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Obesity and the skin: Skin physiology and skin manifestations of obesity

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Obesity is widely recognized as an epidemic in the Western world; however, the impact of obesity on the skin has received minimal attention. The purpose of this article is to highlight the association between obesity and dermatologic conditions. We review the impact of obesity on the skin, including skin physiology, skin manifestations of obesity, and dermatologic diseases aggravated by obesity. Obesity is responsible for changes in skin barrier function, sebaceous glands and sebum production, sweat glands, lymphatics, collagen structure and function, wound healing, microcirculation and macrocirculation, and subcutaneous fat. Moreover, obesity is implicated in a wide spectrum of dermatologic diseases, including acanthosis nigricans, acrochordons, keratosis pilaris, hyperandrogenism and hirsutism, striae distensae, adiposis dolorosa, and fat redistribution, lymphedema, chronic venous insufficiency, plantar hyperkeratosis, cellulitis, skin infections, hidradenitis suppurativa, psoriasis, insulin resistance syndrome, and tophaceous gout. We review the clinical features, evidence for association with obesity, and management of these various dermatoses and highlight the profound impact of obesity in clinical dermatology. (J Am Acad Dermatol 2007;56:901-16.)

Learning objective: After completing this learning activity, participants should be aware of obesity-associated changes in skin physiology, skin manifestations of obesity, and dermatologic diseases aggravated by obesity, and be able to formulate a pathophysiology-based treatment strategy for obesity-associated dermatoses.

INTRODUCTION

Epidemiology of obesity

Obesity is increasingly being recognized as a major public health problem in the United States. The prevalence of obesity, which is defined as a body mass index (BMI) of 30 kg/m² or greater, has significantly increased among the US population over the past 30 years.1 Approximately 119 million Americans, nearly two thirds of adult Americans, are either overweight or obese.2 Recent research estimates that between one fourth and one third of American adults are obese,1,2 and one in six children and adolescents is overweight.1 This increased prevalence of obesity has been noted among all age, gender, and racial groups in all 50 states.2

The total cost attributable to obesity in the United States in 1995 was estimated to amount to nearly $100 billion.3 More than $50 billion were direct medical costs, and over 60 million physician visits were attributable to obesity in 1994.3 It is widely recognized that obesity increases the risk of coronary heart disease, hypertension, hyperlipidemia, osteoarthritis, and diabetes. Obesity is also known to be directly related to increased risk of sleep apnea; breast, endometrial, and colon cancer; gallbladder disease; musculoskeletal disorders; severe pancreatitis, diverticulitis; infertility; urinary incontinence; and idiopathic intracranial hypertension.4 Obesity is indirectly related to anxiety, impaired social interaction, and depression.4 However, the impact of obesity on the skin has received minimal attention.

Pathophysiology of obesity

Obesity results from both environmental and genetic factors. Based on previous studies, approximately 60% to 70% of the variance in BMI can be attributed to environment and 30% to 40% of the variance in BMI can be attributed to genetics.5 The contributions of environmental factors to the etiology of obesity are well known. Dietary choices, socioeconomic status, and behavioral factors, such as inactivity, are all important factors in obese patients. In the United States, high-caloric food is cheap and abundant. Moreover, advances in technology both at home
and in the workplace have dramatically reduced the amount of physical activity compared with previous generations. Obesity results from a chronic imbalance between food intake and energy expenditure. Specifically, 3 metabolic factors have been reported to be predictive of weight gain: (1) low adjusted sedentary energy expenditure; (2) high respiratory quotient (carbohydrate-to-fat oxidation ratio); and (3) low level of spontaneous physical activity.

The interaction between genetics and environment is also important. Individuals may be genetically predisposed to become obese; however, the obesity genotype may only be expressed under certain environmental conditions. In Western countries, exposure to high-fat diets and sedentary lifestyle is common; thus the proportion of the population expressing the obesity genotype has increased.

Molecular genetics of obesity

Although researchers have identified monogenic forms of obesity resulting from mutations in genes involved in central pathways of food intake regulation, the vast majority of obesity cases result from a complex polygenic disease involving interactions between multiple genes and the environment. The genetics of obesity is an ongoing topic of study and we refer the reader to the detailed reviews by Snyder et al and Cancello et al outlining the obesity gene map and various signaling molecules implicated in obesity. For the purpose of this review, we will focus on the two gene products which are known to have direct effects on the skin—the leptin and proopiomelanocortin (POMC) genes.

