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

ARTICLE *in* JOURNAL OF THE AMERICAN ACADEMY OF DERMATOLOGY · JULY 2007

Impact Factor: 4.45 · DOI: 10.1016/j.jaad.2006.12.004 · Source: PubMed

3 AUTHORS, INCLUDING:

Gil Yosipovitch
Wake Forest University
206 PUBLICATIONS **5,090** CITATIONS

SEE PROFILE

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

Gil Yosipovitch, MD,[a,b] Amy DeVore, MD,[a] and Aerlyn Dawn, MD, MBA[a]
Winston-Salem, North Carolina

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/m^2 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

From the Departments of Dermatology[a] and Regenerative Medicine,[b] Wake Forest University School of Medicine.
Funding sources: None.
Conflicts of interest: None declared.
Reprint requests: Gil Yosipovitch, MD, Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, NC 27157. E-mail: gyosipov@wfubmc.edu.
0190-9622/$32.00

doi:10.1016/j.jaad.2006.12.004

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[6]; (2) high respiratory quotient (carbohydrate-to-fat oxidation ratio)[7]; 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.[5]

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[8] and Cancello et al[9] 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.[10] Congenital leptin deficiency has been identified in humans and is associated with a rare, severe early-onset form of obesity.[11] In such patients, treatment with leptin is successful.[12] 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.[13] Leptin receptors (Ob-R) have been located on tissues, including keratinocytes, fibroblasts, endothelial cells, and adipose tissue.[14-16] Many studies have examined the beneficial role of leptin in wound healing. Leptin is acutely up-regulated in injured skin[17] and in vitro promotes fibroblast proliferation and collagen synthesis.[15] 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[18]; 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.[19]

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.[20,21] 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.[20,22] The *POMC*-derived melanocortin peptides bind with different affinity and specificity to a set of 5 homologous melanocortin receptors.[23] MC1 receptor is associated with human pigmentation and mutations in the gene for this receptor are known to cause red hair and fair skin.[24] MC4r deficiency is the most common monogenic cause of obesity, and mutations in this gene affect at least 3% of extremely obese individuals.[23,25] This receptor appears to play a key role in the control of eating behavior in humans.[26] A syndromic variant of *POMC* deficiency has been described with complete loss-of-function mutations of the *POMC* gene.[23,27,28] 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[29] 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,[29] 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.[30-33] 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.[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.[35,36] Obese patients with polycystic ovary syndrome demonstrated significant improvement in acne when treated with pioglitazone,[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.[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.[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.[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.[38] 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[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.[41] Interestingly, neither insulin nor diet restriction restored wound collagen accumulation in phenotypically obese mice.[41] The authors proposed that the decreased wound collagen accumulation may be due in part to structural changes in adipose tissue. Another study demonstrated that increased turnover of type III collagen correlated with obesity, particularly abdominal obesity.[42] Notably, obese patients rarely manifest facial wrinkles, whereas individuals with low BMI often have more evident facial wrinkles.

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.[43] Using bioengineering methods, Loffler, Aramaki, and Effendy[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.[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.[43] Alterations of cardiac vagosympathetic activity in obesity have also been suggested. In nondiabetic obese patients, there is a significant reduction in the cutaneous vasoconstrictive response to sympathetic activation.[45] Agapitov et al[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.[47] Endocrine peptides secreted by adipocytes include leptin and tumor necrosis factor α, among others. In contrast, brown fat is most prominent in newborn infants and its exact role in obese adults is

Table I. Skin disorders in obesity

Insulin resistance
Insulin resistance syndrome
Acanthosis nigricans
Acrochordons
Keratosis pilaris
Hyperandrogenism
Hirsutism
Mechanical
Plantar hyperkeratosis
Striae distensae
Cellulite
Adiposis dolorosa
Lymphedema
Chronic venous insufficiency
Infectious
Intertrigo
Candida
Dermatophytes
Folliculitis
Necrotizing cellulitis/fasciitis
Inflammatory
Hidradenitis suppurativa
Psoriasis
Metabolic
Tophaceous gout

not yet clear. We direct the reader to the comprehensive review series by Avram, Avram, and James[48,49] 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.[50] Hud et al[51] 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.[52] Insulin resistance is also associated with cutaneous virilism.[53] 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.[54]

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.[55,56] 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.[57] Decreased numbers of functional insulin receptors cause a shift to increased binding to IGF receptors contributing to the development of acanthosis nigricans.[55]

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.[58] Other treatments that have been reported to help clear acanthosis nigricans include metformin,[59,60] octreotide,[61] retinoids,[62,63] topical calcipotriol,[64] and laser therapy.[65]

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.[66] In general, acrochordons are more strongly associated with diabetes than with obesity. Kahana et al[67] 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[68]; 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,[69] this benign dermatosis also manifests in those with

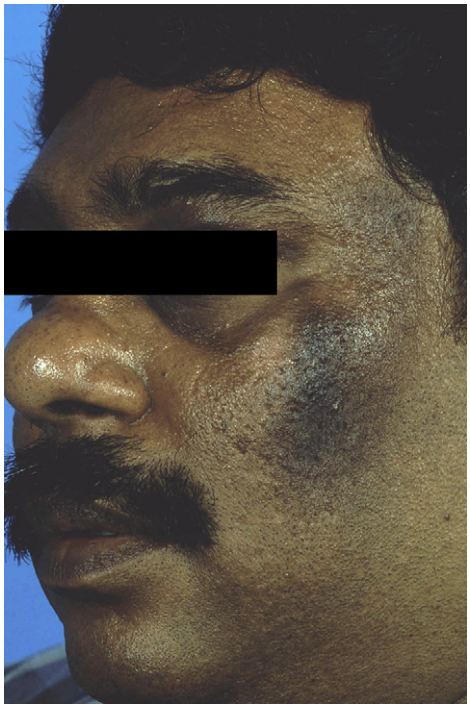

Fig 1. Acanthosis nigricans of the face in a dark-skinned obese patient.

