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# ADIPOSE TISSUE, OBESITY, AND AUTOIMMUNITY

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## ABSTRACT

The rising prevalence of immune-mediated diseases in technologically advanced nations has sparked interest in the intricate connection between obesity and autoimmunity. This review explores how environmental factors, particularly the Western lifestyle characterized by unhealthy dietary habits, have contributed to an obesity epidemic linked to an increased risk of autoimmune diseases. We highlight the significant role of white adipose tissue (WAT) as an endocrine organ that secretes inflammatory mediators known as adipokines. These adipokines, including leptin and adiponectin, play pivotal roles in modulating immune responses, promoting a chronic low-grade inflammatory state that can lead to various immune-related conditions. Additionally, we examine the involvement of immune cells, such as T-helper 17 (Th17) cells and B-regulatory lymphocytes, in the pathophysiological mechanisms by which obesity exacerbates autoimmunity. Clinical evidence correlating obesity with diseases such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus is discussed, along with the shared inflammatory pathways and genetic predispositions that underline this relationship. Despite the growing body of evidence, challenges remain in establishing causative links due to the complexity of these interactions. This review underscores the need for further research to elucidate the underlying mechanisms and potential therapeutic implications of the obesity-autoimmunity nexus, aiming to pave the way for novel strategies in managing autoimmune diseases through lifestyle and metabolic interventions.

## 1. INTRODUCTION

For many years, technologically advanced nations have been witnessing a rise in the occurrence of immune-mediated diseases. These inflammatory conditions are often the result of a complex interplay between one's genetic makeup and various environmental factors. Given that our genetic framework has stayed relatively unchanged, the spotlight has increasingly turned towards environmental contributors, particularly the Western lifestyle is taking the main stage. The shift towards Westernization has drastically altered our food consuming habits, favoring diets rich in fats, sugars, and salts, and leading to an excessive calorie intake [1-3]. This dietary change has been a significant factor behind the obesity epidemic seen over the last two decades. Consequently, the relationship between obesity and autoimmune diseases has come under scrutiny, with a growing body of evidence suggesting obesity's significant role in the escalation of autoimmune conditions. This connection has become even more intriguing with the recent uncovering of adipose tissue's remarkable functions [4-6]. White adipose tissue (WAT), once thought to be merely a passive storage site for energy, is now recognized as a crucial endocrine organ that secretes a variety of soluble factors known as “adipokines” or “adipocytokines”. Initially identified for their roles in metabolism and appetite regulation, adipokines have been found to play roles in immunity and inflammation as well [7-9]. Through their pro-inflammatory effects, these molecules contribute to a “low-grade inflammatory state” in obese individuals, leading to a range of comorbidities including metabolic syndrome, diabetes, and cardiovascular issues. Therefore, understanding the relationship between obesity and autoimmune/inflammatory diseases has become a primary focus. In this review, after providing a brief overview of the mechanisms linking obesity and autoimmunity identified thus far, we will delve into the metabolic and immunological functions of key adipokines. We will then explore the specific roles of obesity, particularly through adipokines, in the development and prognosis of various immune-mediated diseases [10-12].

## 2. SEWING OBESITY AND AUTOIMMUNE DISEASES TOGETHER

Obesity is characterized by an excessive accumulation of fat tissue in the body. The World Health Organization (WHO) estimates that around 35% of the global population is either overweight (with a body mass index, BMI, between 25–30 kg/m^2) or obese (BMI over 30 kg/m^2). It is well-established that individuals with obesity often experience a low-grade, chronic inflammatory state, which can result in various metabolic complications [13,14]. Furthermore, numerous studies have demonstrated a strong link between obesity and an increased risk or severity of several immune-related conditions.

Hence, exploring the immune dysfunctions associated with obesity that contribute to inflammatory autoimmune diseases is a critical area of research. To this end, several mechanisms have been proposed [15-17].

One key area of study has been the role of WAT as a significant source of inflammatory mediators known as "adipokines," which largely promote inflammation. These include well-known cytokines such as interleukin (IL)-6 and Tumor Necrosis Factor alpha (TNFα), along with specific molecules like leptin and adiponectin [18-20]. These substances are released not only by fat cells but also by various immune cells that are found in greater numbers in the adipose tissue of obese individuals. As will be further discussed, adipokines are crucial in mediating the interaction between fat tissue and the immune system [21,22].

