Endocrinological aspects in anorexia nervosa

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Abstract

Anorexia nervosa is a psychiatric illness characterized by restricted calorie intake, self-induced weight loss, and an intense fear of weight gain. The age of onset of the disease appears to be decreasing, placing adolescents and young adults, especially women, at risk, although the prevalence in males is increasing. The state of starvation and chronic stress characteristic of this disorder lead to global endocrine dysregulation with dysfunction of the hypothalamic-pituitary axes (hypogonadotropic hypogonadism; growth hormone resistance with potential detriment to final height; hypercortisolism and relative hypothyroidism), as well as changes in the concentrations of adipokines and appetite-regulating hormones. These adaptive abnormalities in the hormonal axes are reversible with weight recovery. Both hormonal deficiencies and malnutrition negatively affect bone metabolism and lead to decreased bone mineral density, accompanied by impaired bone microarchitecture and an increased risk of fractures. Restoring body weight, normalizing nutritional intake, and recovering menstrual cycles are essential for improving bone health, but low bone density and increased risk of fractures can remain a long-term complication in individuals recovering from anorexia nervosa.

Resumen

La anorexia nerviosa es una enfermedad psiquiátrica caracterizada por una restricción de la ingesta calórica, una pérdida de peso autoinducida y un miedo intenso a la ganancia ponderal. La edad de inicio de la enfermedad parece estar disminuyendo, lo que pone en riesgo a adolescentes y adultos jóvenes, especialmente del género femenino, aunque la prevalencia en varones es cada vez mayor. El estado de inanición y el estrés crónico, propios de este trastorno, conducen a una desregulación endocrina global con disfunción de los ejes hipotálamo-hipofisarios (hipogonadismo hipogonadotropo; resistencia a la hormona de crecimiento con el potencial detrimento en la talla final; hipercortisolismo e hipotiroidismo relativo), así como modificaciones en los niveles de adipoquinas y hormonas reguladoras del apetito. Estas alteraciones adaptativas en los ejes hormonales son reversibles con la recuperación ponderal. Tanto las deficiencias hormonales como la desnutrición afectan negativamente al metabolismo óseo y conllevan una disminución de la densidad mineral ósea, acompañándose de una microarquitectura ósea deteriorada y un mayor riesgo de fracturas. La restauración del peso corporal, la normalización de la ingesta nutricional y la recuperación de los ciclos menstruales son fundamentales para mejorar la salud ósea, pero la baja densidad ósea y el aumento del riesgo de fracturas pueden seguir siendo una complicación a largo plazo en los individuos que se recuperan de la anorexia nerviosa.

Key words: *Anorexia nervosa; Adolescent; Endocrine disorders; Bone density; Weight restoration.*

Palabras clave: Anorexia nerviosa; Adolescente; Alteraciones endocrinológicas; Densidad ósea; Restauración ponderal.

OBJECTIVES

- To understand the main endocrinological manifestations that can affect patients with anorexia nervosa.
- To identify individual risk factors that can enhance and perpetuate endocrinological disorders.
- To promote the restoration of weight, as an essential part of the recovery of the hypothalamic-pituitary-gonadal axis, thus improving bone health.
- To participate in a multidisciplinary approach in the comprehensive care of patients with anorexia nervosa.

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Introduction

The possibility of endocrinological abnormalities in patients with anorexia nervosa should be considered and evaluated as part of the follow-up process.

Anorexia nervosa (AN) is a psychiatric disorder characterized by a restriction of caloric intake, self-induced and maintained weight loss, and a distorted perception of body image, accompanied by an intense fear of weight gain[1].

Although the overall incidence of AN remains stable, it has increased significantly in children under 15 years of age over the past decade. The age of onset of the disease appears to be decreasing, placing adolescents and young adults, especially females, at risk[2]. Prevalence studies indicate wide differences by age and sex, with the prevalence being much higher in young women. The prevalence according to the DSM-5 is estimated at 0.8-6.3% in women and 0.1-0.3% in men, with a peak incidence at 15-19 years of age[3].

The starvation state and chronic stress of AN lead to a variable global endocrine dysregulation. Adaptive hormonal alterations include dysfunction of the hypothalamic-pituitary-gonadal axis, resulting in hypothalamic amenorrhea and relative estrogen and androgen deficiency, with increased cortisol levels and relative hypothyroidism. Furthermore, growth hormone (GH) resistance is observed, with decreased levels of insulin-like growth factor 1 (IGF-1). Appetite regulation and energy metabolism are also affected, perpetuating restrictive eating behaviors[4].

The combination of hormonal deficiencies and malnutrition negatively affects bone metabolism and leads to a decrease in bone mineral density, increasing the risk of osteoporosis and fractures, which increases the morbidity associated with AN[5]. Furthermore, neuropsychiatric comorbidities, such as depressive symptoms or anxiety, are associated with the hormonal changes observed in the disease[6].

