

REVIEW ARTICLE

Obesity and inflammatory skin diseases

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ABSTRACT

Obesity has become a significant public health problem since it may cause many chronic diseases, including type 2 diabetes, liver diseases, cardiovascular diseases, and some cancers. Recent studies show that obesity is a major risk factor for the development of inflammatory skin diseases, including eczema, atopic dermatitis, and psoriasis. Inflammatory cytokines produced from adipose tissue and activation of innate immunity are considered as important factors in obesity-induced inflammation. However, the molecular mechanisms by which obesity affects the development of inflammatory skin diseases are not well understood. In this review, we will discuss the relationship between the underlying mechanisms linking obesity and inflammatory skin diseases based on the latest researches.

Keywords: obesity; psoriasis; inflammation; adipokine; high fat diet; fatty acids

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Introduction

The prevalence of obesity has increased markedly in most developed countries over the past two decades^[1]. By the year 2000, around two-thirds of adults in the United States were overweight (body mass index (BMI) 26–30) or obese (BMI >30)^[2], and there were 300 million of obese adults worldwide. The incidence of type 2 diabetes increased proportionally during this same time period; this trend is presumed to be a direct result of the obesity epidemic^[3]. Even though obesity has long been recognized as a vital cause of diabetes and cardiovascular diseases, the impact of obesity on the skin has received minimal attention. However, recent studies have gradually revealed the close relationships between obesity and various skin diseases and skin homeostasis. For example, the epidermal barrier is reported to be impaired in obesity, so that obese individuals show increased transepidermal water loss (TEWL) and dry skin^[4]. Obese individuals also have larger skin folds and sweat more profusely when overheated^[5]. Obesity inhibits lymphatic flow^[5] and alters collagen formation^[6]. The delayed-type hypersensitivity response is increased in obese individuals and decreases with weight reduction^[7], which may be related to an alteration in the production of cytokines by adipocytes.

This article aims to highlight the association between obesity and dermatologic conditions. We review the impact of obesity on inflammatory skin diseases, including eczema, atopic dermatitis and psoriasis.

Epidemiology of the association between obesity and inflammatory skin diseases

Eczema and atopic dermatitis

Eczema, the most common inflammatory skin disease, is estimated to have affected 245 million people globally in 2015^[8]. In the United States, it affects about 10%–30% of people. Eczema, also known as dermatitis, is a clinical and

histopathological pattern of skin inflammation that presents as pruritus, skin dryness and erythema^[9]. Eczema may result in skin lichenification, and severe eczema is the most common cause of erythroderma. Quality of life for patients and their families may be considerably reduced and occupational issues may add to the financial consequences^[10].

There are some reports regarding the association between obesity and eczema^[11,12]. Silverberg *et al.* reported that BMI-for-age percentiles (BMIP) of 50 to 94 and greater than or equal to 95 are each associated with higher odds of eczema compared with BMIP of 5 to 49^[11]. The incidence of moderate to severe eczema is higher among individuals with BMIP of 50 to 94 and those with BMIP greater than or equal to 95 than among those with BMIP of 5 to 49. There is a significant interaction between race/ethnicity and BMIP in multivariate regression models of eczema severity, such that BMIP remains significant in Hispanics, non-Hispanic whites, Pacific Islanders/Alaskan Natives, Asians, and multiracial/other but not in non-Hispanic blacks or American Indians^[11]. Thus, epidemiologically, it is suggested that the incidence of eczema correlates with BMI.

The above two reports^[11,12] regarding the association between eczema and obesity, however, include many atopic dermatitis patients in the analysis. Therefore, in the next paragraph, we will go into the details about the association between atopic dermatitis and obesity.

Atopic dermatitis is a chronic, relapsing, inflammatory skin condition characterized by itch^[13-16], which affects 20%–30% of schoolchildren and 5%–10% of adults in the UK^[10]. Topical therapy with emollients, corticosteroids, and calcineurin inhibitors remains the mainstay of treatment. For more severe cases, current therapeutic options remain limited. As a result, atopic dermatitis still places a significant quality-of-life and financial burden on society and health care systems worldwide^[10,16].

There are more than 30 studies about the relationships between obesity and atopic dermatitis^[17]. In general, it is reported that patients who are overweight or obese have higher odds of atopic dermatitis than normal weight patients. In sensitivity analyses, children who are overweight or obese and adults who are obese have higher odds of atopic dermatitis. The association is also significant in North America and Asia but not Europe. As the phenotype of atopic dermatitis is different between the regions^[18], the contribution of obesity to the development of atopic dermatitis may be different between the regions. Although the underlying mechanisms by which

obesity causes eczema and atopic dermatitis remain largely unknown, various mechanisms have been proposed, including obesity-induced exacerbation of skin inflammation, which will be discussed later.