Leptin, the product of the Ob gene, is a hormone secreted by adipocytes that regulates energy homeostasis and food intake via specific receptors in the hypothalamus. Congenital leptin deficiency has been identified in humans and is associated with a rare, severe early-onset form of obesity. In such patients, treatment with leptin is successful. However, most obese patients actually have elevated circulating leptin levels in the setting of functional leptin resistance, and treatment with exogenous leptin is ineffective in ameliorating the obesity. Leptin receptors (Ob-R) have been located on tissues, including keratinocytes, fibroblasts, endothelial cells, and adipose tissue. Many studies have examined the beneficial role of leptin in wound healing. Leptin is acutely up-regulated in injured skin and in vitro promotes fibroblast proliferation and collagen synthesis. Leptin has also been shown to promote endothelial cell growth and angiogenesis, but at higher levels it proves toxic to vasculature, leading to capillary leakage and avascular zones. Decreased levels of leptin have also been shown in patients with some forms of lipodystrophy, in mouse models of generalized lipodystrophy, administration of exogenous leptin increases glucose metabolism and restores insulin sensitivity. This suggests a possible role of leptin in the pathophysiology of this disorder as well as in the insulin resistance syndrome.

The second possible genetic contributor towards obesity is the POMC gene. POMC is expressed in various tissues, including the pituitary, immune system, hypothalamus, and skin. In these tissues, POMC is cleaved into smaller peptides including beta-endorphin, adrenocorticotropin, and alpha-, beta- and gamma-melanocyte-stimulating hormones, which play various roles in control of analgesia, inflammation, adrenal steroidogenesis, and skin pigmentation. The POMC-derived melanocortin peptides bind with different affinity and specificity to a set of 5 homologous melanocortin receptors. MC1 receptor is associated with human pigmentation and mutations in the gene for this receptor are known to cause red hair and fair skin. MC4 receptor deficiency is the most common monogenic cause of obesity, and mutations in this gene affect at least 3% of extremely obese individuals. This receptor appears to play a key role in the control of eating behavior in humans. A syndrome variant of POMC deficiency has been described with complete loss-of-function mutations of the POMC gene. The syndrome consists of severe early-onset obesity, adrenal insufficiency, reduced skin pigmentation, and red-orange hair. However, the contribution of the POMC gene to the pathogenesis of nonsyndromic obesity remains unclear.

OBESITY AND SKIN PHYSIOLOGY

Obesity is related to a number of effects on skin physiology, including effects on skin barrier function, sebaceous glands and sebum production, sweat glands, lymphatics, collagen structure and function, wound healing, microcirculation and macrocirculation, and subcutaneous fat.

Skin barrier function

Obesity is associated with a number of significant changes in skin barrier function. Loffler, Aramaki, and Effendy used bioengineering methods to investigate the correlation between BMI and epidermal functions. Obese individuals demonstrated significantly increased transepidermal water loss and erythema compared with control subjects, suggesting a fundamentally altered epidermal barrier. We have previously found that morbidly obese patients have dry skin and impaired skin barrier repair (unpublished data).
Sebaceous glands and sebum production
To our knowledge, there are no epidemiologic studies examining the relationship between obesity and sebum production. This relationship is potentially important because sebum production plays a major role in the pathogenesis of acne.\textsuperscript{30-35} In addition, diet may directly or indirectly influence causes of acne, including increased proliferation of basal keratinocytes within the pilosebaceous duct, incomplete separation of ductal corneocytes from one another and subsequent obstruction of the pilosebaceous duct, and androgen-mediated increases in sebum production.\textsuperscript{34}

Acne is clearly exacerbated by obesity-associated disorders, such as hyperandrogenism and hirsutism. Androgens, insulin, growth hormone, and insulin-like growth factors are frequently elevated in obese patients and have been demonstrated to activate sebaceous glands and influence acne severity.\textsuperscript{35,36} Obese patients with polycystic ovary syndrome demonstrated significant improvement in acne when treated with pioglitazone,\textsuperscript{37} an insulin-sensitizing agent.

Apocrine and eccrine sweat glands
Previous authors have suggested that obesity-associated changes in skin physiology may be related to increased sweat gland activity.\textsuperscript{29} Obese patients have larger skin folds and sweat more profusely after becoming overheated because of thick layers of subcutaneous fat, thereby increasing both the frictional and moisture components.\textsuperscript{38} In diabetic patients, skin surface pH was found to be higher in the skin folds of women with BMI greater than 25 versus women with BMI less than 25.\textsuperscript{39} However, currently there are no specific published data on the structure and function of apocrine and eccrine sweat glands in obesity.

Lymphatics
Obesity impedes lymphatic flow, which leads to collection of protein-rich lymphatic fluid in the subcutaneous tissue. This accumulation frequently results in lymphedema. Lymphedema is associated with dilatation of tissue channels and reduced tissue oxygenation.\textsuperscript{36} Further accumulation of fluid in the setting of decreased oxygen tension leads to fibrosis and a chronic inflammatory state.

