The Role of Obesity in Autoimmune Disease Development

Mohammad Adawi MD MHA[1,2], Amin Adawi MD[3], and Said Abozaid MD[4]

[1]Rheumatic Disease Unit, Sanz Medical Center–Laniado Hospital, Netanya, Israel
[2]Rheumatology Unit, Ariel University, Ariel, Israel
[3]Azrieli Faculty of Medicine, Bar-Ilan University, Safed, Israel
[4]Department of Pediatrics, Tzafon Medical Center, Lower Galilee, Israel

ABSTRACT Obesity is a growing global health concern, with its prevalence contributing to the rise of multiple chronic conditions, including autoimmune diseases. In this review I explore the intricate relationship between obesity and autoimmunity, focusing on how excess adiposity can affect immune responses and promote the development of autoimmune disorders. Obesity alters adipose tissue architecture, promoting chronic low-grade inflammation and triggering the release of pro-inflammatory cytokines, which contribute to immune system dysregulation. Adipose tissue is no longer seen as merely an energy store but as an active endocrine organ that interacts with the immune system. The review delves into mechanisms such as the role of adipokines, altered T cell function, and the recruitment of immune cells to inflamed adipose tissue, which together exacerbate autoimmune risk in obese individuals. Genetic and environmental factors also play a critical role in these processes, as polymorphisms and high-fat diets have been shown to influence both obesity and autoimmune susceptibility. Last, the review explores potential therapeutic strategies, such as lifestyle interventions and targeting obesity-driven inflammatory pathways, which could mitigate autoimmunity. Understanding the connection between obesity and autoimmunity offers insights into more effective interventions for patients suffering from these intertwined conditions.

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The substantial increase in the rate of obesity over the past three decades has had significant ramifications for public health. It has led to a notable upsurge in obesity-related diseases. While obesity primarily affects the adipose tissue and metabolic pathways, it is important to recognize that the skin, as the largest organ in the human body, can also be impacted by this condition. Inflammatory changes associated with obesity within the skin are particularly intriguing as they disrupt the delicate balance within the immune system. This altered immune response within the skin can have far-reaching consequences on its overall function and health [1].

The skin is a remarkable organ, characterized by its robustness and ability to adapt to various environmental factors. It houses metabolically active tissues, structural proteins, and an intricate immune system. Yet, there remain numerous enigmatic aspects of the interplay between obesity and the skin. Exploring the differentiation of skin immune cells, the factors that attract these cells to specific areas of the skin, and the timing of immune responses in the context of obesity poses significant challenges [2].

In addition, the occurrence of obesity in individuals has a profound impact on the release and distribution of free fatty acids throughout the body, including the skin. Technological advancements have paved the way for a more comprehensive understanding of individual fatty acid composition, which can have implications for skin integrity and function. By elucidating the intricate relationships between obesity, energy metabolism, and immune cell distribution and activation, we can begin to speculate on potential effects of obesity on the skin, specifically pertaining to inflammation, fatty acid deposition, and composition [3].

Thus, these obesity-related effects can have profound implications for skin function not only within the context of obesity but also in broader settings. Understanding how obesity influences the skin's ability to respond to infections and other external stimuli is of paramount importance for preventive healthcare strategies. By expanding our knowledge in these areas, we can uncover novel therapeutic targets and interventions to mitigate the adverse effects of obesity on the skin and promote overall well-being. With further research, we can explore the

intricate mechanisms through which obesity affects the skin and pave the way for innovative approaches in treating and managing obesity-related skin conditions [4].

One area of interest lies in unraveling the complex interactions between obesity and the immune system within the skin. The immune response in obese individuals may differ from those who are not obese, leading to altered inflammatory processes that contribute to skin disorders. Understanding the factors that drive the differentiation and activation of immune cells within the skin can provide valuable insights into the pathogenesis of obesity-related skin conditions and guide the development of targeted therapies [5].

OBESITY TRIGGERS CHRONIC LOW-GRADE INFLAMMATION, WHICH DISRUPTS NORMAL IMMUNE FUNCTION, INCREASING THE RISK OF AUTOIMMUNE DISEASES BY ALTERING IMMUNE CELL BEHAVIOR AND PROMOTING INFLAMMATORY RESPONSES IN ADIPOSE TISSUE.