Psoriasis

Psoriasis encompasses a group of related inflammatory skin diseases that affect up to 3% of the population^[19]. These diseases are heritable and over 40 genetic susceptibility loci have been identified, many of which are involved in antigen presentation, cytokine signaling, or innate antimicrobial responses. The most common presentation of psoriasis is plaque psoriasis but the disease is clinically heterogeneous in its manifestations and natural history depending on the age of the patient, environmental triggers, and the sites affected^[10]. Treatments include topical agents for disease of limited extent, phototherapy (UVB and PUVA), and systemic therapy (methotrexate, cyclosporine, acitretin and fumarates) for more extensive disease, and biological treatment (inhibitors for tumor necrosis factor α , IL-23 and IL-17) for severe resistant psoriasis^[10].

Many reports cite an association between obesity and psoriasis. From 1980 to 2012, sixteen observational studies were conducted with a total of 2.1 million study participants^[20]. The frequency of psoriasis varied significantly in relation to BMI (OR = 1.6 and 1.9 for overweight and obese patients, respectively)^[21]. Prospective data on 78,626 women in a nurses' health study found that weight gain placed individuals at an increased risk for the subsequent development of psoriasis. Moreover, the incidence of psoriasis was linearly associated with the BMI, with the greatest relative risk of 2.69 for patients with a BMI of 35 or more compared to patients with a BMI of 21 to 23. The risk of psoriasis at 18 years of age was also linearly associated with BMI^[22]. It is likely that obesity predisposes individuals to the development of psoriasis. Obesity is also associated with the severity of psoriasis. It has been reported that BMI and psoriasis area and severity index (PASI) are correlated^[23]. Unlike other inflammatory diseases, psoriasis has been reported to be associated with obesity in all regions of the world.

Mechanistic links between obesity and skin inflammation

Although there are considerable epidemiological data, as described above, the mechanisms linking obesity with skin inflammation are diverse, and there are many unclear points. In the next section, we will

introduce these mechanisms that are currently under consideration.

Obesity changes cell composition in adipose tissues

As discussed above, inflammatory skin diseases are generally exacerbated by obesity, but the mechanism of this exacerbation has not been fully elucidated. It has been reported, however, that changes in cell composition in adipose tissues are important for the development of systemic diseases such as diabetes in obesity^[24]. Adipose tissues are composed not of adipocytes alone but rather of a variety of other cell types, collectively termed the stromal vascular fraction (SVF). This fraction includes mesenchymal stem cells, vascular endothelial cells, nerve cells, macrophages, T cells and B cells. In 2003, pioneering studies by Xu *et al.* and Weisberg *et al.* reported that obesity is associated with significant increases in the proportion of macrophages in the SVF in both visceral and subcutaneous adipose tissues^[25,26]. Flow cytometric analysis has shown that macrophages account for approximately 40% of the SVF in obese rodents, whereas it accounts for only 10% in lean littermates. The gene expression profile of adipose tissues from multiple obese mouse models demonstrates that macrophage-related genes are upregulated in obese animals^[26]. Recruitment of macrophages into adipose tissues is an early event in obesity-induced adipose inflammation. The monocyte chemoattractant protein-1 (MCP-1)/CCL2, one of the major chemoattractants for macrophages via CCR2, is secreted primarily by macrophages and vascular

endothelial cells, and also by adipocytes^[27]. Adipose tissue macrophages (ATMs) express CCR2 and recruit additional monocytes/macrophages, promoting a feed-forward process^[26,27]. As it is reported that macrophages play an important role in inflammatory skin diseases such as contact dermatitis and psoriasis^[28,29], an increase in ATM in adipose tissues in the skin (subcutaneous and intradermal adipose tissues)^[30] may contribute to the deterioration of inflammatory skin diseases.

Adipokines and inflammation

Presently, the hypothesis that adipose tissues have an endocrine function^[31] is supported by the findings that adipocytes secrete a variety of mediators, namely adipokines, which are involved in the inflammatory network. These mediators include leptin, adiponectin, plasminogen activator inhibitor (PAI)-1, interleukin (IL)-6 and tissue necrosis factor (TNF)- α ^[32] (**Figure 1**). Particularly, not only increased cytokine production but also impaired cytokine catabolism seem to be determinants of obesity-related inflammatory status^[33].

