Cutaneous Signs of Malnutrition Secondary to Eating Disorders

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PRACTICE **POINTS**

- Cutaneous manifestations of malnutrition may be the presenting sign of disordered eating.
- Dermatologists have a unique opportunity for early recognition and intervention in patients with eating disorders (EDs).
- Rapid identification and multidisciplinary management of EDs may improve patient outcomes and potentially attenuate the risk of irreversible damage from malnutrition.

Patients with eating disorders (EDs) frequently experience malnutrition that may lead to nutritional dermatoses. Effects of malnutrition and starvation on the skin may include xerosis, lanugo, pruritus, acrocyanosis, carotenoderma, telogen effluvium, and other hair and mucosal findings. Although these dermatologic sequelae often are reported among patients with EDs, the pathomechanisms of these cutaneous symptoms are poorly understood. This article reviews the existing literature on nutritional dermatoses to clarify visible signs that should heighten clinical suspicion for an underlying ED. The skin may present the first visible signs of an otherwise occult ED diagnosis, offering the dermatologist a special opportunity for early diagnosis and coordination with a multidisciplinary team for ED treatment.

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Eating disorders (EDs) and feeding disorders refer to a wide spectrum of complex biopsychosocial illnesses. The spectrum of EDs encompasses anorexia nervosa (AN), bulimia nervosa (BN), binge eating disorder, and other specified feeding or eating disorders. Feeding disorders, distinguished from EDs based on the absence of body image disturbance, include pica, rumination syndrome, and avoidant/restrictive food intake disorder (ARFID).[1]

This spectrum of illnesses predominantly affect young females aged 15 to 45 years, with recent increases in the rates of EDs among males, patients with skin of color, and adolescent females.[2-5] Patients with EDs are at an elevated lifetime risk of suicidal ideation, suicide attempts, and other psychiatric comorbidities compared to the general population.[6] Specifically, AN and BN are associated with high psychiatric morbidity and mortality. A meta-analysis by Arcelus et al[7] demonstrated the weighted annual mortality for AN was 5.10 deaths per 1000 person-years (95% CI, 3.57-7.59) among patients with EDs and 4.55 deaths for studies that selected inpatients (95% CI, 3.09-6.28); for BN, the weighted mortality was 1.74 deaths per 1000 person-years (95% CI, 1.09-2.44). Unfortunately, ED diagnoses often are delayed or missed in clinical settings. Patients may lack insight into the severity of their illness, experience embarrassment about their eating behaviors, or actively avoid treatment for their ED.[8]

Pica—compulsive eating of nonnutritive substances outside the cultural norm—and rumination syndrome—regurgitation of undigested food—are feeding disorders more commonly recognized in childhood.[9-11] Pregnancy, intellectual disability, iron deficiency, and lead poisoning are other conditions associated with pica.[6,9,10] Avoidant/restrictive food intake disorder, a new diagnosis added to

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the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (*DSM-5*)[1] in 2013, is an eating or feeding disturbance resulting in persistent failure to meet nutritional or energy needs. Etiologies of ARFID may include sensory sensitivities and/or a traumatic event related to eating, leading to avoidance of associated foods.[12]

Patients with an ED or a feeding disorder frequently experience malnutrition, including deficiencies, excesses, or imbalances in nutritional intake, which may lead to nutritional dermatoses.[13] As a result, the skin may present the first visible clues to an ED diagnosis.[8,14-19] Gupta et al[18] organized the skin signs of EDs into 4 categories: (1) those secondary to starvation or malnutrition; (2) cutaneous injury related to self-induced vomiting; (3) dermatoses due to laxative, diuretic, or emetic use; and (4) other concomitant psychiatric illnesses (eg, hand dermatitis from compulsive handwashing, dermatodaxia, onychophagia, trichotillomania). This review will focus on the effects of malnutrition and starvation on the skin.

Skin findings in patients with EDs offer the treating dermatologist a special opportunity for early diagnosis and appropriate consultation with specialists trained in ED treatment. It is important for dermatologists to be vigilant in looking for skin findings of nutritional dermatoses, especially in populations at an increased risk for developing an ED, such as young female patients. The approach to therapy and treatment must occur through a collaborative multidisciplinary effort in a thoughtful and nonjudgmental environment.