Collagen structure and function and wound healing
In animal studies, obesity is also associated with altered collagen structure and function and impaired wound healing. Enser and Avery\textsuperscript{40} demonstrated that the skin of obese mice was mechanically weaker and generated a lower hydrothermal isometric force compared with the skin of lean mice. The authors suggest that the decreased mechanical strength of skin in obese mice resulted from failure of collagen deposition to match the increase in skin surface area. A previous study found that obese mice demonstrated slower wound healing and decreased wound collagen deposition.\textsuperscript{41} Interestingly, neither insulin nor diet restriction restored wound collagen accumulation in phenotypically obese mice.\textsuperscript{41} The authors proposed that the decreased wound collagen accumulation may be due in part to structural changes in the pilosebaceous duct, and androgen-mediated increases in sebum production.\textsuperscript{34}

Microcirculation and macrocirculation
Several studies have demonstrated that obesity is associated with significant changes in cutaneous microcirculation and macrocirculation. Obesity appears to be a primary cause of microvascular dysfunction, which may contribute to the development of obesity-related microangiopathy and hypertension.\textsuperscript{43} Using bioengineering methods, Loffler, Aramaki, and Effendy\textsuperscript{29} demonstrated that higher BMI was significantly correlated with increased cutaneous blood flow. In obese children, there appears to be significantly elevated cutaneous baseline blood flow and peak blood flow and significantly lower peak capillary blood cell velocity compared with healthy control subjects.\textsuperscript{44} These changes in cutaneous microcirculation may be due to physiological compensation. Obese women have been demonstrated to have impaired capillary recruitment and acetylcholine-mediated vasodilation compared with lean women.\textsuperscript{43} Alterations of cardiac vangosympathetic activity in obesity have also been suggested. In non-diabetic obese patients, there is a significant reduction in the cutaneous vasoconstrictive response to sympathetic activation.\textsuperscript{45} Agapitov et al\textsuperscript{46} found that normotensive obese patients exhibited markedly impaired skin microcirculatory responses to mental stress.

Subcutaneous fat
In adults, subcutaneous fat is made up almost entirely of white adipose tissue, which provides insulation and serves as an energy depot. White adipose tissue plays an important role in endocrine functions as well as metabolism of lipids and glucose.\textsuperscript{47} Endocrine peptides secreted by adipocytes include leptin and tumor necrosis factor $\alpha$, among others. In contrast, brown fat is most prominent in newborn infants and its exact role in obese adults is
not yet clear. We direct the reader to the comprehensive review series by Avram, Avram, and James on subcutaneous fat in normal and diseased states.

SKIN MANIFESTATIONS OF OBESITY

Obesity is associated with a number of dermatoses, including acanthosis nigricans, acrochordons, keratosis pilaris, hyperandrogenism and hirsutism, striae distensae, and adiposis dolorosa, and with fat redistribution (Table I).

Acanthosis nigricans

Acanthosis nigricans is the most common dermatological manifestation of obesity. Acanthosis nigricans appears as symmetric, velvety, hyperpigmented plaques that may occur in almost any location. It is most commonly observed in the axilla, groin, and posterior neck but can also be seen on the elbows, knuckles, and face, particularly in ethnic skin (Figs 1 and 2). Acrochordons are frequently observed in the affected areas. The hyperpigmentation observed is secondary to acanthosis and papillomatosis of the epidermis rather than pigment-producing cells. The skin proliferation abnormalities in acanthosis nigricans are frequently associated with hyperinsulinemia and insulin resistance. Hud et al found that 74% of an obese population exhibited acanthosis nigricans along with elevated plasma insulin levels. Obese children with acanthosis nigricans have also been shown to have insulin resistance. Insulin resistance is also associated with cutaneous virilism. Hyperinsulinemia increases the production of ovarian androgens, which may lead to associated hirsutism and acne vulgaris. The clinical triad of polycystic ovaries, hirsutism, and acanthosis nigricans is commonly observed. In obese women with hyperandrogenism and hirsutism, acanthosis nigricans most commonly affects the vulva.

The proposed mechanism of how hyperinsulinemia leads to this epidermal change begins at the cellular level. Increased levels of circulating insulin leads to decreased numbers of functional insulin receptors. These “classic” insulin receptors regulate glucose uptake, cell growth, DNA synthesis, and protein and fat metabolism via tyrosine kinase activity. Keratinocytes and fibroblasts both express insulin-like growth factor (IGF) receptors that are also capable of binding insulin and have growth-promoting effects. Decreased numbers of functional insulin receptors cause a shift to increased binding to IGF receptors contributing to the development of acanthosis nigricans.

Acanthosis nigricans plaques can be managed by improved control of hyperinsulinemia. Treatment with a low-calorie diet and weight reduction can improve the insulin resistance state, thus decreasing the severity of the skin disease. Other treatments that have been reported to help clear acanthosis nigricans include metformin, octreotide, retinoids, topical calcipotriol, and laser therapy.