Additionally, recent research has shed light on the importance of the apoptosis inhibitor of macrophage (AIM) in the development of autoimmune diseases linked to obesity. Produced by tissue macrophages, AIM was initially recognized for helping macrophages resist various stimuli that induce apoptosis. It has been shown that in obesity, elevated levels of AIM in the blood trigger lipolysis, releasing a high volume of saturated fatty acids from fat cells [23-25]. These fatty acids then prompt the production of chemokines in fat cells through the activation of TLR4, leading to an increased infiltration of M1-macrophages in adipose tissue. Furthermore, AIM interacts with naturally occurring auto reactive IgM to form immune complexes, facilitating their attachment to follicular dendritic cells and the presentation of autoantigens to follicular B-lymphocytes. This process results in the generation of IgG autoantibodies [26-28].

T-helper 17 cells (Th17), a subset of CD4 effector T lymphocytes identified recently, are known for their secretion of IL-17 and their role in the development of autoimmune diseases. It has been found that obesity might promote the activation of Th17 cells through an IL-6-dependent mechanism, worsening autoinflammatory conditions such as multiple sclerosis and colitis in various mouse studies. Interestingly, IL-17 has been observed to block the process of forming new fat cells. The exact impact of Th17 cells and IL-17 on inflammation linked to obesity remains to be fully understood [29-32].

The impact of diet, particularly a diet high in salt and fat, on immune-related disorders is another area of keen interest. Studies have indicated that a Western diet can lead to dysbiosis, a disruption in the gut microbiome, which significantly affects immune responses outside the gut, including an imbalance between Th17 and regulatory T cells (Treg). The relationship between dysbiosis and autoimmune diseases, whether causal or consequential, is still under investigation [33-35]. Additionally, the higher incidence of vitamin D deficiency in obese individuals is noteworthy. Vitamin D plays a crucial role in regulating the immune system, promoting Treg cells while inhibiting Th1 and Th17 differentiation. Although the link between vitamin D deficiency and autoimmune diseases has been suggested, the evidence remains debatable [36-38].

Further research is also needed in areas such as the activation of the NLRP3 inflammasome in macrophages by obesity-related factors like ceramides, saturated fats, and reactive oxygen species. This inflammasome, through its release of IL1β and IL18, is implicated in many autoimmune diseases. Recent discoveries include the presence of B-regulatory lymphocytes in adipose tissue, which produce anti-inflammatory cytokines IL-10 and TGF β [39-42]. However, their numbers and the levels of these cytokines decrease in obesity, contributing to inflammation. The role of invariant natural killer T cells (iNK cells), which are abundant in adipose tissue and help maintain its homeostasis, is also not fully understood, as their numbers drop significantly in obesity [43-45].

While these areas require more detailed study, the role of adipokines in the pathology of immune-mediated diseases associated with obesity is well-documented. More than 50 adipokines produced by WAT have been identified, with leptin, adiponectin, resistin, and visfatin being four key players in autoimmune and inflammatory conditions [46,47].

**Table 1. Adipokines and Their Roles in Obesity and Autoimmunity**

| Adipokine | Source | Effect on Immunity | Associated Autoimmune Diseases |
|---|---|---|---|
| **Leptin** | White Adipose Tissue | Promotes inflammation; enhances Th cell differentiation | MS, RA, SLE |
| **Adiponectin** | White Adipose Tissue | Anti-inflammatory; promotes Treg cell function | Reduced levels in RA, SLE |
| **Resistin** | White Adipose Tissue | Pro-inflammatory; enhances macrophage activation | RA, IBD |
| **Visfatin** | White Adipose Tissue | Activates inflammatory pathways, influences T cell responses | Reduces inflammation related to T1DM |

## 3. NEWLY FOUND EVIDENCES OF CONNECTION

Recent research has established a concrete link between obesity and autoimmunity, particularly focusing on the impact of leptin on the immune system. Initial findings revealed that a deficiency in leptin or its receptor leads to a higher risk of infections, as evidenced by ob/ob mice's reduced capacity to eliminate Klebsiella pneumoniae infections. On the other hand, lower levels of leptin have been linked to a decreased risk of developing autoimmune diseases. Animal studies have indicated that leptin promotes the growth and differentiation of CD4+ T helper cells while inhibiting the formation and persistence of regulatory Tregs [48-50].

