, free T4, and leptin concentrations were significantly lower in the women with amenorrhea. Pulse rate, serum T4, free T4, novelty seeking and exercise all remained associated with amenorrhea after controlling for percentage body fat. When entered into a stepwise logistic regression model, only current exercise and low novelty seeking remained significant predictors. The authors suggest that the low novelty seeking scores among patients with amenorrhea may be caused by elevated dopaminergic activity which has an inhibitory effect on GnRH-mediated LH release. Alternatively, novelty seeking was significantly associated with binge eating in the study as well as menstruating, so it may be that individuals with high novelty seeking are consuming more nutrients and therefore are less likely to develop amenorrhea.

Watson and Andersen[27] reported a small number of clinical differences related to menstrual status after conducting a retrospective chart review that included 230 individuals with full syndrome AN and 28 individuals who were menstruating and weighed less than 85% of ideal body weight. In this

sample, the menstruating group had a lower discharge percentage of expected body weight, shorter hospitalization and lower scores on the Eating Attitudes Test-26 (EAT-26) and the Eating Disorder Inventory (EDI) drive for thinness subscale than patients who were amenorrheic. However, the groups had comparable admission percentage of expected body weights and did not differ significantly on most clinical measures.

Another retrospective chart review conducted by Roberto et al.[28] included a large sample ($n = 240$) of consecutively admitted inpatients with AN. The results indicated that the amenorrheic group ($n = 150$) differed significantly from the menstruating group ($n = 47$) only on lowest lifetime BMI and admission BMI, with individuals with amenorrhea having lower BMIs on both measures. The two groups did not significantly differ on age, discharge BMI, previous number of hospitalizations, duration of illness, Beck Depression Inventory (BDI) total score, Beck Anxiety Inventory (BAI) total score, and Eating Disorder Examination (EDE) subscale scores.

A study by Miller et al.[29] included a large sample of 74 women with DSM-IV AN and 42 women who met all DSM-IV criteria for AN except amenorrhea. The authors found that percent ideal body weight (IBW), BMI, duration of AN, age of menarche and hours per week of exercise were not significantly different between the groups. However, fat mass, truncal fat mass, and percent body fat were significantly higher in the menstruating group when compared to the amenorrheic group despite having comparable BMIs and IBWs. In addition, mean serum estradiol, follicle-stimulating hormone (FSH) and leptin levels (which correlated with body fat mass and truncal fat) were higher in the menstruating group compared to the amenorrheic group as were IGF-1 levels (which correlated with BMI, leptin, total fat mass, percent fat mass and estradiol). In terms of psychological variables, surprisingly the EDI subscales of drive for thinness and body dissatisfaction were more severe in the menstruating group compared with the amenorrheic group. In addition, the menstruating patients had greater interoceptive awareness and confusion in recognizing and accurately responding to emotional states, including feelings of hunger and satiety. There were no other differences between the groups on any of the other five EDI subscales.

A study by Abraham et al.[30] provided further evidence that differences among women with eating disorders with or without amenorrhea reflect a variety of indicators of nutritional status. The investigators compared 90 inpatients with secondary amenorrhea to 19 with irregular periods, and 54 who had regular cycles. They found that the best predictors of amenorrhea at admission were a current BMI less than or equal to 18.0 kg/m^2 and having rules for exercising, though it is difficult to draw conclusions about amenorrhea as a criterion for AN since the analyses included patients with AN or bulimia nervosa (BN). A second study by Abraham et al.[31] examined 242 female patients with eating and exercise disorders (defined as exercising excessively and feeling annoyed, angry or agitated if interrupted, continuing to exercise if ill or injured and considering exercise to be of greater than average importance for psychological reasons or to influence energy expenditure, body weight or shape) upon admission to an eating disorder inpatient unit or 12 months later. Again, the study included patients with AN, BN and EDNOS, dividing them into groups based on menstrual status: secondary amenorrhea versus oligomenorrhea/regular menses. The oligomenorrhea/regular menses group was more likely to have an exercise disorder compared to the amenorrhea group, but the results also indicated that older age and higher current BMI were associated with a lower likelihood of amenorrhea, while losing more weight and exercising for reasons of mood, body image or energy utilization were associated with a greater likelihood of amenorrhea. Amenorrhea was also observed to occur at higher body weights when weight loss was more substantial. Current BMI, weight loss, exercise for mood or energy utilization and age predicted 81% of cases of amenorrhea and 82% of noncases without amenorrhea, suggesting that parameters reflecting nutritional status are the best predictors of amenorrhea.