Most of the observed endocrine abnormalities are epiphenomena, resulting from the body's adaptation to the state of low energy and malnutrition. Restoring body weight, normalizing nutritional intake, and correcting hormones are key in this process. Therefore, the primary treatment is of the psychiatric disorder itself. However, low bone density and increased risk of fractures may remain a long-term complication in individuals who recover from the illness[7]. The complexity of AN and its manifestations requires a multidisciplinary intervention, addressing psychological, nutritional, and medical aspects[8].

Endocrinological disorders in anorexia nervosa

Figure 1 shows, in a schematic way, the main endocrinological alterations that occur in AN, both in the hypothalamic-pituitary axis and in the appetite-regulating hormones.

The algorithm, at the end of the article, lists the initial tests that should be considered in a patient with AN to detect the presence of endocrinological disorders.

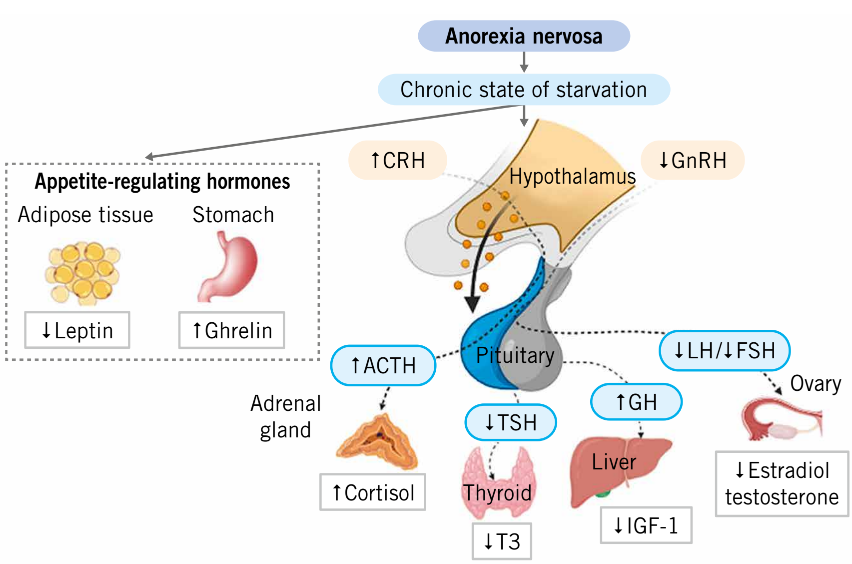

Figure 1. Endocrinological alterations in anorexia nervosa.
ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; FSH: follicle-stimulating hormone; GH: growth hormone; GnRH: gonadotropin-releasing hormone; IGF1: insulin-like growth factor 1; LH: luteinizing hormone; TSH: thyroid-stimulating hormone; T_3: triiodothyronine.

Hypothalamic-pituitary involvement

AN leads to dysfunction of the hypothalamic-pituitary axis, resulting in hypogonadotropic hypogonadism, GH resistance, hypercortisolism, relative hypothyroidism, as well as hyponatremia and decreased oxytocin.

Gonadotropic axis (GnRH-LH/FSH)

Functional hypothalamic amenorrhea (FHA) is one of the most common clinical complications of AN. It results from low energy availability, influenced by multiple interacting factors, and has no organic cause[9,10]. Women with AN frequently present luteinizing hormone (LH) pulsatility patterns reminiscent of those of prepubertal girls, where LH pulses are of low amplitude and occur mainly during nighttime sleep. The alteration in gonadotropin secretion is associated with a decrease in fat mass and, consequently, in leptin. Normal serum leptin levels facilitate gonadotropin secretion and the onset of puberty[6]. FHA leads to decreased levels of estrogen and testosterone. The decrease in gonadal steroid secretion has deleterious effects on bone metabolism, affecting both genders, and hypogonadotropic hypogonadism causes infertility, reversible with recovery from the disease[7].

Diagnosis

Some women experience irregular menstrual periods rather than complete amenorrhea, reflecting the change in energy status over time. Hypogonadotropic hypogonadism is characterized by delayed puberty (primary amenorrhea, absence of secondary sexual characteristics) or arrested puberty (no progression of secondary sexual characteristics, secondary amenorrhea; i.e., absence of menstrual cycles for more than 6 months in a woman with previously well-established cycles and lack of libido in late adolescence). The biochemical pattern will be consistent with hypogonadotropic hypogonadism (low gonadotropins and gonadal steroids).

Treatment

Restoration of normal body weight and increased fat mass have been described as the most important clinical parameters for restoring hypothalamic-pituitary-gonadal function[6,7,10]. Although reproductive function recovers in most women, amenorrhea persists in up to 15% of women despite weight regain[11]. Hormone replacement therapy is described further in the section "Bone health".

