Review

Obesity in autoimmune diseases: Not a passive bystander

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Abstract

In the last decades, autoimmune diseases have experienced a dramatic increase in Western countries. The involvement of environmental factors is strongly suspected to explain this rise. Particularly, over the same period, obesity has followed the same outbreak. Since the exciting discovery of the secretory properties of adipose tissue, the relationship between obesity and autoimmunity and the understanding of the underlying mechanisms have become of major interest. Indeed, the fat tissue has been found to produce a wide variety of “adipokines”, involved in the regulation of numerous physiological functions, including the immune response. By conducting a systematic literature review, we extracted 329 articles regarding clinical, experimental and pathophysiological data on the relationship between obesity, adipokines – namely leptin, adiponectin, resistin, visfatin – and various immune-mediated conditions, including rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), inflammatory bowel disease (IBD), multiple sclerosis (MS), type-1 diabetes (T1D), psoriasis and psoriatic arthritis (PsA), and thyroid autoimmunity (TAI), especially Hashimoto thyroiditis (HT). The strongest levels of evidence support an increased risk of RA (OR = 1.2–3.4), MS (OR = 2), psoriasis and PsA (OR = 1.48–6.46) in obese subjects. A higher risk of IBD, T1D and TAI is also suggested. Moreover, obesity worsens the course of RA, SLE, IBD, psoriasis and PsA, and impairs the treatment response of RA, IBD, psoriasis and PsA. Extensive clinical data and experimental models demonstrate the involvement of adipokines in the pathogenesis of these autoimmune diseases. Obesity appears to be a major environmental factor contributing to the onset and progression of autoimmune diseases.

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1. 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]. Since 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, 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 pro-inflammatory 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.

2. 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/m²) or obese (BMI > 30 kg/m²) [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 that 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. 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 pro-inflammatory 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 as well as 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.

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 auto reactive 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 auto inflammatory diseases like 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 extra intestinal immune responses, including Th17/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 IL1β and IL18 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 anti-inflammatory 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 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 1 and Fig. 2.

3. Adipokines: metabolic and immunological properties

3.1. Leptin

Leptin [33–37] (from the Greek word leptoς = 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 non-glycosylated 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 (LIF). 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, and in immune system cells. Leptin is predominantly produced by WAT, and circulating levels of leptin directly correlate with the body adipose mass as well as 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 anti-diabetic effects and inhibits hepatic lipogenesis. Either ob or db deficient mice develop 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 due to 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 induce them to produce leptokriptien B4, eicosanoids, and pro-inflammatory 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. In mature immune cells, leptin also supports proliferation and maturation of Th1 cells.

3.2. 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), adipQ 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-family, sharing homologies with collagens VIII and X and complement factor C1q. The primary structure of adiponectin contains an N-family, sharing homologies with collagens VIII and X and complement factor C1q. The primary structure of adiponectin contains an N-family, sharing homologies with collagens VIII and X and complement factor C1q. The primary structure of adiponectin contains an N-family, sharing homologies with collagens VIII and X and complement factor C1q.
intracellular adhesion molecule-1 (ICAM-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 anti-atherogenic factor, adiponectin also exhibits its anti-inflammatory effects on immune system cells. Adiponectin inhibits maturation, proliferation and phagocytic activity of macrophages, as well as their TNF-α and IFN-γ production in response to LPS stimulation. Moreover, adiponectin promotes phagocytosis of apoptotic cells by macrophages, whose accumulation can trigger inflammatory disease conditions [38,40]. This bidirectional, anti- and pro-inflammatory 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.

3.3. 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” (RELMs). 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-resident peripheral blood mononuclear cells (PBMC). Moreover, human and rodent resistin 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 is controversial. Some authors report that high serum levels are associated with increased obesity, insulin resistance, and type 2-diabetes, while 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 pro-inflammatory cytokines, such as TNF-α, 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 like glucose or blood lipids being just an indirect effect.

3.4. Visfatin

Visfatin [36,37,41] corresponds to a 52 kDa-protein previously identified as PBEF (Pre-B cell colony-Enhancing Factor) as well as identified to act as an enzyme, NAMPT (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, TNF-α and IL-1β) by leukocytes. 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 pro-inflammatory effects might contribute to the process of atherosclerosis. As resistin, visfatin is upregulated by inflammatory mediators.

4. 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 2 and Fig. 3.