Pinheiro et al.[32] examined data from 1,705 women with eating disorders and similar to Abraham et al.[30,31] included individuals with AN, BN and EDNOS in order to compare menstrual status across these three diagnostic categories. The authors found that menstruating participants had significantly higher values for highest and lowest lifetime BMI, greater binge and vomiting frequency, and more appetite suppressant use. Amenorrheic participants had the greatest caloric restriction and highest frequency of exercising and laxative abuse, but no differences in comorbid Axis I and II psychopathology emerged. However, the normal menstruation group scored significantly lower on eating disorder rituals, personal standards, and harm avoidance, but higher on novelty seeking, which was also found in the Gendall et al.[26] sample.

In a larger population-based study using data from a Twin Registry, Bulik et al.[33] employed latent class analysis and revealed that individuals who had the psychological features of AN with and without amenorrhea clustered naturally together. They reported that the symptom of amenorrhea was equally represented in the "anorexic class" and in the low-weight binge eating class that did not endorse the psychological symptoms of AN.

Finally, a recent study[34] compared 57 inpatients with AN and 16 inpatients meeting all of the criteria for AN except for amenorrhea on a variety of clinical measures including treatment outcome. They found that at baseline, patients who were menstruating were older, had a higher admission BMI, a longer duration of illness, lower EDE global, shape and weight concerns scores, more binge eating and self-induced vomiting and less engagement in intense exercise. The groups did not differ, however, on general psychopathology and personality measures in contrast to previous findings that found lower novelty seeking scores among patients with amenorrhea.[26] They also reported that only baseline BMI and intense exercise were significantly associated with the presence of amenorrhea at admission, suggesting that the criterion may be a function of BMI and exercise. No differences between the two groups in drop out rate or time to drop out from a 20 week inpatient/residential CBT-based hospital program were observed.

Amenorrhea and Bone Health

Amenorrhea is associated with bone health and the risk of fractures is related to a decrease in bone mineral density (BMD) among women.[35–37] Therefore, the inclusion of amenorrhea as a diagnostic criterion has clinical utility because it alerts clinicians to potential deficits in bone mineral density, though weight status may also provide this information. In a large epidemiological sample, Vestergaard et al.[38] found a significant increase in fracture risk among women who received a diagnosis of AN. In addition, the authors note that studies have found the BMD of the spine and hip to be, on average, 15% less in women with AN when compared to normal controls.[39] However, there have not been consistent results to suggest that hormone therapy or oral contraceptives are efficacious in increasing bone density in women. This provides evidence that the mechanism through which osteopenia emerges and may reverse is not mediated solely by hormonal deficiency. While risk factors for low BMD include a long duration of AN and amenorrhea[40] there is also research which indicates that weight restoration may increase BMD independently of resumption of menses.[41]

An early study of bone density among 33 females (8 with AN, 17 with BN, and 8 with EDNOS based on DSM-III-R criteria) ages 20 to 53 years old found that seventy-five percent of the women with AN were amenorrheic and one woman with AN had a fracture history. Bone density analyses of the AN subgroup revealed significant differences from controls in the trochanter and the neck of the femur, and near significant differences in Ward's triangle of the femur and the lumbar spine. However, there was no evidence of a correlation between decreased bone density and estrogen deficiency and/or history of amenorrhea in any of the diagnostic subgroups.[42] In addition, Rigotti et al.[43] found no significant correlation between estradiol levels and bone density among 18 patients with AN, but Treasure et al.[44] observed a negative correlation between duration of amenorrhea and bone density of the femur and spine among 31 patients with AN.

Goebel et al.[45] studied 137 hospitalized women with AN, BN or EDNOS, though the sample contained only 20 individuals with AN-R and 15 with AN-B/P. Comparisons were made to a representative sample of German women though a limited description of this sample is presented. The results indicated that bone density of the lumbar spine was highly correlated with BMI on admission (r = 0.52, $p < .01$) and past minimum BMI (r = 0.49, $p < .01$). In addition, current weight after correction for age and height was the best predictor of current bone mineral density, while menstrual status, reduced caloric intake, binge eating, vomiting, use of estrogen, laxatives, and nicotine did not significantly predict BMD. In contrast, the Miller et al.[29] study described earlier found that bone mineral density was significantly lower at the posterior-anterior lumbar and lateral spine as was total body and radius BMD in the amenorrheic group compared with the menstruating group and these groups were of similar weights. These investigators did not find differences in bone density at the hip. In addition, 61% of women with amenorrhea had osteoporosis compared with 24% of those who were menstruating. However, Watson and Andersen[27] reported that their amenorrheic group and low-weight, menstruating group had comparable bone deficiency when measured on an age and gender-matched bone mineral density test, though this was in a small sample.

