Chapter 35

Obesity in Autoimmune Diseases: Not a Passive Bystander

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INTRODUCTION

For several decades, industrialized countries face an increased prevalence of immune-mediated diseases [1,2]. Most of these inflammatory conditions result from a complex interaction between genetic background and multiple environmental factors [3–8]. Because genetic basis has remained constant over time, there is increasing recognition that environmental factors, especially the Western lifestyle, have a preponderant role in this growing prevalence [9]. Westernization is accompanied by profound changes in dietary habits, promoting high-fat, high-sugar, and high-salt foods [10] with excess calorie intake, leading to obesity outbreak over the past 20 years [11,12]. Therefore, the links between obesity and autoimmunity were questioned and the involvement of obesity in the rise of autoimmune conditions was strongly suggested. This link became even more fascinating in recent years since the discovery of the remarkable properties of adipose tissue. Indeed, the white adipose tissue (WAT), long regarded as an inert energy storage tissue, has been recognized to be an essential endocrine organ, secreting a wide variety of soluble mediators termed "adipokines" or "adipocytokines" [13]. Initially identified for their metabolic and appetite regulation activities, adipokines are known to be involved in various processes including immunity and inflammation [14]. By their proinflammatory action, these molecules contribute to the so-called "low-grade inflammatory state" in obese subjects, resulting in a cluster of comorbidities such as metabolic syndrome, diabetes, or cardiovascular complications [13]. On this basis, it is now of major interest to clarify the relationship between obesity and autoimmune/inflammatory diseases. In this review, following a short overview of the main mechanisms highlighted so far to link obesity and autoimmunity, we will detail metabolic and immunological activities of the main adipokines. Then, we shall focus on obesity and more precisely adipokines involvement in the development and prognosis of several immune-mediated conditions.

CONNECTING OBESITY AND AUTOIMMUNITY

Obesity corresponds to an abnormal accumulation of adipose tissue within the body. According to World Health Organization (WHO), approximately 35% of the world population is estimated to be overweight (body mass index, BMI 25–30 kg/m^2) or obese (BMI > 30 kg/m^2) [12]. As mentioned above, it is widely known that obese persons exhibit a subclinical chronic state of inflammation leading to multiple metabolic disorders [13]. Moreover, as will be discussed further below, a large number of studies found a significant correlation between obesity and a higher prevalence or a worse prognosis of many immune-mediated conditions. Therefore, understanding the underlying immune disorders in obesity, which promote inflammatory autoimmune diseases, is a major topic of research. Thus, to date, several mechanisms have been postulated. These mechanisms are schematically illustrated in Fig. 35.1.

First, numerous studies have documented the properties of WAT as a crucial site in the generation of soluble mediators named "adipokines," most of which carry a proinflammatory activity. These include classical cytokines such as interleukin (IL)-6 and tumor necrosis factor alpha (TNFα) and specific molecules such as leptin and adiponectin [13]. These mediators are secreted by adipocytes and by a diverse set of immune cells found to abundantly infiltrate adipose tissue under obese conditions [15,16]. As will be discussed later in this review, adipokines appear to be key players in the interactions between adipose tissue and the immune system.

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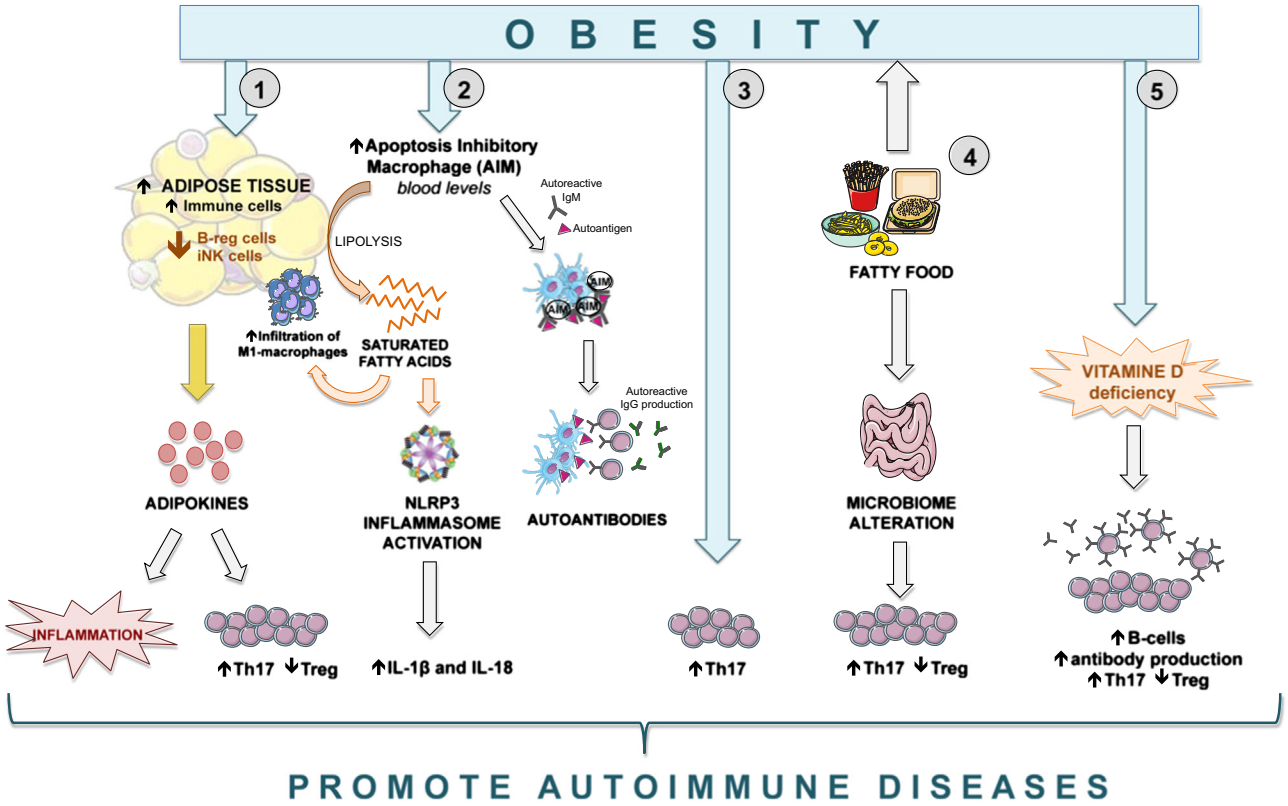

FIGURE 35.1 Representation of the main mechanisms suggested to promote autoimmune diseases in obesity. (1) In obesity, fat mass increases. Both adipocytes and immune cells massively infiltrating adipose tissue secrete high levels of adipokines, responsible for a proinflammatory state and deregulation of Th17/Treg balance. Furthermore, obesity is associated with lower B regulatory and iNK cells within the adipose tissue. (2) AIM blood levels increase under obese conditions. First, AIM induces lipolysis, thereby producing saturated fatty acids. The latter will in turn act on adipose tissue by promoting proinflammatory M1-macrophage infiltration; moreover, saturated fatty acids can activate the NLRP3-inflammasome, which secretes IL-1β and IL-18, both being involved in the pathogenesis of autoimmune diseases. Second, AIM forms immune complexes with natural autoreactive IgM associated with autoantigens, promoting their retention on follicular dendritic cells. Subsequent autoantigens presentation to follicular B cells leads to the production of IgG autoantibodies. (3) Obesity has been found to promote a Th17 profile, a subset implicated in the pathogenesis of immune-mediated conditions. (4) The Western diet, partially responsible for obesity, may also cause dysbiosis, an alteration of gut microbiota, resulting in a modulation of extraintestinal immune responses and subsequent deregulation of the Th17/Treg balance. (5) Obese subjects exhibit a higher prevalence of vitamin D deficiency. Lower vitamin D levels have been associated with increased Th17 cells, B cells, and secretion of antibodies as well as reduced Treg cells. *AIM*, apoptosis inhibitor of macrophage; *Breg cells*, B regulatory cells; *iNK cells*, invariant natural killer T cells; *IL*, interleukin; *NLRP3-inflammasome*, NOD-like receptor protein 3 inflammasome; *Th17*, T helper 17 cells; *Treg*, regulatory T cells.

Recently, several authors have also highlighted the role of the apoptosis inhibitor of macrophage (AIM) in the pathogenesis of obesity-associated autoimmune diseases [17,18]. AIM is produced by tissue macrophages and was initially found to promote the survival of macrophages against various apoptosis-inducing stimuli [19]. Briefly, it was demonstrated that lipolysis induced by increased blood AIM under obese conditions releases large amounts of saturated fatty acids from adipocytes. The latter stimulate chemokine production in adipocytes via TLR4 activation, which results in increased M1-macrophage infiltration in adipose tissue. Moreover, AIM forms immune complexes with natural autoreactive IgM associated with autoantigens. Thus, AIM promotes their retention on follicular dendritic cells and autoantigens presentation to follicular B lymphocytes, leading to production of IgG autoantibodies.

The T helper 17 cells (Th17) are a recently discovered subset of CD4 effector T lymphocytes. Th17 cells secrete IL-17 and are now recognized for their involvement in the pathogenesis of autoimmune diseases [20]. Recently it has been reported that obesity may predispose induction of Th17 cells, at least in part in an IL-6-dependent process, which exacerbates autoinflammatory diseases such as multiple sclerosis and colitis in several mouse models [21]. Paradoxically, IL-17 has also been shown to inhibit adipogenesis [22,23]. The precise role of Th17 cells and IL-17 in obesity-associated inflammatory conditions needs to be clarified.

Another exciting field of investigation is the contribution of nutrients, especially the influence of a high-salt, high-fat diet on immune-mediated conditions [10,24]. Indeed, recent studies suggest that Western diet may cause dysbiosis, an alteration

of intestinal microbiome. This modification induces profound modulation of extraintestinal immune responses, including Th17/T regulatory cells (Treg) imbalance [25]. However, it is not yet clear if dysbiosis contributes to or is a consequence of autoimmune diseases. In the same area, another possibility involves the higher prevalence of vitamin D deficiency among obese subjects [26]. Vitamin D regulates many processes, including immune response. Thus, it has been shown to increase Treg cells and inhibits Th1 and Th17 differentiation [27]. Hence, some studies report an association between vitamin D deficiency and the development of autoimmune diseases, although these observations are still controversial [28,29].

Some areas still require further investigations. It has been demonstrated that the NLRP3 (NOD-like receptor protein 3) inflammasome, a highly regulated protein complex involved via its secretion of IL-1β and IL-18 in the pathogenesis of many autoimmune diseases, can be activated in macrophages by numerous factors associated with obesity, including ceramides, saturated fatty acids, and reactive oxygen species [30]. Additionally, Nishimura et al. [31] recently showed that B regulatory lymphocytes, a subset of B lymphocytes known to hamper inflammation by their secretion of IL-10 and TGF-β, are constitutively present in the adipose tissue. B regulatory cells and subsequent antiinflammatory cytokines are progressively diminished in obese adipose tissue, promoting the development of inflammation. Likewise, the role of invariant natural killer T cells (iNK cells) also remains unclear. iNK cells are a subset of natural killer (NK) cells abundantly present in adipose tissue (10%–20% of resident T lymphocytes). They seem to contribute to the maintenance of adipose tissue homeostasis, and their number decreases significantly in obese patients [32].