Another intriguing aspect is the role of fatty acids in skin health and integrity. Obesity alters the distribution of free fatty acids throughout the body, affecting their availability within the skin. Changes in fatty acid composition can affect the skin's barrier function and overall lipid metabolism. By delving into the specific fatty acid profiles associated with obesity, we can gain a deeper understanding of how these alterations contribute to skin dysfunction and explore potential interventions to restore skin health [6].

Furthermore, the impact of obesity on the skin extends beyond localized effects. Systemic changes induced by obesity, such as insulin resistance and chronic inflammation, can have systemic consequences that are reflected in the skin. These include impaired wound healing, increased susceptibility to infections, and compromised immune responses. It is crucial to examine the broader implications of obesity on the skin and identify strategies to mitigate these systemic effects for improved overall well-being.

Two articles discuss the association between systemic lupus erythematosus (SLE), smoking, and obesity. In the first, Versini and colleagues [7] identified smoking as a significant independent risk factor for SLE but found no correlation between obesity and SLE occurrence. The study emphasized the importance of addressing smoking in SLE management while suggesting further research into its pathogenic role. In the second, Versini and co-authors [8] identified the significant role of obesity in autoimmune diseases, identifying obesity as a major environmental factor that exacerbates these conditions. The article highlights how adipokines (leptin, adiponectin, resistin, visfatin) secreted by adipose tissue influence immune responses, contributing to both the onset and progression of autoimmune diseases like rheumatoid arthritis, lupus, and multiple sclerosis. Furthermore, obesity worsens disease severity and treatment response in autoimmune conditions, underscoring the importance of addressing obesity in patient management [9].

In summary, the intricate relationship between obesity and the skin presents a vast frontier for exploration. By expanding our knowledge of the underlying mechanisms, we can gain insights into the impact of obesity on skin function and design targeted interventions to improve skin health in the context of obesity. This research holds great potential not only for individuals affected by obesity but also for preventive healthcare strategies and the development of novel therapeutic approaches. Through continued investigation, we can unlock the secrets of obesity's influence on the skin and pave the way for a healthier future [10].

Definition and prevalence of obesity and autoimmunity

Obesity is the status of gaining excessive body fat in the modern world due to easy access to fast foods or lack of exercise. Overweight and obesity lead to major non-communicable diseases, especially cardiovascular diseases, diabetes, musculoskeletal disorders, and some cancers.

Autoimmunity indicates a failure of the immune system to yield self-tolerance, thereby causing the removal of its own tissue. When autoimmunity prevails, immune responses are produced against self-proteins, self-cells, or self-tissues. Autoimmune diseases affect over 4% of the general population. It is suggested that unbalanced nutrition, such as high-fat diets, can prompt more severe autoimmune diseases. It is now becoming increasingly recognized that those with obesity have a higher prevalence of autoimmune diseases. The increased adiposity encourages autoimmune risk factors, including complex dynamic processes that may or may not be the consequence of obesity. These aspects are due to fat metabolism quality and the distribution of adipose tissue macrophages, which produce adipose tissue inflammation and antibodies that provoke the immune system [10].

THE IMPACT OF OBESITY ON AUTOIMMUNITY

Obesity is increasingly recognized as a risk factor for numerous autoimmune diseases. Emerging evidence suggests that obesity influences autoimmunity through mechanisms including adipocyte hypertrophy and adipose tissue architecture, altered levels of cytokines and adipokines, increased T cell accumulation, and fewer adipose regulatory

T cells. Although each cell subset has different effects on autoimmunity, most T cell subsets have common defects including increased cell death, impaired suppressive function, and decreased expression of suppressive molecules, suggesting they have shared underlying dysfunction [11].

A number of potential therapeutic strategies are discussed that target obesity-induced signals to control aberrant immunity in autoimmune diseases. Thus, obesity should be considered a modifiable risk factor for the pathogenesis of chronic autoimmune diseases. Therapies targeting obesity by an intended weight-loss treatment or specifically targeting obesity-induced disruption signals may present new approaches to mitigate autoimmunity in the diseases in which the efficacy of current interventions is suboptimal [12].