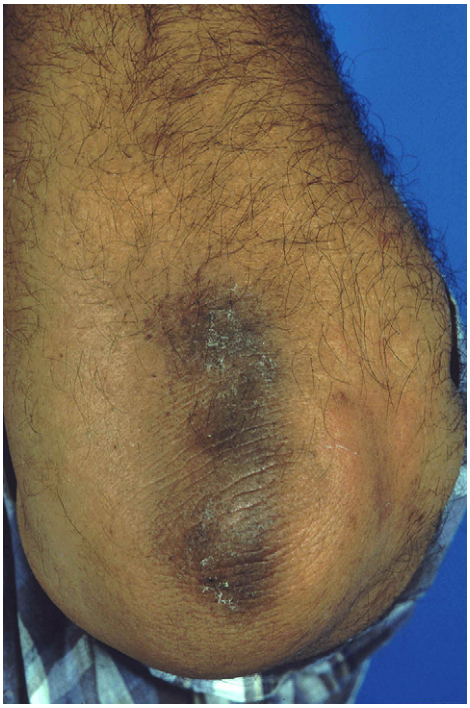

Fig 2. Acanthosis nigricans of the elbow in a dark-skinned obese patient.

greater BMI.[66,70,71] It has been suggested that insulin resistance may play a role in the development of keratosis pilaris.[53,71] 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.[53] Ruutiainen et al[72] 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.[38] In obese women with polycystic ovary syndrome, thiazolidinediones improve insulin resistance and hyperandrogenism.[73,74]

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,[66] and in other clinical settings such as pregnancy, Cushing's syndrome, and topical corticosteroid use.[75] Hsu et al[76] 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[77] 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[78] 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.[79] 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.[80] 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.[81]

Currently available treatment options are unsatisfactory, but include topical agents such as tretinoin

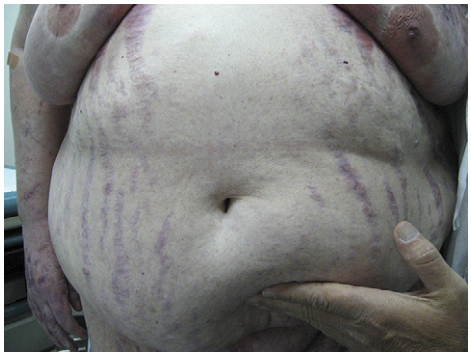

Fig 3. Striae distensae in a morbidly obese woman mimicking cushingoid striae.

0.1% cream,[82] and tretinoin 0.05% cream combined with 20% glycolic acid.[83] Lower dose tretinoin 0.025% cream does not appear to be effective.[84] Intense pulsed light improves striae clinically and histologically with minimal side effects.[85] 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,[86] and the 308-nm excimer laser improves hypopigmentation associated with late-stage striae.[87,88] Striae rubra and alba have been treated with a pulsed dye laser with marginal success.[38] Laser therapy should be avoided for striae in individuals having Fitzpatrick skin types IV through VI because of the resultant hyperpigmentation.[89]

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.[90] 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.[91,92] 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.[93] Diagnosis is often delayed and is made by ultrasonography and magnetic resonance imaging.[94]

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,[95] intravenous lidocaine,[96,97] mexiletine,[97] or analgesics may provide pain relief. Surgical excision or liposuction of painful masses is sometimes effective.[91,92]

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.[98,99] In women, increased androgenicity is strongly associated with an unfavorable body fat distribution and insulin resistance.[100]

Obese patients frequently consult plastic surgeons and dermatologists for liposuction. Liposuction is the most commonly performed cosmetic surgery procedure in North America.[101] 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.[102-104] Large-volume liposuction may decrease weight and body fat mass[105,106]; however, there are conflicting data regarding whether or not it significantly improves insulin resistance and other obesity-associated metabolic abnormalities.[105-107] 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.[102] 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 women[115,116] and men.[117,118] Padberg et al[119] 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]

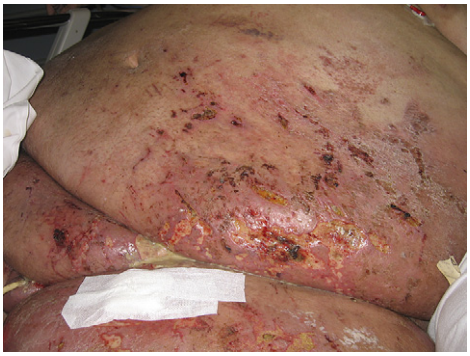

Fig 4. Severe lymphedema involving the lower abdomen in a morbidly obese woman.

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 bandagingl.[126] Itching and inflammation associated with stasis pigmentation, the result of red blood

cells escaping into the tissues, can be treated with corticosteroids.[38]

Plantar hyperkeratosis

Hyperkeratosis of the soles in obesity was first described by Garcia-Hidalgo et al[66] in 1999. The horseshoe-shaped hyperkeratosis overlying the posterior portion of the sole was the most common skin finding in those weighing more than 176% of expected weight. Obese patients have higher plantar pressures during walking and standing[127,128] and increased forefoot width.[127] There is also an abnormal transference of weight during walking that alters the alignment of the foot, causing increased stress over bony prominences.[129] The plantar hyperkeratosis that develops may be regarded as a physiologic response to mechanical trauma.[130]

Eliminating the increased pressure by losing weight should be the primary recommended treatment. Protective insoles may alleviate symptoms while attempting weight reduction.[38]

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.[131] 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.[132] 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.[38] There is a linear trend between the severity of obesity and intertrigo.[66] 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.[39] *Candida* first invades host tissue in the hyphal form, and this form grows best at an alkaline pH.[133] Because pH affects the morphologic form of *Candida albicans*, it may affect how the yeast adheres to and infects intertriginous regions.[134] 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[135]), but candidal vaginitis does not appear to be increased.[136]

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.[137] Candidal superinfection is best treated with topical antifungal agents. Systemic antifungal therapy may be required in some patients. Oral fluconazole is effective[138] 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.[139,140] Oral antifungals are required for nail involvement, and terbinafine has proven to be more effective than itraconazole and fluconazole.[141] 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[142] to more serious infections including erysipelas[143,144] and necrotizing fasciitis[145-148] that

require hospitalization. Erysipelas is most commonly caused by streptococcal species and has been known to complicate lymphedematous limbs.[149] Obesity without coexistent lymphedema has also proven to be an independent risk factor for erysipelas.[144] Penicillin G remains the mainstay of treatment for this infectious complication.[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.[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,[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.[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.[153] Appropriate treatment must include aggressive surgical debridement of all necrotic tissue, nutritional support, and broad-spectrum antibiotics.[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.[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.[155] Obesity has not been consistently found to be associated with this suppurative disease,[156] but likely exacerbates underlying disease by increasing shearing forces and androgen effects.[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,[157] which further supports the role of obesity as an exacerbating factor.

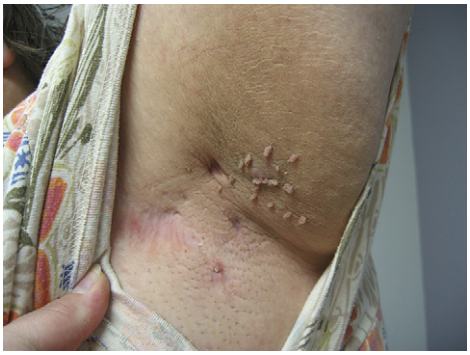

Fig 5. Hidradenitis suppurativa with acanthosis nigricans and acrochordons in an obese patient.