Although these mechanisms require further investigations to be specified, one of the most documented areas to date is the role of adipokines in the pathophysiology of obesity-associated immune-mediated diseases. WAT has been found to produce more than 50 adipokines. Herein, we will consider four of those—leptin, adiponectin, resistin, and visfatin—whose involvement in autoimmune and inflammatory conditions has been reported. The main metabolic, vascular, and immunological effects of these four adipokines are summarized in Table 35.1 and Fig. 35.2.

ADIPOKINES: METABOLIC AND IMMUNOLOGICAL PROPERTIES

Leptin

Leptin [33–37] (from the Greek word leptos = thin) was the first adipokine identified in 1994 by positional cloning of a single gene mutation in the *ob/ob* mouse. It is a 16 kDa nonglycosylated polypeptide hormone, classified as a member of the long-chain helical cytokine family, such as IL-6, IL-11, IL-12, and leukemia inhibitory factor. It is encoded by the obese (*ob*) gene, which is the murine homolog of human Lep gene. Leptin exerts its biological actions through the activation of its OB-Rb long-isoform receptor, encoded by the diabetes (*db*) gene. OB-Rb receptors are expressed in different tissues including the central nervous and the cardiovascular systems, as well as in immune system cells. Leptin is predominantly produced by WAT, and circulating levels of leptin directly correlate with the body adipose mass and adipocyte size. Starvation and hormones such as testosterone and glucocorticoids inhibit its synthesis. It is upregulated by inflammatory mediators (TNFα, IL-1β) insulin and ovarian sex steroids, the latter likely explaining the higher levels of leptin found in women.

Leptin is a major regulator of body weight by promoting satiety and stimulating energy expenditure. It acts on specific hypothalamic nuclei, inducing anorexigenic factors and suppressing orexigenic neuropeptides. Leptin has antidiabetic effects and inhibits hepatic lipogenesis. Either *ob*- or *db*-deficient mice develops severe obese phenotype. This is due to the lack of perception of satiety, together with deregulation of glucose and lipid metabolisms. In addition to its metabolic effects, leptin exerts pleiotropic actions on physiological functions, including fertility, bone metabolism, angiogenesis, inflammation, and immunity.

Leptin is a potent modulator of immune responses. Thus, congenital leptin-deficient patients have a higher incidence of infection-related death because of dysfunctional immune response. Similarly, starvation causes a dramatic decrease in leptin levels, causing immunosuppression. In both cases, the effects can be reversed by leptin replacement therapy. Leptin affects both innate and acquired immunity. In innate immunity, leptin activates proliferation of monocytes, enhances macrophages phagocytosis activity, and induces them to produce leukotriene B4, eicosanoids, and proinflammatory cytokines such as TNFα, IL-6, and IL-12. In neutrophils, it increases chemotaxis and release of oxygen radicals. It promotes proliferation, differentiation, activation, and cytotoxicity of NK cells. Finally, leptin is involved in dendritic cell maturation and survival by activating signaling pathways such as Akt and nuclear factor kappa beta. Leptin is also an important regulator of the acquired response. Indeed, leptin-deficient mice have defective cellular immunity and exhibit thymic and lymphoid atrophy. These effects are reversed by exogenous leptin administration. Leptin stimulates proliferation of naive T cells and promotes memory T cells differentiation toward Th1, producing proinflammatory cytokines such as interferon gamma (IFN-γ) and IL-2 and suppressing the production of the Th2 cytokines IL-4 and IL-10. Furthermore, it inhibits

TABLE 35.1 Major Metabolic, Vascular, and Immune Actions of Adipokines

	Metabolic Effects	Vascular Effects	Innate Immune System Effects	Acquired Immune System Effects
Leptin ↑ in obesity	Anorexigen ↑Resting energy expenditure (REE) Antidiabetic effect ↑Lipolytic activity Hepatic ↓lipogenesis	Proatherogenic: Causes endothelial dysfunction ↑Platelets aggregation	Proinflammatory: Monocytes: ↑ proliferation, ↑ production of IL-1 RA, ↑ CD25, CD71 Macrophages: ↑phagocytosis, ↑ production of IL-6, IL-12, LTB4, NO, eicosanoids, COX2 PMNLs: ↑ chemotaxis, ↑ release of oxygen radicals NK cells: ↑ differentiation ↑ proliferation, activation ↑cytotoxicity, survival Dendritic cells: ↑ maturation, ↑ production of IL-1, IL-6, IL-12, TNF_{α}, ↑survival	Proinflammatory: T cells: ↑ thymocytes maturation, ↑ naive T cells proliferation and activation, ↑ differentiation of memory T cells toward Th1 phenotype ↑ production of IFN-γ, IL-2, ↓ production of IL-4, IL-10 ↓T cells apoptosis B cells: ↑ lymphopoiesis, ↓ IgG2-switch Treg cells, ↓ proliferation, ↑ anergy
Adiponectin ↓ in obesity	↑Appetite ↑Insulin sensitivity, ↑insulin gene expression, ↑ glucose uptake in adipose tissue and skeletal muscle, ↓hepatic glycogenesis ↑Free-fatty acid oxidation in liver and skeletal muscle	Antiatherogenic: ↓Endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin) ↓Macrophage transformation into foam cells	Antiinflammatory: Monocytes: ↓ Secretion of TNFα, IFN-γ IL-6 and ↑IL-10, IL-1 RA Macrophages: ↓ maturation, proliferation, phagocytosis activity, if ↑ phagocytosis of apoptotic cells,↓ production of TNFα, IFN-γ, ↑ M2-profile NK cells: ↓ cytotoxicity Dendritic cells: ↑ maturation, activation	Antiinflammatory: T cells: ↓ activation ↓ proliferation B cells: ↓lymphopoiesis Treg cells: ↑ proliferation Proinflammatory effects suspected in autoimmune diseases
Resistin ↑ in obesity	Anorexigen ↑Insulin resistance ↑Free-fatty release from adipose tissue	Proatherogenic: ↑Endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin)	Proinflammatory: Monocytes: ↑ production of 1L1β, IL-6, IL-12, TNFα Macrophages: ↑ production of IL-12, TNFα	Proinflammatory: Lymphocytes: ↑ production of IL-1β, IL-6, IL-12, TNFα
Visfatin ↑ in obesity	Insulin-like effects suggested	Proatherogenic: ↑Endothelial adhesion molecules (ICAM-1, VCAM-1, E-selectin) ↑Atherosclerotic plaque instability	Proinflammatory: Monocytes: ↑ chemotaxis, ↑ activation, ↑ production of IL-1β, IL-6, IL-12, TNFα PMNLs: ↓ apoptosis	Proinflammatory: Lymphocytes: ↑ maturation, ↑ activation, ↑ production of IL-1β, IL-6, IL-12, TNFα

COX2, cyclooxygenase-2; *ICAM-1*, intercellular adhesion molecule-1; *IL*, interleukin; *IL-1 RA*, interleukin-1 receptor antagonist; *LTB4*, leukotriene B4; *NK cells*, natural killer cells; *PMNL*, polymorphonuclear leukocytes; *Treg cells*, regulatory T cells; *VCAM-1*, vascular cell adhesion molecule-1.

the proliferation of Treg cells, known as critical mediators of immune tolerance. In summary, leptin modulates immune response toward a proinflammatory profile, being critical in infection control. As it is at the crossroad between inflammation and autoimmunity, upsetting the balance may result in immunosuppressed condition or conversely proinflammatory state facilitating the development of autoimmune diseases.

Adiponectin

Adiponectin [33,35–38] was independently characterized by four research groups as a 244-amino acid protein with various names: Acrp30 (adipocyte complement-related protein of 30 kDa), apM1 (adipose most abundant gene transcript 1), adipoQ, or GBP28 (gelatin-binding protein of 28 kDa). The human adiponectin gene is located on 3q27 chromosome. It structurally belongs to the collagen superfamily, sharing homologies with collagens VIII and X and complement factor C1q. The primary structure of adiponectin contains an N-terminal signal sequence, a variable domain, a collagen-like domain, and a C-terminal domain, known as globular adiponectin. The monomeric 30 kDa form of adiponectin seems to be confined to the adipocyte, whereas oligomeric complexes circulate in plasma as low-, middle-, and high molecular weight multimers. Adiponectin can also be found in the plasma as a 16 kDa proteolytic globular form.

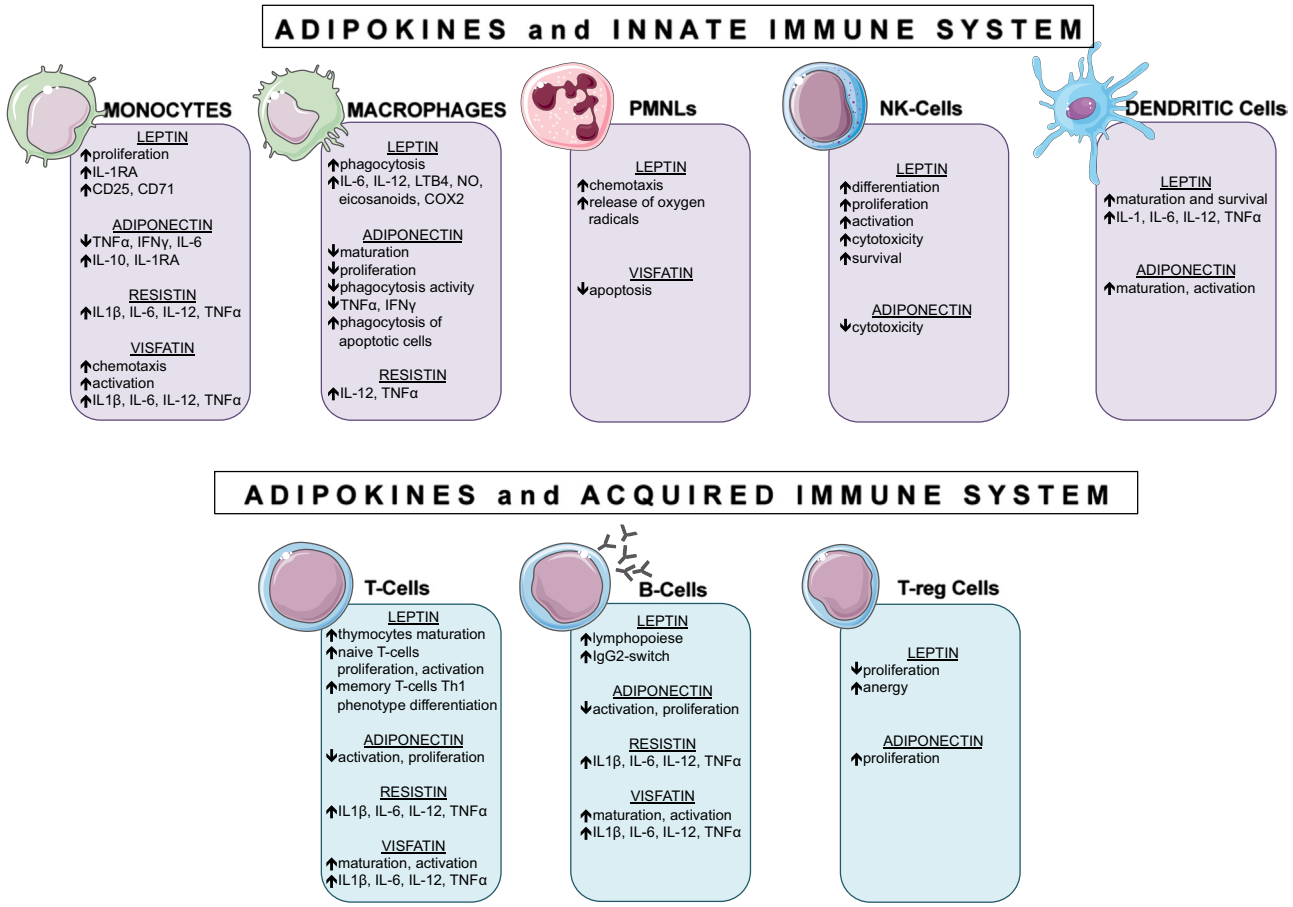

FIGURE 35.2 Main effects of leptin, adiponectin, resistin, and visfatin on cells of the innate and acquired immunity. *COX2*, cyclooxygenase-2; *IL*, interleukin; *IL-1 RA*, interleukin-1 receptor antagonist; *LTB4*, leukotriene B4; *NK cells*, natural killer cells; *PMNLs*, polymorphonuclear leukocytes; *Treg cells*, regulatory T cells.

