Skin changes in the obese patient

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Learning objectives
After completing this learning activity, participants should be able to describe skin changes associated to overweight and obesity, the metabolic and physiologic alterations; identify the most common and rare skin manifestations related to obesity; define skin manifestations related to metabolic disorders seen in obese patients; evaluate inflammatory skin diseases seen in obese patients; and identify the association between obesity and skin cancer.

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Obesity is a worldwide major public health problem with an alarmingly increasing prevalence over the past 2 decades. The consequences of obesity in the skin are underestimated. In this paper, we review the effect of obesity on the skin, including how increased body mass index affects skin physiology, skin barrier, collagen structure, and wound healing. Obesity also affects sebaceous and sweat glands and causes circulatory and lymphatic changes. Common skin manifestations related to obesity include acanthosis nigricans, acrochordons, keratosis pilaris, striae distensae, cellulite, and plantar hyperkeratosis. Obesity has metabolic effects, such as causing hyperandrogenism and gout, which in turn are associated with cutaneous manifestations. Furthermore, obesity is associated with an increased incidence of bacterial and *Candida* skin infections, as well as onychomycosis, inflammatory skin diseases, and chronic dermatoses like hidradenitis suppurativa, psoriasis, and rosacea. The association between atopic dermatitis and obesity and the increased risk of skin cancer among obese patients is debatable. Obesity is also related to rare skin conditions and to premature hair graying. As physicians, understanding these clinical signs and the underlying systemic disorders will facilitate earlier diagnoses for better treatment and avoidance of sequelae. (J Am Acad Dermatol 2019;81:1037-57.)

Key words: acne; atopic dermatitis; epidermal barrier; hidradenitis suppurativa; obesity; psoriasis; rare skin diseases; rosacea; skin cancer; skin changes; skin infections; tophaceous.

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Abbreviations used:

BMI:	body mass index
DD:	adiposis dolorosa/Dercum disease
HS:	hidradenitis suppurativa
MetS:	metabolic syndrome
SC:	stratum corneum
TEWL:	transepidermal water loss

Obesity is a worldwide major public health problem and can be described as a disproportionate body weight for height involving an excessive accumulation of adipose tissue.[1] The body mass index (BMI) is an objective way to define obesity; it is calculated by dividing a person's weight in kilograms by the square of height in meters. A BMI ≥30 kg/m^2 is considered obesity (Table I).[1]

Obesity is a major risk factor for cardiovascular, endocrine, respiratory disorders, and cancers[1-5] and is associated with depression.[1,6,7] Obesity is also a part of metabolic syndrome (MetS), which is associated with insulin resistance and an increased risk of cardiovascular diseases (Table II).[8-12] In this review, we will focus on the skin changes associated with obesity and its metabolic and physiologic alterations.

EPIDEMIOLOGY AND BURDEN

The prevalence of obesity has been alarmingly increasing in the past few decades in the United States.[1] Overall, non-Hispanic black and Hispanic adults had a higher prevalence of obesity than other races.[1]

OBESITY AND SKIN PATHOPHYSIOLOGY

Obesity causes alterations in skin physiology that predisposes obese individuals to the development of various skin manifestations and diseases (Fig 1).

Skin barrier

Various changes in barrier integrity have been linked to obesity, such as xerosis and altered transepidermal water loss (TEWL).[13-19] Xerosis is a common feature in morbidly obese patients related to stratum corneum (SC) hydration changes. In a cross-sectional study of >1300 patients, SC moisture was studied by evaluating skin capacitance, and in this study, obesity was found to significantly affect SC moisture.[14] However, the data presented in a few available studies on TEWL baseline measurements in obese patients was variable. Loffler et al found higher TEWL in obese patients;[16] this finding might be linked to profuse sweating commonly seen in this population. Increased TEWL was also found in a study involving obese children.[18] On the contrary, 1 study demonstrated that TEWL was lower in obese patients,[15] suggesting a lower permeability of the skin to evaporative water loss. The authors attributed this finding to the role of adipokines and leptin. Adipokines induce the replacement of the SC and enhance keratinocyte activation.[15,20] Leptin, a hormone predominantly made by adipocytes that inhibits hunger, is a mitogen factor for keratinocytes, which also promote in vitro fibroblast proliferation and collagen synthesis through signal transducer and activator of transcription 3 phosphorylation.[15,21,22] Monteiro Rodrigues et al found that weight gain causes adaptive physiologic skin changes.[19] Healthy weight and morbidly obese individuals had higher TEWL values than overweight and obesity class I and II individuals, which also translated in lower levels of epidermal hydration.[19] However, TEWL might not accurately reflect skin barrier function. More studies need to be done to better elucidate the role of obesity in impairing or improving the skin barrier function.

Table I. WHO criteria for the classification of the BMI, calculated by the Quetelet formula

Group	BMI, kg/m^2	Category
I	19.9-24.9	Healthy
II	25-29.9	Overweight
III	30-39.9	Obesity
IV	>40	Morbid obesity

Quetelet formula: BMI = mass/height.
BMI, Body mass index.