FAR FROM BEING JUST A FAT STORE, ADIPOSE TISSUE ACTIVELY INTERACTS WITH THE IMMUNE SYSTEM, RELEASING ADIPOKINES AND OTHER SIGNALS THAT INFLUENCE IMMUNE CELL RECRUITMENT AND FUNCTION, FURTHER EXACERBATING AUTOIMMUNE RISKS IN INDIVIDUALS WITH OBESITY.

Influence of adipose tissue on immune response

Adipose tissue, or fat, has functions that go beyond energy storage. One is to serve as a physical support for the proliferation and activation of different immune system cells, like lymphocytes and cytokine-producing cells. Therefore, excess adipose tissue increases the levels of pro-inflammatory cytokines released in the organism and the immune cell infiltration. Recent data show that subsets of T cells and macrophages related to obesity originate inside the adipose tissue and have their activity influenced by the new molecules released by adipocytes, which can be an important factor in the occurrence of obesity-related metabolic and autoimmune diseases. Molecules released by the immune cells located inside the adipose tissue can also alter the differentiation of stem cells located close to them. This influence can be observed in children and young adults, affecting the development and expansion of different cell lineages and their eventual connection with other areas of the organism. The relationships between adipose tissue, inflammation, and the immune system need to be deeply understood to help expand our comprehension of the relationship between metabolic and inflammatory diseases like obesity and autoimmune diseases that develop when immune cells are inappropriately activated [13].

THE ROLE OF INFLAMMATION IN OBESITY-RELATED AUTOIMMUNITY

Both obesity and autoimmunity are considered inflammatory diseases. Because T cells are involved in both, obesity-associated adipose tissue-specific antigens have been thought to cause autoimmune diseases. Researchers have demonstrated that dominant negative T cell receptor transgenic mice, which have diminished T suppressive effects, developed obesity-related autoimmune diseases and that the lifespan of obese mice was increased when T cell frequency was reduced by DN-TcR introduction. In obese patients, a high number of autoantibodies are observed along with obesity-related inflammation. Autoantibodies under obese inflammation are produced not only by autoantibodies themselves but also by regulatory B cells and T follicular helper cells. Regulatory B cells work with suppressive cytokines and relevant cellular loss molecules to produce a high number of autoantibodies. Like clinical obese patients, obesity-induced CV systolic pressure over 150 mmHg in mice with a supplement of aquaporin-4 or S100B, and these T cells expressed the gut-associated chemokine adhesion molecule and co-stimulatory molecules. The high-risk T cells were recruited to the meninges, activated autoreactive T and B cells, and increased sympathetic innervation with hepatic steatosis. These obesity-increased brain sympathetic innervated hepatic effects were inhibited by gut-targeted T cell depletion. Obese inflammatory T cells are correlated with the development and progression of neuroinflammation and promote systemic diseases [14].

Chronic low-grade inflammation in obesity

Chronic low-grade inflammation is currently considered a critical condition in obesity, and it is associated with high expression levels of inflammatory mediators such as interleukin (IL)-1, IL-6, and tumor necrosis factor alpha as well as down-regulation of adiponectin. In the past, adipose tissue was thought to be just an energy-storing organ, but recently, it has been recognized as an active player in the endocrine system, as well as an immune and inflammation organ. Overweight and obese patients exhibit an increased level of macrophages in adipose tissue, which is very closely associated with the inflammatory state. IL-1 serves as an initiator and helper of inflammation. IL-6 has been widely studied in the context of obesity, insulin resistance, and obesity-related adipose tissue inflammation [15].

IL-6 may play divergent roles in the occurrence and development of obesity and obesity-related metabolic disorders. It has been verified that adipose tissue IL-6

production, which is tightly linked to white adipose tissue inflammation, peaks in obese humans. However, adipose-specific IL-6 knockout mice are only obese, without noticeable pathological changes. These mice have higher insulin and leptin levels compared with their wild-type littermates. They are protected from obesity-related moderately impaired glucose tolerance and peripheral insulin sensitivity but do not show adipose tissue inflammation. In contrast to IL-6 knockout mice, evidence from activation or local administration studies strongly supports a favorable role of IL-6 on adipose tissue insulin sensitivity and lipid metabolism [16].