Somatotropic axis (GHRH-GH)

Chronic malnutrition leads to a state of acquired GH resistance, with increased GH secretion but decreased IGF-1. Low IGF-1 levels may be an adaptive response to preserve energy by decreasing energy expenditure for growth[6]. IGF-1 is also an important bone anabolic factor; therefore, GH resistance, together with decreased IGF-1 levels, contribute to altered bone metabolism[7]. Decreased insulin levels, characteristic of malnutrition, may play a role in GH resistance through decreased expression of GH receptors on the liver surface[12]. Dietary restriction accompanied by weight loss and excessive exercise, lead to the depletion of glycogen stores and impaired hepatic gluconeogenesis, resulting in hypoglycemia. In the presence of this disorder, which often occurs in severe cases of AN, insulin levels are appropriately decreased. Furthermore, it is important to consider that AN cases are increasingly occurring in patients with previously established type 1 diabetes mellitus, which represents a challenge for the management of these patients, impairing glycemic control[13]. Abnormalities in GH secretion and low levels of IGF-I and IGFBP-3 contribute to poor growth in prepubertal patients, a reduced pubertal growth spurt, and a reduction in their adult height[14]. Recently, a reduction in the PAPP-A2 protease, involved in the cleavage of IGF transporter proteins (IGFBP-3 and IGFBP-5), has also been described in patients with AN. This decrease would limit the release of free IGF-I, thus reducing its bioavailability, which reinforces the functional state of GH resistance characteristic of these patients[15].

Diagnosis

Decreased growth velocity for the patient's pubertal stage. Affected children and adolescents may have short stature relative to their age and sex. Blood IGF-1 levels will be decreased, as will insulin levels. In cases of severe anorexia nervosa, hypoglycemia may be observed.

Treatment

IGF-1 levels increase with refeeding, and weight gain induces normalization of GH secretion. During the active disease phase, administration of supraphysiological doses of recombinant GH does not appear to elevate IGF-1 levels and could instead be detrimental through a reduction in fat mass secondary to GH-stimulated lipolysis in a patient who remains cachectic[16]. In cases of sustained hypoglycemia, treatment should be with glucose supplements, since severe hypoglycemia has been associated with sudden death due to liver failure and depletion of the stores needed to maintain glycemia[13].

Corticotropic axis (CRH-ACTH)

The hypothalamic-pituitary-adrenal axis is chronically stimulated in at least one-third of women with AN. Although the degree of hypercortisolism is inversely related to body mass index (BMI) and fat mass, cortisol measurements rarely exceed twice the upper limit of normal. Increased cortisol levels are influenced by chronic stress related to malnutrition and are also an adaptive mechanism to maintain euglycemia in a state of low energy availability[6,7]. Furthermore, increased ghrelin levels in AN contribute to the stimulation of corticotropin-releasing hormone (CRH)[17]. This hormone has an anorexigenic role that aggravates weight loss[18]. Hypercortisolism is associated with lower lean mass and bone mineral density, as occurs in Cushing's syndrome, although Cushingoid stigmata are not observed in patients with AN[19].

Diagnosis

In clinical practice, adrenocorticotropic hormone (ACTH) and cortisol are not routinely determined.

Treatment

No pharmacological treatment is currently recommended for the management of relative hypercortisolism in AN. This is understood as part of the adaptive changes that occur in the disease, and not as a contributor to the Cushingoid state, as opposed to pathological hypercortisolemia[7]. However, hypercortisolism may not completely resolve despite weight recovery, so in these cases, continued endocrine monitoring is recommended until the axis is restored[4].

Thyrotropic axis (TRH-TSH)

The severe weight loss that occurs in AN is accompanied by thyroid abnormalities, similar to the euthyroid sick syndrome observed in various systemic diseases. It is also a result of adaptation to a state of lower energy and metabolism. It is characterized by decreased total triiodothyronine (T_3) levels, with normal or borderline-low levels of free thyroxine (FT_4) and thyroid-stimulating hormone (TSH), and increased reverse T_3 (R_3T_3) due to increased peripheral conversion of thyroxine (T_4) to inactive T_3. Decreased free T_3 (FT_3) concentrations and a lower FT_3/FT_4 ratio have also been observed to be associated with greater severity of depressive symptoms.

Diagnosis

Blood tests for thyroid hormones (total and free T_3, free T_4, FT_3/FT_4, and TSH).

Treatment

Hormonal treatment is not required, as the changes are adaptive and will improve with weight restoration. In fact, the use of thyroid hormone can aggravate weight loss and promote drug abuse[6]. Sometimes, thyroid hormone levels may be delayed in returning to normal, even after achieving a healthy weight.

Posterior pituitary (antidiuretic hormone, oxytocin) and kidney function

- Antidiuretic hormone (ADH): it is characteristically elevated in some psychiatric pathologies, such as depression. In AN, a slight increase is also observed, although not as pronounced as in other disorders. ADH has a stimulatory role on ACTH; however, it does not appear to be the main contributor to the hyperactivity of this axis in AN[18]. However, inappropriate ADH secretion leads in some patients to free water retention by the kidneys and decreased levels of natremia, which are generally not severe[20]. Other causes of hyponatremia in AN include excessive water consumption, hypovolemia related to malnutrition and vomiting, as well as some drugs that lead to the syndrome of inappropriate antidiuretic hormone secretion (SIADH)[21].