Dominguez et al.[14] built on past research to investigate how bone density changed with weight-restoration. They studied 28 women with AN (one

who maintained her menstrual cycle at low weight) before and after they normalized their weight and compared them to 11 control subjects matched for age and percentage IBW. They also obtained data from a second comparison group comprising 30 reference control subjects who were healthy, postpubertal white girls of Spanish descent with similar BMIs. Patients were divided into those who had a resumption of menses upon reaching 90% IBW (n = 8) and those who remained amenorrheic. While the small sample size makes it difficult to detect differences, the amenorrheic group did differ significantly on lower spine and total BMDs compared to the control subjects. In addition to bone density, the investigators measured osteocalcin, a biochemical marker of bone formation and N-telopeptide (NTX) a marker of bone resorption. Osteocalcin levels rose with weight gain, but did not differ significantly between the differing menstrual status groups, though the amenorrheic group had higher levels than reference controls. Those with persistent amenorrhea had higher NTX levels compared to the reference controls, but not the healthy controls, while patients who were menstruating had a fall in NTX that was within healthy ranges. The amenorrheic group had significantly lower LH and FSH levels at baseline; these increased with weight gain, but not significantly when compared to controls. Those patients who experienced a return of menses had an increase in estradiol levels which was not significantly different than controls, while those with persistent amenorrhea also had an increase in estradiol, but it remained significantly lower than those in the recovered menses group. The authors concluded that while osteocalcin levels increased with weight gain for all participants, elevated NTX levels fell into the normal range only for those individuals who had a resumption of menses. They suggest that this would likely lead to larger increases in BMD among this group over time.

Overall, it appears difficult to determine whether the link between amenorrhea and bone mineral density is largely accounted for by weight status or other factors.

Predictors of Resumption of Menses

Finally, another important research agenda has been the quest for predictors of the resumption of menses in individuals with AN. This research is relevant to understanding the diagnostic utility of amenorrhea because it provides information about whether the likelihood of amenorrhea is simply related to weight or to other features of the disorder. In an effort to clarify which factors are associated with the return of menses, Golden et al.[7] followed a cohort of 100 adolescents with AN who received treatment largely on an outpatient basis. Sixty-nine of these individuals were followed for up to one year, while 59 of these were followed for 2 years. The resumption of menses occurred on average at 9.4 (S.D. 8.2) months after patients presented for treatment. In addition, the weight at which menses returned was on average, 2.04 kg greater than the weight at which menses were lost. They reported that 86% of the sample resumed menses within 6 months of obtaining a weight which was at or above 90% of standard body weight based on National Center for Health Statistics tables. At the one year follow-up time point, there were no significant differences in weight, percent standard body weight (SBW), body mass index or percent body fat between those who had resumed menstruating and those who continued to be amenorrheic. However, estradiol levels were significantly lower in the amenorrheic group. In terms of baseline predictors of return of menses, those who were amenorrheic one year later did not differ in age, age of menarche, duration of amenorrhea, duration of illness, amount of weight loss, or on psychological measures such as the EAT, EDI or BDI or in amount of exercise performed. The amenorrheic individuals one year later were, however, of lower weight and lower percent body fat at baseline. They also had lower FSH levels and undetectable LH levels.

The authors observed that one-fifth of the adolescents in their sample experienced amenorrhea prior to weight loss, but these individuals were not more likely to remain amenorrheic after one year follow-up. They note that if hypothalamic dysfunction were primary, these individuals would have been more likely to remain amenorrheic for a longer period of time, but this was not supported by that data. Therefore, they concluded that hypothalamic dysfunction in AN is likely secondary to malnutrition.