Xerosis

Xerosis, or dry skin, is the most common dermatologic finding in both adult and pediatric patients with AN and BN.[14,19] It presents as skin roughness, tightness, flaking, and scaling, which may be complicated by fissuring, itching, and bleeding.[20] In healthy skin, moisture is maintained by the stratum corneum and its lipids such as ceramides, cholesterol, and free fatty acids.[21] Natural moisturizing factor (NMF) within the skin is composed of amino acids, ammonia, urea, uric acid, inorganic salts, lactic acid derivatives, and pyrrolidine-3-carboxylic acid.[20-22] Disruptions to this system result in increased transepidermal water loss and impaired barrier function.[23]

In patients with ED, xerosis arises through several mechanisms. Chronic illness or starvation can lead to euthyroid sick syndrome with decreased peripheral conversion of thyroxine (T_4) to triiodothyronine (T_3).[24,25] In the context of functional hypothyroidism, xerosis can arise from decreased eccrine gland secretion.[26] Secretions of water, lactate, urea, sodium, and potassium from eccrine glands help to maintain NMF for skin hydration.[27] Persistent laxative or diuretic abuse and fluid intake restriction, which are common behaviors across the spectrum of EDs, lead to dehydration and electrolyte imbalances that can manifest as skin dryness.[20] Disrupted keratinocyte differentiation due to insufficient stores of vitamins and minerals involved in keratinocyte differentiation, such as vitamins A and C, selenium, and zinc, also may contribute to xerosis.[25,28,29]

Severely restrictive eating patterns may lead to development of protein energy malnutrition (PEM). Cutaneous findings in PEM occur due to dysmaturation of epidermal keratinocytes and epidermal atrophy.[30] Patients with severe persistent depletion of macronutrients—carbohydrates, fat, and protein—may experience marasmus, resulting in loss of subcutaneous fat that causes the appearance of dry loose skin.[29,31]

Xerosis is exceedingly common in the general population and has no predictive value in ED diagnosis; however, this finding should be noted in the context of other signs suggestive of an ED. Treatment of xerosis in the setting of an ED should focus on correction of the underlying malnutrition. Symptomatic alleviation requires improving skin hydration and repairing barrier function. Mild xerosis may not need treatment or can be ameliorated with over-the-counter moisturizers and emollients. Scaling secondary to dry skin can be improved by ingredients such as glycerol, urea, lactic acid, and dexpanthenol.[20,32] Glycerol and urea are small hydrophilic molecules that penetrate the stratum corneum and help to bind moisture within the skin to reduce transepidermal water loss. Urea and lactic acid are keratolytics of NMF commonly found in moisturizers and emollients.[33,34] Dexpanthenol may be used for soothing fissures and pruritus; in vitro and in vivo studies have demonstrated its ability to upregulate dermal fibroblast proliferation and epidermal re-epithelization to promote faster wound healing.[35]

Lanugo

Lanugo is clinically apparent as a layer of fine, minimally pigmented hair. It is physiologically present on the skin surface of fetuses and newborns. In utero, lanugo plays an essential role in fetal skin protection from amniotic fluid, as well as promotion of proper hydration, thermoregulation, and innate immune development.[36-38] Although it may be found on approximately 30% of newborns as normal variation, its presence beyond the neonatal period signals underlying systemic disease and severe undernutrition.[16,36,39] Rarely, hypertrichosis lanuginosa acquisita has been reported in association with malignancy.[40,41] The finding of lanugo beyond the neonatal period should prompt exclusion of other medical disorders, including neoplasms, chronic infections, hyperthyroidism, malabsorption syndromes, and inflammatory bowel disease.[41-47]