Collagen structure and wound healing

Obesity has been found to be associated with altered collagen structure and impaired wound healing in animal models.[23,24] In obesity, collagen deposition fails to match the expansion of the skin surface area, which translates into decreased mechanical strength of the skin.[23] Leptin promotes wound healing, and obesity is associated with leptin resistance contributing to the pathologic cycle of impaired wound repair.[25-28] Interestingly, a BMI of >40 kg/m^2, along with a Braden scale (pressure ulcer risk tool) score of ≤16 were found to have an independent and statistically significant association with pressure ulcer occurrence.[29]

Sebaceous glands and sebum production

Sebum production plays a major role in acne development.[30-34] Androgens, insulin, growth hormone, and insulin-like growth factors are frequently elevated in obese patients and affect acne severity by increasing sebum production.[35,36]

Table II. Definition of the metabolic syndrome

Adult Treatment Panel III report	World Health Organization
Presence of 3 of the following traits: • Waist circumference >102 cm for men and >88 cm for women • Triglycerides ≥ 1.7 mmol/L • High-density lipoprotein cholesterol <1.04 mmol/L for men and <1.30 mmol/L for women • Blood pressure ≥130/≥85 mmHg • Fasting glucose ≥6.1 mmol/L	Insulin resistance identified by • Type 2 diabetes • Impaired fasting glucose • Impaired glucose tolerance or, for those with fasting glucose levels <6.1 mmol/L, glucose uptake below the lowest quartile for the background population under investigation under hyperinsulinemic, euglycemic conditions Plus any 2 of the following: • Antihypertensive medication or high blood pressure (≥140 mm Hg systolic or ≥90 mm Hg diastolic) • Plasma triglycerides ≥1.7 mmol/L • High-density lipoprotein cholesterol <0.9 mmol/L for men or <1.0 mmol/L for women • Body mass index >30 kg/m^2 or waist-to-hip ratio >0.9 in men and >0.85 in women • Urinary albumin excretion rate ≥20 μg/min or albumin-to-creatinine ratio ≥3.4 mg/mmol

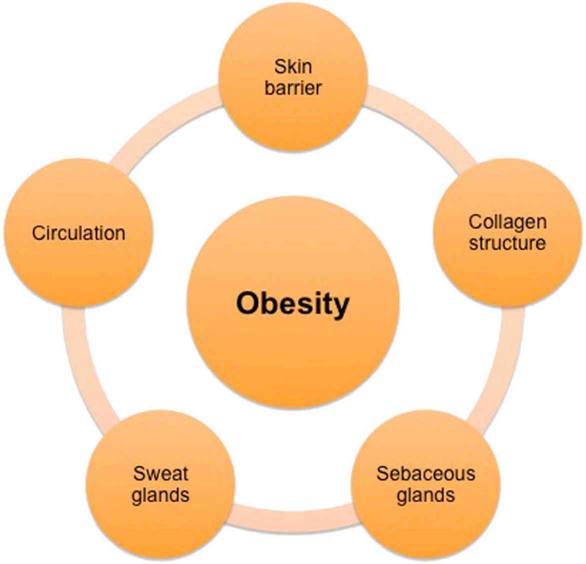

Fig 1. Obesity and skin pathophysiology. Obesity affects skin barrier integrity, which gets translated into clinical xerosis. It also causes altered collagen structure and impaired wound healing due to decreased mechanical strength. Sebum and sweat production are increased with augmented incidence of acne and dermatoses, such as intertrigo. Obesity is associated with microvascular dysfunction, chronic venous disease, and lymphedema.

Sweat glands

Obese patients sweat more profusely because they have larger skin folds and thicker layers of subcutaneous fat.[15,16,37,38] Cramer and Jay in 2015 found that heat production, evaporative heat balance, and increased body size explained their higher rectal temperatures and evaporative heat balance.[39]

In addition, augmented subcutaneous fat increases the frictional and moisture components of the skin.[17] This humid environment exacerbates local inflammation, predisposing obese patients to dermatoses, such as intertrigo, with secondary overgrowth of bacteria, *Candida* species, and dermatophytes.[15,40,41]

Obesity, diabetes, and intertrigo are conditions that promote bacterial overgrowth and the development of bromhidrosis.[42] Bromhidrosis is a chronic condition of the sweat glands that presents clinically with an unpleasant body odor.[42]

Circulatory and lymphatic changes

Obesity appears to be a primary cause of microvascular dysfunction, contributing to the development of microangiopathy and hypertension,[17,43] and this medical condition might negatively affect the clinical severity of chronic venous disease.[44] Obesity is related to vascular stress and further venous insufficiency due to valve failure and high intra-abdominal pressure.[45-49] Venous insufficiency can lead to varicose eczema and ulceration (Fig 2).[45-49] In addition, the cutaneous capillaries of obese patients are maximally recruited at rest, with no functional capillary reserve, contributing to the development of ulcers.[50] Furthermore, increased weight affects lymphatic flow, which leads to lymphedema,