GENETIC AND ENVIRONMENTAL FACTORS IN OBESITY-RELATED AUTOIMMUNITY

Obesity influences autoimmunity mainly by inducing chronic low-grade inflammation. Several studies have suggested that increased fat mass and obesity-associated factors, such as adipokines, free fatty acids, and gut microbiota, promote the breakdown of immune tolerance, activation of autoreactive T and B cells, and the development of chronic inflammatory conditions, which may eventually lead to the development of autoimmunity. Genetic and environmental factors responsible for increased obesity risk have also been linked to a higher risk for autoimmunity development. Some studies identified gene polymorphisms associated with both obesity and different autoimmune diseases. Individuals at the beginning of the subsequent autoimmune process have some shared common pathogenic pathways, but not all molecular circuits are balanced in the same way and with the same relevance for all autoimmune diseases [17].

ADDRESSING OBESITY THROUGH LIFESTYLE INTERVENTIONS AND TARGETING OBESITY-RELATED INFLAMMATORY PATHWAYS MAY HELP REDUCE THE INCIDENCE AND SEVERITY OF AUTOIMMUNE DISEASES, OFFERING A PROMISING APPROACH TO TREATMENT AND PREVENTION.

Many of the obesity-associated characterizations, such as modifying adipokine levels and activation of innate immune cells in adipose tissue, change in T and B lymphocyte gene regulation and require the understanding of how these mechanisms are able to prime the immune system to unleash an autoimmune process. The obesity-dependent increase in inflammation and changes in the gut microbiota can even individually or synergistically induce systemic changes that favor the depauperation of oral and lung immune tolerance, and their commensal microflora promotes the development of autoimmune inflammation not only in the intestine but also in systemic organs and tissue sites, revealing the complex interdependent relationship between nutrients and the immune system. However, many uncertainties remain, and much research is ongoing to understand obesity-promoted autoimmune activation to use these insights in the future in the prevention and treatment of autoimmune diseases [18].

GENETIC SUSCEPTIBILITY AND GENE-ENVIRONMENT INTERACTIONS

Many common complex diseases, such as autoimmunity and obesity, have both genetic and environmental causes. Genes contributing to a low-penetrance predisposition for most complex phenotypes have been linked to a few true monogenic syndromes. Candidate genes often relate to various immune systems and can highlight some similarities in several traits found in autoimmunity and obesity, which include the health and functionality of fat deposits. Several of the proposed genes control the balance between T helper effector cells, T regulatory cells, and macrophages. Genes that have a specific contribution to obesity mostly concern the development of the central nervous system, the behavior of an individual, and the release of various neurotransmitters. Genes may control or lead to defects in glucose or lipid metabolism. In addition, genes that are responsible for the leptin-melanocortin pathway and determine the structural and functional properties of white adipose cells have also been linked to obesity [19].

The genetics of obesity and of autoimmunity are presently mapped to many of the same regions of the human genome. Overlap in the genes causing the different diseases is suggested by several polymorphic genetic systems in concordance signals that are observed in multiple autoimmune diseases and in the body weight distribution of human and preclinical obesity models. To date, most genomic data are derived from heterogeneous populations that are typically examined in the context of genetic studies in obesity. However, at the 40 loci, common genetic variants that influence the predisposition to develop the following phenotypes are recognized: a blood lipid profile, glucose and insulin concentrations, fat distribution, and energy expenditure components. Most of the responsible genes belong to the central nervous system and immune regulatory systems. When a small group of obesity candidate variants is re-evaluated in multiple autoimmune diseases, significant segregations remain restricted to the main traits. This result suggests that many of our categories may require further revision. Some

support angles are given by existing homologies between obesity and systemic autoimmunity [20].

POTENTIAL THERAPEUTIC STRATEGIES

A constantly growing body of evidence supports and strengthens the reciprocal relationship between obesity and the immune system. The adipose tissue has become a well-recognized secretory organ that secretes a plethora of pleiotropic adipocytokines with pivotal roles in obesity-associated low-grade chronic inflammation. Although the link between the adipose tissue–immunity relationship and autoimmunity has not yet been directly proven. The development of potential therapeutic strategies focusing on obesity and its related immune system dysfunctions that might also slow down the acceleration of any hypertension-related autoimmune disorders is important. Several popular cardio-protective drugs have shown anti-inflammatory and immunosuppressive effects, while some of them are able to prevent obesogenic effects too. Therefore, the direct treatment with cardio-protective molecules already used in clinical practice might represent a more successful strategy to solve complex, chronic, lifestyle-related diseases compared to laboriously individual, disease-based multitargeting. Last, strategies exploiting the gastrointestinal tract leading to energy harvesting manipulation, inflammation, or satiety can be developed and involve dietary modifications, prebiotic or probiotic applications, or fecal microbiota transplantation [21].