- Other electrolyte disturbances may occur: hypokalemia, hypomagnesemia, and hypophosphatemia. It is especially important to be vigilant of refeeding syndrome, characteristic of rapid nutritional rehabilitation, in which the increase in carbohydrates in the blood and, consequently, insulin, introduces electrolytes (potassium, magnesium and phosphorus) into the cells, with their corresponding decrease in plasma[22].
- Oxytocin: AN is also associated with altered secretion of oxytocin, a hormone with anorexigenic effects in the hypothalamus. Postprandial oxytocin levels are higher in women with AN compared with normal-weight controls, indicating an adaptive response to decreased central postprandial oxytocinergic satiety signals. Furthermore, increased levels of this hormone have been associated with greater severity of anxiety and depression symptoms in these patients. However, nocturnal serum oxytocin levels are decreased in AN compared with normal-weight controls[23].

Adipokines, peptides and appetite-regulating hormones

The state of starvation that accompanies AN entails adaptive changes that affect appetite regulation and metabolism. Characteristically, decreased levels of leptin and insulin are observed, while, conversely, increased levels of ghrelin and peptide YY (PYY).

- Leptin: leptin is an adipokine mainly produced by the adipose tissue, which regulates appetite and energy metabolism, with anorexigenic action. A direct relationship has been shown between serum leptin concentration and the amount of body fat mass, in both children and adults, although there is great individual heterogeneity for a given BMI. Studies in our hospital described how adolescents with AN present significantly lower plasma leptin levels compared to healthy controls of the same age and sex[24]. Furthermore, leptin stimulates the secretion of gonadotropin-releasing hormone (GnRH) and hypoleptinemia contributes to hypothalamic amenorrhea in AN[6]. Endogenous leptin levels increase with refeeding and weight gain[25].
- Insulin: insulin, similar to leptin, has an anorexigenic effect. Insulin levels in AN are also found decreased, in response to the chronic state of malnutrition and, especially, in cases of hypoglycemia, contributing to maintaining normal blood glucose values[12,13].
- Ghrelin: Ghrelin is an orexigenic hormone secreted by oxyntic cells in the stomach and is elevated in AN, both fasting and at night[7]. In addition, it stimulates the secretion of GH and ACTH, which also contributes to maintaining euglycemia[17]. Elevated levels of ghrelin are an adaptive response to chronic nutritional deprivation and decrease with weight gain[6].
- Peptide YY (PYY): PYY is an orexigenic hormone secreted by enteroendocrine cells of the intestine in response to food intake. Physiologically, PYY levels are low during fasting, whereas they increase rapidly in the postprandial period. Therefore, it is expected that, in AN, PYY levels would be decreased. However, elevated levels have been observed, which could enhance the low nutrient intake, as well as the psychopathology of this eating disorder[6,7].

Diagnosis

Serum measurement of appetite-regulating peptides (leptin, insulin, ghrelin, and PYY). Although these hormones are not generally assessed in clinical practice, they have been proposed, among others, as potential diagnostic biomarkers for identifying AN cases[26].

Treatment

Appetite-regulating peptides will, to a greater or lesser extent, return to normal levels with refeeding and weight gain. However, there are some peculiarities, such as ghrelin, where it has been shown that, despite weight restoration, levels remain higher compared to healthy controls[6]. However, beyond the isolated values of these markers, and encompassing them as part of the broad pathogenesis of the disease, they are proposed as potential therapeutic targets for AN[26], which currently has no approved pharmacological treatment. This is the case of metreleptin, a recombinant human analogue of leptin, which could represent a future therapeutic option for AN, given the role of the characteristic hypoleptinemia in these patients[26]. However, further studies are needed to advance in this line.

Bone health

The combination of hormonal deficiencies and malnutrition present in AN is associated with decreased bone mineral density, which increases the risk of osteoporosis and fractures. The best therapeutic strategy to preserve bone density is weight restoration and gonadal function.

Adolescents with AN present with decreased bone mineral density (BMD), which is accompanied by impaired bone microarchitecture and an increased risk of fractures. As previously mentioned, the etiology of decreased BMD is multifactorial. Along with low weight, changes in lean mass and fat stores, alterations in the hypothalamic-pituitary axis, and variations in the levels of adipokines and appetite-regulating peptides negatively affect bone health[5-8,27].

Hormones produced in the anterior pituitary gland are important determinants of BMD, including GH resistance and relative IGF-1 deficiency, which is a major contributor to net bone loss[27]. Hypercortisolemia, characteristic of this disorder, has multiple deleterious effects on bone, decreasing formation and increasing bone resorption[5]. Estrogens, along with testosterone, have anabolic effects on bone and inhibitory effects on bone resorption; however, both are decreased in AN. Patients with primary amenorrhea show more severe bone loss than those with secondary amenorrhea[8,27].

Regarding adipokines and appetite-regulating peptides, leptin levels are characteristically decreased in AN, which is associated with lower fat mass and bone density. Similarly, insulin, which has an anabolic effect on bone, is decreased in AN, which is associated with lower levels of bone formation and lower bone density[28].

Adolescence is a crucial period, with changes in bone structure and peak bone mass. It has been shown that adolescents with AN have a lower peak bone mass compared to normal-weight controls, resulting in suboptimal peak bone mass and poorer future bone health[5]. It should also be noted that regular exercise (weight bearing) is healthy for bone, but very intense exercise, as performed by some patients with AN, can be detrimental.