Fig 2. Venous insufficiency and venous leg ulcer. Varicosities, venous dermatitis, dermatosclerosis, atrophie blanche, and classic venous leg ulcer in the medial ankle are appreciated in an obese white woman.

dilatation of tissue channels, and reduced tissue oxygenation (Fig 3). Lymphedema increases the risk of infection due to the collection of a protein-rich fluid in tissues.[25,51-54]

Lipodermatosclerosis

Lipodermatosclerosis is a chronic form of panniculitis associated with venous insufficiency (Fig 2). Several case series have documented an association of lipodermatosclerosis with obesity.[55-57]

COMMON SKIN MANIFESTATIONS RELATED TO OBESITY

Obesity is associated with a variety of skin manifestations, acanthosis nigricans,[58-65] achrocordons,[17,61,64-68] keratosis pilaris,[17,61,64,65,69-72] striae distensae,[73-79] cellulite,[80-83] and palmoplantar keratoderma-plantar hyperkeratosis,[17,61,64,69,84-88] which are explained in detail in Table III and Figs 4-9.

Palmoplantar keratodermas

Horseshoe plantar hyperkeratosis involving the heel, foot arch area, and great toe is associated with obesity.[64] Plantar hyperkeratosis results as a compensatory mechanism due to thickening of the SC[87] (Fig 8). Excess weight alters the foot anatomy and transfers high pressure over weight-bearing areas and bony prominences of the soles, causing mechanical trauma and injury.[87] Keratoderma climactericum, a common form of acquired palmoplantar keratoderma, is also frequently associated with obesity.[87,88]

SKIN INFECTIONS

Obesity increases the risk of infectious diseases in general, including skin infections, and obesity has been shown to negatively influence the outcome.[89,90] The possible mechanisms of this predisposition are the association of obesity with a proinflammatory state, decreased cell-mediated immune responses, and pharmacologic interactions with antimicrobial agents.[90,91] Moreover, poor mobility and the inability to maintain adequate levels of hygiene might exacerbate this problem.[25]

Fig 3. Lymphedema and erosions on a morbidly obese Hispanic woman.

The incidence of candidiasis, intertrigo, *Candida* folliculitis, furunculosis, erysipelas, cellulitis, erythrasma, tinea cruris, folliculitis, necrotizing fasciitis, and gas gangrene is increased in patients with higher BMIs.[17,92,93] Also, methicillin-resistant *Staphylococcus aureus* infections are more common in obese patients.[25,94] In a retrospective cohort study of 318 patients with diabetic foot ulcers and methicillin-resistant *S. aureus* infection, obesity was found in 49% of the patients.[95]

Intertrigo is an inflammatory (infectious or noninfectious) condition of 2 closely opposed skin surfaces (intertriginous area).[40,71] It presents as macerated erythematous plaques developing within skin folds (inframammary, genitocrural, axillary, and abdominal). Obese patients have larger skin folds and sweat more profusely, which increases friction and moisture that leads to maceration and inflammation.[17,64] Interestingly, it was shown that skin surface pH was higher in the inguinal folds of diabetic women with BMI >25 kg/m^2, which increases the risk of developing skin infections.[17,96]

Cellulitis has a higher incidence in obese patients[17,25,37,97] and arises more commonly on the legs in patients with coexisting lymphoedema.[98] The association between obesity and severe cellulitis in

Table III. Common skin manifestations related to obesity

Category	Clinical presentation	Pathogenesis	Histologic findings	References
Acanthosis nigricans	Symmetric hyperpigmented, verrucose, hypertrophic, sometimes papillamatous patches and plaques; localized in face, perioral, posterior neck, axilla, flexor surface of the upper and lower extremities, umbilicus, inframammarian folds, groin, and perianal; lesions might completely regress with weight reduction; might develop as a sign of internal malignancy (eg, aggressive adenocarcinomas of the gastrointestinal tract)	Associated with obesity and diabetes mellitus; contributing factors: IGFR1, fibroblast growth factor receptors, and epidermal growth factor receptor; elevated levels of insulin might stimulate keratinocyte and dermal fibroblast proliferation via interaction with IGFR1.	Hyperkeratosis, acanthosis, and mild papillomatosis; usually the dermis is normal-appearing.	58-65
Acrochordons	Pedunculated lesions with narrow stalks; localized in sites of friction: neck, axilla, inframammary folds, and inguinal regions; associated symptoms: itching, pain, and rubbing against clothes	Associated with insulin resistance; mast cells, leptin, growth factors, inflammatory mediators, estrogens, androgens, and human papilloma virus infection might also be implicated.	Papillary dermis composed of loose collagen fibers, dilated capillaries, and lymphatic vessels without appendage structures	17,61,64-68
Keratosis pilaris	Disorder of follicular keratinization with variable perifollicular erythema; spiny keratotic papules; localized in the extensor aspects of proximal arms, thighs, and cheeks	Related to obesity, not fully understood; hypothesis: genetic disorder of keratinization that results in the formation of horny plugs in the hair follicle orifices	Orthokeratotic keratin plug that might contain $\geq$1 twisted hairs; sometimes-mild perivascular lymphocytic infiltrate in the upper dermis	17,61,64,65,69,71
Striae distensae	Erythematous, violaceous, or hypopigmented linear striations; localized in the abdomen, breasts, medial upper arms, hips, lower back, buttocks, and thighs	Physical factor: mechanical stress on skin; altered skin structure: reduced procollagen and fibronectin gene expression, disruption of elastic fiber network, thin disorganized tropoelastin-rich fibrils, impaired migration and proliferation of fibroblasts; hormonal factors: increased expression of estrogen, androgen, and glucocorticoid receptors; cortisol leads to alterations in collagen and elastic fibers.	Epidermal atrophy, thin dermal collagen bundles, and loss of rete ridges	73-79