4.1. Obesity and rheumatoid arthritis (RA)

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 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 to the general population mainly due to 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/m²) to develop an ACPA (Anti-Citrullinated 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 ACR 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/m² [56]. Recently, a large prospective study [57] using two cohort of women, Nurses’ Health Study (NHS, 109,896 women) and Nurses’ Health Study II (NHSII, 108,727 women), observed a significant association between being overweight and obese and developing seropositive and seronegative RA, that appeared to be stronger among women diagnosed at younger ages (≤ 55 years) with a HR = 1.45–1.65. They also observed that a BMI ≥ 25 kg/m² 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 < 1.5), 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, nor 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/m² was directly correlated with higher disease activity, indicated by higher HAQ (Health Assessment Questionnaire) score, DAS28, VAS (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] nor 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/m²) 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.
Table 2
Synthesis of clinical and experimental data regarding the effects of obesity and adipokines in several autoimmune diseases.

<table>
<thead>
<tr>
<th>Disease</th>
<th>Obesity as a risk factor</th>
<th>Obesity as a worsening factor</th>
<th>Experimental data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight loss: risk of RA [58]</td>
<td>Paradoxic protective role on radiographic damage [67,73,98–100]</td>
<td>Mice: Leptin-KO mice and inhibition of visfatin, severity [95–97]</td>
</tr>
<tr>
<td>Systemic lupus erythematosus (SLE)</td>
<td>Insufficient data</td>
<td>Obesity correlated with renal and cognitive involvement, quality of life [134,145,146,151,152] and CVD [134,156]</td>
<td>Patients: leptin levels in SLE not correlated with disease activity [138–140]</td>
</tr>
<tr>
<td></td>
<td>One negative study but several bias [126]</td>
<td>No correlation with disease activity [133–135]</td>
<td>Mice: leptin [lupus autoimmunity, Th17 and Treg, Leptin deficiency, severity, Th17 and Treg [127–130]</td>
</tr>
<tr>
<td>Type-1 diabetes (T1D)</td>
<td>High birthweight, early weight gain, childhood and adult obesity: risk of T1D (OR = 2)</td>
<td>No clinical data</td>
<td>Mice: Inhibition of visfatin, severity [219] Adiponectin-KO mice: severity, and Treg [217]</td>
</tr>
<tr>
<td></td>
<td>[126,236,237,241]</td>
<td></td>
<td>Strong data for a key role of leptin in induction and progression of the disease [220–223]</td>
</tr>
<tr>
<td></td>
<td>Earlier onset rather than risk?</td>
<td></td>
<td>Mice: High birthweight, risk of T1D [238]</td>
</tr>
</tbody>
</table>

Abbreviations: ACPA: Anti-Citrullinated Protein Antibodies; CVD: Cardiovascular Diseases; KO: Knock-Out; OR: Odds Ratio; TAI: Thyroid Autoimmunity; Th17: T-helper 17 cells; Treg: regulatory T cells

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 pro-inflammatory action of adiponectin and visfatin in RA is widely recognized, but conflicting data are reported regarding on leptin and resistin effects. It may be due to 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 pro-inflammatory 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 effect of obesity for radiographic joint damage in RA [67,73,98–100]. Possible explanations for this phenomena include stimulation of bone synthesis due the increased mechanical loading [101], the higher levels of estrogens in obese individuals [102], known to exhibit bone protective effects, as well as 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 to 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 pro-inflammatory effects of these adipokines on synovial fibroblasts and chondrocytes by enhancing the secretion of numerous chemokines (IL-3, IL-8), pro-inflammatory cytokines (IL-1β), IL-6 and 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/m²). 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 pro-inflammatory action of adipokines, most of which increase their circulating levels along with the fat mass. However, further studies are needed to confirm these observations.

4.2. Obesity and systemic lupus erythematosus (SLE)

SLE is a chronic autoimmune disorder characterized by multisystem organ involvement, ranging from relatively mild manifestations (skin rash or non-erosive 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 body mass index 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, due to 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 SLEDAI (Systemic Lupus Erythematosus 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], as well as 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, since 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 pro-inflammatory and anti-atherosclerotic effects.

4.3. Obesity and inflammatory bowel disease (IBD)

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 extra-intestinal 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 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, that 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. Second, 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 pro-inflammatory 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, and 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.

4.4. Obesity and multiple sclerosis (MS)

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 non-traumatic 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/m² 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, Mungler 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/m²) 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/m² 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/m² rendered an OR = 13.8–16.2 in the two cohorts.