Regarding bone microarchitecture, both trabecular and cortical bone are affected, although general data suggest that, in women, trabecular bone is affected more than cortical bone. This has been attributed to the profound estrogen deficiency that often accompanies this disorder[5,27]. In contrast to women, men with AN have greater bone involvement in areas where cortical bone predominates[5].

Diagnosis

BMD assessment by dual-energy X-ray absorptiometry (DXA) at L1-L4 level is recommended after 6-12 months of amenorrhea. However, some groups perform baseline DXA, even in the presence of menstrual cycles, to assess initial data[29]. BMD should be corrected for bone age and/or height. Until menses resume, L1-L4 DXA should be repeated annually. In all patients with AN, the presence of low BMD should be used to raise awareness of the importance of bone health, as well as to encourage weight gain.

Treatment

Table I summarizes the main therapies studied and their effectiveness for the management of decreased BMD in adolescent and young women with AN.

The most effective strategy for improving bone density is weight normalization and restoring menstrual cycles. To achieve this, it is paramount to follow psychiatric guidelines and participate in a multidisciplinary approach. It is important to optimize calcium and vitamin D intake according to age-specific daily requirements (e.g., in adolescents who do not meet at least two dairy products per day, supplement with 1,300 mg of elemental calcium and 600 IU of vitamin D); however, supplementation alone is not an effective therapy for increasing bone density[5].

Drug therapy should be considered in women with AN, amenorrhea, and low BMD z-scores (≤-2 or individualized in cases with a z-score ≥-2 but long-standing secondary amenorrhea) or bone fractures, and whenever weight gain strategies have not been effective. Treatment is usually continued for at least 1 year, after which BMD testing is repeated. Although BMD has not usually normalized after 1 year, treatment should be individualized for each patient depending on psychiatric and weight outcomes. Oral estrogens have not been shown to be effective in increasing BMD, but therapy with transdermal 17β-estradiol patches at a dose of 100 µg/day (it is a high dose, especially considering the tendency to use low doses of estradiol, especially in adolescents) and cyclic progesterone did show an increase in BMD in the spine and hips (Misra 2011). Despite this, in clinical practice it is common to use transdermal ethinylestradiol at a dose of 34 mg/day + progestogen (Evra® patch). However, this therapy is not sufficient to normalize BMD, probably because it does not correct other hormonal abnormalities that are important for bone health[27]. This would be the case of IGF-1 deficiency, a characteristic of malnutrition present in AN, for which therapeutic options have been explored, such as the administration of recombinant IGF-1 (rhIGF-1). Some studies indicate that rhIGF-1 therapy may increase bone formation and improve BMD, especially when combined with other interventions such as hormone therapy. However, these authors emphasize that the available evidence is limited and not without risks[5]. Similarly, in relation to the hypoleptinemia present in AN, the administration of subcutaneous leptin has been evaluated and, although it apparently improves BMD, it seems that the effects are not directly produced by leptin and, furthermore, given that weight loss is enhanced with this therapy, exhaustive monitoring is necessary[27].

Bone-activating drugs approved for the treatment of postmenopausal osteoporosis, including antiresorptives (bisphosphonates) and bone anabolics (teriparatide), have also been studied in AN. Bisphosphonates have not been approved by the FDA for women of childbearing age due to limited knowledge of their long-term efficacy. Teriparatide, a parathyroid hormone analogue, has also not been approved due to the risk of osteosarcoma, especially in the pediatric population where bone epiphyses remain open[5,27]. No data are available in AN for denosumab (a monoclonal antibody used to treat osteoporosis in postmenopausal women and other conditions with risk of fractures).

Cholesterol metabolism

Hypercholesterolemia is frequently present in patients with AN, but does not pose an increased cardiovascular risk.

Hypercholesterolemia, a common finding in patients with AN, is a consequence of increased lipolysis, increased fat mobilization, and decreased hepatic lipid metabolism, among others. However, recent studies suggest that these patients do not have an advanced atherogenic lipid profile, and although some alterations persist with partial weight recovery, most are reversed[30].

Diagnosis

Elevated concentrations of total cholesterol and high, low and very low-density lipoproteins (HDL, LDL and VLDL).

Treatment

It is usually not necessary.