Continued

Table III. Cont'd

Category	Clinical presentation	Pathogenesis	Histologic findings	References
Cellulite	Skin dimpling, orange-peel appearance; localized in thighs, buttocks, and legs	Polymorphism associated with angiotensin converting enzyme; fibrous septa and increased subcutaneous adipose tissue thickness; microvascular dysfunction; chronic inflammation leads to reduced expression of the adipokine adiponectin in subcutaneous adipose tissue.	Herniation of subcutaneous fat within fibrous connective tissue	80-83
Plantar hyperkeratosis	Horseshoe plantar hyperkeratosis, involving the heel, foot arch, and great toe, was the most common skin manifestation.	Excess weight alters the foot anatomy and transfers high pressure over weight-bearing areas and bony prominences of the soles, causing mechanical trauma and injury.	Thickening of the stratum corneum	17,61,64,69,84-88

IGFR1, Insulin-like growth factor receptor-1.

the lower limbs was also shown in a large longitudinal cohort study.[99] Obesity is a known risk factor for erysipelas and its complications.[97,100,101] In sub-Saharan Africa, obesity was determined to be an independent risk factor for this condition in the lower legs.[102] In a retrospective chart review of patients hospitalized for primary and recurrent erysipelas, it was found that obesity prolongs the time of hospitalization.[103] Moreover, obesity was associated with erysipelas recurrence after prophylactic treatment with benzathine penicillin G 1,200,000 U once every 3 weeks.[104] *Candida albicans* infection is also more prevalent in obese patients and might cause folliculitis, intertrigo, furunculosis, or paronychia of the hands or feet.[17,25,92,105]

Erythrasma is a superficial, localized skin infection caused by *Corynebacterium minutissimum*.[69] The interdigital form is one of the most common causes of interdigital foot infection, and obese patients are especially susceptible.[106]

Also, elephantiasis nostras verrucosa might occur because of recurrent bacterial infections secondary to impaired lymphatics.[107]

Obesity is also a risk factor for onychomycosis.[108] In a study conducted in 2002 with >1000 patients, obesity (along with vascular disease and diabetes) was observed to be one of the most prevalent predisposing factors in patients with onychomycosis.[109] Obesity, MetS, high triglyceride levels, and poor glycemic control were associated with onychomycosis in a study of 1245 diabetic Taiwanese patients.[110] In addition, in 2011, researchers of a podiatry clinic sought to determine the frequency of toenail onychomycosis in diabetic patients and found a strong association with obesity.[111] In another study, topical antifungal treatment was shown to be less effective in patients who were overweight or obese than those with healthy weight ($P = .05$).[112] Complete cure rates at week 52 were 15.9% in the obese patients and 22.0% in the patients with healthy BMIs.[112]

Less common infections seen in obese patients include necrotizing fasciitis and gas gangrene.[17,25,113] In a retrospective study by Klbadi et al on patients with necrotizing fasciitis, obesity was found to be a risk factor in 29% of the cases.[93] In another retrospective study, necrotizing fasciitis was found to have a female predominance, and obesity was a risk factor.[114]

INFLAMMATORY SKIN DISEASES

Hidradenitis suppurativa

Hidradenitis suppurativa (HS) presentation varies from recurrent inflamed nodules and abscesses to draining sinus tracts associated with severe scar formation, pain, malodor, drainage, and disfigurement.[115] HS is associated with obesity because obese patients have larger intertriginous folds.[116-121] The increased mechanical friction at flexural sites causes injured follicular openings, narrowed follicular outlets due to intrafollicular keratin hydration from skin

Fig 4. Acanthosis nigricans and acrochordons on the posterior neck of an obese black woman.

Fig 5. Acrochordons in the axilla of an obese woman.