There is a limited understanding of the pathomechanism behind lanugo development in the context of malnutrition. Intentional starvation leads to loss of subcutaneous fat and a state of functional hypothyroidism.[48] Studies hypothesize that lanugo develops as a response to hypothermia, regulated by dermal papillae cell–derived exosomes that may stimulate hair growth via paracrine signaling to outer root sheath cells.[36,49] Molecular studies have found that T_3 impacts skin and hair

differentiation and proliferation by modulating thyroid hormone receptor regulation of keratin expression in epithelial cells.[50,51] Lanugo may be a clinical indicator of severe malnutrition among ED patients, especially children and adolescents. A study of 30 patients aged 8 to 17 years with AN and BN who underwent a standard dermatologic examination found significant positive correlation between the presence of lanugo hair growth and concomitant amenorrhea ($P<.01$) as well as between lanugo hair and body mass index lower than 16 kg/m^2 ($P<.05$).[19] Discovery of lanugo in the dermatology clinical setting should prompt a thorough history, including screening questions about eating patterns; attitudes on eating, exercise, and appearance; personal and family history of EDs or other psychiatric disorders; and screening for depression and anxiety. Given its association with other signs of severe malnutrition, a clinical finding of lanugo should prompt close physical examination for other potential signs of an ED and laboratory evaluation for electrolyte levels and blood counts.[52] Resolution of lanugo secondary to an ED is achieved with restoration of normal total body fat.[18] Treatment should be focused on appropriate weight gain with the guidance of an ED specialist.

Pruritus

The prevalence and pathomechanism of pruritus secondary to EDs remains unclear.[16,53,54] There have been limited reports of pruritus secondary to ED, with Gupta et al[53] providing a case series of 6 patients with generalized pruritus in association with starvation and/or rapid weight loss. The study reported remission of pruritus with nutritional rehabilitation and/or weight gain of 5 to 10 pounds. Laboratory evaluation ruled out other causes of pruritus such as cholestasis and uremia.[53] Other case reports have associated pruritus with iron deficiency, with anecdotal evidence of pruritus resolution following iron supplementation.[55-59] Although we found no studies specifically relating iron deficiency, EDs, and pruritus, iron deficiency routinely is seen in ED patients and has a known association with pica.[9,10,60] As such, iron deficiency may be a contributing factor in pruritus in ED patients. A UK study of 19 women with AN and a body mass index lower than 16 kg/m^2 found that more than half of the patients (11/19 [57.9%]) described pruritus on the St. Thomas' Itch Questionnaire, postulating that pruritus may be a clinical feature of AN.[61] Limited studies with small samples make it difficult to conclude whether pruritus arises as a direct consequence of malnutrition.

Treatment of pruritus should address the underlying ED, as the pathophysiology of itch as it relates to malnutrition is poorly understood. Correction of existing nutritional imbalances by iron supplementation and appropriate weight gain may lead to symptom resolution. Because xerosis may be a contributing factor to pruritus, correction of the xerosis also may be therapeutic. More studies are needed on the connection between pruritus and the nutritional imbalances encountered in patients with EDs.

Acrocyanosis

Acrocyanosis is clinically seen as bluish-dusky discoloration most commonly affecting the hands and feet but also may affect the nose, ears, and nipples. Acrocyanosis typically is a sign of cold intolerance, hypothesized to occur in the context of AN due to shunting of blood centrally in response to hypothermia.[39,62] The diminished oxyhemoglobin delivery to extremity sites leads to the characteristic blue color.[63] In a study of 211 adolescent females (age range, 13–17 years) with AN, physical examination revealed peripheral hypothermia and peripheral cyanosis in 80% and 43% of patients, respectively.[48] Cold intolerance seen in EDs may be secondary to a functional hypothyroid state similar to euthyroid sick syndrome seen in conditions of severe caloric deficit.[25]

It is possible that anemia and dehydration can worsen acrocyanosis due to impaired delivery of oxyhemoglobin to the body's periphery.[63] In a study of 14 ED patients requiring inpatient care, 6 were found to have underlying anemia following intravenous fluid supplementation.[64] On admission, the mean (SD) hemoglobin and hematocrit across 14 patients was 12.74 (2.19) and 37.42 (5.99), respectively. Following intravenous fluid supplementation, the mean (SD) hemoglobin and hematocrit decreased to 9.88 (1.79)($P<.001$) and 29.56 (4.91) ($P=.008$), respectively. Most cases reported intentional restriction of dietary sodium and fluid intake, with 2 patients reporting a history of diuretic misuse.[64] These findings demonstrate that hemoglobin and hematocrit may be falsely normal in patients with AN due to hemoconcentration, suggesting that anemia may be underdiagnosed in inpatients with AN.