In studies involving leptin-deficient ob/ob mice, these mice displayed an immunosuppressive profile upon mitogenic stimulation. They showed lower levels of pro-inflammatory cytokines such as IFN-γ, TNF, IL-2, and IL-18, and higher levels of TH2-type cytokines, including IL-4 and IL-10. This immunosuppressive state in ob/ob mice has been protective against the onset of autoimmunity in mouse models prone to autoimmune diseases, such as experimental autoimmune encephalomyelitis (EAE), which is characterized by demyelination, experimentally induced glomerulonephritis (EINN), antigen-induced arthritis (AIA), experimentally induced hepatitis (EIH), and experimentally induced colitis (EIC) [51,52]. In many of these autoimmune model studies, administering leptin to ob/ob mice reinstated their susceptibility to these diseases to levels observed in normal mice.

Further research has delved into how impaired leptin signaling affects mice genetically predisposed to systemic lupus erythematosus (SLE), specifically the MRL/Mp-Fas(lpr) mouse model. This model, which naturally exhibits symptoms similar to those of human SLE, including lesion development, autoantibody production, proliferative glomerulonephritis, and low complement levels, is characterized by a deficiency in the Fas protein essential for initiating apoptosis, leading to lymphoproliferation and an accumulation of Treg cells [53-55]. Inhibiting leptin signaling by breeding MRL/Mp-Fas(lpr) mice with leptin-deficient C57BL/6J-ob/ob mice resulted in reduced spleen enlargement and fewer double negative (CD4−, CD8−) T cells. Serum analysis from these mice showed decreased levels of anti-dsDNA autoantibodies and healthier kidney tissue, suggesting that blocking leptin signaling could offer therapeutic advantages for SLE patients [56,57].

The relationship between leptin levels and SLE can be further understood based on a recent study, which compared the susceptibility of leptin-deficient (ob/ob) mice to lupus symptoms and SLE disease with that of leptin-sufficient wild-type mice. Pristane was used to induce autoimmunity in the leptin-deficient mice, which then exhibited protection against kidney disease, reduced autoantibody production, and an increase in Treg cell counts in comparison to wild-type mice [58,59]. These results were corroborated in the spontaneous SLE mouse model, the New Zealand Black/New Zealand White F1 (NZB/W), where higher leptin levels were associated with more severe disease symptoms. For instance, leptin administration exacerbated autoantibody production and kidney disease, whereas leptin inhibition delayed disease progression and extended survival. In vitro experiments demonstrated that leptin enhanced effector T-cell responses by promoting the presentation of self-antigens to T cells, further supporting the link between leptin, CD4+ Treg cell activity, and immune function [60,61].

Leptin, a hormone, has been identified in T cells and macrophages within lymph nodes and the central nervous system's (CNS) inflammatory areas during acute and relapsing episodes of EAE. Individuals with active Multiple Sclerosis (MS) show higher levels of leptin in both the CNS's inflammatory lesions and their serum before a relapse occurs. Freshly isolated human regulatory T (Treg) cells exhibit high leptin and leptin receptor levels even when not activated. Furthermore, it was found that leptin negatively affects Treg cell proliferation [62-64]. In vitro studies where human Treg cells were treated with anti-leptin antibodies demonstrated an increase in their proliferation when stimulated. This is supported by observations in leptin- or leptin receptor-deficient mice, which show an increase in Treg cell proliferation, indicating that leptin and its receptor act as inhibitors of Treg cell proliferation. These findings offer insights into previous research which suggested that chronic deficiency in leptin or its receptor could lead to higher susceptibility to infections and resistance to autoimmune diseases [65,66].