Hidradenitis suppurativa has a high degree of morbidity, most significantly due to the pain and pustular discharge associated with the disease.[158]

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

Psoriasis

Recent data demonstrate a significantly higher prevalence of obesity among psoriasis patients than in the general population.[170] Inverse psoriasis appears to be particularly associated with obesity (Fig 6) and sometimes can be indistinguishable from intertrigo in obese patients.[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.[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.[170]

Obesity appears to be associated with morbidity of psoriasis.[172-174] Sakai et al[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[176] found that BMI ≥ 30 was associated with an odds ratio of 1.9. Other studies have also

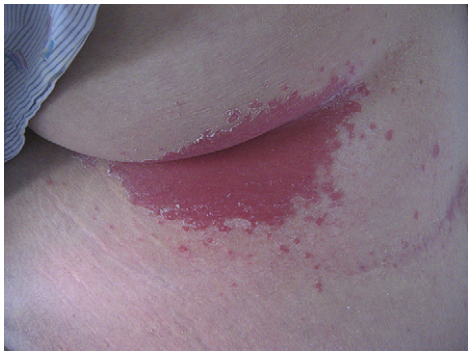

Fig 6. Inverse psoriasis of the breast in an obese woman.

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 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.[198,199] In obese patients, systemic methotrexate therapy is associated with a higher risk of hepatotoxicity.[200-202]

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.[203] 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.[203-206]

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.

REFERENCES

1. Baskin ML, Ard J, Franklin F, Allison DB. Prevalence of obesity in the United States. Obes Rev 2005;6:5-7.
2. F as in fat: how obesity policies are failing in America 2005. Trust for America's Health. Available at: http://healthyamericans.org/reports/obesity2005/. Accessed August 30, 2005.
3. Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. Obes Res 1998;6:97-106.
4. Pender JR, Pories WJ. Epidemiology of obesity in the United States. Gastroenterol Clin North Am 2005;34:1-7.
5. Pi-Sunyer FX. The obesity epidemic: pathophysiology and consequences of obesity. Obes Res 2002;10(Suppl 2): 97S-104S.
6. Ravussin E, Lillioja S, Knowler WC, Christin L, Freymond D, Abbott WG, et al. Reduced rate of energy expenditure as a risk factor for body-weight gain. N Engl J Med 1988;318: 467-72.
7. Zurlo F, Lillioja S, Esposito-Del PA, Nyomba BL, Raz I, Saad MF, et al. Low ratio of fat to carbohydrate oxidation as predictor of weight gain: study of 24-h RQ. Am J Physiol 1990;259: E650-7.
8. Snyder EE, Walts B, Perusse L, Chagnon YC, Weisnagel SJ, Rankinen T, et al. The human obesity gene map: the 2003 update. Obes Res 2004;12:369-439.
9. Cancello R, Tounian A, Poitou C, Clement K. Adiposity signals, genetic and body weight regulation in humans. Diabetes Metab 2004;30:215-27.
10. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763-70.
11. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, et al. Congenital leptin deficiency is associated with severe early-onset obesity in humans. Nature 1997;387: 903-8.
12. Farooqi IS, Jebb SA, Langmack G, Lawrence E, Cheetham CH, Prentice AM, et al. Effects of recombinant leptin therapy in a child with congenital leptin deficiency. N Engl J Med 1999;341:879-84.
13. Fine JB, Fine RM. Leptin levels in obesity. Int J Dermatol 1997;36:727-8.
14. Margetic S, Gazzola C, Pegg GG, Hill RA. Leptin: a review of its peripheral actions and interactions. Int J Obes Relat Metab Disord 2002;26:1407-33.
15. Li P, Jin H, Liu D, Gao L, Xu Z, Nan W, et al. [Study on the effect of leptin on fibroblast proliferation and collagen synthesis in vitro in rats.] Zhongguo Xiu Fu Chong Jian Wai Ke Za Zhi 2005;19:20-2. Chinese.
16. Goren I, Pfeilschifter J, Frank S. Determination of leptin signaling pathways in human and murine keratinocytes. Biochem Biophys Res Commun 2003;303:1080-5.
17. Murad A, Nath AK, Cha ST, Demir E, Flores-Riveros J, Sierra-Honigmann MR. Leptin is an autocrine/paracrine regulator of wound healing. FASEB J 2003;17:1895-7.
18. Pardini VC, Victoria IM, Rocha SM, Andrade DG, Rocha AM, Pieroni FB, et al. Leptin levels, beta-cell function, and insulin sensitivity in families with congenital and acquired generalized lipoatropic diabetes. J Clin Endocrinol Metab 1998;83: 503-8.
19. Shimomura I, Hammer RE, Ikemoto S, Brown MS, Goldstein JL. Leptin reverses insulin resistance and diabetes mellitus in mice with congenital lipodystrophy. Nature 1999;401:73-6.
20. Bertagna X. Proopiomelanocortin-derived peptides. Endocrinol Metab Clin North Am 1994;23:467-85.
21. Wintzen M, Yaar M, Burbach JP, Gilchrest BA. Proopiomelanocortin gene product regulation in keratinocytes. J Invest Dermatol 1996;106:673-8.
22. Yeo GS, Farooqi IS, Challis BG, Jackson RS, O'Rahilly S. The role of melanocortin signalling in the control of body weight: evidence from human and murine genetic models. QJM 2000;93:7-14.
23. Krude H, Biebermann H, Schnabel D, Tansek MZ, Theunissen P, Mullis PE, et al. Obesity due to proopiomelanocortin deficiency: three new cases and treatment trials with thyroid hormone and ACTH4-10. J Clin Endocrinol Metab 2003;88:4633-40.
24. Schaffer JV, Bolognia JL. The melanocortin-1 receptor: red hair and beyond. Arch Dermatol 2001;137:1477-85.
25. Cone RD. Haploinsufficiency of the melanocortin-4 receptor: part of a thrifty genotype? J Clin Invest 2000;106:185-7.
26. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003;348: 1085-95.
27. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Gruters A. Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. Nat Genet 1998;19:155-7.
28. Yaswen L, Diehl N, Brennan MB, Hochgeschwender U. Obesity in the mouse model of pro-opiomelanocortin deficiency responds to peripheral melanocortin. Nat Med 1999;5: 1066-70.
29. Loffler H, Aramaki JU, Effendy I. The influence of body mass index on skin susceptibility to sodium lauryl sulphate. Skin Res Technol 2002;8:19-22.
30. Zouboulis CC. Acne and sebaceous gland function. Clin Dermatol 2004;22:360-6.