Three receptors mediate adiponectin signaling: AdipoR1, found predominantly in skeletal muscle; AdipoR2, expressed more abundantly in the liver; and T-cadherin, mainly expressed in the cardiovascular system. It is important to note that adiponectin isoforms differ in their biological function, possibly depending on tissue and receptor subtype. Adiponectin is mainly secreted by WAT. Of all adipokines, it has the highest serum levels, ranging from 0.5 to 30 mg/mL in human, which accounts for about 0.01% of all plasma proteins in humans [39]. Unlike most adipokines, plasma levels of adiponectin are decreased in obese individuals and increase with weight loss. Adiponectin exerts important effects on metabolic modulation and energy homeostasis. Adiponectin is, together with leptin, an insulin-sensitizing adipokine. Besides enhancing insulin sensitivity, it decreases hepatic glycogenesis and promotes insulin gene expression and glucose uptake in skeletal muscle and in adipose tissue. Furthermore, adiponectin increases free fatty acid oxidation in the liver and in the skeletal muscle.

While leptin has proinflammatory activity, adiponectin has been consistently shown to be an antiinflammatory adipokine, especially with regard to protective effects on the vascular wall. Indeed, adiponectin acts on endothelial cells by inhibiting the expression of TNFα-induced adhesion molecules, such as vascular cell adhesion molecule-1, endothelial–leukocyte adhesion molecule-1, and intracellular adhesion molecule-1. It results in reduced monocyte adhesion to endothelial cells. Furthermore, adiponectin can modulate transformation of macrophages into foam cells. Thus, low circulating adiponectin levels are closely associated with obesity-linked metabolic and cardiovascular disorders, including insulin resistance, type 2 diabetes, hypertension, and coronary artery disease.

Besides acting as a metabolic and antiatherogenic factor, adiponectin also exhibits its antiinflammatory effects on immune system cells. Adiponectin inhibits maturation, proliferation, and phagocytic activity of macrophages, as well as their TNFα and IFN-γ production in response to lipopolysaccharide stimulation. Moreover, adiponectin promotes phagocytosis of apoptotic cells by macrophages, whose accumulation can trigger inflammation or immune system dysfunction.

It reduces the secretion and activity of TNFα and IL-6 and induces production of antiinflammatory mediators, such as IL-10 and IL-1 receptor antagonist, in monocytes, macrophages, and dendritic cells. Adiponectin also increases the number of Treg cells. Conversely, it promotes the maturation and activation of dendritic cells. Interestingly, both TNFα and IL-6 are potent inhibitors of adiponectin secretion, which suggests the existence of a negative feedback between adiponectin and proinflammatory cytokines. Further antiinflammatory effects of adiponectin involve suppression of IL-2-induced NK cell cytotoxic activity. In acquired immunity, it inhibits the activation and proliferation of T lymphocytes and B cell lymphopoiesis. Surprisingly, some reports suggest a proinflammatory action of adiponectin. It has been proven that the serum concentration of adiponectin is elevated in patients with autoimmune inflammatory conditions [38,40]. This bidirectional, anti-, and proinflammatory effects of adiponectin may in part result from the changes in the relative proportion of its various isoforms, as much as the different molecular weight and truncated forms of adiponectin exert differential activities.

Resistin

Resistin [35,37,41], also known as ADSF (adipocyte-secreted factor) or FIZZ3 (found in inflammatory zone 3), was discovered in 2001. It is a 12.5 kDa polypeptide that belongs to a family of cysteine-rich proteins called "resistin-like molecules." The term "resistin" was originally proposed for its role as a mediator of insulin resistance. To date, resistin receptor and its signaling pathways have not been identified. The study of resistin in human disease is complicated by the fact that there are marked interspecies differences in the source of production and structure of this protein. Indeed, while in rodents the major source of resistin is WAT, human resistin is mainly produced by circulating and WAT-resident peripheral blood mononuclear cells (PBMC). Moreover, human and rodent resistins only share 59% identity at the amino acid level. Serum resistin levels are known to increase with obesity in both rodents and humans. In animal models, resistin has consistently been shown to promote insulin resistance. Yet, data on the role of this adipokine in the regulation of glucose homeostasis and insulin sensitivity in humans are controversial. Some authors report that high serum levels are associated with increased obesity, insulin resistance, and type 2 diabetes, whereas other groups failed to observe such correlations.

In humans, resistin may instead be involved in inflammatory processes rather than in the modulation of glucose homeostasis. Recent studies showed that resistin induces the secretion by PBMC and is induced by several proinflammatory cytokines, such as TNFα, IL-1β, and IL-6, indicating that resistin can increase its own activity by a positive feedback mechanism. Resistin also increases the expression of cytokines and adhesion molecules in vascular endothelial cells, thereby contributing to atherogenesis. Metabolic syndrome by itself is associated with inflammation. Some authors suggest that resistin may be associated with inflammatory markers of metabolic syndrome, its correlation with metabolic parameters such as glucose or blood lipids being just an indirect effect.

Visfatin

Visfatin [36,37,41] corresponds to a 52 kDa-protein previously identified as pre-B cell colony-enhancing factor as well as identified to act as an enzyme, nicotinamide phosphoribosyl transferase. It was originally discovered in liver, skeletal muscle, and bone marrow as a growth factor for B lymphocyte precursors. Adipose tissue and leucocytes also secrete visfatin. The role of this adipokine on glucose metabolism remains unclear, although most studies indicate insulin-like effects. Visfatin appears to be increased in obese subjects, even if these data are also controversial. Certainly, it is a potent mediator of inflammation. Visfatin increases the production of inflammatory cytokines (IL-6, TNFα, and IL-1β) by leucocytes. Additionally, it promotes activation of T cells by enhancing the expression of co-stimulatory molecules, such as CD40, CD54, and CD80, on monocytes. Visfatin acts as a chemotactic factor on monocytes and lymphocytes. It strongly affects the development of both T and B lymphocytes. Moreover, its proinflammatory effects might contribute to the process of atherosclerosis. As resistin, visfatin is upregulated by inflammatory mediators.

OBESITY AND IMMUNE-MEDIATED DISEASES

An association between obesity and various inflammatory/autoimmune conditions has been suggested in many observational studies. Recently, the discovery of adipokines and better knowledge of their pleiotropic role, particularly on the immune system, has led to major advances in the understanding of the relationships between obesity and autoimmune diseases. Below, we summarize and discuss the data in this field in several immune-mediated conditions. An overview of experimental and clinical data from the literature is presented in Table 35.2 and Fig. 35.3.

TABLE 35.2 Synthesis of Clinical and Experimental Data Regarding the Effects of Obesity and Adipokines in Several Autoimmune Diseases

	Obesity as a Risk Factor	Obesity as a Worsening Factor	Experimental Data
Rheumatoid arthritis (RA)	Obesity ↑ risk (OR = 1.2–3.4) of ACPA- > ACPA + RA in women > men [50–57], weight loss ↓ risk of RA [58]	Obesity ↑ severity, comorbidities [67–72] and ↓ treatment efficacy [114–119] Paradoxical protective role on radiographic damage [67,73,98–100]	Patients: ↑ leptin, adiponectin, resistin, and visfatin levels in RA correlated with severity [79–94] Mice: Leptin-KO mice and inhibition of visfatin ↓ severity [95–97]
Systemic lupus erythematosus (SLE)	Insufficient data; one negative study but several bias [126]	Obesity correlated with renal and cognitive involvement,↓quality of life [134,145,146,151,152] and ↑CVD [134,156] No correlation with disease activity [133–135]	Patients: ↑ leptin levels in SLE not correlated with disease activity [138–140] Mice: leptin ↑ lupus autoimmunity, Thl7 and ↓Treg. Leptin deficiency ↓ severity, Thl7 and,↑ Treg [127–130] ↑ Leptin, resistin and ↓adiponectin levels correlated with ↑ renal damage and CVD [128,136,137,141,142,144,147–149,160,161]
Inflammatory bowel disease	Conflicting results [126,167–169]; overall data suggesting obesity as a risk factor	Obesity correlated with an unfavorable course of the disease and ↓ treatment efficacy [174,175,194–197]	Patients: ↑ leptin, resistin and visfatin levels in plasma, visceral adipose tissue, or gut lumen [176–180,183–186] Mice: Leptin-KO mice ↓colitis [181,182] High-fat diet ↑ intestinal inflammation [172,173]
Multiple sclerosis (MS)	Childhood and adolescent obesity ↑ risk (OR ≈ 2) of MS in women > men [204–207]; risk potentiated by genetic predisposition [208]	No clinical data Experimental data suggesting a harmful role	Patients: ↑ leptin, resistin, visfatin and ↓adiponectin levels correlated with ↑ inflammation and ↓Treg Mice: Inhibition of visfatin ↓ severity [219] Adiponectin-KO mice ↑ severity and ↓Treg [217] Strong data for a key role of leptin in induction and progression of the disease [220–223]
Type 1 diabetes (T1D)	High birthweight, early weight gain, childhood, and adult obesity ↑ risk of T1D (OR ≈ 2) [126,236,237,241]; earlier onset rather than ↑ risk?	No clinical data	Mice: High birthweight ↑ risk of T1D [238] Pregnancy calorie restriction ↓birthweight and subsequent T1D [239] ↑ leptin, resistin and ↓adiponectin levels: ↑ βcell autoimmunity [258–261]
Psoriasis and psoriatic arthritis (PsA)	Obesity ↑ risk of psoriasis and PsA (OR = 1.48–6.46) [126,271,273–275]; risk potentiated by genetic predisposition [286,287]	Obesity ↑ severity, CVD, metabolic syndrome and ↓ biologic therapies efficacy [277,288–290,322,326,328–330] Weight loss ↓ severity, CVD and ↑ treatment efficacy [296–302,332]	Patients: ↑ leptin and resistin levels in psoriasis and PsA correlated with severity [305–309,315] ↑ leptin levels in skin lesions [313,314]
Hashimoto thyroiditis (HT)	Childhood obesity ↑ risk of HT (OR = 1.21) [357] Obesity ↑ TAI [356]	No clinical data	Patients: ↑ leptin levels correlated with Thl7 [356,358]

ACPA, anticitrullinated protein antibodies; *CVD*, cardiovascular diseases; *KO*, knockout; *OR*, odds ratio; *TAI*, thyroid autoimmunity; *Th17*, T helper 17 cells; *Treg*, regulatory T cells.