A unique subset of dendritic cells, rich in perforin-containing granules (perf-DCs), has been identified and is thought to play a regulatory role in the immune mechanisms that manage fat tissue metabolism. Early studies outside the body suggested these cells might promote immune tolerance. Further in vivo studies, particularly in chimeric mice treated with radiation and lacking perf-DCs, showed these mice developed metabolic syndrome, a condition that was entirely prevented by depleting T cells in vivo [67-72]. Further research indicated that perf-DCs help regulate inflammatory T cells within WAT, thus controlling inflammation in fat tissue. Mice without perf-DCs, when fed a high-fat diet, showed a worsened metabolic condition. This was also observed in the EAE model, where mice lacking perf-DCs had a significant increase in autoimmune-associated T cell clones compared to control mice. These discoveries highlight the existence of specific myeloid dendritic cell subpopulations that could help understand how immune dysregulation is linked to metabolic issues and the development of autoimmune diseases [73,74]

**Table 2. Clinical Evidence Linking Obesity with Autoimmune Conditions**

| Autoimmune Disease | Main Clinical Findings | Impact of Obesity |
|---|---|---|
| Multiple Sclerosis | Higher incidence in obese youth; elevated leptin and inflammatory markers | Increased risk of disease onset and severity |
| Rheumatoid Arthritis | Elevated adipokines in serum and synovial fluid; exacerbated symptoms with obesity | Higher risk (20%); less radiographic damage |
| Systemic Lupus Erythematosus | Increased disease severity in obese patients; alterations in adipokine levels | Correlates with hyperleptinemia and greater comorbidities |
| Psoriasis | Strong association with obesity; improved PASI scores with weight loss | Increased pro-inflammatory cytokines; synergistic relationship |
| Type 1 Diabetes | Uncertain relationship; variable adipokine levels | Potentially doubles risk; complex interaction |
| Hashimoto Thyroiditis | Elevated TSH in obesity; linkage with increased anti-TPO autoantibodies | Increased risk of HT; correlations with leptin levels |

## 4. CONCRETE CLINICAL EVIDENCE: FIRM LINK BETWEEN AUTOIMMUNITY AND OBESITY

Millions of individuals globally suffer from autoimmune diseases, yet the root causes remain elusive despite extensive research. Given the multifaceted roles of adipose tissue, including its immunomodulatory and metabolic functions, it's not surprising that links between autoimmune diseases and obesity aroused. Both conditions share commonalities in inflammation, genetic and epigenetic predispositions [75,76]. In obesity, dysfunctional visceral adipose tissue (VAT) plays a role in the development of various conditions including cancer, allergies, and notably, autoimmune diseases, through shared mechanisms. Numerous studies support this connection, demonstrating a strong correlation through clinical observations in humans [77,78].

MS, a chronic inflammatory demyelinating disease of the central nervous system of unknown cause, predominantly affects young individuals. Its development is influenced by a combination of genetic susceptibility, environmental factors, and immune responses. With the increasing prevalence of both MS and obesity, obese children and adolescents, especially girls with a genetic predisposition, face a doubled risk of developing MS [79,80]. Key mechanisms include decreased levels of adiponectin, elevated leptin levels, low vitamin D, and a shift towards an M2/M1 macrophage phenotype. Several studies have confirmed these findings, showing increased serum levels of leptin, visfatin, and resistin alongside decreased adiponectin levels. These changes are also associated with higher levels of inflammatory markers such as TNF-α, high-sensitivity C-reactive protein (hs-CRP), and IL-1b, as well as a decrease in Tregs [81,82].

Rheumatoid arthritis (RA) is an inflammatory autoimmune disease marked by swelling in the synovial fluid, with an increase in pro-inflammatory cytokines in the affected joints. Elevated levels of adipokines such as leptin, resistin, and visfatin have been detected in the serum and synovial fluids of individuals with RA. These adipokines can locally stimulate the production of chemokines like IL-2 and IL-8, cytokines including IL-1b and IL-6, and matrix metalloproteinases (MMPs) such as MMP-1, MMP-3, and MMP-9 [83-85]. Obesity has been linked to a 20% higher risk of developing RA, especially the anti-citrullinated protein antibody-negative form of the disease, and is associated with more severe symptoms and active disease. This is evidenced by higher levels of CRP and erythrocyte sedimentation rate, worse scores on health assessment questionnaires and visual analog scales, and a lack of response to infliximab treatment. Interestingly, individuals with obesity tend to show less radiographic joint damage, possibly due to the increased mechanical load stimulating bone production and higher estrogen levels [86-88].