31. Zouboulis CC, Xia L, Akamatsu H, Seltmann H, Fritsch M, Hornemann S, et al. The human sebocyte culture model provides new insights into development and management of seborrhoea and acne. Dermatology 1998;196:21-31.
32. Harris HH, Downing DT, Stewart ME, Strauss JS. Sustainable rates of sebum secretion in acne patients and matched normal control subjects. J Am Acad Dermatol 1983;8:200-3.
33. Brown SK, Shalita AR. Acne vulgaris. Lancet 1998;351:1871-6.
34. Cordain L. Implications for the role of diet in acne. Semin Cutan Med Surg 2005;24:84-91.
35. Deplewski D, Rosenfield RL. Growth hormone and insulin-like growth factors have different effects on sebaceous cell growth and differentiation. Endocrinology 1999;140:4089-94.
36. Cappel M, Mauger D, Thiboutot D. Correlation between serum levels of insulin-like growth factor 1, dehydroepiandrosterone sulfate, and dihydrotestosterone and acne lesion counts in adult women. Arch Dermatol 2005;141:333-8.
37. Romualdi D, Guido M, Ciampelli M, Giuliani M, Leoni F, Perri C, et al. Selective effects of pioglitazone on insulin and androgen abnormalities in normo- and hyperinsulinaemic obese patients with polycystic ovary syndrome. Hum Reprod 2003;18:1210-8.
38. Garcia-Hidalgo L. Dermatological complications of obesity. Am J Clin Dermatol 2002;3:497-506.
39. Yosipovitch G, Tur E, Cohen O, Rusecki Y. Skin surface pH in intertriginous areas in NIDDM patients. Possible correlation to candidal intertrigo. Diabetes Care 1993;16:560-3.
40. Enser M, Avery NC. Mechanical and chemical properties of the skin and its collagen from lean and obese-hyperglycaemic (ob/ob) mice. Diabetologia 1984;27:44-9.
41. Goodson WH III, Hunt TK. Wound collagen accumulation in obese hyperglycemic mice. Diabetes 1986;35:491-5.
42. Rasmussen MH, Jensen LT, Andersen T, Breum L, Hilsted J. Collagen metabolism in obesity: the effect of weight loss. Int J Obes Relat Metab Disord 1995;19:659-63.
43. de Jongh RT, Serne EH, Ijzerman RG, de Vries G, Stehouwer CD. Impaired microvascular function in obesity: implications for obesity-associated microangiopathy, hypertension, and insulin resistance. Circulation 2004;109:2529-35.
44. Chin LC, Huang TY, Yu CL, Wu CH, Hsu CC, Yu HS. Increased cutaneous blood flow but impaired post-ischemic response of nutritional flow in obese children. Atherosclerosis 1999; 146:179-85.
45. Valensi P, Smagghue O, Paries J, Velayoudon P, Lormeau B, Attali JR. Impairment of skin vasoconstrictive response to sympathetic activation in obese patients: influence of rheological disorders. Metabolism 2000;49:600-6.
46. Agapitov AV, Correia ML, Sinkey CA, Dopp JM, Haynes WG. Impaired skeletal muscle and skin microcirculatory function in human obesity. J Hypertens 2002;20:1401-5.
47. Morrison RF, Farmer SR. Hormonal signaling and transcriptional control of adipocyte differentiation. J Nutr 2000;130: 3116S-21S.
48. Avram AS, Avram MM, James WD. Subcutaneous fat in normal and diseased states: 2. Anatomy and physiology of white and brown adipose tissue. J Am Acad Dermatol 2005;53:671-83.
49. Avram MM, Avram AS, James WD. Subcutaneous fat in normal and diseased states: 1. Introduction. J Am Acad Dermatol 2005;53:663-70.
50. Geffner ME, Golde DW. Selective insulin action on skin, ovary, and heart in insulin-resistant states. Diabetes Care 1988;11: 500-5.
51. Hud JA Jr, Cohen JB, Wagner JM, Cruz PD Jr. Prevalence and significance of acanthosis nigricans in an adult obese population. Arch Dermatol 1992;128:941-4.
52. Fu JF, Liang L, Dong GP, Jiang YJ, Zou CC. [Obese children with benign acanthosis nigricans and insulin resistance: analysis of 19 cases.] Zhonghua Er Ke Za Zhi 2004;42:917-9. Chinese.
53. Barth JH, Ng LL, Wojnarowska F, Dawber RP. Acanthosis nigricans, insulin resistance and cutaneous virilism. Br J Dermatol 1988;118:613-9.
54. Grasinger CC, Wild RA, Parker IJ. Vulvar acanthosis nigricans: a marker for insulin resistance in hirsute women. Fertil Steril 1993;59:583-6.
55. Rendon MI, Cruz PD Jr, Sontheimer RD, Bergstresser PR. Acanthosis nigricans: a cutaneous marker of tissue resistance to insulin. J Am Acad Dermatol 1989;21:461-9.
56. Cruz PD Jr, Hud JA Jr. Excess insulin binding to insulin-like growth factor receptors: proposed mechanism for acanthosis nigricans. J Invest Dermatol 1992;98(Suppl):82S-5S.
57. Hermanns-Le T, Scheen A, Pierard GE. Acanthosis nigricans associated with insulin resistance: pathophysiology and management. Am J Clin Dermatol 2004;5:199-203.
58. Kuroki R, Sadamoto Y, Imamura M, Abe Y, Higuchi K, Kato K, et al. Acanthosis nigricans with severe obesity, insulin resistance and hypothyroidism: improvement by diet control. Dermatology 1999;198:164-6.
59. Tankova T, Koev D, Dakovska L, Kirilov G. Therapeutic approach in insulin resistance with acanthosis nigricans. Int J Clin Pract 2002;56:578-81.
60. Walling HW, Messingham M, Myers LM, Mason CL, Strauss JS. Improvement of acanthosis nigricans on isotretinoin and metformin. J Drugs Dermatol 2003;2:677-81.
61. Lunetta M, Di Mauro M, Le Moli R, Burrafato S. Long-term octreotide treatment reduced hyperinsulinemia, excess body weight and skin lesions in severe obesity with acanthosis nigricans. J Endocrinol Invest 1996;19:699-703.
62. Akovbyan VA, Talanin NY, Arifov SS, Tukhvatullina ZG, Musabayev AN, Baybekov IM, et al. Successful treatment of acanthosis nigricans with etretinate. J Am Acad Dermatol 1994;31:118-20.
63. Weisshaar E, Bonnekoh B, Franke I, Gollnick H. [Successful symptomatic tazarotene treatment of juvenile acanthosis nigricans of the familial obesity-associated type in insulin resistance.] Hautarzt 2001;52:499-503. German.
64. Bohm M, Luger TA, Metze D. Treatment of mixed-type acanthosis nigricans with topical calcipotriol. Br J Dermatol 1998;139:932-4.
65. Rosenbach A, Ram R. Treatment of acanthosis nigricans of the axillae using a long-pulsed (5-msec) alexandrite laser. Dermatol Surg 2004;30:1158-60.
66. Garcia-Hidalgo L, Orozco-Topete R, Gonzalez-Barranco J, Villa AR, Dalman JJ, Ortiz-Pedroza G. Dermatoses in 156 obese adults. Obes Res 1999;7:299-302.
67. Kahana M, Grossman E, Feinstein A, Ronnen M, Cohen M, Millet MS. Skin tags: a cutaneous marker for diabetes mellitus. Acta Derm. Venereol 1987;67:175-7.
68. Muscelli E, Mingrone G, Camastra S, Manco M, Pereira JA, Pareja JC, et al. Differential effect of weight loss on insulin resistance in surgically treated obese patients. Am J Med 2005;118:51-7.
69. Tay YK, Kong KH, Khoo L, Goh CL, Giam YC. The prevalence and descriptive epidemiology of atopic dermatitis in Singapore school children. Br J Dermatol 2002;146:101-6.
70. Yosipovitch G, Hodak E, Vardi P, Shraga I, Karp M, Sprecher E, et al. The prevalence of cutaneous manifestations in IDDM patients and their association with diabetes risk factors and microvascular complications. Diabetes Care 1998;21:506-9.
71. Yosipovitch G, Mevorah B, Mashiach J, Chan YH, David M. High body mass index, dry scaly leg skin and atopic conditions are