Obesity and Rheumatoid Arthritis

RA is an inflammatory autoimmune disease characterized by chronic synovial inflammation. If left untreated, RA ultimately leads to irreversible erosive joint destruction, responsible for disability and impaired quality of life. Extra-articular manifestations may include cutaneous, pulmonary, cardiac, ocular, renal, and hematological involvement [42]. It is the most common inflammatory joint disease, affecting almost 1% of the population, and it has experienced an increase over the last decades. RA has a higher prevalence in women than in men [43,44]. Most RA patients are recognized to have altered

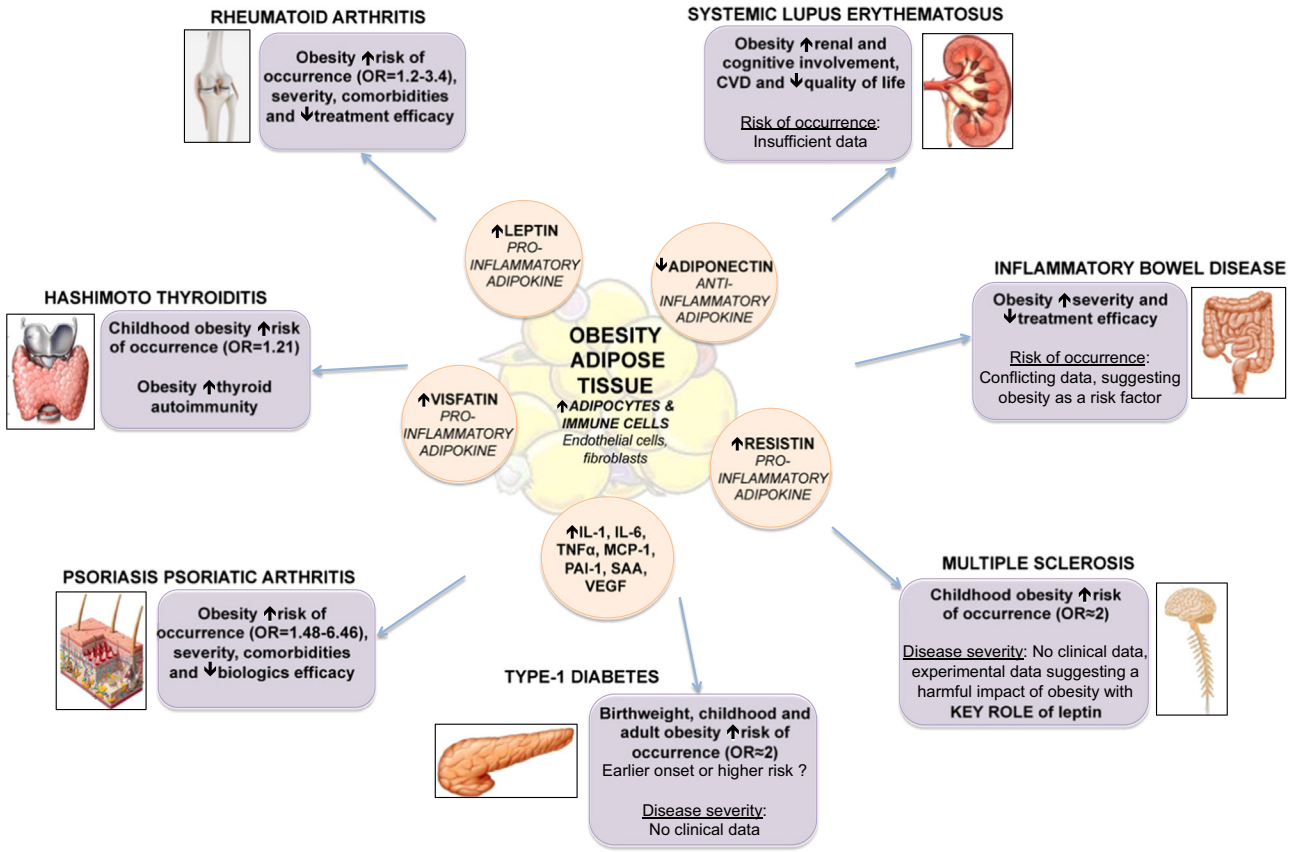

FIGURE 35.3 Schematic overview of the actions of adipose tissue on several immune-mediated diseases during obesity. Adipose tissue consists primarily of adipocytes and many other cell types. In obesity, there is an increase in the number of adipocytes and a major infiltration of adipose tissue by a variety of immune cells. Both adipocytes and immune cells are responsible for the secretion of multiple inflammatory mediators called "adipokines" including conventional molecules (IL-1, IL-6, TNF, MCP-1, PAI-1, SAA, VEGF) and specific hormones, such as leptin, adiponectin, resistin, and visfatin. In obesity, the levels of leptin, resistin, and visfatin, three proinflammatory molecules, increase proportionally to fat mass. Conversely adiponectin, a mostly antiinflammatory adipokine, decreases. The boxes present the major effects of obesity on the onset and progression of several autoimmune diseases. This partially results from the harmful action of adipokines. *CVD*, cardiovascular diseases; *IL*, interleukin; *MCP-1*, monocyte chemotactic protein-1; *OR*, odds ratio; *PAI-1*, plasminogen activator inhibitor-1; *SAA*, serum amyloid A; *VEGF*, vascular endothelial growth factor.

body composition. This change is characterized by reduced lean tissue and preserved or increased fat mass with stable or increased body weight, a condition known as "rheumatoid cachexia" [45], believed to accelerate morbidity and mortality [46]. This state has received significant scientific attention, but less is known about the relation between obesity and RA. However, both conditions—obesity and RA—share several common features. Indeed, RA is characterized by chronic inflammation, with reduced life expectancy compared with the general population mainly because of increased prevalence of cardiovascular diseases [47]. Similarly, obese patients exhibit a chronic subclinical inflammatory state, resulting in an increased incidence of various comorbidities, especially cardiovascular diseases [48,49].

First, concerning obesity as a risk factor for RA onset, several studies associated obesity with a higher risk for the occurrence of RA [50–55]. In a large retrospective case–control study, Crowon et al. [53] found that a history of obesity more than obesity at incidence date was modestly correlated (OR = 1.24; CI 1.01–1.53) with the likelihood of developing RA. Interestingly, their findings indicate that obesity could explain 52% of the recent rise in incidence of RA in Minnesota. Two additional large case–control studies [51,55] brought out an increased risk in obese individuals (BMI ≥30 kg/m^2) to develop an ACPA (anticitrullinated protein antibodies)–negative RA (OR ranging 1.6–3.45), this rise affecting only women in one of these studies [55]. There is no biologic explanation for this specific association. It should be noted that, in both studies, patients fulfilled old 1987 American College of Rheumatology criteria for RA diagnosis, and the authors cannot exclude misdiagnosed osteoarthritis, which is positively correlated with BMI. The association between obesity and risk of seronegative RA was recently found again in a population-based study from the European Prospective Investigation of Cancer Norfolk and Norfolk Arthritis Register (EPIC-2-NOAR Study) with an hazard ratio (HR) = 2.75 for BMI ≥30 kg/m^2 [56]. Recently, a large prospective study [57] using two cohort of women, Nurses' Health Study (NHS, 109,896 women) and

Nurses' Health Study II (NHS II, 108,727 women), observed a significant association between being overweight and obese and developing seropositive and seronegative RA, which appeared to be stronger among women diagnosed at younger ages (≤55 years) with an HR = 1.45–1.65. They also observed that a BMI ≥25 kg/m^2 at 18 years of age was associated with a 35% increased risk of developing RA, and an almost 50% increased risk of developing seropositive RA in adulthood. Finally, they reported a "dose effect" of obesity years on risk of RA at age 55 years or younger with a 37% increased risk of RA associated with a history of 10 years of being obese. Interestingly, an intensive prevention program in Finland reported a decline in the incidence of RA accompanying weight reduction [58]. Conversely, many studies failed to show obesity as being a predisposing factor for RA [59–65]. Several reasons have been discussed to account for this discrepancy, including the lack of power of some studies (insufficient number of patients) to detect a modest risk (OR b1.5), methodological variability across studies, many biases or confounding factors, particularly in case–control studies, and the relevance of BMI as a measuring tool of obesity especially in RA patients [66]. Indeed, BMI is not a good marker of body fat content because it neither distinguishes between the tissues that comprise it or consider abdominal obesity, which is a key prognostic factor.

Regarding the impact of obesity on RA activity, available data suggest a correlation between obesity and disease severity. In 2013, Ajeganovic et al. [67] followed a cohort of 1596 patients with early RA for a mean duration of 9.5 years. They found that a BMI ≥30 kg/m^2 was directly correlated with higher disease activity, indicated by higher HAQ (Health Assessment Questionnaire) score, DAS28, visual analog scale pain, CRP (C-reactive protein), and ESR (erythrocyte sedimentation rate) levels. BMI was also correlated with worse global health scores, decreased probability of remission, and higher prevalence of comorbidities, such as type 2 diabetes, cardiovascular disease, and chronic pulmonary disease. These results are consistent with previous studies [68–72]. In contrast, several authors do not correlate obesity with increased disease activity [73–75] or with cardiovascular disease [76,77]. However, some results may be biased by a well-described phenomenon. Indeed, all studies report a paradoxical association between a low BMI (<18–20 kg/m^2) and a higher morbidity and mortality of RA [46,78]. Actually, this is more likely related to a state of rheumatoid cachexia, mentioned above, which is the result of a more active disease. This association may distort the results, finding a more severe disease in lean subjects and ignoring the deleterious effect of fat.

In addition, a correlation between the increase in fat mass and disease activity seems consistent in the light of recently acquired knowledge on adipokines. Indeed, despite some conflicting results, most studies report higher levels of serum leptin [79–83], adiponectin [79,84,85], resistin [81,86–92], and visfatin [79,93,94] in patients with RA when compared with control subjects. This rise is commonly correlated with severity parameters, such as DAS28, HAQ score, radiographic damage, and with inflammation markers ESR and CRP. These data are supported by different mouse models, including leptin-deficient mice [95] or mice treated by pharmacological inhibition of visfatin [96,97], exhibiting a milder form of experimental arthritis. It is important to note that the proinflammatory action of adiponectin and visfatin in RA is widely recognized, but conflicting data are reported regarding leptin and resistin effects. It may be because of various biases, including differences in race, age, sex, BMI, body fat distribution, and medication used between the studies. However, the overall findings and the experimental data are in favor of higher levels and proinflammatory effects of adipokines in RA. Thus, considering that the rate of three of these adipokines (leptin, resistin, and visfatin) is correlated with fat mass in obese subjects, these data argue for a more severe RA activity in obese patients.