Finally, Copeland et al.[46] obtained a sample of 229 females seeking outpatient treatment, who met DSM-III-R criteria for AN (n = 41), BN (n = 98) or AN/BN (n = 90) and were followed for one year. They found that low body weight was the major associated feature of amenorrhea. In addition, those with amenorrhea tended to be younger and to have higher rates of affective disorders (though this may be attributed to their lower weight status). However, the groups did not differ on age of onset and duration of illness. There was also an association between Axis II diagnosis and menstruation, though the authors hypothesized that this may be due to the higher prevalence of Axis II disorders

among older individuals. Binge eating was also associated with menstruation. Amenorrhea appeared to persist at follow-up among those who had a longer duration of illness and who met criteria for an anxiety disorder.

Discussion

Most differences between individuals with AN who do and do not meet the amenorrhea criterion appear to reflect nutritional status. These differences include measures of current and lowest lifetime BMI as well as exercise habits. Psychologically, these two groups of patients appear quite similar, with some mixed findings on novelty seeking scores and some differences on a few eating disorder-related questionnaires. These differences tend to favor higher scores, indicating greater illness severity, in the menstruating groups, but this paradoxical finding may be explained by the fact that some eating disorder pathology, such as binge eating, may be associated with better nutritional status in an AN sample. In addition, there is some emerging evidence that these groups do not differ on various measures of treatment outcome. While there are mixed findings related to bone health, some studies also conclude that nutritional rehabilitation plays a key role in restoring BMD, rather than something specific to the return of menses. Finally, studies examining the resumption of menses also point to nutritional factors being essential to restoration of normal function.

By retaining the amenorrhea criterion, DSM-V would emphasize to clinicians that individuals with AN are at greater risk of medical complications such as bone mineral loss and are likely to have low BMIs and therefore be more severely ill. Amenorrhea also serves as a potentially important marker of biological abnormalities, therefore potentially providing enhanced clinical utility. However, the criterion can only be applied to post-menarchal/pre-menopausal women who are not taking exogenous hormones. In addition, some women share many of the features of AN but continue to have some menstrual activity; assigning such women a diagnosis of AN might increase the chances of their receiving appropriate treatment.

The following options for DSM-V are possible regarding the requirement for amenorrhea for AN:

- Retain the amenorrhea criterion. DSM-V could retain the amenorrhea criterion as amenorrhea is present in the majority of individuals with the other diagnostic features of AN. This option is the most conservative; it would require that clinicians evaluate menstrual status and emphasize the potential for clinical complications such as bone loss.
- Eliminate the amenorrhea criterion. Much of the available literature indicates that the presence of amenorrhea does not usefully distinguish clinically a category of low weight patients. When it develops, amenorrhea in AN generally appears to be secondary to weight loss, malnutrition and exercise behavior rather than a primary or predisposing element of the illness. Additionally, amenorrhea is not a relevant feature in several sub-groups of individuals who exhibit other features of AN such as male patients, female patients taking exogenous hormones and female patients who have not reached menarche.
- Eliminate the amenorrhea criterion, but include amenorrhea in DSM-V text as one of several medical signs and symptoms frequently associated with AN. Amenorrhea could be described in the DSM-V text as being frequently associated with a diagnosis of AN and with additional medical complications such as low BMD. Alternatively, amenorrhea could be included in a severity dimension. If this option is considered, amenorrhea will likely need to be included together with other significant medical findings (bradycardia, low BMD, etc) which are relevant to males and to pre-menarchal females.

This literature review documents that amenorrhea is a physiologically important disturbance often seen in association with AN and a useful indicator of clinical severity. However, there is compelling evidence that it not be included as a diagnostic criterion in DSM-V.

References

1. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 4th ed. Washington, DC: American Psychiatric Association, 1994.
2. Mitchell J, Cook-Myers T, Wonderlich S. Diagnostic criteria for anorexia nervosa: Looking ahead to DSM-V. Int J Eat Disord 2005;37:595–597.