Adipokines and psoriasis

As mentioned above, adipokines have the function of regulating inflammation. Several basic and clinical studies have been published on adipokines' role in the pathology of inflammatory skin diseases (especially psoriasis).

Leptin is one of the main adipose-derived cytokines. Leptin has been investigated primarily for its

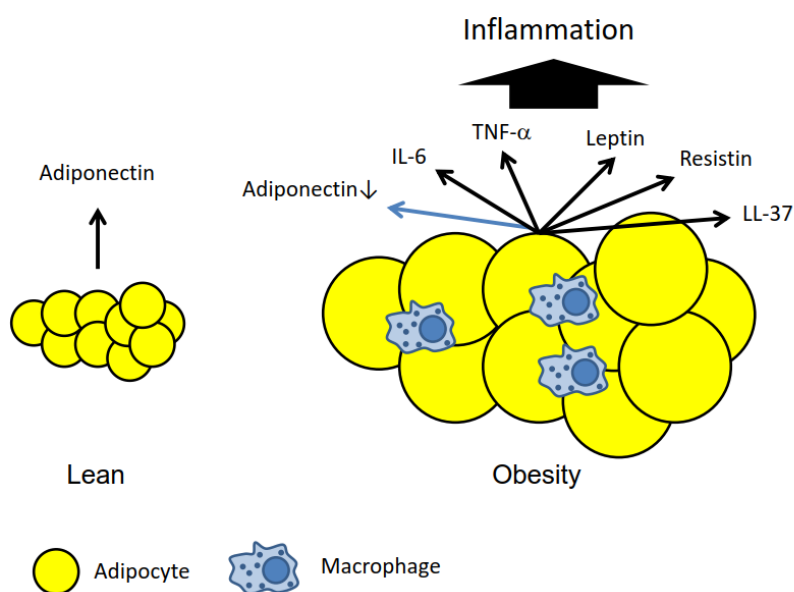


Figure 1. Hypertrophic adipose tissue produces inflammatory cytokines. Obesity increases the proportion macrophages in adipose tissue. In obesity, production of inflammatory cytokines from adipose tissue increases, causing inflammation.

role in controlling energy homeostasis by regulating appetite^[34]. Leptin is also essential for cell-mediated immunity. Previous studies reported that CD4⁺ T cells are hyporeactive in leptin-deficient mice^[35]. In psoriasis patients, leptin levels showed correlation with psoriasis severity^[36]. Furthermore, leptin-deficient (ob/ob) mice exhibit impaired IL-17A and IL-22 mRNA expression as well as reduced epidermal hyperplasia in an imiquimod (IMQ)-induced psoriasis model^[37]. *In vitro*, leptin induces proliferation and production of several pro-inflammatory proteins on human keratinocytes^[37]. These results suggest that leptin may exacerbate the condition in psoriasis.

Adiponectin is an anti-inflammatory cytokine mainly produced by adipocytes. Low serum levels of adiponectin have been reported in several chronic diseases, for example obesity and psoriasis^[38]. High levels of cytokines (eg. TNF- α and IL-6) may decrease adiponectin production in patients affected by inflammatory diseases^[38]. Low serum levels of adiponectin have been observed in obese psoriatic patients as compared with non-obese psoriatic patients^[39,40]. Shibata *et al.* reported that mice with adiponectin deficiency are present with severe psoriasiform skin inflammation with increased infiltration of IL-17-producing T cells^[41]. Adiponectin suppresses IL-17 synthesis via AdipoR1 on murine T cells. Adiponectin levels in skin tissue as well as in subcutaneous fat are decreased in psoriasis patients^[41]. IL-17 production from human CD4- or CD8-positive T cells is also suppressed by adiponectin^[41].

Zhang *et al.* reported that LL-37 (cathelicidin), one of the inducers of psoriasis^[42], is produced from the intradermal adipocytes under *Staphylococcus aureus* infection^[42]. This LL-37 production is inhibited by an adipocyte-differentiation inhibitor (peroxisome proliferator-activated receptor γ inhibitor). Interestingly, in the mice with high fat diet (HFD)-induced obesity, the numbers of intradermal adipocytes and their production of LL-37 are increased^[43]. Therefore, the immunological and metabolic alterations associated with obesity may be associated with the pathophysiology of psoriasis.