Acrochordons

Acrochordons are pedunculated soft brown papules most commonly seen on the neck and in the axillae and groin; they are frequently seen in association with acanthosis nigricans. In a study of 156 obese patients, the percentage of those with acrochordons increased with the severity of obesity. Kahana et al did not find an increased incidence with obesity but did report that those patients with acrochordons had greater impairment of carbohydrate metabolism. Insulin sensitivity improves with weight loss; therefore the increased incidence seen at higher BMI may be due to greater insulin resistance. Further studies are warranted in this area. Simple scissor excision, electrodesiccation, and cryotherapy are successful therapeutic options.

Keratosis pilaris

Keratosis pilaris often presents as small, perifollicular, spiny papules on extensor aspects of extremities. Often associated with atopic diathesis, this benign dermatosis also manifests in those with...
It has been suggested that insulin resistance may play a role in the development of keratosis pilaris. Treatments are of varying success and include keratolytics, retinoids, and mild topical corticosteroids.

### Hyperandrogenism and Hirsutism

Hyperandrogenism can be the result of increased production of endogenous androgens due to increased volumes of adipose tissue (which synthesizes testosterone) and hyperinsulinemia (which increases the production of ovarian androgens). Cutaneous virilism can include hirsutism, acne vulgaris, hidradenitis suppurativa, and androgenic alopecia. There appears to be an association between cutaneous virilism, acanthosis nigricans, keratosis pilaris, and insulin resistance. Ruutiainen et al found that facial hirsutism is significantly correlated with BMI independently of age and testosterone level.

Treatment of hyperandrogenism should be centered on controlling insulin levels; weight loss, oral contraceptives, and antiandrogenic therapies are also treatment options. In obese women with polycystic ovary syndrome, thiazolidinediones improve insulin resistance and hyperandrogenism.

### Striae Distensae

Striae distensae, stretch marks, are linear atrophic plaques that are distributed perpendicular to the force of greatest tension and are commonly found on the breasts, buttocks, abdomen, and thighs (Fig 3). They begin with an erythematous phase before turning violet, then finally becoming white depressed plaques. The exact pathogenesis of striae has yet to be elucidated, but mechanical, hormonal, and genetic factors may play a role. They are present in obese patients, and in other clinical settings such as pregnancy, Cushing’s syndrome, and topical corticosteroid use. Hsu et al diagnosed striae in 40% of children with moderate to severe obesity, and incidence was higher in those with a longer duration of obesity. Simkin and Arce found higher levels of urinary adrenocorticosteroids in obese patients with striae as opposed to obese patients without striae. The clinical appearance of striae, however, was found by Angeli et al to be lighter, narrower, and less atrophic than in those with Cushing’s syndrome. Striae can be regarded as “scars” that result from dermal connective tissue injury in which the newly generated collagen aligns in response to local stress forces. In the early stage of development, elastolysis, mast cell degranulation, and macrophage engulfment of elastic tissue have all been documented by light and electron microscopy. Typical histopathologic features also include densely packed eosinophilic thin collagen bundles parallel to epidermis, effacement of rete ridges, and lack of adnexal structures, thus reinforcing striae as forms of scars.

Currently available treatment options are unsatisfactory, but include topical agents such as tretinoin.
0.1% cream, and tretinoin 0.05% cream combined with 20% glycolic acid. Lower dose tretinoin 0.025% cream does not appear to be effective. Intense pulsed light improves striae clinically and histologically with minimal side effects. Laser therapies are effective and depend upon stage of striae that is being treated. The 585-nm flash-pumped laser decreases erythema of early-stage lesions, and the 308-nm excimer laser improves hypopigmentation associated with late-stage striae. Striae rubra and alba have been treated with a pulsed dye laser with marginal success. Laser therapy should be avoided for striae in individuals having Fitzpatrick skin types IV through VI because of the resultant hyperpigmentation.

**Adiposis dolorosa**

Adiposis dolorosa, or Dercum’s disease, is a rare progressive condition characterized by multiple, painful, subcutaneous lipomas that usually occur in obese, postmenopausal women. The painful lipomas are symmetrically distributed and are either diffuse or localized. These fatty deposits have been reported to occur in any location, except on the head and the neck; however, the trunk and lower extremities, especially around the knees, are the most commonly involved sites. Characteristically, pain is out of proportion to physical findings. Pain increases with BMI, and patients are usually 50% above normal weight for their age. Other findings in adiposis dolorosa include hyperalgesia to light pressure, acral swelling, bruising, and telangiectasia. The syndrome is also associated with fatigability and weakness as well as depression, confusion, and dementia. The etiology is unknown; however, a metabolic or autoimmune mechanism is suspected to be involved. Diagnosis is often delayed and is made by ultrasonography and magnetic resonance imaging.

Treatment is often ineffective. A combination of medications, surgery, and psychiatric care is usually needed. The goals of therapy are to relieve the pain and restore normal appearance. Available medications only treat symptoms and do not change the course of the disease. Corticosteroids, intravenous lidocaine, mexiletine, or analgesics may provide pain relief. Surgical excision or liposuction of painful masses is sometimes effective.