Furthermore, data unanimously show a surprising protective action of obesity for radiographic joint damage in RA [67,73,98–100]. Possible explanations for these phenomena include stimulation of bone synthesis because of the increased mechanical loading [101], the higher levels of estrogens in obese individuals [102], known to exhibit bone protective effects, and the involvement of adiponectin. Indeed, regarding the role of adipokines in erosive joint damage, studies report increased rates of four previously cited adipokines—that is, leptin, adiponectin, resistin, and visfatin—in the synovial fluid of patients compared with healthy controls or osteoarthritis patients [82,84,87,103,104]. High synovial rates were most frequently correlated with joint damage [94,105–107]. Moreover, in vitro data demonstrate proinflammatory effects of these adipokines on synovial fibroblasts and chondrocytes by enhancing the secretion of numerous chemokines (IL-2, IL-8), proinflammatory cytokines (IL-1β, IL-6), and matrix metalloproteinases (MMP-1, MMP-3, MMP-9) [85,93,108–113]. Adiponectin, the most abundant adipokines in human, is inversely correlated with body fat. We can therefore assume that the decreased levels of adiponectin in obese individuals are partly responsible for the paradoxical relationship between obesity and protection against radiographic damage.

Finally, all the studies investigating the consequences of obesity on treatment efficacy in RA suggest a poorer remission rate in obese conditions [114–119]. Thus, in a cohort of 495 patients with early RA, Sandberg et al. [119] showed that there were significantly lower odds of remission at 6 months (OR = 0.49) among overweight or obese patients (BMI ≥25 kg/m^2). This effect appears to be even more pronounced with infliximab, which is consistent with previous studies [114,115,118]. It is postulated that the adipose tissue leads to an inflammatory and therapy-resistant state. In this regard, however, studies investigating the effect of TNF blockade on adipokine plasma levels in patients with RA are not conclusive, most of these

failing to demonstrate an impact of anti-TNFα therapy on the levels of adipokines [120–122]. Further clarification is needed regarding the reason why obesity mostly affects RA outcome in patients treated with infliximab.

In conclusion, data suggest that obesity may modestly predispose RA, especially ACPA-negative RA, and is associated with higher severity of the disease and lower response rate to treatment. These effects seem to be partially related to the proinflammatory action of adipokines, most of which increase their circulating levels along with the fat mass. However, further studies are needed to confirm these observations.

Obesity and Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a chronic autoimmune disorder characterized by multisystem organ involvement, ranging from relatively mild manifestations (skin rash or nonerosive arthritis) to severe or life-threatening complications, such as lupus nephritis, neuropsychiatric disorders, cardiac involvement, and a wide profile of autoantibodies [123]. SLE affects people worldwide, though the incidence and prevalence may diverge across different countries. Young women are predominantly affected, representing about 80%–90% of patients [124]. Although the pathogenesis of SLE is still poorly understood, various genetic and environmental factors appear to be involved in the onset as in disease activity.

To date, no study has demonstrated an epidemiological link between obesity and the risk of developing lupus. However, while other environmental factors such as hormones or chemical exposures have been widely investigated [125], it is important to specify that data on the role of obesity in the onset of lupus are extremely rare. Only one large prospective cohort study recently investigated the association between BMI and the risk of 43 autoimmune diseases [126]. In a cohort of 75,008 Danish women followed for a mean duration of 11 years, the authors found no correlation between obesity and the risk of developing SLE. However, despite the power of this study, no definite conclusion can be made from these data because of several methodological limitations that may bias the results. Moreover, several recent studies [127–130] demonstrated that leptin, commonly elevated in obese subjects, could promote the survival and proliferation of autoreactive T lymphocytes, as well as the expansion of Th17 cells, while decreasing Treg cells in lupus-prone mice. Conversely, fasting-induced hypoleptinemia [130] or leptin-deficient mice [128,129] exhibit decreased Th17 cells and higher Treg cells.

Several studies have examined the impact of obesity on various parameters of SLE. This is even more important considering that the prevalence of obesity in patients with SLE is very high, ranging from 28% to 50% depending on the measurement methods [131,132]. None found an association between high BMI and disease activity, generally defined by the SLE disease activity index [133–135]. Similarly, many [136–141], but not all studies [142,143], have demonstrated that leptin rates were enhanced in SLE patients, as in obese individuals, and this was not correlated with disease activity [138–140]. However, in a lupus-prone murine model [128], leptin deficiency was shown to ameliorate lupus severity and was associated with decreased concentrations of anti-dsDNA antibodies. Regarding other adipokines, less data are available, but none showed a direct correlation between circulating levels and lupus activity in SLE patients. Only one experiment in a strain of lupus-prone mice suggests that adiponectin deficiency is correlated with a more severe disease [144].

Nevertheless, some studies associated obesity with a higher risk of renal impairment (lupus nephritis), as measured by increased proteinuria [134], and a significant increase in inflammatory markers (TNFα, CRP, IL-6) [133,145]. This corroborates experimental data on mouse models of SLE, reporting that high-fat diet [146], as well as increased levels of leptin [128], resistin [147,148], and reduced levels of adiponectin [144,149] as found in obese subjects are associated with more severe renal impairment. However, observations on adiponectin are contradictory because another study [150] found that plasma levels and urinary adiponectin levels were higher in patients with lupus renal disease. Furthermore, several studies have clearly linked obesity with worsened functional and cognitive capacities, decreased physical activity, more fatigue, and altered quality of life [134,145,151,152]. Even more interesting are the findings that high inflammation markers and leptin levels appear to be related to cognitive impairment in the general population [153–155]. Finally, obesity appears to predispose cardiovascular risk factors (hypertension, dyslipidemia) and atherosclerosis [134,156]. This is a key observation considering the increased prevalence of atherosclerosis and metabolic syndrome in SLE [157] and that cardiovascular disease is a major cause of mortality in SLE patients [158,159]. Here again, high levels of leptin [136,137,141,160] and resistin [161] and low levels of adiponectin [136,137,141,142] were correlated with an increased risk of cardiovascular disease and metabolic syndrome.

In summary, despite suggestive experimental data, the relationship between obesity and the likelihood of developing SLE has not been really investigated to date. However, it appears that a high BMI is associated with more severe cognitive and renal involvement, alteration of the quality of life, and contributes to the enhanced cardiovascular risk in SLE patients. Indeed, pathophysiological data provide evidence on the involvement of adipokines in the pathogenesis of SLE through their proinflammatory and proatherosclerotic effects.

Obesity and Inflammatory Bowel Disease

Crohn's disease (CD) and ulcerative colitis (UC) are the main forms of IBD, a group of chronic, idiopathic, pathological conditions affecting the gut, characterized by a relapsing-remitting course and the frequent development of various intestinal and extraintestinal complications. Despite some shared characteristics, these forms can be distinguished by differences in genetic predisposition, risk factors, and clinical, endoscopic, and histological features. The precise cause of inflammatory bowel disease (IBD) is unknown; however, genetically susceptible individuals seem to have a dysregulated mucosal immune response to commensal gut flora, which results in bowel inflammation [162–165]. The prevalence of IBD has increased mainly in Western countries in the past 50 years up to 120–200/100,000 and 50–200/100,000 for UC and CD, respectively [166]. The reasons for this rise are unknown, but environmental factors are likely to have a preponderant role. Similar to IBD, obesity has followed the same upward curve in industrialized countries, which seems obvious to discuss its involvement in the recent outbreak of IBD.

A single very large international prospective study, including 300,724 participants, investigated the link between BMI and the risk of developing IBD [167]. The findings revealed no association of obesity measured by BMI and the risk of incident UC or CD. Yet, a previous retrospective study suggested a link between BMI and CD in subjects aged 50–70 years [168]. This correlation between obesity and an increased risk of CD was also found in a recent large study (OR = 1.02–3.47) [126]. Moreover, a recent systematic literature review of epidemiological data from 19 studies comprising 1269 CD and 1340 UC patients concluded that a high dietary intake of fat increases the risk of IBD development [169]. Several deficiencies in the first-mentioned cohort study should be pointed out [167]. First, BMI alone is a poor measuring tool of adiposity fat, especially to assess visceral adipose tissue. Secondly, only one measurement of BMI was performed when participants were recruited, sometimes several years before diagnosis. Lastly, the population was predominantly middle to elderly aged (median age of recruitment: 50–53 years), although classically IBD presents in younger patients. Thus, this study, although major, does not enable us to have a formal conclusion regarding the relationship between obesity and the risk of developing IBD, given the conflicting data from other studies.

Obesity has previously been considered to be uncommon in IBD. As the prevalence of obesity has increased worldwide, this epidemic has also influenced the IBD patients population [170]. Moreover, mesenteric adipose depots, so-called "creeping fat," have long been recognized as hallmarks of CD, its extent being correlated with the severity of intestinal inflammation [171]. Due to the proinflammatory state induced by the adipose tissue, it is necessary to clarify its impact on disease progression. Studies on this topic are unfortunately rare. Some experiments in murine models of IBD have shown that high-fat diet-induced obesity aggravates intestinal and systemic inflammation [172,173]. Furthermore, only two clinical studies have correlated a high BMI with an unfavorable course of IBD, including a higher risk of relapses, abscesses, surgical complications, and therefore hospitalizations [174,175]. These findings seem consistent with several studies reporting a link between the level of some adipokines and the severity of inflammation in IBD. Indeed, higher leptin levels are found in the plasma [176], the mesenteric visceral adipose tissue [177,178], and the gut lumen [179,180] of IBD subjects. Moreover, leptin-deficient mice are protected from inflammation in experimental colitis [181,182]. Similarly, the plasma [183,184] and adipose tissue levels [185] of resistin, as visfatin serum levels [183,186], are elevated in patients with IBD. Regarding adiponectin, results are contradictory on mouse models [187–190], as well as with serum [183,184,191] and tissue levels [178,192]. These discrepancies may be related to methodological variations and the various actions of adiponectin isoforms. Conversely, Suibhne et al. [193] recently failed to correlate obesity with disease activity score in CD. Only CRP concentration was increased in obese IBD patients. Finally, several studies found worse responses to treatment with adalimumab [194,195], infliximab [196], and azathioprine [197] in obese patients, respectively, for both diseases, CD and UD.

To summarize, data are still too sparse to conclude regarding the involvement of obesity in the risk of IBD. Nevertheless, in our opinion, despite a negative large cohort study [167] affected by some noteworthy bias, much evidence argues for obesity as a risk factor of IBD: it includes several positive studies [126,168,169], including a broad review reporting a promoting effect of a high-fat diet on the risk of IBD [169], knowledge acquired on the involvement of adipokines in this disease, and, last but not the least, the troubling outbreak of IBD concomitantly with increase in obesity worldwide, particularly with the dramatic rise in prevalence of obesity in IBD patients. Moreover, experimental and pathophysiological data prove that adipose tissue, particularly visceral mesenteric adipose tissue, plays an important role in the pathogenesis of IBD and could result in more severe presentations. However, clinical studies are lacking on this topic and further studies will likely clarify its involvement.