Fig 6. Striae distensae on an obese woman.

occlusion, increased levels of proinflammatory cytokines, and sweat retention that produces skin irritation.[122-124] Moreover, the dietary choices (eg, high glycemic food) that increase the risk of HS also contributes to obesity.[125] In a case–control study of 302 patients with HS, 21% of patients had a BMI $\geq$30 kg/m^2, and 22% of patients had a BMI 25-29 kg/m^2.[126] Better outcomes, including remission, were reported in (obese and nonobese) patients with weight reduction.[127]

Acne vulgaris and HS often occur together and are important features of the acne tetrad.[124] Obesity is associated with relative androgen excess, which promotes follicular plugging and worsens HS presentation.[128] Moreover, HS is associated with immune system changes that result in a sustained proinflammatory environment, which might be behind the elevated rates of MetS in patients with HS.[129]

Psoriasis

Psoriasis severity has been linked to obesity.[130,131] The clinical response to biologics and systemic therapy used for the treatment of moderate-to-severe psoriasis appears to be less effective in patients with higher BMI (Tables IV and V).[132-157] This observation might be associated with the higher treatment doses required to treat these patients. There is evidence that progressive weight loss decreases psoriasis severity.[17,25,158-161] Moderate-to-severe psoriasis is also associated with metabolic disorders, including diabetes, dyslipidemia, nonalcoholic fatty liver disease, and MetS.[131,162-166] Jensen et al performed a prospective observational follow-up study to evaluate the effect of weight loss in obese patients with psoriasis; they found significant positive changes in the severity of psoriasis after weight loss, and the improvement was maintained for 64 weeks.[167] Psoriasis and obesity share many

Fig 7. Cellulite in the left thigh of an obese man.

Fig 8. Plantar hyperkeratosis in an obese woman.

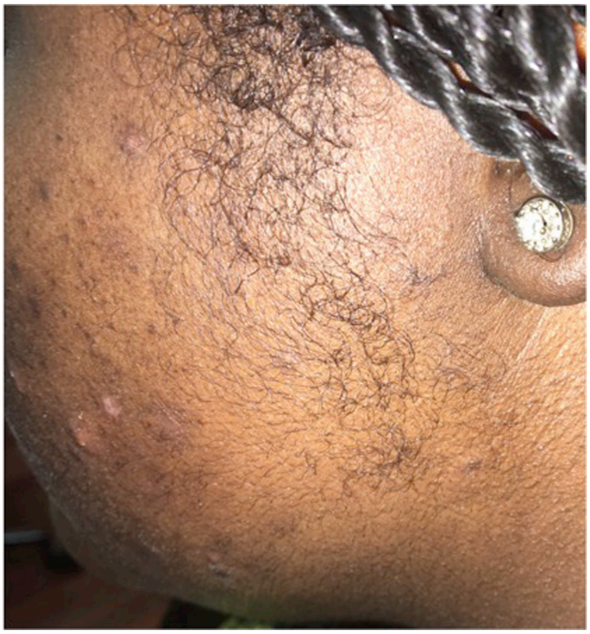

Fig 9. Hirsutism and acne on an obese woman.

pathologic pathways, such as the transcription of renin, cytotoxic T-lymphocyte antigen 4, and toll-like receptor 3.[131,168] There is also evidence that the proinflammatory mediators involved in the pathogenesis of psoriasis get circulated systemically, inducing insulin resistance, endothelial dysfunction, and hypercoagulation and increasing oxidative stress.[131]

Rosacea

The association between obesity and rosacea is not clear; the few epidemiologic studies performed have shown mixed results.[169-172] However, in a recent study of a large cohort of US women, a positive correlation was found.[170] A significantly increased risk for rosacea was described for patients with high BMIs. Moreover, the risk of rosacea was increased among those with weight gained since age 18 years, independently of BMI, suggesting that weight changes early in life were more important than total weight gain. The authors also found a positive association between rosacea and waist and hip circumferences.[170] It is important to mention that all patients in the study were women and most were white; thereby, caution is necessary when extrapolating these results into the general population.

Atopic dermatitis

There has been an increase in the prevalence of obesity that might be paralleling the same trend in

Table IV. Impact of obesity in psoriasis with biologic treatment

Drug class	Drug	Type of study	Obesity impact in efficacy of the drug	References
Anti-IL-17A monoclonal antibodies	Secukinumab	Phase 3, double-blind, global trial	• Intervention: placebo, 150-mg and 300-mg secukinumab treatment groups • Patients of healthy BMI have more rapid and better response than overweight patients. • Weight, waist, and hip circumference were significantly different between good responders (PASI-75 at week 4) and poor responders under secukinumab 300 mg.	137
		Case report	• First case: male patient with a BMI ≥30 kg/m^2 and severe psoriasis on secukinumab 450 mg after a partial response to a standard 300-mg dose. Patient significantly improved with 450 mg. • Second case: female patient with a BMI of 31.6 kg/m^2 with treatment-resistant psoriasis relapsed after receiving the standard dose, which was increased to 450 mg. Psoriasis did not resolve.	138
	Ixekizumab	Integrated database of 3 randomized, controlled phase 3 studies	• Intervention: subcutaneous placebo, 80 mg ixekizumab every 2 weeks or every 4 weeks after a starting dose of 160 mg ixekizumab, or 50 mg etanercept twice weekly • Ixekizumab is efficacious regardless of bodyweight. • The safety profile was similar across bodyweight categories.	139-141
Human IL-12/23 monoclonal antibody	Ustekinumab	Retrospective analysis	• Intervention: ustekinumab 45 mg • Patients with BMI ≥25 kg/m^2 and BMI <25 kg/m^2 had comparable PASI-50 and PASI-75 response rates. • Patients with BMI ≥25 kg/m^2 had significantly lower PASI-90 and PASI-100 response rates. • BMI was negatively correlated with percent reduction in PASI, whereas body weight was not.	142
		Retrospective analysis	• 45 mg via subcutaneous injection at weeks 0, 4, and every 12 weeks • Intervention: ustekinumab subcutaneous injection at weeks 0 and 4 and every 12 weeks • Patients with body weight >80 kg, BMI >25 kg/m^2, or smoking habit >20 cigarettes/day had a higher proportion of insufficient responders. • Patients with previous exposures to biologics had a significantly lower response to the treatment.	143