highly associated with keratosis pilaris. Dermatology 2000; 201:34-6.
72. Ruutiainen K, Erkkola R, Gronroos MA, Irjala K. Influence of body mass index and age on the grade of hair growth in hirsute women of reproductive ages. Fertil Steril 1988;50:260-5.
73. Ortega-Gonzalez C, Luna S, Hernandez L, Crespo G, Aguayo P, Arteaga-Troncoso G, et al. Responses of serum androgen and insulin resistance to metformin and pioglitazone in obese, insulin-resistant women with polycystic ovary syndrome. J Clin Endocrinol Metab 2005;90:1360-5.
74. Sepilian V, Nagamani M. Effects of rosiglitazone in obese women with polycystic ovary syndrome and severe insulin resistance. J Clin Endocrinol Metab 2005;90:60-5.
75. Rogalski C, Haustein UF, Glander HJ, Paasch U. Extensive striae distensae as a result of topical corticosteroid therapy in psoriasis vulgaris. Acta Derm Venereol 2003;83:54-5.
76. Hsu HS, Chen W, Chen SC, Ko FD. Colored striae in obese children and adolescents. Zhonghua Min Guo. Xiao Er Ke Yi Xue Hui Za Zhi 1996;37:349-52.
77. Simkin B, Arce R. Steroid excretion in obese patients with colored abdominal striae. N Engl J Med 1962;266:1031-5.
78. Angeli A, Boccuzzi G, Frajria R, Bisbocci D. [Adrenal gland function test in the differential diagnosis of sthenic obesity with pink striae.] Folia Endocrinol 1970;23:566-78. Italian.
79. Arem AJ, Kischer CW. Analysis of striae. Plast Reconstr Surg 1980;65:22-9.
80. Sheu HM, Yu HS, Chang CH. Mast cell degranulation and elastolysis in the early stage of striae distensae. J Cutan Pathol 1991;18:410-6.
81. Zheng P, Lavker RM, Kligman AM. Anatomy of striae. Br J Dermatol 1985;112:185-93.
82. Kang S. Topical tretinoin therapy for management of early striae. J Am Acad Dermatol 1998;39(Suppl):S90-2.
83. Ash K, Lord J, Zukowski M, McDaniel DH. Comparison of topical therapy for striae alba (20% glycolic acid/0.05% tretinoin versus 20% glycolic acid/10% L-ascorbic acid). Dermatol Surg 1998;24:849-56.
84. Pribanich S, Simpson FG, Held B, Yarbrough CL, White SN. Low-dose tretinoin does not improve striae distensae: a double-blind, placebo-controlled study. Cutis 1994;54: 121-4.
85. Hernandez-Perez E, Colombo-Charrier E, Valencia-Ibiett E. Intense pulsed light in the treatment of striae distensae. Dermatol Surg 2002;28:1124-30.
86. Jimenez GP, Flores F, Berman B, Gunja-Smith Z. Treatment of striae rubra and striae alba with the 585-nm pulsed-dye laser. Dermatol Surg 2003;29:362-5.
87. Goldberg DJ, Sarradet D, Hussain M. 308-nm Excimer laser treatment of mature hypopigmented striae. Dermatol Surg 2003;29:596-8.
88. Alexiades-Armenakas MR, Bernstein LJ, Friedman PM, Geronemus RG. The safety and efficacy of the 308-nm excimer laser for pigment correction of hypopigmented scars and striae alba. Arch Dermatol 2004;140:955-60.
89. Nouri K, Romagosa R, Chartier T, Bowes L, Spencer JM. Comparison of the 585 nm pulse dye laser and the short pulsed CO2 laser in the treatment of striae distensae in skin types IV and VI. Dermatol Surg 1999;25:368-70.
90. Dercum FX. Three cases of a hitherto unclassified affection resembling in its grosser aspects obesity, but associated with special symptoms: adiposis dolorosa. Am J Med Sci 1892; 104:521-35.
91. Brodovsky S, Westreich M, Leibowitz A, Schwartz Y. Adiposis dolorosa (Dercum's disease): 10-year follow-up. Ann Plast Surg 1994;33:664-8.
92. DeFranzo AJ, Hall JH Jr, Herring SM. Adiposis dolorosa (Dercum's disease): liposuction as an effective form of treatment. Plast Reconstr Surg 1990;85:289-92.
93. Wortham NC, Tomlinson IP. Dercum's disease. Skinmed 2005;4:157-62.
94. Amine B, Leguilchard F, Benhamou CL. Dercum's disease (adiposis dolorosa): a new case-report. Joint Bone Spine 2004;71:147-9.
95. Palmer ED. Dercum's disease: adiposis dolorosa. Am Fam Physician 1981;24:155-7.
96. Iwane T, Maruyama M, Matsuki M, Ito Y, Shimoji K. Management of intractable pain in adiposis dolorosa with intravenous administration of lidocaine. Anesth Analg 1976;55:257-9.
97. Petersen P, Kastrup J. Dercum's disease (adiposis dolorosa). Treatment of the severe pain with intravenous lidocaine. Pain 1987;28:77-80.
98. Goodpaster BH, Krishnaswami S, Harris TB, Katsiaras A, Kritchevsky SB, Simonsick EM, et al. Obesity, regional body fat distribution, and the metabolic syndrome in older men and women. Arch Intern Med 2005;165:777-83.
99. Kahn SE, Prigeon RL, Schwartz RS, Fujimoto WY, Knopp RH, Brunzell JD, et al. Obesity, body fat distribution, insulin sensitivity and Islet beta-cell function as explanations for metabolic diversity. J Nutr 2001;131:354S-60S.
100. Haffner SM. Sex hormones, obesity, fat distribution, type 2 diabetes and insulin resistance: epidemiological and clinical correlation. Int J Obes Relat Metab Disord 2000;24(Suppl 2): S56-8.
101. Dolsky RL. State of the art in liposuction. Dermatol Surg 1997;23:1192-3.
102. Matarasso A, Kim RW, Kral JG. The impact of liposuction on body fat. Plast Reconstr Surg 1998;102:1686-9.
103. Matarasso SL. A regional approach to patient selection and evaluation for liposuction. Dermatol Clin 1990;8:401-14.
104. Commons GW, Halperin B, Chang CC. Large-volume liposuction: a review of 631 consecutive cases over 12 years. Plast Reconstr Surg 2001;108:1753-63.
105. Giese SY, Bulan EJ, Commons GW, Spear SL, Yanovski JA. Improvements in cardiovascular risk profile with large-volume liposuction: a pilot study. Plast Reconstr Surg 2001; 108:510-9.
106. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med 2004;350:2549-57.
107. Giugliano G, Nicoletti G, Grella E, Giugliano F, Esposito K, Scuderi N, et al. Effect of liposuction on insulin resistance and vascular inflammatory markers in obese women. Br J Plast Surg 2004;57:190-4.
108. Schissel DJ, Hivnor C, Elston DM. Elephantiasis nostras verrucosa. Cutis 1998;62:77-80.
109. Chernosky ME, Derbes VJ. Elephantiasis nostras of the abdominal wall. Arch Dermatol 1966;94:757-62.
110. Azam M, Saboorian H, Bieligk S, Smith T, Molberg K. Cutaneous angiosarcoma complicating morbid obesity. Arch Pathol Lab Med 2001;125:531-3.
111. Krause KI, Hebert AA, Sanchez RL, Solomon AR Jr. Anterior abdominal wall angiosarcoma in a morbidly obese woman. J Am Acad Dermatol 1986;15:327-30.
112. Ko DS, Lerner R, Klose G, Cosimi AB. Effective treatment of lymphedema of the extremities. Arch Surg 1998;133: 452-8.
113. Beebe-Dimmer JL, Pfeifer JR, Engle JS, Schottenfeld D. The epidemiology of chronic venous insufficiency and varicose veins. Ann Epidemiol 2005;15:175-84.