Obesity and Multiple Sclerosis

Multiple sclerosis (MS) is the most common chronic inflammatory demyelinating disease of the central nervous system. It is characterized by localized areas of inflammation, demyelination, axonal loss, and gliosis in the brain and spinal cord,

resulting in a variety of neurological symptoms disseminated in time and space. MS mainly affects young people with onset usually at the age of 20–50 and a mean age of onset of 30, although the disease may develop also in childhood and after the age of 60 [198]. The total number of people living with MS worldwide is estimated to be 2.3 million in 2013, with increasing prevalence in recent decades. In many countries, it is the leading cause of nontraumatic disability in young adults [199]. The cause of MS is still unknown. However, genetic, environmental, and immunological factors have been implicated in the etiology of the disease [200,201]. Childhood and adolescence are thought to be a critical period of susceptibility to promoting factors. Concomitant with the rise of MS is the increased prevalence of overweight and obese children over the past decades; thus, in some countries the number of overweight children has tripled since 1980. Globally, 170 million children (aged <18 years) are estimated to be overweight [202,203].

Therefore, several studies investigated obesity during childhood and late adolescence as a risk factor of developing MS [204–208]. Thereby, two large studies, one using two cohorts of over 200,000 American women [204] and the other based on a Swedish population case–control study [205], reported a twofold increased risk of developing MS among subjects with a BMI ≥30 kg/m^2 at age 18 and 20, respectively, compared with normal weight subjects in both men and women in the second study (the first including only women). Although these studies are limited by several biases, including retrospective self-report of body size, this trend was confirmed in subsequent studies [206,207] with a more pronounced risk in women than in men. Indeed, in a prospective cohort study, Munger et al. [206] found that a higher BMI at ages 7–13 was associated with a significant 1.61–1.95-fold increased risk of MS only among girls. Similarly, another study [207] identified a higher risk of pediatric MS and clinically isolated syndrome (encompassing optic neuritis and transverse myelitis) in extremely obese adolescent girls (BMI ≥35 kg/m^2) with an OR = 2.57.

The explanation for the higher female-to-male risk observed in MS is still unknown. However, it is likely that an interaction between childhood obesity and estrogens or the X chromosome may contribute to this phenomenon [207].

Interestingly, one study [208] investigated the interactions between human leukocyte antigen (HLA) genotype and BMI status. Many genes have been identified for predisposition to MS [201], HLA-DRB1*15 allele conferring a threefold higher risk and HLA-A*02 being protective with a twofold lower risk. Using two case–control studies, the authors showed that subjects with a BMI <27 kg/m^2 and the two risk genotypes (carriage of DRB1*15 and absence of A*02) displayed an OR = 5.1–5.7, whereas the same genotype for subjects with BMI ≥27 kg/m^2 rendered an OR = 13.8–16.2 in the two cohorts.

Different hypotheses were suggested attempting to explain this association. First, vitamin D has been found to reduce the incidence and progression of an animal model of MS [209]. Moreover, high levels of circulating 25-hydroxyvitamin D have been associated with lower risk of MS [210]. It is well established that obese people, including obese children, have decreased serum levels of vitamin D metabolites [26,211,212], which may offer a partial explanation for the increased risk of MS in this population. Furthermore, adipose tissue macrophages infiltrating adipose tissue during obesity under high-fat feeding switch from an antiinflammatory M2 polarization state to a proinflammatory M1 polarization [213]. A recent study [214] demonstrated that imbalance toward M1 monocytes promotes relapsing experimental autoimmune encephalomyelitis (EAE), whereas administration of ex vivo activated M2 monocytes suppressed ongoing severe EAE.

The most exciting field of investigation is the role of adipokines in the pathogenesis of MS. Indeed, several studies [215,216] reported increased levels of leptin, resistin, and visfatin and decreased levels of adiponectin, a profile also observed among obese subjects, in MS patients. This profile was correlated with higher levels of inflammatory mediators (CRP, TNFα, IL-1β) [216] and lower Foxp3 Treg cells [215,216]. Using an EAE mice model, the most commonly used animal model for MS, Piccio et al. [217] showed that adiponectin-deficient mice developed worse clinical and histological disease, with higher amounts of IFN-γ, IL-17, TNFα, and IL-6, and fewer Treg cells than wild-type mice. Treatment with globular adiponectin almost completely suppressed the development of EAE and increased Treg cells. Moreover, prior study [218] found that calorie restriction ameliorated murine EAE and was associated with higher adiponectin plasma levels and lower concentrations of leptin and IL-6. In the same way, pharmacological inhibition of visfatin decreased the clinical manifestations of EAE by reducing T lymphocytes IFN-γ and TNFα production [219].

However, the stronger body of evidence has been shown with leptin. Indeed, Matarese et al. investigated the role of leptin in several experimental studies in murine models of MS [220–223] (reviewed in Refs. [224,225]). First, using a leptin-deficient *ob*/*ob* mice [220], they showed that leptin is required in the induction and progression of EAE; leptin replacement converted disease resistance to susceptibility by shifting the Th2 to a Th1 response and by inducing production of myelin-specific antibodies. Additionally, [221], they demonstrated in C57BL/6J and SJL/J mice, two EAE-susceptible strains of mice, that a marked surge in serum leptin levels, starting after immunization with myelin antigens, anticipates the onset of the acute phase of EAE; interestingly, this increase was accompanied by in situ production of leptin by pathogenic T cells and macrophages in demyelinating lesions in the brain and the spinal cord. A 48-h starvation at this time prevented rise in serum leptin along with EAE onset and clinical symptoms by inducing a Th2 cytokine switch. The effects of starvation could be reversed by administration of recombinant leptin. Finally [222,223], leptin neutralization with either

antileptin antibodies or leptin receptor-Fc fusion protein reduced EAE onset, severity, and mortality by promoting a Th2 and Treg profile. Moreover, in patients with MS, leptin levels were found enhanced in both the serum and the cerebrospinal fluid (CSF), correlating with IFN-γ production in CSF [222].

To summarize, there is strong evidence linking obesity with the risk of developing MS. The pathophysiological mechanisms are likely to be complex but clearly involve adipokines by promoting a proinflammatory Th1 profile and reducing Treg cells. Although to date there is no clinical study investigating the involvement of obesity on the course and prognosis of MS, experimental data detailed above suggest a harmful impact. This issue needs to be investigated in subsequent studies.

Obesity and Type 1 Diabetes

Diabetes mellitus refers to a group of diseases characterized by dysregulation of glucose metabolism, resulting from defects in insulin secretion, decreased insulin sensitivity, or a combination of both; it leads to chronic hyperglycemia and subsequent acute and chronic complications. It has traditionally been subdivided into type 1 diabetes (T1D, previously named insulin-dependent or juvenile-onset diabetes), a childhood acute disorder characterized by autoimmune destruction of insulin-secreting β-cells, and type 2 diabetes (T2D, formerly known as non–insulin-dependent diabetes), a slow-onset, middle-life disorder presenting with insulin resistance and features of metabolic syndrome, including overweightness [226,227]. Autoantibodies associated with T1D include islet cell autoantibodies, glutamic acid decarboxylase autoantibodies, insulinoma-associated 2 autoantibodies, insulin autoantibodies, and zinc transporter-8 autoantibodies.

However, distinctions between type 1 and type 2 diabetes are becoming increasingly blurred both clinically and etiologically. Indeed, the last decades have been marked by profound changes in epidemiological and clinical features of "diabetic diseases," giving rise to an intense debate on the underlying pathophysiological mechanisms. First, incidence and prevalence of both T1D and T2D are dramatically increasing worldwide. Thus, the number of people with diabetes rose from 153 million in 1980 to 347 million in 2008 [228]. T1D is the most common (90%) type of diabetes in children and adolescent. Its incidence is increasing by approximately 4% per year [2]. As genetic changes cannot cause such a rapid rise, environmental factors are strongly suspected to be involved in this outbreak. Second, clinical presentations are becoming more complex and overlapping. In addition to the "classical" type 1 and type 2 diabetes, the following are described: overweight or obese T1D, T2D in adolescents, latent autoimmune diabetes in adults, enclosing a group of patients over 35 years with features of T2D but with T1D autoimmunity markers, and conversely "double diabetes" or "1.5 diabetes," characterized by the presence of overlapping T1D and T2D symptoms in children or adolescents [227]. One common point is noted: obesity has experienced the same dramatic increase as diabetes in recent decades [11,12] and is found as a common characteristic in the overlapping forms of diabetes mentioned above.

These findings led Wilkin to propose a provocative and controversial theory in 2001, the "Accelerator Hypothesis" [229]. It postulates that T1D and T2D are the same disorder of insulin resistance set against different genetic background. Both diseases are distinguishable only by their rate of β-cell loss and the "accelerators" responsible; at the end, all diabetes progress to a final insulin-dependent state. Thus, the difference between T1D and T2D would only rely on the tempo of disease progression, depending on the presence of the various accelerators. Three accelerators are described: genetic susceptibility, insulin resistance, and β-cell autoimmunity. Insulin resistance would be a common accelerator, resulting from weight gain, and is widely believed to explain the epidemic rise of both T1D and T2D.

To focus on T1D, the question of the relationship between obesity and the risk of developing T1D has long been raised [230]. The Accelerator Hypothesis puts overweightness at the heart of the pathogenesis of T1D in a continuum with T2D [229]. It has sparked renewed interest in this topic and has been investigated in subsequent studies. Several questions are raised: does obesity influence the occurrence of T1D, partly driving its recent outbreak? If so, what are the mechanisms involved? The literature on this subject is not uniform, this issue being addressed at different levels. According to the studies, authors analyze the influence of maternal weight and weight gain during pregnancy, birthweight, weight gain in the early years of life, or childhood obesity, on the occurrence of T1D.

Prenatal factors (including maternal obesity and weight gain during pregnancy) will not be discussed herein. Briefly, studies are scarce and contradictory [231], some correlating maternal obesity and weight gain during pregnancy with increased islet autoimmunity and higher risk of T1D in offspring [232,233] and others failing to evidence an association [234,235]. Two large metaanalyses [236,237] were made regarding the role of birthweight and early weight gain during the first years of life, one of these investigating 29 studies [237]. A significant positive relation was found between higher birthweight or increased early weight gain and the risk of developing subsequent T1D. Children with birthweight >4000 g exhibit an increased risk of T1D ranging from 10% [237] to 43% [236]. The observed association is supported by several studies in non-obese diabetic mice, an animal model spontaneously developing T1D. A higher risk of diabetes was seen with increased birthweight [238], whereas calorie restriction during pregnancy leads to reduced birthweight and lower risk

of diabetes in mice at 24 weeks [239]. However, it is worth mentioning that despite the adjustment for potential confounders in these large metaanalyses, it is impossible to exclude all exposure factors that may affect both birthweight and risk of T1D, such as maternal diseases, weight, and nutrition, or some HLA predisposing both conditions [240]. Similarly, childhood obesity has been investigated as a potential risk factor for T1D and reviewed in a recent metaanalysis [241]. Despite heterogeneous data, there is overall evidence for a positive association between childhood obesity and increased risk of T1D, with a calculated pooled OR = 2.03.