SLE is a chronic inflammatory condition that affects multiple systems and predominantly occurs in women, who make up 80 to 90% of all SLE patients. Epidemiological studies have found that approximately one-third of women with SLE are obese, which is linked to increased disease severity, including cognitive issues, lupus nephritis, and cardiovascular disease (CVD). Notably, atherosclerosis and CVD are more common in SLE patients. Additionally, SLE patients with CVD often exhibit hyperleptinemia and hyperresistinemia along with low levels of adiponectin, a pattern also seen in individuals with obesity [89,90].

Psoriasis and obesity are both chronic inflammatory conditions that are closely linked, creating a harmful cycle and exhibiting a synergistic relationship. Obesity contributes to a higher level of inflammation, marked by an increase in pro-inflammatory adipokines and cytokines, such as IL-17A and IL-23, which play a significant role in psoriasis but are less studied in the context of obesity [91-93]. Recent comprehensive reviews on the link between psoriasis and obesity have revealed that: (1) a genetically higher body mass index (BMI) is associated with an increased risk of developing psoriasis; (2) there is a connection between obesity and a higher incidence and prevalence of psoriasis; (3) obesity affects the effectiveness of anti-TNF-α medications and may lead to the discontinuation of biological treatments; and (4) dietary and physical exercise-induced weight loss can improve existing psoriasis and reduce the risk of developing the condition [94-97]. Both psoriasis and psoriatic arthritis show an increase in Th1, Th17, Th22, TNF-α, and INF-γ cells, leading to a rise

in pro-inflammatory cytokines such as IL-6, IL-17, IL-22, TNF-α, and INF-γ. Additionally, observational studies have found higher levels of serum leptin, resistin, and visfatin in individuals with both psoriasis and obesity. The data on adiponectin levels in those with psoriasis and obesity is mixed, indicating the need for further research to clarify this relationship [98-100]. The severity of psoriasis, measured by the Psoriasis Area and Severity Index (PASI), has been linked to obesity, as determined by BMI, waist circumference, and other metrics. It was found that among patients with psoriasis and excess body weight, those who lost weight saw a 48% improvement in their PASI score, compared to a 25.5% improvement in the control group who received only counseling without a dietary plan [101-103].

The relationship between type 1 diabetes mellitus (T1DM) and obesity presents conflicting evidence. While there are suggestions that high birth weight and obesity during childhood and adolescence could potentially double the risk of T1DM, it remains uncertain whether obesity acts as a causative or accelerating factor for this condition. The increasing prevalence of obesity in young populations adds complexity to understanding this relationship [104-106]. In T1DM patients, the serum levels of adipokines, including leptin, have shown varied results, being either increased, decreased, or unchanged. Notably, adipokines might play a role in triggering an autoimmune response against the pancreatic β-cells. However, to date, neither adipokines nor inflammatory markers have provided definitive insights [107-109].

Hashimoto thyroiditis (HT) is a common autoimmune disorder that leads to hypothyroidism, characterized by goiter, lymphocytic infiltration, and the presence of autoantibodies against thyroid-peroxidase (anti-TPO) and/or thyroglobulin (anti-TG). Obesity is linked to elevated thyroid stimulating hormone (TSH) levels, a response from the hypothalamus-pituitary axis partly regulated by leptin, aimed at boosting energy expenditure [110-112]. Recent studies, including meta-analyses, have identified a connection between obesity and an increased risk of both overt and subclinical hypothyroidism, HT, and the presence of anti-TPO autoantibodies. Specifically, research by Wang et al. has found an association between HT and obesity with elevated serum leptin levels, which also correlates with an increase in Th17 cells [113-116].

Recent research has established a link between obesity and the development and severity of inflammatory bowel diseases (IBD), such as ulcerative colitis and Crohn's disease, as well as a diminished response to anti-TNF-α treatments. Additionally, both animal and human studies have highlighted the significance of adipokines in IBD pathogenesis. Individuals with IBD exhibit increased levels of leptin, resistin, and visfatin in their serum, VAT or intestinal lumen, which correlates with gut inflammation [117-119].