114. Lacroix P, Aboyans V, Preux PM, Houles MB, Laskar M. Epidemiology of venous insufficiency in an occupational population. Int Angiol 2003;22:172-6.
115. Maffei FH, Magaldi C, Pinho SZ, Lastoria S, Pinho W, Yoshida WB, Rollo HA. Varicose veins and chronic venous insufficiency in Brazil: prevalence among 1755 inhabitants of a country town. Int J Epidemiol 1986;15:210-7.
116. Malhotra SL. An epidemiological study of varicose veins in Indian railroad workers from the South and North of India, with special reference to the causation and prevention of varicose veins. Int J Epidemiol 1972;1:177-83.
117. Jawien A. The influence of environmental factors in chronic venous insufficiency. Angiology 2003;54(Suppl 1):S19-31.
118. Musil D, Herman J. [Chronic venous insufficiency—outpatient study of risk factors.] Vnitr Lek 2004;50:14-20. Czech.
119. Padberg F Jr, Cerveira JJ, Lal BK, Pappas PJ, Varma S, Hobson RW. Does severe venous insufficiency have a different etiology in the morbidly obese? Is it venous? J Vasc Surg 2003;37:79-85.
120. Angle N, Freischlag JA. Venous disease. In: Townsend CM Jr, Beauchamp RD, Evers BM, Mattox KL, editors. Sabiston textbook of surgery. London (UK): Elsevier; 2004. p. 2060.
121. Bull RH, Mortimer PS. Acute lipodermatosclerosis in a pendulous abdomen. Clin Exp Dermatol 1993;18:164-6.
122. Abbade LP, Lastoria S. Venous ulcer: epidemiology, physiopathology, diagnosis and treatment. Int J Dermatol 2005; 44:449-56.
123. Danielsson G, Eklof B, Grandinetti A, Kistner RL. The influence of obesity on chronic venous disease. Vasc Endovascular Surg 2002;36:271-6.
124. Duque MI, Yosipovitch G, Chan YH, Smith R, Levy P. Itch, pain, and burning sensation are common symptoms in mild to moderate chronic venous insufficiency with an impact on quality of life. J Am Acad Dermatol 2005;53:504-8.
125. Smith PC, Sarin S, Hasty J, Scurr JH. Sequential gradient pneumatic compression enhances venous ulcer healing: a randomized trial. Surgery 1990;108:871-5.
126. Jull A, Waters J, Arroll B. Pentoxifylline for treatment of venous leg ulcers: a systematic review. Lancet 2002;359:1550-4.
127. Birtane M, Tuna H. The evaluation of plantar pressure distribution in obese and non-obese adults. Clin Biomech 2004;19:1055-9.
128. Hills AP, Hennig EM, McDonald M, Bar-Or O. Plantar pressure differences between obese and non-obese adults: a biomechanical analysis. Int J Obes Relat Metab Disord 2001;25: 1674-9.
129. Mann RA, Mann JA. Keratotic disorders of the plantar skin. Instr Course Lect 2004;53:287-302.
130. Stott JR, Hutton WC, Stokes IA. Forces under the foot. J Bone Joint Surg Br 1973;55:335-44.
131. Rossi AB, Vergnanini AL. Cellulite: a review. J Eur Acad Dermatol Venereol 2000;14:251-62.
132. Draelos ZD, Marenus KD. Cellulite. Etiology and purported treatment. Dermatol Surg 1997;23:1177-81.
133. Buffo J, Herman MA, Soll DR. A characterization of pH-regulated dimorphism in Candida albicans. Mycopathologia 1984;85:21-30.
134. Odds FC. Ecology and epidemiology of Candida species. Zentralbl Bakteriol Mikrobiol Hyg 1984;257:207-12.
135. Ross EV, Baxter DL Jr. Widespread Candida folliculitis in a nontoxic patient. Cutis 1992;49:241-3.
136. Knippenberger H, Vanselow H, Barth H, Scheffzek HD, Ruttgers H. [Investigation of the epidemilogy of fungal vaginitis in 1000 patients (author's transl).] Geburtshilfe Frauenheilkd 1979;39:676-81.
137. Chapman MS, Brown JM, Linowski GJ. 0.1% tacrolimus ointment for the treatment of intertrigo. Arch Dermatol 2005;141:787.
138. Nozickova M, Koudelkova V, Kulikova Z, Malina L, Urbanowski S, Silny W. A comparison of the efficacy of oral fluconazole, 150 mg/week versus 50 mg/day, in the treatment of tinea corporis, tinea cruris, tinea pedis, and cutaneous candidosis. Int J Dermatol 1998;37:703-5.
139. Chan MK, Chong LY. A prospective epidemiologic survey on the prevalence of foot disease in Hong Kong. J Am Podiatr Med Assoc 2002;92:450-6.
140. Cheng S, Chong L. A prospective epidemiological study on tinea pedis and onychomycosis in Hong Kong. Chin Med J (Engl) 2002;115:860-5.
141. Gupta AK, Ryder JE, Lynch LE, Tavakkol A. The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence. J Drugs Dermatol 2005;4:302-8.
142. Scheinfeld NS. Obesity and dermatology. Clin Dermatol 2004;22:303-9.
143. Amal S, Houass S, Laissaoui K, Moufid K, Trabelsi M. [Epidemiology, clinical features, and evolution of Erysipelas in the Marrakech region (100 cases).] Med Mal Infect 2004;34:171-6.
144. Dupuy A, Benchikhi H, Roujeau JC, Bernard P, Vaillant L, Chosidow O, et al. Risk factors for erysipelas of the leg (cellulitis): case-control study. BMJ 1999;318:1591-4.
145. Angelici AM, Nasti AG, Montesano G, Simonelli I, Palumbo P. [Necrotizing fasciitis: our experience.] G Chir 2004;25:167-70. Italian.
146. Gallup DG, Freedman MA, Meguiar RV, Freedman SN, Nolan TE. Necrotizing fasciitis in gynecologic and obstetric patients: a surgical emergency. Am J Obstet Gynecol 2002;187:305-10.
147. Roujeau JC. [Necrotizing fasciitis. Clinical criteria and risk factors.] Ann Dermatol Venereol 2001;128:376-81. French.
148. Francis KR, Lamaute HR, Davis JM, Pizzi WF. Implications of risk factors in necrotizing fasciitis. Am Surg 1993;59:304-8.
149. Vaillant L, Gironet N. [Infectious complications of lymphedema]. Rev Med Interne 2002;23(Suppl 3):403s-7s. French.
150. Zaraa I, Zeglaoui F, Zouari B, Ezzine N, Fazaa B, Kamoun MR. [Erysipelas. Retrospective study of 647 patients.] Tunis Med 2004;82:990-5. French.
151. Granier F. [Management of erysipelas.] Ann Dermatol Venereol 2001;128:429-42. French.
152. Gozal D, Ziser A, Shupak A, Ariel A, Melamed Y. Necrotizing fasciitis. Arch Surg 1986;121:233-5.
153. Majeski J, Majeski E. Necrotizing fasciitis: improved survival with early recognition by tissue biopsy and aggressive surgical treatment. South Med J 1997;90:1065-8.
154. Jemec GB. Medical treatment of hidradenitis suppurativa. Expert Opin Pharmacother 2004;5:1767-70.
155. Slade DE, Powell BW, Mortimer PS. Hidradenitis suppurativa: pathogenesis and management. Br J Plast Surg 2003;56: 451-61.
156. Brown TJ, Rosen T, Orengo IF. Hidradenitis suppurativa. South Med J 1998;91:1107-14.
157. Harrison BJ, Read GF, Hughes LE. Endocrine basis for the clinical presentation of hidradenitis suppurativa. Br J Surg 1988;75:972-5.
158. von der Werth JM, Jemec GB. Morbidity in patients with hidradenitis suppurativa. Br J Dermatol 2001;144:809-13.
159. Jemec GB, Heidenheim M, Nielsen NH. Hidradenitis suppurativa—characteristics and consequences. Clin Exp Dermatol 1996;21:419-23.
160. Jansen I, Altmeyer P, Piewig G. Acne inversa (alias hidradenitis suppurativa). J Eur Acad Dermatol Venereol 2001;15:532-40.