### Fat redistribution in obesity

In obesity, there is redistribution of fat in specific patterns. Women generally have a higher percentage of body fat than men, and adipose tissue is distributed differently in men and women. Men tend to accumulate fat in an android or upper body (abdominal) distribution. In contrast, women tend to accumulate fat in a gynoid or lower body distribution that predominantly involves the hips and thighs. The etiology of these dramatic differences in body fat distribution between men and women is not well understood; however, differences in fat distribution have significant implications for obesity-associated diseases. In both normal-weight and obese men and women, increased accumulation of fat in the intra-abdominal cavity (visceral adiposity) is independently associated with insulin resistance and coronary artery disease. In women, increased androgenicity is strongly associated with an unfavorable body fat distribution and insulin resistance.

Obese patients frequently consult plastic surgeons and dermatologists for liposuction. Liposuction is the most commonly performed cosmetic surgery procedure in North America. It is most appropriately viewed as a procedure to improve the body contour and is not recommended as a treatment for generalized obesity. So-called large-volume liposuction or mega-liposuction for obese patients is highly controversial. Large-volume liposuction may decrease weight and body fat mass; however, there are conflicting data regarding whether or not it significantly improves insulin resistance and other obesity-associated metabolic abnormalities. Large-volume liposuction can be associated with significant increases in the proportion of visceral adipose tissue, which is a risk factor for metabolic complications of obesity. In obese patients, much larger cannulae and volume of anesthesia must be used and the risks to the patient are significant. Common complications occurring after liposuction in obese patients include rippling of excess skin, constrictive bands, and unsightly skin folds.

### SKIN DISEASES AGGRAVATED BY OBESITY

Skin diseases aggravated but not directly caused by obesity include lymphedema, chronic venous
insufficiency, plantar hyperkeratosis, cellulite, skin infections, hidradenitis suppurativa, psoriasis, insulin resistance syndrome, and tophaceous gout.

**Lymphedema**

In obese patients, lymphedema results from impedance to lymphatic flow. In such patients, lymphedema presents clinically as initially soft, pitting edema most commonly beginning in the feet and spreading proximally (Fig 4). With time, further accumulation of fluid, decreased oxygen tension, and macrophage function lead to fibrosis and a chronic inflammatory state. In this setting of reduced tissue oxygenation, lymphedema provides a culture medium for bacterial growth.38

The patient is subject to repeated bacterial infections in the affected tissue that causes further perilymphatic scarring and impedance to lymphatic flow, thus entering the patient in a downward spiral. Chronic lymphedema can lead to elephantiasis nostras verrucosa, defined by hyperkeratosis and papillomatosis of the epidermis overlying an indurated dermis and subcutaneous tissue.108 This end-stage process can occur in any location affected by lymphedema, including the lower extremities and the abdomen of obese patients.109 A further, more threatening complication of lymphedema is the development of angiosarcoma—a malignant vascular tumor. There have been reports of abdominal wall angiosarcomas complicating chronic lymphedema of obesity.110,111

Treatment of lymphedema is directed toward reducing the limb girth and weight as well as the prevention of infection.38 Treatment consists of weight reduction, meticulous skin care, and elevation and compression by elastic stockings or pneumatic compression devices. Noninvasive complex lymphedema therapy, consisting of physical therapy, manual lymph drainage, and compressive bandages, has shown significant promise in lymphedema care.112

**Chronic venous insufficiency**

Obesity is a recognized risk factor for the development of chronic venous insufficiency.113,114 Multiple studies have documented this association in both women115,116 and men.117,118 Padberg et al119 could not demonstrate definitive venous valvular disease in obese patients with chronic venous insufficiency, which suggests that obesity alone may be inducing the morbidity associated with this disease.

The increased intra-abdominal pressure found in obese patients causes an oppositional force to venous return from the lower extremities. Valvular incompetence and venous dilation leading to varicosities may result; however, the relationship between obesity and varicose veins is controversial.38

Because of increased hydrostatic pressure, components of intravascular fluid may leak into tissue. Red blood cells extravasated from veins deposit hemoglobin within the dermis and incite an inflammatory reaction with erythema and warmth. Pitting edema, brown macular hyperpigmentation, and scaling are also typically clinically apparent.38 Stasis dermatitis is the result of irritation of superficial nerve fibers by the increased pressure and metabolic break-down products increasing local pH.120

Lipodermatosclerosis and venous ulcerations may complicate chronic venous insufficiency. The fibrosing panniculitis of lipodermatosclerosis presents as bound-down, brawny skin overlying an indurated dermis and subcutaneous tissue. The legs are the most common location for this process; however, the abdomen can also be affected in obese individuals.121 Venous ulcerations are found most commonly along the medial aspect of the lower extremity between mid-calf and the medial malleolus along the course of the greater saphenous vein. They account for approximately 70% of ulcerations found on the lower extremities.122 Overweight individuals have a greater risk for ulceration compared with those of normal body mass with comparable venous reflux severity.123

Itch and burning pain, which are common symptoms of mild to moderate venous insufficiency, have not been found to be associated with BMI.124 Treatment includes compression and leg elevation. In cases with ulceration, surgical debridement of devitalized tissue along with occlusive dressings to promote autolytic debridement should be used.122 Zinc-impregnated dressings are often applied as sequential gradient compression, which has been shown to hasten healing via stimulating fibrinolytic activity.125 Pentoxifylline (800 mg 3 times daily) also seems to be an effective adjunct to compression bandaging.126 Itching and inflammation associated with stasis pigmentation, the result of red blood
cells escaping into the tissues, can be treated with corticosteroids.  