Different hypothesis 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 anti-inflammatory M2 polarization state to a pro-inflammatory M1 polarization [213]. A recent study [214] demonstrated that imbalance toward M1 monocytes promotes relapsing 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 experimental autoimmune encephalomyelitis (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 IFNγ, 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 IFNγ 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 [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-hour-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 anti-leptin 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 IFNγ 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 pro-inflammatory 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.

4.5. Obesity and type-1 diabetes (T1D)

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 (ICA), glutamic acid decarboxylase autoantibodies (GADA), insulinoma associated-2 autoantibodies (IA-2A), insulin autoantibodies (IAA), and zinc transporter-8 autoantibodies (ZnT8A).

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 (LADA), 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 meta-analysis [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 (NOD)-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 meta-analyses, 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 meta-analysis [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/m²). 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, overweight 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 gluco toxicity 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 due to 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 anti-inflammatory 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. Hyperadiponectinemia 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 pro-inflammatory 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 lead 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 “adipokinic profile” observed in obese subjects has been shown to aggravate both metabolic and autoimmune processes involved in T1D.
4.6. Obesity, psoriasis and psoriatic arthritis (PsA)

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 papulo-squamous 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 spondyloarthritids, 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 meta-analysis [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 matter of debate. Several authors suggest that obesity may be a risk factor predisposing the development of psoriasis [271–273] and PsA [274–276], while 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 bodyweight 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 Nurses’ Health Study I [273] and Nurses’ Health Study 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 psoriatic patients, 976 incident PsA) [274] and the other from the Nurses’ Health Study II (89,049 women, 146 incident PsA) [275] provide evidence linking obesity with the risk of incident PsA, with a 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 have 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 psoriatic arthritis [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 by-pass [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 to 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 adipocyties. 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 pro-inflammatory mediators, including IFNγ, TNFα, IL6, IL17 and IL22 [303,305]. As it is now recognized that fat cells secrete a wide variety of mediators, including TNFα and IL6 [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 meta-analysis 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 pro-inflammatory 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 pro-inflammatory 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 pro-atherogenic 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 meta-analysis [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 ciclosporin, 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 [322]. Alternatively, the distribution volume of cyclo-
spirone, 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 cyclospirone 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
in 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 (MDA) in PsA patients treated
by anti-TNFα blockers. Similarly, large trials found that in psoriasis
patients, a weight >100 kg was associated with decreased serum levels
and efficacy of ustekinumab, an anti-IL12 and IL23 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,
reasons for the pro-inflammatory 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 pro-inflammatory 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.

4.7. Obesity and thyroid autoimmunity (TAI)

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 post-partum thyroid-
itis. Herein, we will focus on HT, since there are no sufficient data on
the relationship between obesity and the other autoimmune thyroid
diseases. HT (also named chronic autoimmune thyroiditis and autoim-
mune hypothyroidism) is the most common autoimmune disease
[335], the most common endocrine disorder [336], as well as 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-thyroidperoxidase (anti-TPO)
and anti-thyroglobulin (anti-Tg) antibodies – and systemic manifesta-
tion 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 environmen-
tal 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 (thyrotrphin, TSH) concentra-
tion 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
either increased, decreased or in the normal range [344–346].
Moreover, in most studies, 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
adaptation process of the hypothalamic–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 child-
hood 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 hypothy-
roidism 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.

5. 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 are 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 pathophys-
iological studies have demonstrated their pathogenic action in various
diseases, including immune-mediated diseases, mostly through their
pro-inflammatory 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 pathophysiologial 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 autoinflammation. Altogether, these mechanisms may lead to a breakdown of self-tolerance, promoting the development of autoimmune and subsequent autoimmune disease. On the other hand, obesity is recognized to result in a strong pro-inflammatory 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 already suggest the involvement of obesity and adipokines.

Take-home messages

- White adipose tissue is an active endocrine organ secreting soluble mediators called “adipokines”.
- Adipokines are responsible for a pro-inflammatory state in obese subjects promoting and worsening various pathological conditions.
- Obesity promotes autoimmunity through variety of mechanisms including the secretion of adipokines.
- Obesity may aggravate the course of RA, systemic lupus erythematosus, and juvenile idiopathic arthritis.
- Obesity would affect the treatment response of RA, IBD, psoriasis and COVID-19.
- Obesity may aggravate the course of RA, systemic lupus erythematosus, and juvenile idiopathic arthritis.
- Obesity would affect the treatment response of RA, IB, psoriasis and PsA.

References