Beyond treatment of the underlying ED, acrocyanosis therapy is focused on improvement of circulation and avoidance of exacerbating factors. Pharmacologic intervention rarely is needed. Patients should be reassured that acrocyanosis is a benign condition and often can be improved by dressing warmly and avoiding exposure to cold. Severe cases may warrant trial treatment with nicotinic acid derivatives, α-adrenergic blockade, and topical minoxidil, which have demonstrated limited benefit in treating primary idiopathic acrocyanosis.[63]

Carotenoderma

Carotenoderma—the presence of a yellow discoloration to skin secondary to hypercarotenemia—has been described in patients with EDs since the 1960s.[65,66] Beyond its clinical appearance, carotenoderma is asymptomatic. Carotenoids are lipid-soluble compounds present in the diet that are metabolized by the intestinal mucosa and liver to the primary conversion product, retinaldehyde, which is further converted to retinol, retinyl esters, and other retinoid metabolites.[67,68] Retinol is bound by lipoproteins and transported in the plasma, then deposited in

peripheral tissues,[69] including in intercellular lipids in the stratum corneum, resulting in an orange hue that is most apparent in sites of increased skin thickness and sweating (eg, palms, soles, nasolabial folds).[70] In an observational study of ED patients, Glorio et al[14] found that carotenoderma was present in 23.77% (29/122) and 25% (4/16) of patients with BN and other specified feeding or eating disorder, respectively; it was not noted among patients with AN. Prior case reports have provided anecdotal evidence of carotenoderma in AN patients.[66,71] In the setting of an ED, increased serum carotenoids likely are due to increased ingestion of carotene-rich foods, leading to increased levels of carotenoid-bound lipoproteins in the serum.[70] Resolution of xanthoderma requires restriction of carotenoid intake and may take 2 to 3 months to be clinically apparent. The lipophilic nature of carotenoids allows storage in body fat, prolonging resolution.[71]

Hair Changes

Telogen effluvium (TE) and hair pigmentary changes are clinical findings that have been reported in association with EDs.[14,16,19,72] Telogen effluvium occurs when physiologic stress causes a large portion of hairs in the anagen phase of growth to prematurely shift into the catagen then telogen phase. Approximately 2 to 3 months following the initial insult, there is clinically apparent excessive hair shedding compared to baseline.[73] Studies have demonstrated that patients with EDs commonly have psychiatric comorbidities such as mood and anxiety disorders, obsessive compulsive disorder, posttraumatic stress disorder, and panic disorder compared to the general population.[6,74-76] As such, stress experienced by ED patients may contribute to TE. Despite TE being commonly reported in ED patients,[16-18] there is a lack of controlled studies of TE in human subjects with ED. An animal model for TE demonstrated that stressed mice exhibited further progression in the hair cycle compared with nonstressed mice ($P<.01$); the majority of hair follicles in stressed mice were in the catagen phase, while the majority of hair follicles in nonstressed mice were in the anagen phase.[77] Stressed mice demonstrated an increased number of major histocompatibility complex class II^+ cell clusters, composed mostly of activated macrophages, per 12.5-mm epidermal length compared to nonstressed mice (mean [SEM], 7.0 [1.1] vs 2.0 [0.3][$P<.05$]). This study illustrated that stress can lead to inflammatory cell recruitment and activation in the hair follicle microenvironment with growth-inhibitory effects.[77]

The flag sign, or alternating bands of lesser and greater pigmentation in the hair, has been reported in cases of severe PEM.[31] In addition, PEM may lead to scalp alopecia, dry and brittle hair, and/or hypopigmentation with periods of inadequate nutrition.[29,78] Scalp hair hypopigmentation, brittleness, and alopecia have been reported in pediatric patients with highly selective eating and/or ARFID.[79,80] Maruo et al[80] described a 3-year-old boy with ASD who consumed only potato chips for more than a year. Physical examination revealed reduced skin turgor overall and sparse red-brown hair on the scalp; laboratory testing showed deficiencies of protein, vitamin A, vitamin D, copper, and zinc. The patient was admitted for nutritional rehabilitation via nasogastric tube feeding, leading to resolution of laboratory abnormalities and growth of thicker black scalp hair over the course of several months.[80]