**Plantar hyperkeratosis**

Hyperkeratosis of the soles in obesity was first described by Garcia-Hidalgo et al. in 1999. The horseshoe-shaped hyperkeratosis overlying the posterior portion of the sole was the most common skin finding in those weighing more than 170% of expected weight. Obese patients have higher plantar pressures during walking and standing and increased forefoot width. There is also an abnormal transference of weight during walking that alters the alignment of the foot, causing increased stress over bony prominences. The plantar hyperkeratosis that develops may be regarded as a physiologic response to mechanical trauma.

Eliminating the increased pressure by losing weight should be the primary recommended treatment. Protective insoles may alleviate symptoms while attempting weight reduction.

**Cellulite**

Cellulite occurs mainly in women on the thighs, buttocks, pelvic region, and abdomen. It is characterized by skin dimpling and other changes in skin topography and often a padded or “orange peel” appearance. Cellulite largely results from changes in the epidermis and dermis rather than changes in adipose tissue. Although cellulite is often present in healthy, nonobese patients, it is exacerbated by obesity.

There is no satisfactory treatment for cellulite. Authors have reported some success with topical retinoids, mechanized physical massage, and aminophylline cream, among other products. Although weight loss may improve the appearance of cellulite in some patients, this is not universally true.

**Skin infections**

Obesity increases the incidence of cutaneous infections, including candidiasis, intertrigo, candida folliculitis, furunculosis, erythrasma, tinea cruris, and folliculitis. Less common infections include erysipelas, cellulitis, necrotizing fasciitis, and gas gangrene. Although none of the following infectious complications are specific to obesity, previous studies have documented increased incidence within this population and clinical relevance. A heightened awareness of these infections could lead to earlier diagnosis and treatment in an at-risk population.

**Intertrigo**

Although intertrigo is not primarily an infectious disease, it is included in this category because of the frequent coexistence of yeast, bacteria, or fungi within the plaques. The macerated erythematous plaques developing within skin folds, such as inframammary, genitocrural, axillary, and abdominal folds, are due to both increased friction and moisture within these areas. Obese patients have larger skin folds and sweat more profusely after becoming overheated because of thick layers of subcutaneous fat, thus increasing both frictional and moisture components. There is a linear trend between the severity of obesity and intertrigo. In a study evaluating intertrigo in diabetic patients, skin surface pH was found to be higher in the inguinal folds of women with BMI higher than 25 compared with women with BMI less than 25. *Candida* first invades host tissue in the hyphal form, and this form grows best at an alkaline pH. Because pH affects the morphologic form of *Candida albicans*, it may affect how the yeast adheres to and infects intertriginous regions. A potassium hydroxide preparation can be used to diagnose candidal infection; however, the appearance of satellite papules and pustules is usually clinically distinct. Candidal species may appear independent of intertrigo in obese patients (eg, candidal folliculitis), but candidal vaginitis does not appear to be increased.

Mid- and low-potency topical steroids with silvadene as well as low pH creams can be used to treat intertrigo for a limited period. Using cleansers with low pH rather than alkaline soaps is highly recommended. Twice-daily application of tacrolimus 0.1% ointment has been shown to be effective in clearing patients of intertrigo and may prove beneficial for long-term treatment because of the lack of atrophy and striae with use. Candidal superinfection is best treated with topical antifungal agents. Systemic antifungal therapy may be required in some patients. Oral fluconazole is effective and can be used in those cases resistant to topical medications.

Dermatophyte infections can also complicate intertrigo or arise in nails or other cutaneous locations in this population. Obesity has repeatedly been shown to be a risk factor for tinea pedis and toenail onychomycosis. Oral antifungals are required for nail involvement, and terbinafine has proven to be more effective than itraconazole and fluconazole. Topical antifungal agents are first-line therapy for cutaneous infections lacking nail infection.