Continued

Table IV. Cont'd

Drug class	Drug	Type of study	Obesity impact in efficacy of the drug	References
PDE-4 inhibitor	Apremilast	Prospective analysis	• Intervention: apremilast starting 10 mg/day stepwise to increase to 30 mg twice a day • Patient weight inversely correlated with a PASI-50 response ($P < .05$, n = 37) • None of the obese patients (BMI >30.0 kg/m^2, n = 6) reached PASI-75.	144,145
TNF-α inhibitor	Adalimumab	Randomized, double-blind, placebo-controlled, phase 3 multicenter study	• Intervention: adalimumab 80 mg at week 0 then 40 mg every other week starting at week 1, methotrexate up to 25 mg/wk orally, or placebo • The adalimumab-treated group had higher PASI-75 and PASI-90 response rates and more improvements in DLQI scores at week 16 than the methotrexate or placebo groups, regardless of baseline BMI.	146
		Retrospective study	• Obesity did not affect the efficacy of adalimumab in terms of PASI response. • Patients with a BMI ≥30 kg/m^2 discontinued treatment earlier.	147
	Etanercept + NB-UVB	Pilot randomized comparison study	• Intervention: etanercept 50 mg twice weekly for 12 weeks and then randomized to receive etanercept monotherapy or etanercept + NB-UVB 3 times weekly for an additional 12 weeks • Etanercept + NB-UVB had similar efficacy as etanercept monotherapy in obese patients. • Even in the setting of obesity, most patients respond well to etanercept, with or without NB-UVB.	148
	Etanercept	Randomized placebo-controlled study	• Intervention: subcutaneous injection of 50 mg etanercept 2X/wk for 12 weeks, followed by 50 mg 1X/wk and placebo (group A) or subcutaneous placebo 2X/wk for 12 weeks, followed by etanercept 50 mg 2X/wk for 12 weeks (group B) • At week 12, a significantly higher proportion of patients achieved PASI-75 with etanercept than placebo, regardless of baseline BMI.	149
	Infliximab	Prospective study	• Intervention: 5 mg/kg at weeks 0, 2, and 6 (induction phase), followed by maintenance therapy every 8 weeks • Obesity was associated with a delayed and less effective response to treatment.	151

Combined biologics	Infliximab, efalizumab, alefacept, etanercept	Literature review	• Weight-based–dosed medications do not seem to lose efficacy with increasing weight. • Etanercept and alefacept might have compromised efficacy in heavier individuals.	150
	Adalimumab, etanercept, infliximab	Retrospective analysis	• Disease activity and clinical response to anti–TNF-α therapy in psoriatic arthritis do not seem to be affected by BMI.	152
	Adalimumab, etanercept, ustekinumab	Prospective, comparative, long-term drug-survival study from the BioCAPTURE registry	• Higher BMI is a predictor for discontinuation due to ineffectiveness in etanercept and ustekinumab. • Female sex is a predictor for discontinuation due to side effects for 3 biologics.	153

BMI, Body mass index; *DLQI*, Dermatology Life Quality Index; *IL*, interleukin; *NB-UVB*, narrowband ultraviolet B; *PASI*, Psoriasis Area Severity Index; *PASI-50*, ≥50% improvement from baseline PASI score; *PASI-75*, ≥75% improvement from baseline PASI score; *PASI-90*, ≥90% improvement from baseline PASI score; *PASI-100*, ≥100% improvement from baseline PASI score; *PDE4*, phosphodiesterase 4; *TNF*, tumor necrosis factor.

atopic dermatitis.[79,173,174] Few studies have demonstrated an association between obesity and atopic dermatitis.[175-183] The results of a meta-analysis suggested that increased weight is associated with increased prevalence of atopic dermatitis both in children and adults in North America and Asia.[177] However, further research is necessary to determine a temporal relationship between obesity and atopic dermatitis and to clarify causation.

Hair and scalp

Obesity might be related to premature hair graying (ie, graying before 30 years of age).[184,185] Shin et al performed a cross-sectional study and concluded that the odds of having premature hair graying proportionally increased with BMI.[184] Scalp hair cortisol levels have also been associated with obesity and MetS. Papafotiou et al showed that obese prepubertal girls had higher scalp hair cortisol levels,[186] and these findings were also replicable in children 6-9 years of age.[187]

Cutis verticis gyrata is a rare disorder characterized by thickening of the scalp with ridges and furrows that resembles the cerebral gyri.[188] It has been described in association with insulin resistance syndrome,[188] which has obesity as one of its features.