Neuroendocrine control of keratin expression by thyroid-stimulating hormone (TSH) and thyroid hormones likely plays a role in the regulation of hair follicle activities, including hair growth, structure, and stem cell differentiation.[81,82] Altered thyroid hormone activity, which commonly is seen in patients with EDs,[24,25] may contribute to impaired hair growth and pigmentation.[26,51,83-85] Using tissue cultures of human anagen hair follicles, van Beek et al[85] provided in vitro evidence that T_3 and T_4 modulate scalp hair follicle growth and pigmentation. Both T_3- and T_4-treated tissue exhibited increased numbers of anagen and decreased numbers of catagen hair follicles in organ cultures compared with control ($P<.01$); on quantitative Fontana-Masson histochemistry, T_3 and T_4 significantly stimulated hair follicle melanin synthesis compared with control ($P<.001$ and $P<.01$, respectively).[85] Molecular studies by Bodó et al[83] have shown that the human scalp epidermis expresses TSH at the messenger RNA and protein levels. Both studies showed that intraepidermal TSH expression is downregulated by thyroid hormones.[83,85] Further studies are needed to examine the impact of malnutrition on local thyroid hormone signaling and action at the level of the dermis, epidermis, and hair follicle.

Discovery of TE, hair loss, and/or hair hypopigmentation should prompt close investigation for other signs of thyroid dysfunction, specifically secondary to malnutrition. Imbalances in TSH, T_3, and T_4 should be corrected. Nutritional deficiencies and dietary habits should be addressed through careful nutritional rehabilitation and targeted ED treatment.

Oral and Mucosal Symptoms

Symptoms of the oral cavity that may arise secondary to EDs and feeding disorders include glossitis, stomatitis, cheilitis, and dental erosions. Mucosal symptoms have been observed in patients with vitamin B deficiencies, inflammatory bowel disease, and other malabsorptive disorders, including patients with EDs.[86-88] Patients following restrictive diets, specifically strict vegan diets, without additional supplementation are at risk for developing vitamin B_{12} deficiency. Because vitamin B_{12} is stored in the liver, symptoms of deficiency appear when hepatic stores are depleted over the course of several years.[89] Insufficient vitamin B_{12} prevents the proper functioning of methionine synthase, which is required for the conversion of homocysteine to methionine and for the conversion of methyl-tetrahydrofolate to tetrahydrofolate.[89] Impairment of this process impedes the synthesis

of pyrimidine bases of DNA, disrupting the production of rapidly proliferating cells such as myeloid cells or mucosal lining cells. In cases of glossitis and/or stomatitis due to vitamin B_{12} deficiency, resolution of lesions was achieved within 4 weeks of daily oral supplementation with vitamin B_{12} at 2 µg daily.[90,91] Iron deficiency, a common finding in EDs, also may contribute to glossitis and angular cheilitis.[29] If uncovered, iron deficiency should be corrected by supplementation based on total deficit, age, and sex. Oral supplementation may be done with oral ferrous sulfate (325 mg provides 65 mg elemental iron) or with other iron salts such as ferrous gluconate (325 mg provides 38 mg elemental iron).[29] Mucosal symptoms of cheilitis and labial erythema may arise from irritation due to self-induced vomiting.[88]

Dental erosion refers to loss of tooth structure via a chemical process that does not involve bacteria; in contrast, dental caries refer to tooth damage secondary to bacterial acid production. Patients with EDs who repeatedly self-induce vomiting have persistent introduction of gastric acids into the oral cavity, resulting in dissolution of the tooth enamel, which occurs when teeth are persistently exposed to a pH less than 5.5.[92] Feeding disorders also may predispose patients to dental pathology. In a study of 60 pediatric patients, those with rumination syndrome were significantly more likely to have dental erosions than age- and sex-matched healthy controls (23/30 [77%] vs 4/30 [13%][$P<.001$]). The same study found no difference in the frequency of dental caries between children with and without rumination syndrome.[92] These findings suggest that rumination syndrome increases the risk for dental erosions but not dental caries. The distribution of teeth affected by dental erosions may differ between EDs and feeding disorders. Patients with BN are more likely to experience involvement of the palatal surfaces of maxillary teeth, while patients with rumination syndrome had equal involvement of maxillary and mandibular teeth.[92]