Obesity induces dysfunction of skin barrier

Obesity is associated with a number of significant changes in skin barrier functions. Obese individuals showed significantly increased TEWL, skin blood flow and skin color (*i.e.* redness) as compared to a control group in a study examining clinically unaffected skin in the middle of the flexor side of one forearm^[44], suggesting a fundamentally altered

epidermal barrier. Consistently, in obese mice, TEWL is also increased^[45]. Their numbers of keratinocytes are reduced, and their epidermis has a flattened and thinner appearance in obese mice^[45]. The epidermal structure is exacerbated by factors in the obese environment as demonstrated by altered E-cadherin localization and impaired cell-cell adhesion^[45]. A dysfunction of the skin barrier allows for more opportunities for antigen sensitization, which can cause various allergic diseases. In fact, obesity is a risk factor not only for atopic dermatitis, but also for asthma^[46].

Obesity and the inflammasome

The emergence of chronic inflammation during obesity in the absence of overt infection or well-defined autoimmune processes is a confusing phenomenon. The NOD-like receptor (NLR) family of innate immune cell sensors, for example, the nucleotide-binding domain, the leucine-rich-containing family, and the pyrin domain-containing-3 (Nlrp3) inflammasome, are implicated in recognizing certain nonmicrobially-originated “danger signals” leading to caspase-1 activation and subsequent IL-1 β and IL-18 secretion. The expression levels of IL-1 β and Nlrp3 in the adipose tissue correlate with body weight and insulin resistance (**Figure 2**). Ablation of Nlrp3 in mice avoids obesity-induced inflammasome activation in fat depots and the liver and enhances insulin signaling^[47,48].

The inflammasome may be also important in obesity-induced exacerbation of psoriasis-like skin inflammation. Vasseur *et al.* reported that imiquimod-induced psoriasiform dermatitis is exacerbated in obese mice as compared to lean mice^[49]. Scale formation and acanthosis are aggravated in correlation with increased IL-17A and IL-22 expressions in inflamed skins. Moreover, obesity is associated with the epidermal activation of caspase-1 and the cutaneous overexpression of IL-1 β ^[49] (**Figure 2**), suggesting that obesity induces inflammasome activation in the skin.

Obesity and lymphatic dysfunction

Recent studies reported that obesity impairs lymphatic functions in both mice and humans^[50,51]. For instance, obese mice have reduced ability to transport interstitial fluid via cutaneous lymphatics and have remarkably reduced trafficking of antigen-presenting cells to regional lymph nodes^[52]. Obese mice have impaired lymphatic collecting vessel pumping functions^[53]. These findings are supported by clinical studies reporting that obese patients have decreased clearance of macromolecules from

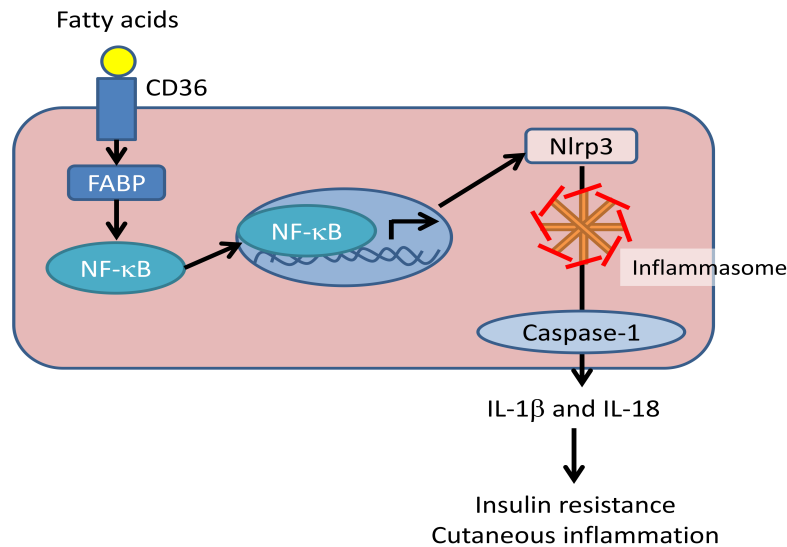


Figure 2. Fatty acids induce inflammasome activation. Fatty acids bind to CD36 and activate NF-κB. NF-κB activates Nlrp3 and the inflammasome to produce IL-1β and IL-18.

fat depots compared with normal controls, and that massively obese patients spontaneously develop lymphedema^[51]. Savetsky *et al.* reported that obesity-induced lymphatic dysfunction regulates contact hypersensitivity^[54]. Obese mice have impaired lymphatic functions and intensified dermatitis responses to inflammatory skin stimuli. Injection of recombinant vascular endothelial growth factor-C remarkably increased lymphangiogenesis, and lymphatic functions, while decreasing inflammation. These results propose that obesity-induced changes in the lymphatic system cause an amplified and prolonged inflammatory response in the skin.