Table I. Studies on therapies to treat low bone mineral density (BMD) in adolescent and young women with anorexia nervosa

Therapies	*Age (years)*	*n*	*Changes in BMD*	*Duration (months)*	*Reference*
Weight restoration and menstruation	18-40	75	Increases BMD of the hip (1.8%) and spine (3.1%) compared to baseline	12	Miller 2006
Oral estrogens/ progesterone	16-42	48	No change compared to placebo	19	Klibanski 1995
	12-21	50	No change compared to placebo	12	Golden 2002
	18-38	60	No change compared to placebo	9	Grispoon 2002
	11-17	112	No change compared to placebo	12	Strokosch 2006
Transdermal estrogen replacement	12-18	110	Increase in spine BMD compared to placebo (2.6% *vs.* 0.3%). Hip BMD remained stable compared to placebo, but decreased (0.004% *vs.* 1.2%)	18	Misra 2011
Recombinant IGF1	18-38	60	Increase in spine BMD compared to placebo (1.1% *vs.* -0.6%)	9	Grispoon 2002
Recombinant IGF1 + OCP	18-38	60	Increase in spine BMD compared to placebo (1.8% *vs.* -1%)	9	Grispoon 2002
Testosterone	19-49	77	No change compared to placebo	12	Miller 2011
DHEA	14-28	61	No changes compared to the OCP group. Similar increase in hip BMD (1.7%), but no significant changes after controlling for weight gain	12	Gordon 2002
DHEA + OCP	13-27	94	BMD of the spine and hip is maintained compared to the control group, where they decrease	18	Divasta 2012
Risedronate	19-49	77	Increased BMD of the spine (3-4%) and hip (2%) compared to placebo	12	Miller 2011
Alendronate	12-21	32	No changes compared to placebo, although both groups gained weight and increased BMD of the spine and hip	12	Golden 2005
Teriparatide	35-58	32	Increase in BMD compared to placebo (6% *vs.* 0.6%). No change in hip BMD compared to placebo	6	Fazeli 2014

Modified from: references[6,28]. OCP: oral contraceptive; DHEA: dehydroepiandrosterone; BMD: bone mineral density; rhIGF-I: recombinant insulin-like growth factor 1.

Anorexia nervosa in males

The prevalence of AN in males is increasing. Similar to women, they present with hypothalamic-pituitary and bone health problems.

Although AN is most commonly diagnosed in adolescent females, its prevalence in males is underestimated and increasing. AN should be suspected in cases with a history of weight loss, especially if other psychiatric comorbidities or substance abuse are present, a BMI lower than the age- and sex-appropriate level, symptoms of hypogonadism, bone fragility, or multiple endocrinopathies not otherwise explained.

Similar to females, males present with hypothalamic-pituitary axis involvement (hypogonadotropic hypogonadism with decreased testosterone and estradiol levels, hypercortisolism, and sick euthyroid syndrome). Fat stores are decreased, as are leptin levels. A particularity is that men with AN have a higher percentage of trunk fat and a higher trunk/extremity fat ratio compared to normal-weight men. This finding is attributable to hypogonadism with decreased testosterone levels.

Bone health is also affected in males; however, compared with adolescent females with AN, males have lower BMD z-scores at the hip and femoral neck, whereas females have lower lumbar BMD. These sex-specific characteristics suggest that not everything that occurs in female AN is attributable to males[6]. Further studies are needed to clarify the characteristic alterations of AN in males.

Role of the Primary Care pediatrician

A crucial role in the early detection of the disease, as well as the underlying endocrinological aspects, and in coordinating patient follow-up and rehabilitation with specialists.

The role of the primary care pediatrician is crucial, from the initial diagnosis of AN, through the monitoring of the disease and associated endocrinological disorders, to nutritional, psychological, and medical rehabilitation within a multidisciplinary approach. Their main functions include:

- Primary prevention: health education on nutrition and exercise.
- Knowledge of the illness. If an eating disorder is suspected, referral to child and adolescent psychiatry should be made.
- Frequent monitoring of the patient, facilitating the early detection of endocrinopathies and other medical disorders, characteristic of AN. Evaluation of growth velocity, pubertal stage, menstrual cycles, and weight development.
- In the event of endocrine disorder suspicion, referral to a pediatric endocrinologist is essential, ensuring proper communication for comprehensive patient management.
- Promoting weight recovery and, with it, the restoration of hypothalamic-pituitary axes, supporting the patient and their family throughout this process.

Conflict of interest

There is no conflict of interest in the preparation of this manuscript or source of funding.

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The asterisks show the authors' opinion of the article's interest.

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Recommended bibliography

– Schorr M, Miller KK. The endocrine manifestations of anorexia nervosa: mechanisms and management. Nat Rev Endocrinol. 2017; 13: 174-86.

A comprehensive review of the main endocrinological disorders in anorexia nervosa, including practical and highly visual summary figures and tables.

– Misra M, Klibanski A. Anorexia nervosa and bone. J Endocrinol. 2014; 221: R16376.

A review focusing on bone health in relation to anorexia nervosa, including general guidelines for the treatment of low bone mineral density.

Clinical case

A 14-year-old female adolescent with anorexia nervosa, referred to the endocrinology clinic for secondary amenorrhea.

Family history: nothing relevant to the case. The mother had a height of 167 cm and menarche at 13 years, and the father had a height of 182 cm and normal pubertal development.

Personal background: onset of restrictive eating behavior at the age of 12 years old, reaching a minimum weight of 42 kg (BMI: 15.67 kg/m^2, -1.75 SDS) at age 13, which required admission to the psychiatric ward. Menarche tood place at 11 years of age, with regular cycles initially.

Current illness: two years of amenorrhea. Slow and progressive weight recovery. Adequate nutrition, not following a specific menu presently, and she has scheduled physical exercise at school.