METABOLIC SKIN MANIFESTATIONS

Obesity is associated with MetS and peripheral insulin resistance, which can lead to compensatory hyperinsulinemia.[8-12,17] Insulin resistance is believed to be a cause of obesity itself and is linked to other disorders, including type 2 diabetes, hypertension, dyslipidemia, and coronary artery disease. Many dermatologic diseases (eg, acne, acrochordons, acanthosis nigricans, keratosis pilaris, hyperandrogenism, hirsutism, androgenic alopecia, and HS) might be exacerbated by MetS and insulin resistance (Table III).[17,58-68,189-192] The severity of psoriasis has been linked with MetS.[192,193]

Hyperandrogenism and acne

Adipose tissue synthesizes testosterone, contributing to the hyperandrogenism seen in obesity.[17] Furthermore, obesity is associated with reduced sex hormone–binding globulin synthesis and increased circulatory blood levels of androgens.[194] In women, obesity is associated with polycystic ovary syndrome.[189] Polycystic ovary syndrome might cause hirsutism (Fig 9), menstrual irregularities, acanthosis nigricans, acne, HS, androgenic alopecia, seborrhea, and hyperinsulinism.[17,190] Hirsutism might be the initial and possibly only sign of androgen excess.

The data relating acne to obesity is sparse and controversial. However, there are studies suggesting

Table V. Impact of obesity in psoriasis with systemic treatment

Drug	Type of study	Intervention	Obesity effects	References
Cyclosporine	Randomized controlled clinical trial	2.5 mg/kg for all groups; low caloric diet	Intervention group: PASI-75 response was achieved in 67%, and PASI-50 was achieved in 87%. Nonintervention group: PASI-75 response was achieved in 48% and PASI-50 was achieved in 29%. Weight loss improves response of obese patients with moderate-to-severe chronic plaque psoriasis to low-dose cyclosporine	154
Methotrexate	Tissue collection, 71 patients, 169 liver biopsies	Medium cumulative dose: 1500 mg	Overweight (n = 15): liver fibrosis developed in 93%. Overweight: severe liver fibrosis developed in 5 patients ($P < .0132$). Patients with psoriasis and overweight patients treated with methotrexate are at high risk of liver fibrosis.	155
Phototherapy	Prospective study	Narrowband UVB: Waldmann 7001K cabinets; phototherapy-induced erythema grade 1 or 2	Patients with high BMIs and large waist circumferences had increased risk of phototherapy-induced erythema.	156
Acitretin, cyclosporine, methotrexate, PUVA	Cohort study	A nationwide cohort study of patients receiving a new systemic treatment for plaque psoriasis in Italy	The proportion of patients achieving PASI-75 decreased with higher BMI values, from 41.7% in patients with BMIs <20 kg/m^2 to 29.1% in those with BMIs ≥30 kg/m^2 at 8 weeks and from 59% in patients with BMIs <20 kg/m^2 to 42.2% in patients with BMIs ≥30 kg/m^2 at 16 weeks.	133
Acitretin, cyclosporine, methotrexate, PUVA	Literature review		Dermatologists should be cautious about long-term courses of methotrexate in obese patients with psoriasis because of their increased risk of nonalcoholic fatty liver disease. There is an increased risk of nephrotoxicity, hypertriglyceridemia, and hypercholesterolemia in obese patients receiving treatment with cyclosporine.	157

BMI, Body mass index; *PASI*, Psoriasis Area Severity Index; *PASI-50*, ≥50% improvement form baseline PASI score; *PASI-75*, ≥75% improvement from baseline PASI score; *PUVA*, psoralen ultraviolet A; *UVB*, ultraviolet B.

that increased BMI is associated with increased risk of acne, as well as insulin resistance and early onset menarche.[195-199]

Gout and the skin

Tophaceous gout is caused by the collection of solid urate, resulting in destructive changes in the surrounding connective tissue and chronic inflammation.[200] Tophi are typically tender and can be visualized or palpated on soft tissues or articular structures. Obesity favors the development of gout because obesity is associated with increased uric acid levels.[17,201-205] In fact, weight loss is associated with lower levels of uric acid.[17,203,206,207] In a study conducted in Mexico that included 316 patients with tophaceous gout, 62% were found to be obese.