Fatty acids and inflammation

Fatty acids, such as saturated fatty acids and trans fatty acids, are abundantly contained in HFD, which is considered a cause of obesity^[55]. There are several papers that show the direct effects of fatty acids on immune functions. For example, GPR120, which is a receptor for ω3 fatty acid, is expressed in macrophages and adipocytes, and inhibits inflammation by suppressing Toll-like receptor signals and TNF signals^[56]. On the other hand, CD36, which is a receptor of unsaturated fatty acid, is expressed in vascular endothelial cells and macrophages and is known to cause the production of TNF and IL-1 via NF-κB^[57].

Stelzner *et al.* reported that the concentration of fatty acid is increased in the HFD-fed mice, and that the concentration of fatty acid is correlated with the severity of the imiquimod-induced psoriasis model^[58]. Kanemaru *et al.* reported that saturated

fatty acids activate keratinocyte to up-regulate the IL-17A downstream molecule, regenerating islet-derived 3γ, which has been suggested as a critical molecule for epidermal hyperplasia in psoriasis^[59]. It is also reported that dietary fatty acids induce obesity-associated inflammasome activation in the skin and cause skin inflammation (**Figure 2**). Zhang *et al.* reported that mice fed with HFD for six months spontaneously develop detectable skin lesions^[60]. In mice, langerin-positive dendritic cells are increased in both the epidermis and the dermis where they produce IL-1β and IL-18. The activation of the inflammasome depends on the concentration of fatty acids. Fatty acid binding protein 5, the transporter of fatty acids, is reported to mediate such fatty acids-induced skin inflammation, because mice without fatty acid binding protein 5 did not exhibit any of the above symptoms while receiving HFD^[60] (**Figure 2**). As the fatty acid binding protein 5 was first identified as being upregulated in the psoriasis tissue, a similar mechanism may be involved in the deterioration of psoriasis caused by obesity.

There is a report that fatty acids are involved in the differentiation of Th17 cells, a critical cell subset in the pathogenesis of psoriasis^[61]. Endo *et al.* reported that Th17 is increased in the spleens of obese mice. Increased fatty acid synthesis in Th17 cells was suggested as the mechanism of increased Th17 differentiation in obese mice, since inhibition of fatty acid synthesis reversed the obesity-induced increase of Th17 differentiation while the addition of fatty acids facilitated Th17 cell differentiation *in vitro*^[61]. These results suggest that high intake of fatty acids can increase Th17 cell differentiation in humans,

which may explain one mechanism linking obesity and psoriasis.

Fatty acids may also be important for the survival of the cutaneous resident memory T cells (T_{RM})^[62]. T_{RM} are a recently described subset of memory T cells that persist long-term in peripheral tissues^[63]. T_{RM} undergo a distinct differentiation program that discriminates them from circulating T cells; this program likely evolved to populate epithelial barrier tissues—the skin, gut, lung, and reproductive tracts—with highly protective T cells specific for the pathogens most commonly encountered through each tissue^[63]. T_{RM} have been directly demonstrated in psoriasis, mycosis fungoides, and fixed drug reactions^[63]. Cutaneous T_{RM} express fatty acid binding proteins 4 and 5, and the number of T_{RM} are decreased in the fatty acid binding protein 4- and 5-deficient mice^[63]. Unlike other memory T cells, T_{RM} actually produce ATP by β -oxidation of fatty acid. The protection against virus infection is reduced in through the fatty acid 4- and 5-deficient mice as well as β -oxidation inhibitor-treated mice, suggesting that fatty acids are essential for the protection of the host from virus infection via maintenance of T_{RM} . Fatty acid binding proteins 4 and 5 are also expressed in the human T_{RM} in psoriasis patients^[62]. However, the relationships between obesity and T_{RM} are unknown; increased quantities of fatty acid due to obesity may have some effects on the T_{RM} .

Conclusion

Obesity is one of the important causal factors of many inflammatory diseases. In the skin, functional changes in both adipocytes and lymphatic vessels and epidermal keratinocytes are suspected to be involved in the obesity-induced exacerbation of skin inflammation. How obesity causes inflammation is still not well understood, but future research will reveal these mechanisms, enabling the development of new treatments for inflammatory skin diseases is expected.

Conflict of interest

The authors declare no potential conflict of interest with respect to the research, authorship, and/or publication of this article.

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