3. Vigersky RA, Anderson AE, Thompson RH, Loriaux DL. Hypothalamic dysfunction in secondary amenorrhea associated with simple weight loss. N Eng J Med 1977;297:1141–1145.
4. Golden N, Carlson J. The pathophysiology of amenorrhea in the adolescent. Ann N Y Acad Sci 2008;1135:163–178.
5. Halmi KA. Anorexia nervosa: Demographic and clinical features in 94 cases. Psychosom Med 1974;36:18–26.
6. Hurd HP, Palumbo PJ, Gharib H. Hypothalamic-endocrine dysfunction in anorexia nervosa. Mayo Clin Proc 1977;52: 711–716.
7. Golden N, Jacobson M, Schebendach J, Solanto M, Hertz S, Shenker R. Resumption of menses in anorexia nervosa. Arch Pediatr Adolesc Med 1997;151:16–21.
8. Falk JR, Halmi KA. Amenorrhea in anorexia nervosa: Examination of the critical body weight hypothesis. Biol Psychiatry 1982;17:799–806.
9. Brambilla F, Monteleone P, Bortolotti F, Grave R, Todisco P, Favaro A, et al. Persistent amenorrhoea in weight-recovered anorexics psychological and biological aspects. Psychiatry Res 2003; 118:249–257.
10. DiCarlo C, Tommaselli G, Filippo E, Pisano G, Nasti A, Bifulco G, et al. Menstrual status and serum leptin levels in anorectic and in menstruating women with low body mass indexes. Fertil Steril 2002;78:376–382.
11. Germain N, Galusca B, Le Roux C, Bossu C, Ghatei M, Lang F, et al. Constitutional thinness and lean anorexia nervosa display opposite levels of peptide YY, Glucagon like peptide 1, leptin and ghrelin. Am J Clin Nutr 2007;85:967–971.
12. Bossu C, Galusca B, Normand S, Germain N, Collet P, Frere D, et al. Energy expenditure adjusted for body composition differentiates constitutional thinness from both normal subjects and anorexia nervosa. Am J Physiol Endocrinol Metab 2007;292: 132–137.
13. Falsetti L, Gambera A, Barbetti L, Specchia C. Long-term follow-up of functional hypothalamic amenorrhea and prognostic factors. J Clin Endocrinol Metab 2008;87:500–505.
14. Dominguez J, Goodman L, Gupta S, Mayer L, Etu S, Walsh BT, et al. Treatment of anorexia nervosa is associated with increases in bone mineral density, and recovery is a biphasic process involving both nutrition and return of menses. Am J Clin Nutr 2007;86:92–99.
15. Miller KK, Parulekar Ms, Schoenfeld E, Anderson E, Hubbard J, Klibanski A, et al. Decreased leptin levels in normal weight women with hypothalamic amenorrhea: The effects of body composition and nutritional intake. J Clin Endocrinol Metab 199883:2309–2312.
16. Warren MP, Voussoughian F, Geer EB, Hule EP, Adberg CL, Ramos RH. Functional hypothalamic amenorrhea: Hypoleptinemia and disordered eating. J Clin Endocrinol Metab 1999;84:873–877.
17. Laughlin GA, Yen SSC. Nutritional and endocrine-metabolic aberrations in amenorrheic athletes. J Clin Endocrinol Metab 1996;31:4301–4309.
18. Biller BMIK, Federoff HJ, Koenig JI, Klibanski A. Abnormal cortisol secretion and responses to corticotrophin-releasing hormone in women with hypothalamic amenorrhea. J Clin Endocrinol Metab 1990;70:311–317.
19. Berga SL, Girton LJ. The psychoneuroendocrinology of functional hypothalamic amenorrhea syndrome. Psychiatr Clin North Am 1989;12:105–116.
20. Petraglia F, Panerai AE, Rivier C, Cocchi D, Genazzani AR. Opioid control of gonadotropin secretion. In: Genazzani AR, Montemagno U, Nappi C, Petraglia F, editors. Brain and Female Reproductive Function. Carnforth, UK: Parthenon Publishing Group, 1988, pp. 65–72.
21. Kadva A, Djahanbakhch O, Monson J, Di WL, Silman R. Elevated nocturnal melatonin is a consequence of gonadotropin-releasing hormone deficiency in women with hypothalamic amenorrhea. J Clin Endocrinol Metab 1998;83:3653–3662.
22. Barry V, Klawans HL. On the role of dopamine in the pathophysiology of anorexia nervosa. J Neural Transm 1976;38:107–121.
23. Golden N, Shenker IR. Amenorrhea in anorexia nervosa neuroendocrine control of hypothalamic dysfunction. Int J Eat Disord 1994;16:53–60.