161. Jemec GB, Wendelboe P. Topical clindamycin versus systemic tetracycline in the treatment of hidradenitis suppurativa. J Am Acad Dermatol 1998;39:971-4.
162. Clemmensen OJ. Topical treatment of hidradenitis suppurativa with clindamycin. Int J Dermatol 1983;22:325-8.
163. Lebwohl B, Sapadin AN. Infliximab for the treatment of hidradenitis suppurativa. J Am Acad Dermatol 2003; 49(Suppl):S275-6.
164. Sullivan TP, Welsh E, Kerdel FA, Burdick AE, Kirsner RS. Infliximab for hidradenitis suppurativa. Br J Dermatol 2003;149:1046-9.
165. Adams DR, Gordon KB, Devenyi AG, Ioffreda MD. Severe hidradenitis suppurativa treated with infliximab infusion. Arch Dermatol 2003;139:1540-2.
166. Rosi YL, Lowe L, Kang S. Treatment of hidradenitis suppurativa with infliximab in a patient with Crohn's disease. J Dermatolog Treat 2005;16:58-61.
167. Brown CF, Gallup DG, Brown VM. Hidradenitis suppurativa of the anogenital region: response to isotretinoin. Am J Obstet Gynecol 1988;158:12-5.
168. Dicken CH, Powell ST, Spear KL. Evaluation of isotretinoin treatment of hidradenitis suppurativa. J Am Acad Dermatol 1984;11:500-2.
169. Banerjee AK. Surgical treatment of hidradenitis suppurativa. Br J Surg 1992;79:863-6.
170. Herron MD, Hinckley M, Hoffman MS, Papenfuss J, Hansen CB, Callis KP, et al. Impact of obesity and smoking on psoriasis presentation and management. Arch Dermatol 2005;141:1527-34.
171. McGowan JW, Pearce DJ, Chen J, Richmond D, Balkrishnan R, Feldman SR. The skinny on psoriasis and obesity. Arch Dermatol 2005;141:1601-2.
172. Krueger GG, Duvic M. Epidemiology of psoriasis: clinical issues. J Invest Dermatol 1994;102(Suppl):14S-8S.
173. Raychaudhuri SP, Gross J. Psoriasis risk factors: role of lifestyle practices. Cutis 2000;66:348-52.
174. Henseler T, Christophers E. Disease concomitance in psoriasis. J Am Acad Dermatol 1995;32:982-6.
175. Sakai R, Matsui S, Fukushima M, Yasuda H, Miyauchi H, Miyachi Y. Prognostic factor analysis for plaque psoriasis. Dermatology 2005;211:103-6.
176. Naldi L, Chatenoud L, Linder D, Belloni FA, Peserico A, Virgili AR, et al. Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Invest Dermatol 2005;125:61-7.
177. Marino MG, Carboni I, De Felice C, Maurici M, Maccari F, Franco E. Risk factors for psoriasis: a retrospective study on 501 outpatients' clinical records. Ann Ig 2004;16:753-8.
178. Lindegard B. Diseases associated with psoriasis in a general population of 159,200 middle-aged, urban, native Swedes. Dermatologica 1986;172:298-304.
179. Zamboni S, Zanetti G, Grosso G, Ambrosio GB, Gozzetti S, Peserico A. Dietary behaviour in psoriatic patients. Acta Derm Venereol Suppl (Stockh) 1989;146:182-3.
180. Fleischer AB Jr, Feldman SR, Rapp SR, Reboussin DM, Exum ML, Clark AR. Alternative therapies commonly used within a population of patients with psoriasis. Cutis 1996;58:216-20.
181. Rucevic I, Perl A, Barisic-Drusko V, dam-Perl M. The role of the low energy diet in psoriasis vulgaris treatment. Coll Antropol 2003;27(Suppl 1):41-8.
182. Higa-Sansone G, Szomstein S, Soto F, Brasecsco O, Cohen C, Rosenthal RJ. Psoriasis remission after laparoscopic Roux-en-Y gastric bypass for morbid obesity. Obes Surg 2004;14: 1132-4.
183. Varani J, Bhagavathula N, Ellis CN, Pershadsingh HA. Thiazolidinediones: potential as therapeutics for psoriasis and perhaps other hyperproliferative skin disease. Expert Opin Investig Drugs 2006;5:1453-68.
184. Ellis CN, Varani J, Fisher GJ, Zeigler ME, Pershadsingh HA, Benson SC, et al. Troglitazone improves psoriasis and normalizes models of proliferative skin disease: ligands for peroxisome proliferator-activated receptor-gamma inhibit keratinocyte proliferation. Arch Dermatol 2000;136:609-16.
185. Pershadsingh HA, Sproul JA, Benjamin E, Finnegan J, Amin NM. Treatment of psoriasis with troglitazone therapy. Arch Dermatol 1998;134:1304-5.
186. Shafiq N, Malhotra S, Pandhi P, Gupta M, Kumar B, Sandhu K. Pilot trial: Pioglitazone versus placebo in patients with plaque psoriasis (the P6). Int J Dermatol 2005;44:328-33.
187. Cordain L, Eades MR, Eades MD. Hyperinsulinemic diseases of civilization: more than just Syndrome X. Comp Biochem. Physiol A Mol Integr Physiol 2003;136:95-112.
188. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). JAMA 2001; 285:2486-97.
189. Grundy SM, Hansen B, Smith SC Jr, Cleeman JI, Kahn RA. Clinical management of metabolic syndrome: report of the American Heart Association/National Heart, Lung, and Blood Institute/American Diabetes Association conference on scientific issues related to management. Circulation 2004; 109:551-6.
190. Meigs JB. The metabolic syndrome. BMJ 2003;327:61-2.
191. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med 2002;346:393-403.
192. Roubenoff R. Gout and hyperuricemia. Rheum Dis Clin North Am 1990;16:539-50.
193. Roubenoff R, Klag MJ, Mead LA, Liang KY, Seidler AJ, Hochberg MC. Incidence and risk factors for gout in white men. JAMA 1991;266:3004-7.
194. Campion EW, Glynn RJ, DeLabry LO. Asymptomatic hyperuricemia. Risks and consequences in the Normative Aging Study. Am J Med 1987;82:421-6.
195. Choi HK, Atkinson K, Karlson EW, Curhan G. Obesity, weight change, hypertension, diuretic use, and risk of gout in men: the health professionals follow-up study. Arch Intern Med 2005;165:742-8.
196. Dessein PH, Shipton EA, Stanwix AE, Joffe BI, Ramokgadi J. Beneficial effects of weight loss associated with moderate calorie/carbohydrate restriction, and increased proportional intake of protein and unsaturated fat on serum urate and lipoprotein levels in gout: a pilot study. Ann Rheum Dis 2000;59:539-43.
197. Snaith ML. Gout: diet and uric acid revisited. Lancet 2001; 358:525.
198. Sun YN, Lu JF, Joshi A, Compton P, Kwon P, Bruno RA. Population pharmacokinetics of efalizumab (humanized monoclonal anti-CD11a antibody) following long-term subcutaneous weekly dosing in psoriasis subjects. J Clin Pharmacol 2005;45:468-76.
199. Korman NJ, Ticho B. Weight-based and extended dosing as alternative alefacept treatment regimens for patients with psoriasis who weigh between 100 and 150 kg [abstract]. Poster presented at the American Academy of Dermatology 63rd Annual Meeting, February 18-22, 2005.
200. Langman G, Hall PM, Todd G. Role of non-alcoholic steatohepatitis in methotrexate-induced liver injury. J Gastroenterol Hepatol 2001;16:1395-401.