Lifestyle interventions and weight management

Lifestyle interventions that consist of dietary changes combined with physical activity are of great importance in the long-term treatment of obesity. Recommended dietary advice involves a modest reduction of dietary fat and a vast increase in the consumption of carbohydrates, especially whole grain, fiber-rich carbohydrates, vegetables, and fruits, all of which are important for lowering the total energy intake. Weight maintenance is necessary for those who have lost weight. Physical activity regulation is a major part of successful weight maintenance, revealing beneficial effects on body weight, abdominal obesity, physical fitness, lipid profile, glucose regulation, and disease risk. Moderate caloric restriction, which leads to a 5–12% weight loss, constitutes an effective tool to ameliorate obesity and age-related immune dysfunction; however, not only weight reduction, but also weight loss maintenance is an important key factor in the amelioration of obesity and its consequences. It is also very important to remember that total energy density is less important than energy balance for immune function because prolonged fasting, heavy exercise, as well as overeating can impair immune function, independent of body composition or specific nutrients. This finding suggests caution in the promotion of severe dieting in obesity and rigorous resistance to the idea of organ-specific foods since all components of the diet seem able to modulate the immune response. Furthermore, the overall metabolic state of the individual is instrumental in determining immune responsiveness. It is also important to recognize that the consequences of obesity may vary from individual to individual, and customized treatments for each patient must be considered first in therapy [22].

Correspondence

Dr. M. Adawi
Rheumatic Disease Unit, Sanz Medical Center–Laniado Hospital, Netanya 42150, Israel
Email: adawimo1802@gmail.com

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Capsule

Evaluating the risk of digestive system cancer in autoimmune disease patients

There is emerging evidence that certain autoimmune diseases can modulate the risk for digestive system cancer. However, limitations of non-experimental studies may lead to diverging results. **Reizner** and colleagues evaluated the available evidence and provided bias-minimized estimates for the associations between celiac disease (CD), systemic lupus erythematosus (SLE), multiple sclerosis (MS), and type 1 diabetes (T1D) and different digestive system cancers. This study included 237 estimates from 47 studies covering over 1.5 million cases of any ethnicity. CD, SLE, and T1D were positively associated with pancreatic, esophageal, colon, liver, and hepatobiliary cancers. In addition, T1D was positively associated with stomach and colorectal cancers. The strongest bias-corrected association was found between CD and small intestine cancer (relative risk = 4.19; 95% confidence interval 2.71–6.50). MS was inversely associated with pancreatic, esophageal, rectal, and colorectal cancer. This study provides new insights into the evidence for digestive system cancer risk related to autoimmune diseases by adjusting for multiple sources of bias. As a next step, potential mechanisms responsible for the different associations should be investigated.

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Eitan Israeli

Capsule

Synovial fluid as a complex molecular pool contributing to knee osteoarthritis

During knee osteoarthritis (KOA), synovial fluid becomes modified with drivers of disease that contribute to symptoms (pain) and joint-related pathology. Acting as a sink of factors from both systemic circulation and local tissues, including articular cartilage, subchondral bone, synovium, and the infrapatellar fat pad, the synovial fluid enables bidirectional communication promoting KOA pathogenesis. Synovial fluid constituents might also be detected in circulation, functioning not only as accessible biomarkers but also as potential mediators of KOA-driven systemic effects. Factors deposited in synovial fluid can affect nervous system activity, acting at the neuronal projections that are integrated into joint tissues from dorsal root ganglia. Non-coding RNAs (microRNAs, long non-coding RNAs, circular RNAs), metabolites, cytokines, and other secreted proteins of the synovial fluid in KOA have emerged as biomarkers of disease progression, therapeutic efficacy, and pain. These molecules might also function as molecular mediators of KOA, supporting them as candidates for therapeutic intervention. This review by **Peters** and colleagues consolidates literature published primarily within the past 4 years, focusing on factors identified within synovial fluid as biomarkers and molecular mediators of KOA symptoms and pathology.

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