24. Garfinkel P, Lin E, Goering P, Spegg C, Goldbloom D, Kennedy S, et al. Should amenorrhea be necessary for the diagnosis of anorexia nervosa? Evidence from a Canadian community sample. Br J Psychiatry 1996;168:500–506.
25. Cachelin F, Maher B. Is amenorrhea a critical criterion for anorexia nervosa? J Psychosom Res 1998;44:435–440.
26. Gendall K, Joyce P, Carter F, McIntosh V, Jordan J, Bulik C: The psychobiology and diagnostic significance of amenorrhea in patients with anorexia nervosa. Fertil Steril 2006;85:1531–1535.
27. Watson T, Andersen A. A critical examination of the amenorrhea and weight criteria for diagnosing anorexia nervosa. Acta Psychiatr Scand 2003;108:175–182.
28. Roberto CA, Steinglass J, Mayer LES, Attia E, Walsh BT. The clinical significance of amenorrhea as a diagnostic criterion for anorexia nervosa. Int J Eat Disord 2008;41:559–563.
29. Miller K, Grinspoon S, Gleysteen K, Grieco J, Ciampa J, Breu J, et al. Preservation of neuroendocrine control of reproductive function despite severe undernutrition. J Clin Endocrinol Metab 2004;89:4434–4438.
30. Abraham S, Pettigrew B, Boyd C, Russell J, Taylor A. Usefulness of amenorrhoea in the diagnoses of eating disorder patients. J Psychosom Obstet Gynaecol 2005;26:211–215.
31. Abraham S, Pettigrew B, Boyd C, Russell J. Predictors of functional and exercise amenorrhoea among eating and exercise disordered patients. Hum Reprod 2006;21:257–261.
32. Pinheiro A, Thornton L, Plotonicov K, Tozzi F, Klump K, Berrettini W, et al. Patterns of menstrual disturbance in eating disorders. Int J Eat Disord 2007;40:424–434.
33. Bulik C, Sullivan P, Kendler K. An empirical study of the classification of eating disorders. Am J Psychiatry 2000;157: 886–895.
34. Grave D, Calugi S, Marchesini G. Is amenorrhea a clinically useful criterion for the diagnosis of anorexia nervosa? Behav Res Ther 2008;46:1290–1294.
35. Grinspoon S, Miller K, Coyle C, Krempin J, Armstrong C, Pitts S, et al. Severity of osteopenia in estrogen-deficient women with anorexia nervosa and hypothalamic amenorrhea. J Clin Endocrinol Metab 1999;84:2049–2055.
36. Seeman E, Szmukler GI, Formica C, Tsalamandris C, Mestrovic R. Osteopororsis in anorexia nervosa: The influence of peak bone density, bone loss, oral contraceptive use, and exercise. J Bone Miner Res 1992;7:1467–1474.
37. Marshall D, Johnell O, Wedel H. Meta-analysis of how well measures of bone mineral density predict occurrence of osteoporotic fractures. Br Med J 1996;312:1254–1259.
38. Vestergaard P, Emborg C, Stoving R, Hagen C, Mosekilde L, Brixen K. Fractures in patients with anorexia nervosa, bulimia nervosa and other eating disorders-a nationwide register study. Int J Eat Disord 2002;32:301–308.
39. Vestergaard P, Emborg C, Stoving R, Hagen C, Mosekilde L, Brixen K. Patients with eating disorders: A high risk group for fractures. Orthop Nurs 2003;22:325–331.
40. Rigotti NA, Neer RM, Skates SJ, Herzog DB, Nussbaum SR. The clinical course of osteopororis in anorexia nervosa. JAMA 1991; 265:1133–1138.
41. Bachrach LK, Katzman DK, Litt IF, Guido D, Marcus R. Recovery from osteopenia in adolescent girls with anorexia nervosa. J Clin Endocrinol Metab 1991;72:602–606.

42. Joyce J, Warren D, Humphries L, Smith A, Coon J. Osteoporosis in women with eating disorders: Comparison of physical parameters, exercise and menstrual status with SPA and DPA evaluation. J Nucl Med 1990;31:325–331.
43. Rigotti NA, Nussbaum SR, Herzog DB, Neer MN. Osteoporosis in women with anorexia nervosa. N Engl J Med 1984;311:1601–1606.
44. Treasure J, Fogelman I, Russel GF. Osteopaenia of the lumbar spine and femoral neck in anorexia nervosa. Scott Med J 1986;31:206–207.
45. Goebel G, Schweiger U, Kruger R, Fichter M. Predictors of bone mineral density in patients with eating disorders. Int J Eat Disord 1999;25:143–150.
46. Copeland PM, Sacks NR, Herzog DB. Longitudinal follow-up of amenorrhea in eating disorders. Psychosom Med 1995;57:121–126.