Interestingly, only one study [126] examining the association between obesity and certain autoimmune diseases in a cohort of 75,000 adult women (mean age 30 years) followed during a median time of 11 years reported a twofold increased risk of T1D among obese women (BMI ≥30 kg/m^2). Unfortunately, BMI was only measured once at the start of the follow-up, and no data were available on eventual childhood obesity and weight change throughout the duration of the follow-up.

Yet, it remains unclear if increased birthweight and childhood obesity are acting as real risk factors or simply as accelerators, leading to an earlier presentation of T1D in genetically susceptible subjects. Although a number of studies demonstrated that among heavier children T1D occurs at a younger age [242–244], several authors argue that this is balanced by a decreased incidence among older age groups, resulting in a stable overall risk [245,246]. Thus, obesity may decrease the age at onset of T1D without necessarily changing lifetime risk. According to the Accelerator Hypothesis, overweightness would be a precipitating factor rather than an etiological factor.

Nevertheless, the mechanisms underlying this effect are still poorly understood. Increased body weight may promote T1D in a number of ways. Overload Hypothesis [247] suggests that overload of the β-cell, mediated by a variety of mechanisms, may sensitize them to immune damage and apoptosis and accelerate ongoing autoimmune processes leading to their destruction. Thus, obesity-induced insulin resistance, by increased insulin demand on β-cells at a critical period in early life, leads to β-cell overload by making them work harder metabolically. Both glucotoxicity and β-cell stress may accelerate their apoptosis, rendering β-cells more immunogenic. Therefore, individuals with susceptible genotypes will subsequently mount an autoimmune response, further accelerating β-cell loss.

Adipokines may also have a crucial role in the relationship between T1D and obesity, their action being at the crossroads of metabolism, immunity, and obesity. Leptin and adiponectin are two major insulin-sensitizing mediators and regulate glucose metabolism through various mechanisms, including promotion of insulin secretion and storage of glucose and inhibition of glucagon secretion and hepatic gluconeogenesis [33]. According to the studies, leptin is found to be increased [248], reduced [249], or unchanged [250] among T1D patients, possibly because of variations in insulin levels that regulate leptin. Concerning adiponectin, most studies report high levels [251,252], suggesting that increased adiponectin is a compensatory mechanism secondary to hyperglycemia and loss of endogenous insulin secretion in T1D patients [253]. Paradoxically, although adiponectin has antiinflammatory and vascular protective properties, high adiponectin levels appear to be associated with microvascular and macrovascular complications [254,255] and increased cardiovascular and overall mortality in diabetes [256]. Several explanations have been proposed to this observation. Hyperadiponectimenia may reflect poorly controlled diabetes, thus at high risk of complications, or it may be a compensatory mechanism, the adiponectin exhibiting cardioprotective effects. Conversely, resistin, known to promote insulin resistance, is found at increased levels in T1D [257], suggesting a pathophysiological involvement.

The most exciting point concerns the action of adipokines on the autoimmune destruction of β-cells. Indeed, adiponectin has been shown to protect β-cells from apoptosis and islet immunoreactivity [258,259]; inversely, leptin, by its proinflammatory effects, accelerates autoimmune destruction of β-cells in murine models [260], and resistin decreases β-cell viability [261]. Considering now the adipokine profile observed among obese patients, low adiponectin and high leptin and resistin promote both insulin resistance via decreased adiponectin and elevated resistin; it also leads to the immune-mediated destruction of β-cell through the joint action of the three mediators.

Thus, an extensive literature suggests that childhood and adolescence obesity leads to an overall twofold increase in the risk of subsequent T1D. However, it remains unclear whether this trend reflects an earlier onset of T1D in obese subjects or an enhanced risk of developing the disease. In all cases, prevention of obesity may have substantial benefits on preventing late complications of T1D by delaying or preventing its occurrence. Even more, the "adipokine profile" observed in obese subjects has been shown to aggravate both metabolic and autoimmune processes involved in T1D.

Obesity, Psoriasis, and Psoriatic Arthritis

Psoriasis is a highly common chronic inflammatory skin disease, its prevalence ranging from 1% to 8.5% of the population according to the countries [262]. Psoriasis is associated with a wide range of comorbid conditions [263] and responsible for significant impairment of the quality of life [264]. Its common variant, termed psoriasis vulgaris, affects 90% of all patients and is characterized by papulosquamous well-delineated plaques [265]. However, the disease is not necessarily restricted

to skin and nails; notably, about 30% of patients may develop a chronic inflammatory arthritis, included in the group of spondyloarthritis, namely psoriatic arthritis (PsA) [266]. The pathogenesis of both psoriasis and PsA is thought to result from the interplay between a strong genetic background, environmental factors, and immune dysfunction [267].

The existence of an association between obesity and both psoriasis and PsA has long been suggested [268] and has been strongly confirmed in many studies since [269,270]. Indeed, a recent metaanalysis [269] of 16 observational studies with a total of 2.1 million subjects (including 201,831 psoriasis patients) analyzed the epidemiological association between psoriasis and obesity; the findings conclude that compared with the general population, psoriasis patients are at significantly higher odds of obesity, with a pooled OR = 1.46 for mild-psoriasis and an OR = 2.23 for severe-psoriasis patients. However, the direction of this relationship is still a matter of debate. Several authors suggest that obesity may be a risk factor predisposing the development of psoriasis [271–273] and PsA [274–276], whereas others argue that overweightness is a consequence of these conditions rather than a predisposing factor [277,278]. To date, available data suggest that both phenomena are intricate in a bidirectional relationship [279].

First, psoriasis and PsA are thought to promote weight gain, which may partly explain the high prevalence of obesity among these patients. Thus, Herron et al. [277] reported in a retrospective study of 557 psoriatic patients that obesity at 18 years did not increase the risk of subsequent psoriasis; conversely, patients who developed psoriasis were more likely to become obese compared with Utah population (OR = 2.39). This study was based on a recall method and despite the controversy of this design, the observation seems consistent as numerous studies have demonstrated that psoriasis and PsA promote increased social isolation, depression [280], overeating and high-fat diets [281], alcohol consumption [282], and physical inactivity [283], all of which may lead to excess weight gain. Moreover, some studies have suggested that anti-TNFα treatments could result in a significant increase in body weight in psoriasis patients [284,285].

Furthermore, strong evidence suggests that obesity is an independent risk factor for both psoriasis and PsA [271–276]. In support of this hypothesis are two large prospective cohort studies [271,273] of American female nurses including 67,300 and 76,626 women (with 809 and 892 incident cases of psoriasis) followed, respectively, for 12 and 14 years in NHS [273] and NHS II [271] The studies report that higher BMI and weight gain since the age of 18 years are strong risk factors for incident psoriasis in both young [271] and old [273] women (mean age of 36 and 62 years). The relative risks (RR) of psoriasis are 1.48–1.63 for a BMI of 30–34.9 and 2.03–2.68 for a BMI of 35 or greater. BMI is also suggested as a risk factor for psoriasis in a recently published Danish cohort of over 75,000 women [126]. Similarly, two simultaneous large prospective studies [274,275], one from a UK population database (about 2 million individuals, 75,395 psoriasis patients, 976 incident PsA) [274] and the other from the NHS II (89,049 women, 146 incident PsA) [275], provide evidence linking obesity with the risk of incident PsA, with an RR among all individuals (regardless of psoriasis) of 1.57–3.12 for BMI 30–34.9 and 1.96–6.46 for BMI over 35. Interestingly, the influence of BMI on the risk of developing psoriasis could partially depend on the genetic background as suggested by two studies which demonstrated that the risk of subsequent psoriasis was influenced by the interaction between BMI and several genetic risk factors [286,287].

Moreover, the potential pathogenic role of obesity in psoriasis is strengthened by several studies [277,288–290] reporting a positive correlation between obesity measured by various parameters (BMI, waist circumference, bioelectrical impedance analysis) and psoriasis severity determined by the Psoriasis Area and Severity Index (PASI) score. Furthermore, besides its potential direct pathogenic role in psoriasis and PsA, obesity is also known to aggravate cardiovascular risk and increase the prevalence of metabolic syndrome features [48,49,291]. These comorbidities are more commonly seen in subjects with inflammatory diseases, especially psoriasis and PsA [292–294].

Supporting this hypothesis, a recent review [295] examining the impact of weight loss intervention found that losing weight through decreased calorie intake [296,297] or gastric bypass [298,299], alone or in conjunction with other treatments [300,301], significantly improved psoriasis or PsA severity, as well as the cardiovascular risk profile in both diseases [302]. Naldi et al. [296] recently conducted a randomized controlled trial including overweight or obese patients with moderate-to-severe psoriasis, randomized to receive either a dietary plan associated with physical exercise or simple information counseling. At 20 weeks, a significant improvement of psoriasis severity was shown in the dietary intervention arm when compared with the information-only arm, with a PASI score reduction of 48% versus 25.5%.

Thus, there is strong evidence suggesting a pathogenic role of obesity on both the occurrence and the severity of psoriasis and PsA. This is supported by extensive data acquired on the proinflammatory role of adipocytes. First, we must remember that psoriasis and PsA are characterized by the expansion of Th1, Th17, and Th22 cells, resulting in the production of large amounts of proinflammatory mediators, including IFN-γ, TNFα, IL-6, IL-17, and IL-22 [303,305]. As it is now recognized that fat cells secrete a wide variety of mediators, including TNFα and IL-6 [304], it might contribute to the inflammatory state in psoriasis. Moreover, many studies have demonstrated that high levels of both leptin and resistin, two adipokines enhanced in obese subjects, were found in psoriasis and PsA patients [305–309] and were correlated to the severity of the disease. Furthermore, resistin plasma levels have been shown to decrease under treatment [309–311].

Regarding leptin, a recent metaanalysis of 11 studies [305] confirmed that psoriasis patients exhibit increased levels of leptin compared with controls. Both leptin and resistin are known to promote the production of proinflammatory mediators involved in the pathogenesis of psoriasis, such as TNFα and CXCL8 [307,312]. Interestingly, tissue levels of leptin are also enhanced in the skin of psoriasis patients [313,314] and induce secretion of proinflammatory cytokines by human keratinocytes in vitro [314]. Moreover, leptin is increased in PsA patients and correlates with both the severity score of PsA and soluble mediators of osteoclastogenesis [315]. Studies investigating the role of visfatin in psoriasis are sparse. However, some data [316,317] suggest that high levels of visfatin are associated with more severe psoriasis and, considering its proatherogenic role, visfatin may contribute to the cardiovascular morbidity in psoriasis.