**Bacterial infections**

Obesity may be associated with a multitude of bacterial infections, ranging from less complicated infections such as folliculitis and furunculosis to more serious infections including erysipelas and necrotizing fasciitis that
require hospitalization. Erysipelas is most commonly caused by streptococcal species and has been known to complicate lymphedematous limbs.\textsuperscript{149} Obesity without coexistent lymphedema has also proven to be an independent risk factor for erysipelas.\textsuperscript{144} Penicillin G remains the mainstay of treatment for this infectious complication.\textsuperscript{150,151}

Necrotizing infections of the skin include necrotizing cellulitis and necrotizing fasciitis. Necrotizing fasciitis is a deep gangrenous infection of subcutaneous tissue that leads to progressive destruction of fascia and fat, but occasionally spares the skin.\textsuperscript{152} Characteristics of necrotizing cellulitis and necrotizing fasciitis include extensive tissue destruction, systemic toxicity, and high mortality. Pathophysiologic features include thrombosis of blood vessels, bacteria spreading along fascial planes, and limited infiltration of acute inflammatory cells. In a study by Gallup et al,\textsuperscript{146} 88\% of women hospitalized for necrotizing fasciitis were obese. More than 3 risk factors, including obesity, diabetes, hypertension, and advanced age, were predictive of 50\% mortality due to this rapidly progressive infection.\textsuperscript{148}

Accurate diagnosis is key, but early clinical diagnosis is difficult. Necrotizing fasciitis should be considered in the setting of fever, toxicity, skin involvement with pain out of proportion to skin findings, and elevated levels of creatine phosphokinase. When necrotizing fasciitis is suspected, surgical exploration with appropriate cultures is the only means to make the diagnosis. Some authors advocate the use of punch biopsy for frozen section to establish the diagnosis.\textsuperscript{153} Appropriate treatment must include aggressive surgical debridement of all necrotic tissue, nutritional support, and broad-spectrum antibiotics.\textsuperscript{148,153}

Hidradenitis suppurativa

Hidradenitis suppurativa is a chronic recurrent disease manifested by abscesses, fistulas, and scarring tracts along predominantly apocrine gland-bearing skin (Fig 5). It is a common skin disease affecting an estimated 2\% of the population.\textsuperscript{154} The etiology of hidradenitis suppurativa is still poorly understood; however, it appears to be caused primarily by follicular occlusion with secondary involvement of the apocrine glands.\textsuperscript{155} Obesity has not been consistently found to be associated with this supplicative disease,\textsuperscript{156} but likely exacerbates underlying disease by increasing shearing forces and androgen effects.\textsuperscript{155} Studies attempting to demonstrate primary hyperandrogenism as a cause of the disease have been complicated by the fact that the majority of these patients are obese,\textsuperscript{157} which further supports the role of obesity as an exacerbating factor.

Hidradenitis suppurativa has a high degree of morbidity, most significantly due to the pain and pustular discharge associated with the disease.\textsuperscript{158} Hidradenitis suppurativa is notoriously difficult to treat. Medical management includes encouraging weight loss for patients with active disease.\textsuperscript{155,159} Topical antiseptics, antibiotics, and corticosteroids are usually of minimal benefit.\textsuperscript{160} Antibiotics, including topical clindamycin,\textsuperscript{161,162} systemic tetracycline,\textsuperscript{161} and dapsone, may have an effect in some patients.\textsuperscript{154} Infliximab appears to be a promising treatment for hidradenitis suppurativa, and several studies have demonstrated its efficacy.\textsuperscript{163-166} Oral retinoids\textsuperscript{167,168} and systemic or intralesional steroids have variable results.\textsuperscript{155} Surgical excision of all apocrine gland-bearing tissue is the only treatment proven effective on the natural history of the disease.\textsuperscript{155,169}

Psoriasis

Recent data demonstrate a significantly higher prevalence of obesity among psoriasis patients than in the general population.\textsuperscript{170} Inverse psoriasis appears to be particularly associated with obesity (Fig 6) and sometimes can be indistinguishable from intertrigo in obese patients.\textsuperscript{170} An examination of two nationally representative datasets at our institution also demonstrated a higher frequency of overweight and obese patients in the psoriatic population.\textsuperscript{171} Interestingly, data from the Utah Psoriasis Initiative suggests that obesity may be a consequence of psoriasis rather than a risk factor for triggering onset of disease.\textsuperscript{170}

Obesity appears to be associated with morbidity of psoriasis.\textsuperscript{172-174} Sakai et al\textsuperscript{175} analyzed a cohort of 169 psoriasis patients over more than 10 years and found that elevated BMI (>25) was significantly associated with long-term prognosis of psoriasis. In a large case-control study with 560 psoriasis patients, Naldi et al\textsuperscript{176} found that BMI $\geq$ 30 was associated with an odds ratio of 1.9. Other studies have also
found a significant association between obesity and increased morbidity of psoriasis.\(^{177,178}\) Diet also appears to have a significant influence on psoriasis. A previous study from Italy found that psoriasis patients consumed a higher proportion of high-fat foods and saturated fats.\(^{179}\) Moreover, dietary modification can alleviate psoriasis.\(^{180,181}\) A recent case report described an example of complete resolution of severe psoriasis without medication in a patient who underwent a Roux-en-Y gastric bypass.\(^{182}\) However, prospective studies are needed to determine whether weight control reduces psoriasis morbidity.