Table VI. Rare skin conditions associated or aggravated by obesity

Skin condition	Clinical presentation	Pathogenesis	Histologic findings	References
Keratosis follicularis squamosa (Dohl)	Keratinizing disorder; most common in Asians; scaly patches with brownish follicular plug in the center, and slightly razed margin; localized in the trunk, buttocks and thighs	Bacterial infections, irritation from clothing, genetics, and hormone imbalances; genetics: novel locus on chromosome 7p14.3−7p12.1	Dilated follicles with keratotic plugs surrounded by lamellar orthohyperkeratosis; dermoscopy: lotus-leaves-on-the-water appearance and follicular plug in the center	25,209-211
Adiposis dolorosa/Dercum disease	Multiple, painful, subcutaneous lipomas; associated with systemic findings: hyperalgesia, acral swelling, telangiectasia, bruising, fatigability, weakness, depression; different presentations: generalized diffuse form, generalized nodular form, localized nodular form, juxta-articular form; localized in trunk and lower extremities	Genetics: autosomal dominant with incomplete penetrance; sometimes due to a new mutation; occurs in obese, postmenopausal women; metabolic, autoimmune mechanisms or altered neuropeptides might play a role.	The same findings as in lipomas: mature fat cells	25,212-216
Granular parakeratosis	Self-limited condition; grouped erythematous to brown, scaly, crusted, hyperkeratotic papules that can coalesce into plaques; can be unilateral or bilateral; often asymptomatic, but might be pruritic, burning, or painful; localized to intertriginous body sites	2 theories: physical irritation or contact allergy possibly to deodorants and antiperspirants, which interrupt the breakdown of profilaggrin to filaggrin during epidermal differentiation; acquired disorder of cornification, unrelated to contact agents; aggravating factors: occlusion in warm moist environments, maceration of skin, mechanical irritation exacerbated by obesity	Hyperkeratosis, compact parakeratosis and retention of keratohyalin granules confined to the stratum granulosum; Some areas of agranular parakeratosis or orthokeratosis may also be observed; occasional vacuolization of keratinocytes or mild spongiosis in epidermis, often described as acanthotic or psoriasiform	25,217-227
Chronic obesity lymphedematous mucinosis	Subtype of pretibial myxedema; 4 variants: diffuse nonpitting edema (43%), plaque (27%), nodular (18%) , and elephantiasis (5%); might exhibit peau d'orange (orange-peel) appearance; localized in the lateral or anterior leg and dorsa of the feet; typically asymptomatic, might be associated with hyperhidrosis or hypertrichosis	Abnormal collection of mucin in the interstitium due to a defect in lymphatic drainage	Epidermal atrophy with loss of rete ridges; separation of collagen bundles associated with edema; extension of lymph space in the reticular dermis; mucin deposition in the superficial papillary dermis and around the vessels	25,231-233

Interestingly, few obese patients had severe tophaceous gout (>5 tophi).[208]

OBESITY AND RARE SKIN CONDITIONS

Obesity is also associated with an increased incidence or aggravation of the symptoms of rare skin disorders, such as keratosis follicularis squamosa (Dohi),[25,209-211] adiposis dolorosa/Dercum disease (DD),[25,212-216] granular parakeratosis,[25,217-227] lipedema,[228-230] and lymphedematous mucinosis (Table VI).*

DD is a rare condition characterized by multiple painful fatty lipomas.[234] The most common locations are the extremities, trunk, pelvic area, and buttocks.[205-209,234] DD has been associated with obesity.[216,235-237]

Obesity-associated lymphedematous mucinosis is a rare disorder that clinically mimics pretibial myxedema. However, it is not associated with thyroid disease.[238] It presents as bilateral lower extremity pitting edema sparing the feet with semitranslucent papules, nodules, or both and sometimes vesicles.[232] Obesity-associated lymphedematous mucinosis has been reported in association with obesity in a few case reports.[232,233,239-241] The pathogenesis is believed to be secondary to lymphatic stasis caused by obesity, which leads to local hypoxia and mucin accumulation.[242]

Lipedema is a disorder of adipose tissue with increased deposition of subcutaneous fat that presents with swelling and enlargement of the lower limbs.[228,229] Most patients with lipedema have a high BMI.[228-230] Unlike lymphedema, lipedema presents exclusively in women, has a bilateral symmetrical presentation with minimal involvement of the feet (reverse shouldering), is not associated with pain or tenderness, and involves minimal pitting edema.[228-230]

OBESITY AND SKIN CANCER

Studies evaluating the association of anthropometric measures and nonmelanoma skin cancer have shown contradictory results.[243-252] A few large prospective studies found a lower risk of basal cell carcinoma with increasing weight and BMI for both men and women.[243,248-250,252] This finding can be explained, as obese patients tend to avoid outdoors and have lower levels of sun exposure. On the other hand, some studies showed no association between weight or BMI and incidence of basal cell carcinoma or squamous cell carcinoma.[244-247]

The correlation between obesity and malignant melanoma also yielded contradictory results. Some studies found an increased risk of malignant melanoma among obese patients.[4,246,253-255] Nonetheless, data from other studies, including some recent prospective studies, suggested no relation.[244,256-258]

CONCLUSIONS

Obesity and its metabolic comorbidities are associated with various skin manifestations. As the incidence of obesity continues to increase, so will the accompanying cutaneous conditions. Dermatologists will face an increase in patient visits due to conditions that are caused or aggravated by increased weight. Understanding these clinical signs and the underlying systemic disorders will facilitate better treatment and avoidance of sequelae. Obesity requires a multidisciplinary approach by the primary care physician, dermatologist, and others to reduce harmful effects and complications.

*25,209-211,213-227,231-233

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Answers to CME examination

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