There is limited literature on the role of dentists in the care of patients with EDs and feeding disorders, though existing studies suggest inclusion of a dental care professional in multidisciplinary treatment along with emphasis on education around a home dental care regimen and frequent dental follow-up.[76,93,94] Prevention of further damage requires correction of the underlying behaviors and ED.

Other Dermatologic Findings

Russell sign refers to the development of calluses on the dorsal metacarpophalangeal joints of the dominant hand due to self-induced vomiting. Due to its specificity in purging-type EDs, the discovery of Russell sign should greatly increase suspicion for an ED.[17] Patients with EDs also are at an increased risk for self-harming and body-focused repetitive behaviors, including skin cutting, superficial burning, onychophagia, and trichotillomania.[19] It is important to recognize these signs in patients for whom an ED is suspected. The role of the dermatologist should include careful examination of the skin and documentation of findings that may aid in the diagnosis of an underlying ED.

Final Thoughts

A major limitation of this review is the reliance on small case reports and case series reporting cutaneous manifestations of ED. Controlled studies with larger cohorts are challenging in this population but are needed to substantiate the dermatologic signs commonly associated with EDs. Translational studies may help elucidate the pathomechanisms underlying dermatologic diseases such as lanugo, pruritus, and alopecia in the context of EDs and malnutrition. The known association between thyroid dysfunction and skin disease has been substantiated by clinical and basic science investigation, suggesting a notable role of thyroid hormone and TSH signaling in the skin local environment. Further investigation into nutritional and neuroendocrine regulation of skin health will aid in the diagnosis and treatment of patients impacted by EDs.

The treatment of the underlying ED is key in correcting associated skin disease, which requires interdisciplinary collaboration that addresses the psychological, behavioral, and social components of the condition. Following a diagnosis of ED, assessment should be made of the nutritional rehabilitation required to restore weight and nutritional status. Inpatient treatment may be indicated for patients requiring close monitoring to avoid refeeding syndrome, or those who meet the criteria for extreme AN in the *DSM-5* (ie, body mass index <15 kg/m^2),[1] or demonstrate signs of medical instability or organ failure secondary to malnutrition.[62] Long-term recovery for ED patients should focus on behavioral therapy with a multidisciplinary team consisting of a psychiatrist, therapist, dietitian, and primary care provider. Comparative studies in large-scale trials of cognitive behavioral therapy, focal psychodynamic psychotherapy, and specialist supportive clinical management have shown little to no difference in efficacy in treating EDs.[75,95,96]

Dermatologists may be the first providers to observe sequelae of nutritional and behavioral derangement in patients with EDs. Existing literature on the dermatologic findings of EDs report great heterogeneity of skin signs, with a very limited number of controlled studies available. Each cutaneous symptom described in this review should not be interpreted as an isolated pathology but should be placed in the context of patient predisposing risk factors and the constellation of other skin findings that may be suggestive of disordered eating behavior or other psychiatric illness. The observation of multiple signs and symptoms at the same time, especially of symptoms uncommonly encountered or suggestive of a severe and prolonged imbalance (eg, xanthoderma with vitamin A excess, aphthous stomatitis with vitamin B deficiency), should heighten clinical suspicion for an underlying ED. A clinician's highest priority should be to

resolve life-threatening medical emergencies and address nutritional derangements with the assistance of experts who are well versed in EDs. The patient should undergo workup to rule out organic causes of their nutritional dermatoses. Given the high psychiatric morbidity and mortality of patients with an ED and the demonstrated benefit of early intervention, recognition of cutaneous manifestations of malnutrition and EDs may be paramount to improving outcomes.

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