In addition, medications developed for diabetes are undergoing clinical trials for use in therapy for psoriasis.\(^{183,184}\) Thiazolidinediones are a novel class of insulin-sensitizing drugs that have demonstrated promise for treatment of psoriasis. Thiazolidinediones activate peroxisome proliferator-activated receptors, a type of steroid/thyroid ligand-activated nuclear receptor that is expressed on human keratinocytes. In culture, ligands for peroxisome proliferator-activated receptor inhibit proliferation of both normal and psoriatic human keratinocytes.\(^{184}\) An earlier drug in this class was associated with hepatotoxicity and was subsequently withdrawn.\(^{184,185}\) Nevertheless, newer thiazolidinediones, pioglitazone and rosiglitazone, are not associated with hepatotoxicity and are effective for treatment of psoriasis.\(^{186}\)

**Insulin resistance syndrome**

Insulin resistance syndrome, also known as syndrome X or metabolic syndrome, is characterized by peripheral insulin resistance that leads to compensatory hyperinsulinemia. Insulin resistance syndrome is a well-recognized metabolic disturbance and is thought to be a root cause of obesity as well as disorders including hypertension, type 2 diabetes, dyslipidemia, coronary artery disease, and abnormal glucose tolerance.\(^{187}\) Hyperinsulinemia is thought to cause shifts in critical endocrine pathways, such as IGF-1 and androgens, that lead to altered cellular proliferation and growth in a variety of tissues, including the skin.\(^{187}\) Dermatologic diseases that may be induced or exacerbated by insulin resistance syndrome include acne, some epithelial cell carcinomas, acrochordons, acanthosis nigricans, keratosis pilaris, hyperandrogenism, hirsutism, and polycystic ovary syndrome.\(^{187}\)

The two major therapeutic goals in patients with insulin resistance syndrome are to treat underlying causes, such as obesity and physical inactivity, through weight management and increased physical activity and to treat cardiovascular risk factors.\(^{188,189}\) Insulin resistance can be treated with medications that enhance insulin action, such as thiazolidinediones and metformin; however, in clinical trials, such medical therapy has not been shown to improve outcomes versus weight reduction and exercise alone.\(^{190,191}\)

**Tophaceous gout**

Obesity has been thought to be a risk factor for gout for centuries. Tophi are most commonly observed on the ears or in soft tissues. Tophaceous gout is characterized by collections of solid urate in connective tissues. The development of tophi is correlated with the duration of gout and degree of hyperuricemia. Tophi may or may not be calcified and are usually painless, visible, and palpable. In concert with the current obesity epidemic, the prevalence of gout in the United States has been rising steadily.\(^{192}\) Several prospective studies have demonstrated the strong association between obesity and gout.\(^{193-195}\)

In addition to medical treatment of gout, treatment of tophi requires long-term therapy with antihyperuricemic medications. For patients with complications due to tophaceous disease, surgical intervention may also be necessary. Treatment with anti-inflammatory and prophylactic drugs alone is not adequate for tophi. Weight reduction and reduced dietary protein intake may also help reduce hyperuricemia and prevent tophaceous complications.\(^{196,197}\)

**OBESITY AND DERMATOLOGIC PHARMACOLOGY**

Obesity is known to significantly affect both skin and systemic physiology. With growing numbers of obese patients, it will be increasingly important for dermatologists to be able to modify and adapt topical and systemic dermatologic therapies for obese patients. Common medications, such as oral isotretinoin and griseofulvin, require body weight—adjusted dosing; however, dermatologists often prescribe them in suboptimal doses for obese patients. As a result, the efficacy and tolerability of these medications in obese patients may be compromised.
patients because of concerns about toxicity. In addition, obese patients are particularly vulnerable to risks associated with treatment, such as elevation of serum triglyceride levels with oral isotretinoin. Body weight—adjusted dosing is also sometimes necessary with the biologics. In obese patients, systemic methotrexate therapy is associated with a higher risk of hepatotoxicity.

Drug-induced weight gain is also a significant side effect of many medications commonly prescribed by dermatologists. Such weight gain can lead to patient noncompliance as well as exacerbation of comorbid conditions related to obesity. Medications that may promote weight gain include oral corticosteroids, oral antihistamines, oral contraceptives, antidepressants such as amitriptyline, and serotonin reuptake inhibitors, including mirtazapine and paroxetine.

**CONCLUSION**

Although obesity is recognized as a major public health problem and is increasing in prevalence, little attention has been paid to the impact of obesity on the skin. Obesity is responsible for a variety of changes in skin physiology and is implicated in a wide spectrum of dermatologic diseases. Given the growing numbers of obese patients, dermatologists must work with primary care physicians and patients to reduce the detrimental effects of obesity on the skin.

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