201. Newman M, Auerbach R, Feiner H, Holzman RS, Shupack J, Migdal P, et al. The role of liver biopsies in psoriatic patients receiving long-term methotrexate treatment. Improvement in liver abnormalities after cessation of treatment. Arch Dermatol 1989;125:1218-24.
202. Berends MA, Snoek J, de Jong EM, van de Kerkhof PC, van Oijen MG, van Krieken JH, Drenth JP. Liver injury in long-term methotrexate treatment in psoriasis is relatively infrequent. Aliment Pharmacol Ther 2006;24: 805-11.
203. Ness-Abramof R, Apovian CM. Drug-induced weight gain. Timely Top Med Cardiovasc Dis 2005;9:E31.
204. Hecht OM, Cole JO, Friedman L, Bird M, McEachern J. Weight changes in antidepressants: a comparison of amitriptyline and trazodone. Neuropsychobiology 1986;15(Suppl 1):28-30.
205. Hinze-Selch D, Schuld A, Kraus T, Kuhn M, Uhr M, Haack M, et al. Effects of antidepressants on weight and on the plasma levels of leptin, TNF-alpha and soluble TNF receptors: A longitudinal study in patients treated with amitriptyline or paroxetine. Neuropsychopharmacology 2000;23:13-9.
206. Kraus T, Haack M, Schuld A, Hinze-Selch D, Koethe D, Pollmacher T. Body weight, the tumor necrosis factor system, and leptin production during treatment with mirtazapine or venlafaxine. Pharmacopsychiatry 2002;35:220-5.