Finally, on adiponectin, its role is still uncertain. Indeed, despite several studies [318–320] suggesting that psoriasis patients exhibit lower rates inversely correlated to the severity, a recent metaanalysis [321] found no difference between serum adiponectin levels in patients and controls. However, the authors state that most studies have a case–control design and small sample sizes. In addition, as mentioned above, the action of adiponectin is different depending on the isoform considered, and studies may not all measure the same isoform. Larger studies are needed to clarify the role of adiponectin.

Equally important, obesity has also been shown to significantly affect the efficacy and safety of psoriasis and PsA treatments; several reviews summarize literature data on this topic [279,322]. First, conventional systemic drugs, especially methotrexate and cyclosporine, exhibit a higher risk of toxicity in overweight patients. Indeed, nonalcoholic steatohepatitis, usually associated with obesity, may potentiate the hepatotoxicity of methotrexate, requiring closer hepatic monitoring in obese individuals [323]. Alternatively, the distribution volume of cyclosporine, a highly lipophilic drug, seems to be influenced by increased fat mass, leading to higher concentrations and subsequent nephrotoxicity in psoriasis patients [324]. Thus, it is recommended to adjust the dose of cyclosporine to the ideal weight instead of the actual weight of the patient to reduce the risk of toxicity [325].

Regarding biologic therapies, non–weight-adjusted drugs may be less effective in overweight patients [322,326]. Thus, infliximab weight-adjusted regimen provides constant results in psoriasis according to the weight [327]. Conversely, in most studies, response to etanercept and adalimumab, two fixed dose anti-TNFα treatments, was lower in heavier psoriasis patients, with an inverse correlation between BMI or weight and response rate [328,329]. Moreover, a prospective trial [330] concluded that obesity is a negative predictor of achieving and maintaining minimal disease activity in PsA patients treated by anti-TNFα blockers. Similarly, large trials found that in psoriasis patients, a weight N100 kg was associated with decreased serum levels and efficacy of ustekinumab, an anti–IL-12 and IL-23 inhibitor. The switch for a double dose of ustekinumab restored its efficacy [331]. The lower efficiency is likely related to the modification of the drug distribution, as well as the secretion of proinflammatory factors, including TNFα, by adipose tissue.

In support of this hypothesis, Mutairi et al. [332] carried out a randomized controlled prospective trial including 262 psoriasis patients under biologic therapies and demonstrated the beneficial effects of weight reduction on the efficacy of biologics. They reported that PASI-75 (a 75% reduction in PASI score) was achieved by 85.9% in the diet group and 59.3% in the control group. These results are consistent with previous studies reporting a positive effect of weight loss on the response to treatment, both in psoriasis and PsA [300,301]. Therefore, the treatment of obese patients with psoriasis and PsA is associated with decreased effectiveness and higher risk of adverse events, which may lead to drug discontinuation [333,334]. Consequently, it clearly appears that the type and the dose of treatment should be considered and adapted according to the patient's weight.

In conclusion, there is strong evidence suggesting that obesity, through its proinflammatory action, predisposes the development of psoriasis and PsA, aggravates the evolution of both diseases, increases the risk of cardiovascular and metabolic comorbidities, and decreases biologic therapy efficacy. This should make nutritional care a central part of the management of psoriasis and PsA patient, particularly as the beneficial effects of weight loss have been demonstrated.

Obesity and Thyroid Autoimmunity

Autoimmune thyroid diseases encompass a spectrum of disorders characterized by an autoimmune attack on the thyroid gland, including Hashimoto thyroiditis (HT), Grave's disease, and postpartum thyroiditis. Herein, we will focus on HT, as there are no sufficient data on the relationship between obesity and the other autoimmune thyroid diseases. HT (also named chronic autoimmune thyroiditis and autoimmune hypothyroidism) is the most common autoimmune disease [335], the most common endocrine disorder [336], and the most common cause of hypothyroidism [337]. Its incidence ranges from 27 to 448/100,000 per year according to the studies and the geographic areas, and women show to be at least 8 times more affected than men [335]. It is an organ-specific autoimmune disease characterized by the presence of a goiter with lymphocytic infiltration, associated with serum thyroid antibodies—including anti–thyroid peroxidase (anti-TPO) and antithyroglobulin (anti-Tg) antibodies – and systemic manifestation related to hypothyroidism [338]. The etiopathogenesis of HT

has not been fully elucidated; however, it is clearly a multifactorial disease, resulting from a complex interaction between genetic and environmental factors, such as excess iodine, synthetic chemicals, or infections [339,340].

Thyroid function was extensively investigated in obese subjects. Relationship between obesity and thyroid is complex and several processes seem to be intricate [341]. On the one hand, an elevated serum thyroid-stimulating hormone (thyrotropin, TSH) concentration is frequently reported in obese individuals and positively correlated with BMI [342,343]. However, this elevation is not always indicative of hypothyroidism, as peripheral thyroid hormones (T3 and T4) might be increased, decreased, or in the normal range [344–346]. Moreover, in most studies, these hormonal changes do not appear to be related to an autoimmune process in the thyroid, insofar as these patients with raised serum TSH exhibit low prevalence of HT-related autoantibodies [344–346]. Some authors initially postulated that thyroid dysfunction was responsible for obesity [347]. However, it seems unlikely, as the treatment of severe hypothyroidism was found to result only in a minimal improvement in weight [348]. Conversely, weight loss by hypocaloric diet or by bariatric surgery led to a significant reduction in TSH levels [349,350]. Thus, this hyperthyrotropinemia appears to be the consequence rather than the cause of excess weight. Several mechanisms have been suggested. It might correspond to an adaptive process of the hypothalamus–pituitary–thyroid axis in obese individuals, elevated thyroid hormones promoting the resting energy expenditure [351]. Furthermore, there is increased evidence that leptin is contributing to TSH elevation [352], as it has been shown that leptin regulates, at least partially, TSH secretion in humans [353,354] and is correlated both with BMI and TSH [355].

Besides these hormonal changes associated with obesity, some studies have suggested that obese people could also be more prone to develop HT [356,357]. Ong et al. [357] reported on a cohort study including almost 2500 subjects that childhood weight gain and childhood overweightness conferred a slightly increased risk (OR = 1.21) of HT at the age of 60–64 years particularly in women. Similarly, Marzullo et al. [356] recently showed a greater prevalence of hypothyroidism and HT-related autoantibodies among obese individuals, correlated with increased leptin levels. In support of this concept is a recently published study [358] describing higher leptin levels in HT patients, positively correlating with the percentage of Th17 cells, which are suggested to be involved in the pathogenesis of HT [359,360].

In conclusion, it is now recognized that variations in thyroid hormones during obesity are mostly related to a deregulation of the hypothalamic–pituitary axis, without underlying autoimmune process. This does not exclude that overweightness might also lead to an excess risk of autoimmune thyroiditis, with leptin playing a major role in this process. Given the frequency of HT, future studies will probably help clarify this relationship.

CONCLUSION

Currently, many efforts are underway to attempt to explain the recent outbreak of autoimmune diseases, which is a hot topic today. The combination of variety of environmental factors is highly suspected to promote this phenomenon. Of these environmental factors, available data provide strong evidence for the deleterious impact of obesity on several immune-mediated conditions. Thus, obesity clearly appears to increase the risk of developing RA, MS, psoriasis, and PsA and could also promote the occurrence of IBD, T1D, and TAI. Furthermore, obese patients are prone to experience a more severe course of RA, SLE, IBD, psoriasis, and PsA and reduced therapeutic response in RA, IBD, psoriasis, and PsA.

Multiple and complex pathophysiological processes are likely to be engaged and result in these harmful effects. In this review, we focused on the key role of adipokines. Indeed, extensive clinical and pathophysiological studies have demonstrated their pathogenic action in various diseases, including immune-mediated diseases, mostly through their proinflammatory properties. More than a passive storage area, adipose tissue is an active endocrine organ responsible for the promotion and the worsening of pathological conditions in obese subjects. When considering globally all of the pathogenic mechanisms suggested to affect the immune system under obese conditions, it provides pathophysiological arguments, in addition to clinical data, to answer two major issues: do obese individuals have more autoimmune disorders? And is obesity aggravating these conditions? Schematically, on the one hand, obesity has been associated with decreased Treg and B regulatory subsets, expansion of Th17 cells, and promotion of autoantibodies. Altogether, these mechanisms may lead to a breakdown of self-tolerance, promoting the development of autoimmunity and subsequent autoimmune disease. On the other hand, obesity is recognized to result in a strong proinflammatory environment, which once the autoimmune disease has occurred may worsen its progression and its treatment.

Despite abundant literature, this review also highlights several limitations and gaps in this topic. Thus, studies are often heterogeneous, and their interpretation may be limited by numerous biases, related to an insufficient number of patients, retrospective methodology, inadequate measure of body fat, and variations in considering potential confounders.

In conclusion, in the light of recent advances, obesity appears to be a new component of the complex mosaic of autoimmunity. Although some trends are emerging, further studies are needed to confirm these observations and specify the effects and pathogenic mechanisms involved. Furthermore, the impact of obesity should be investigated in a wide range of

autoimmune diseases, such as antiphospholipid syndrome, inflammatory myopathies, and juvenile idiopathic arthritis, in which a few data [361–364] already suggest the involvement of obesity and adipokines.

TAKE-HOME MESSAGES

- WAT is an active endocrine organ secreting soluble mediators called "adipokines."
- Adipokines are responsible for a proinflammatory state in obese subjects promoting and worsening various pathological conditions.
- Obesity promotes autoimmunity through variety of mechanisms including the secretion of adipokines.
- Obesity may increase the risk of several autoimmune diseases, especially RA, MS, psoriasis, PsA, IBD, T1D, and HT.
- Obesity may aggravate the course of RA, SLE, IBD, psoriasis, and PsA.
- Obesity would affect the treatment response of RA, IBD, psoriasis, and PsA.

LIST OF ABBREVIATIONS

ACPA Anticitrullinated protein antibodies
ACR American College of Rheumatology
AIM Apoptosis inhibitor of macrophage
Anti-Tg Antithyroglobulin antibodies
Anti-TPO Antithyroperoxidase antibodies
BMI Body mass index
CCL Chemokine ligand
CD Crohn's disease
CSF Cerebrospinal fluid
CRP C-reactive protein
EAE Experimental autoimmune encephalomyelitis
ESR Erythrocyte sedimentation rate
Foxp3 Forkhead box protein 3
HAQ Health Assessment Questionnaire
HLA Human leukocyte antigen
HT Hashimoto thyroiditis
HR Hazard ratio
IBD Inflammatory bowel disease
IFN-γ Interferon gamma
IL Interleukin
iNK cells Invariant natural killer T cells
MS Multiple sclerosis
NLRP3-inflammasome NOD-like receptor protein 3 inflammasome
OR Odds ratio
PASI Psoriasis Area and Severity Index
PBMC Peripheral blood mononuclear cell
PsA Psoriatic arthritis
RA Rheumatoid arthritis
RR Relative risk
SLE Systemic lupus erythematosus
T1D Type 1 diabetes
T2D Type 2 diabetes
TAI Thyroid autoimmunity
Th17 cells T helper 17 cells
TNFα Tumor necrosis factor alpha
Treg cells T regulatory cells
TSH Thyroid-stimulating hormone
UC Ulcerative colitis
WAT White adipose tissue

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