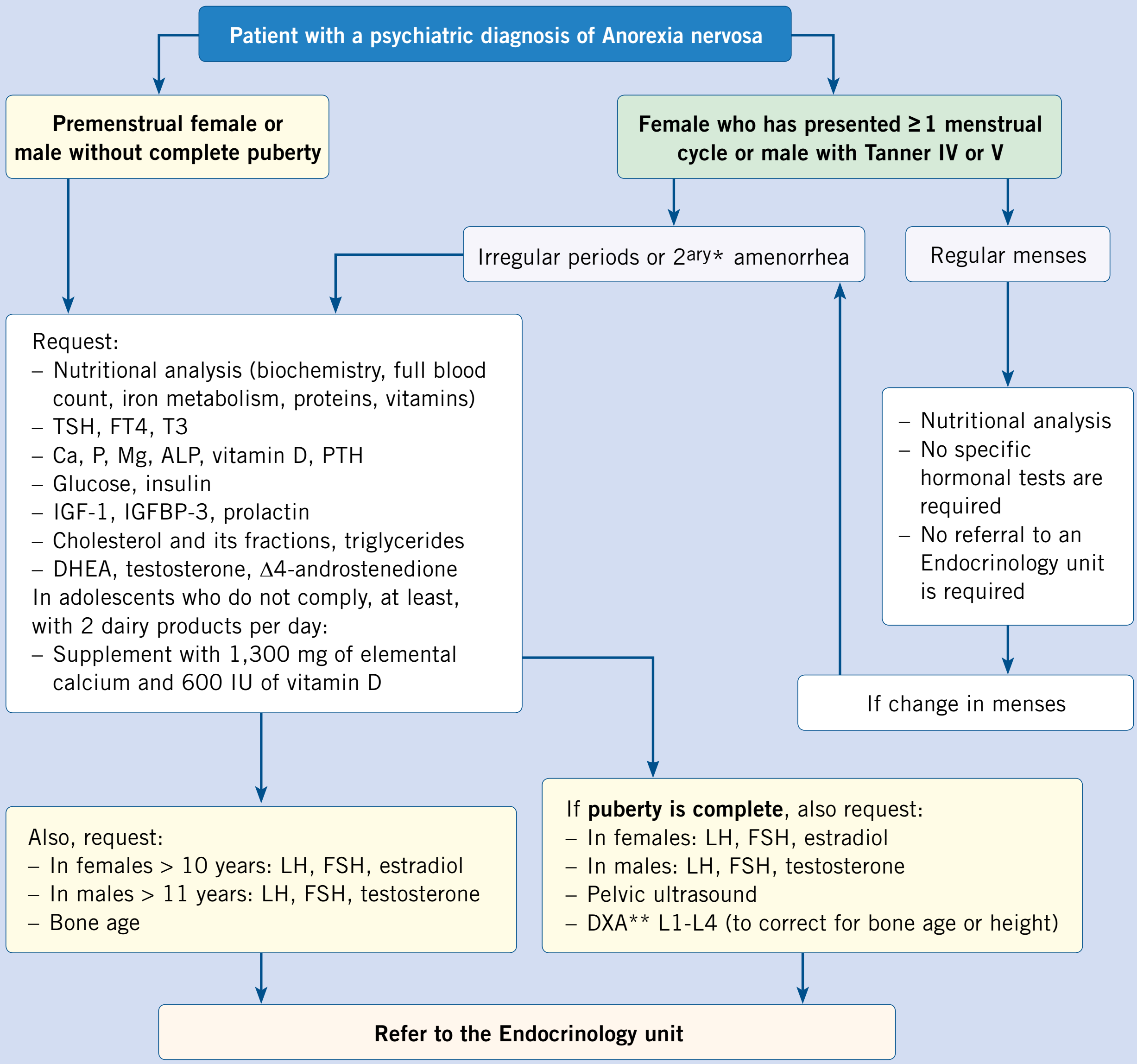
Physical examination: weight: 43.9 kg (19th centile, -0.88 SDS); Height: 163 cm (81st centile, 0.89 SDS); BMI: 16.52 kg/m^2 (7th centil, -1.51 SDS according to Hernández et al. Spanish growth chart). HR: 72 bpm. Normal female external genitalia, Tanner pubertal stage IV (B4, P4, A3). Breasts of intermediate consistency. The rest of the examination was unremarkable.

Additional tests: pelvic ultrasound: postpubertal uterus with a thin endometrial echogenic lining. Ovaries of normal size and echostructure (right: 5.1 ml; left: 6.8 ml) with multiple small follicular cysts. Nutritional and hormonal analysis: fasting glucose: 76 mg/dl (60-100); insulin: *0.8 µIU/ml (4-11); sodium: *133 mEq/L (135-145); total cholesterol: *260 mg/dl (120-200); TSH: 3.24 µU/l (0.36-5.5); FT4: 0.92 ng/dl (0.65-1.4); T3: *0.53 ng/ml (0.9-2); IGF-1: *99 ng/ml (201 ± 78); IGFBP-3: 2.74 mcg/ml (3.1 ± 0.5); PRL: 17.3 ng/ml (3.5-25); LH: *0.12 IU/L (0.61-56); FSH: *1.84 IU/L (2-22); estradiol: *8.4 pg/ml (10-500); 25-Hydroxyvitamin D: 26.3 ng/ml (20-60). Bone age: 14 years and 6 months (chronological age 14 years). DEXA scan (L1-L4): 0.738 g/cm^2 (-2.1 z-score).