However, the direct cause-and-effect relationship between obesity and autoimmunity remains unclear. Key observations include: (1) the pro-inflammatory state of adipose tissue, marked by chronic low-grade inflammation, which leads to the activation and attraction of immune cells; (2) a reduction in Tregs and a rise in Th17 cells, both of which encourage autoimmunity; and (3) gut dysbiosis triggered by an obesogenic diet, altering the balance of Th17 to Tregs. Additionally, the conversion of androgens to estrogens in adipose tissue may shed light on why autoimmunity is more common in females [120-122].

Despite considerable evidence from clinical studies supporting the connection between obesity and autoimmune diseases, there are notable limitations, including: (1) small patient sample sizes that reduce statistical significance; (2) the retrospective nature of studies, which limits the ability to establish causality; and (3) imprecise methods for measuring body fat [123-125].

In summary, obesity and autoimmune diseases are linked by a common inflammatory foundation, with increasing evidence pointing to their interaction from cellular mechanisms to clinical outcomes and potentially influencing treatment strategies.

## 5. ARISING AUTOIMMUNITY TRIGGERING MECHANISMS: YET TO BE PROVEN LINKS TO OBESITY

Numerous studies have identified previously unexplored mechanisms that trigger autoimmunity, which, while not directly studied in the context of obesity, have been independently associated with it. These mechanisms include: 1) persistent activation of platelets in obese women, 2) the movement of harmful gut bacteria outside the gut, and 3) changes in immune function due to aging. Below are some intriguing potential links between these mechanisms and obesity [126,127].

Research has found a connection between android obesity in women and both increased lipid peroxidation and ongoing platelet activation. Furthermore, recent findings suggest that platelet activation could play a significant role in the development of SLE [128].

Other studies have demonstrated that the movement of harmful gut bacteria from the gastrointestinal (GI) tract to other parts of the body can trigger autoimmunity in individuals who are genetically predisposed. Obesity can lead to an imbalance in gut bacteria, which in turn can increase the likelihood of these bacteria leaking into the body. Additionally, as people age, they not only face a higher risk of obesity and changes in immune function but also an increased risk of autoimmunity. Older individuals tend to have more active T cells and higher levels of DNA circulating in their bodies under normal conditions, which can activate immune sensors inside cells [129-131]. Specifically, the KU complex, which is usually

found in the nucleus, has been observed in the cytoplasm of aged human and mouse CD4+ cells, facilitating a DNA-sensing pathway that boosts T cell activation and the severity of EAE in older mice. With aging, immune cells function less effectively, leading to an accumulation of age-associated B cells (ABCs) in patients with autoimmune diseases, older mice, and mice prone to autoimmune conditions. The removal of the transcription factor T-bet from B cells in mice predisposed to autoimmune diseases prevented the development of such diseases. Although these findings are not directly related to obesity, they shed light on the processes behind age-related autoimmunity. Further research is necessary to fully understand the relationship between aging, obesity, and autoimmunity [132,133].

## CONCLUSION

In conclusion, the evidence linking obesity to the development and exacerbation of autoimmune diseases is becoming increasingly compelling. The interplay between excess adipose tissue and the immune system, primarily mediated through the release of adipokines and the recruitment of immune cells, underpins a chronic low-grade inflammatory state that fosters autoimmune dysfunction. Conditions such as multiple sclerosis, rheumatoid arthritis, and systemic lupus erythematosus exemplify the profound impact of obesity on immune-mediated pathologies, highlighting shared inflammatory mechanisms and genetic susceptibilities

While significant strides have been made in understanding these connections, several areas require further investigation to clarify the causal relationships and underlying biological mechanisms. Future research should focus on longitudinal studies with larger cohorts to better establish the order of events leading from obesity to autoimmunity. Additionally, exploring how lifestyle modifications, such as dietary interventions and physical activity, can mitigate the risk of developing autoimmune diseases in obese individuals remains a critical avenue for therapeutic development.

Ultimately, addressing obesity not only has the potential to improve metabolic health but also to reduce the burden of autoimmune diseases on individuals and healthcare systems. A multidisciplinary approach integrating immunology, nutrition, and metabolic research will be essential in uncovering novel strategies for prevention and treatment, fostering a healthier future for those at risk of or suffering from autoimmune conditions.

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