Accreditation quiz

The Accreditation Questionnaires for FC topics can be done at "On line" through the web: www.sepeap.org and www.pediatriaintegral.es. To obtain the single continuous training accreditation from the accreditation system for health professionals for the entire national health system, 70% of the questions must be answered correctly. The accreditation questionnaires on the different issues in the journal may be carried out during the period stated in the online questionnaire.

Initial diagnostic algorithm for endocrinological disorders in anorexia nervosa



*The hormonal profile is usually requested when the patient has had an eating disorder for at least 12 months.

**DXA is usually performed after 6-12 months of amenorrhea.

2ary: secondary; ALP: alkaline phosphatase; DHEA: dehydroepiandrosterone; DXA: dual-energy X-ray absorptiometry; FSH: follicle-stimulating hormone; FT4: free thyroxine; IGF-1: insulin-like growth factor 1; IGFBP-3: insulin-like growth factor binding protein 3; LH: luteinizing hormone; PTH: parathyroid hormone; T3: triiodothyronine; TSH: thyroid-stimulating hormone.

Accreditation quiz

Subsequently, the following accreditation quiz of Pediatría Integral collects questions on this topic, which must be answered online through the website: www.sepeap.org.
In order to obtain certification by the Spanish "formación continuada" national health system for health professionals, 70% of the questions must be answered correctly. The accreditation quizzes of the different numbers of the journal may be submitted during the period indicated in the "on-line" quiz.

Endocrinological aspects in anorexia nervosa

17. Which of the following is CHARACTERISTIC of chronic starvation state and malnutrition in anorexia nervosa?

a. Hypothyroidism.
b. Hypothalamic amenorrhea.
c. Hypogonadotropic hypogonadism.
d. Hyponatremia.
e. All of the above.

18. Which of the following statements is CORRECT regarding the endocrine dysregulation in anorexia nervosa?

a. Hypocortisolism is characteristic.
b. Hypercortisolism is a common finding and should always be treated.
c. Hypercortisolism is characteristic of this disorder and is accompanied by the following: typical cushingoid stigmata.
d. Hypercortisolism is characteristic of this disorder and has multiple deleterious effects on bone.
e. None of the above.

19. Please indicate the INCORRECT answer:

a. Hypoleptinemia contributes to hypothalamic amenorrea in anorexia nervosa.
b. Peptide YY (PYY) is an orexigenic hormone and is therefore decreased in anorexia nervosa.
c. Insulin is decreased in response to chronic malnutrition.
d. Ghrelin´s increased levels contribute to the maintance of euglycemia.
e. Endogenous leptin levels increase with refeeding and weight gain.

20. Which of the following statements is CORRECT regarding anorexia nervosa in men?

a. Similar to females, males have hypothalamic-pituitary axis involvement.
b. Bone health is not affected.
c. The prevalence is underestimated and increasing.
d. Testosterone levels are increased.
e. Answers a and c are correct.

21. Regarding the treatment of decreased bone mineral density, indicate the CORRECT answer:

a. Oral contraceptive therapy increases spine and hipbone mineral density (BMD).
b. Bisphosphonates are approved in women with anorexia nervosa for the treatment of decreased BMD.
c. 17β-estradiol transdermal patches and progesterone have proven to increase hip BMD.
d. The most effective strategy for improving bone density is normalizing weight and restoring menstrual cycles.
e. Options c and d are correct.

Clinical case

22. What endocrinological ABNORMALITIES can be observed in the patient in the clinical case?

a. Hypergonadotropic hypogonadism.
b. Hypogonadotropic hypogonadism.
c. Hypogonadotropic hypogonadism, growth hormone (GH) resistance with decreased insulin-like growth factor 1 (IGF-1) and insulin levels, hyponatremia, and decreased triiodothyronine (T_3) levels.
d. Sick euthyroid syndrome.
e. Hypothalamic amenorrhea exclusively.

23. In your opinion, are there any other disrupted parameters? Indicate the CORRECT answer:

a. Pelvic ultrasound and bone density are normal for age and patient's development.
b. Pelvic ultrasound shows multiple cysts and ovaries with decreased volume, which are the main cause of the patient's amenorrhea.
c. Lower bone mineral density for age in association with hypovitaminosis D.
d. Increased bone mineral density.
e. Lower bone mineral density of multifactorial etiology.

24. What therapeutic strategy is APPROPRIATE in this case to preserve bone mineral density?

a. Weight restoration.
b. Recovery of gonadal function.
c. It is important to optimize the intake of calcium and vitamin D, according to daily requirements.
d. In those feamles low with Z-scores, physiological replacement with transdermal patches has been shown to be effective.
e. All of the above are true.