

Obesity: an Additional Piece in the Mosaic of Autoimmunity

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The recent outbreak of autoimmune diseases in industrialized countries has brought into question the factors contributing to this increased prevalence. Given the constancy of genetics, growing attention has focused on environmental factors [Figure 1], especially the western lifestyle [1]. Indeed, in the last few decades significant changes in western dietary habits have led to the parallel rise in obesity. White adipose tissue (WAT), previously believed to be an inert tissue, was recently found to secrete numerous soluble mediators called adipokines that are involved in many processes including immunity and inflammation [2]. Thus, a link between obesity and autoimmune diseases was strongly suggested. In a systematic literature review we analyzed the relationship between obesity, adipokines and several immune mediated conditions [3].

FROM OBESITY TO AUTOIMMUNITY

Several mechanisms have been suggested to explain how obesity could promote autoimmune disease. One of them is the secretion by WAT of adipokines, which encompass both classical cytokines and specific molecules such as leptin, adiponectin, resistin and visfatin. In addition to their role in various physiologic processes, adipokines modulate the immune response and contribute to the “low grade inflammation state” in obese subjects. Leptin, resistin and visfatin exhibit pro-inflammatory activity and their levels are directly correlated with adipose mass. Conversely, adiponectin is an anti-inflammatory molecule and its secretion is reduced in obese persons [2]. Other mechanisms may link obesity and autoimmunity, but these require further research. Thus, the frequently found vitamin D deficiency in obese subjects, alteration of gut microbiota due to a western diet, or obesity itself may be responsible for a dysregulation of T helper (Th)17/T-regulatory cell (Treg) balance, contributing to the development of autoimmunity. Some authors highlighted the role of the apoptosis inhibitory macrophage (AIM), a macrophage-derived blood protein

whose circulating levels are increased in obesity. AIM has been found to promote autoantibody formation, M1-macrophage infiltration in WAT, as well as inflammasome activation, leading to both inflammation and autoimmune response.

OBESITY AND AUTOIMMUNE DISEASES

• Obesity and rheumatoid arthritis (RA)

RA is an inflammatory autoimmune disease characterized by synovial inflammation and joint destruction. Most studies, including two recent large prospective studies, reported a higher risk of RA developing, especially anticitrullinated protein antibody (ACPA)-negative RA, among obese individuals with an odds ratio (OR) ranging from 1.2 to 3.4 [4]. Furthermore, obesity is associated with a more severe disease and a higher prevalence of comorbidities, as well as a worse therapeutic response, particularly for infliximab. This is consistent with pathophysiological data indicating that increased levels of pro-inflammatory adipokines, as found in obese subjects, correlate with severity parameters. Conversely, a paradoxical protective effect of obesity on radiographic joint damage was observed.

• Obesity and multiple sclerosis (MS)

MS is the most common chronic inflammatory demyelinating disease of the central nervous system and it affects mainly young adults. A strong body of evidence supports obesity as a risk factor for developing MS. First, several large clinical studies found an overall twofold increased risk of MS associated with obesity during childhood or late adolescence – critical periods of susceptibility for MS. This risk seems to be more pronounced among women. Moreover, adipokine involvement in the pathogenesis of MS was strongly demonstrated, particularly for leptin [5]. Thus this hormone, whose levels are elevated in obese subjects, is critical for induction and progression of murine models of MS, notably by promoting a Th1 pro-inflammatory profile and reducing Treg cells. Similarly, low adiponectin and high visfatin levels have been shown to promote the onset and severity of murine MS.

• Obesity, psoriasis and psoriatic arthritis (PsA)

Psoriasis is a common chronic inflammatory skin disease that in a third of cases may be complicated by articular involvement, namely PsA. The association between obesity and both psoriasis and PsA is widely recognized. It appears to result

from bidirectional phenomena. First, psoriasis and PsA promote weight gain by changes in lifestyle such as depression, overeating and physical inactivity. Second, several large prospective studies have demonstrated that obesity is an independent risk factor for psoriasis and PsA (OR 1.48–6.46) [6]. In addition, obesity has been shown to worsen psoriasis and PsA evolution, increase cardiovascular comorbidities, and impair therapeutic response. This is likely partly due to the pro-inflammatory and pro-atherogenic effects of adipokines. Indeed, high rates of leptin and resistin were observed in the serum and skin of psoriatic patients and correlated positively with disease activity. In support of these data, weight loss has been shown to lessen disease severity and improve treatment efficacy.

• **Obesity and systemic lupus erythematosus (SLE)**

SLE is a systemic autoimmune disorder. Data on the risk of occurrence of SLE under obese conditions are scarce and do not allow a definite conclusion. With regard to disease severity, although obesity has not been found to correlate with SLE activity scores, it appears to be associated more with lupus nephritis, cognitive impairment, cardiovascular morbidities, and an impaired quality of life [7]. The high levels of leptin and resistin and low levels of adiponectin observed in both SLE and obese subjects, by their pro-inflammatory and pro-atherogenic effects, are thought to contribute to this association.

• **Obesity and inflammatory bowel disease (IBD)**

IBD is a group of inflammatory diseases affecting the gut whose main forms are Crohn's disease (CD) and ulcerative colitis (UC). Despite some conflicting results, a body of clinical and experimental evidence points to obesity as a risk and aggravating factor of IBD. First, epidemiologic data highlight the simultaneous outbreak of both IBD [8] and obesity in western countries. In addition, several studies have correlated obesity with the risk of occurrence as well as a more severe course of IBD. Moreover, experimental data in mice models and patients support the involvement of adipokines, as found in obese individuals, in the pathogenesis of IBD. Indeed, high levels of leptin, resistin and visfatin in plasma, visceral adipose tissue or gut lumen were found to be associated with intestinal inflammation. Finally, obese IBD patients also exhibit a worse therapeutic response, especially to anti-tumor necrosis factor- α (TNF α) therapies.

• **Obesity and type 1 diabetes (T1D)**

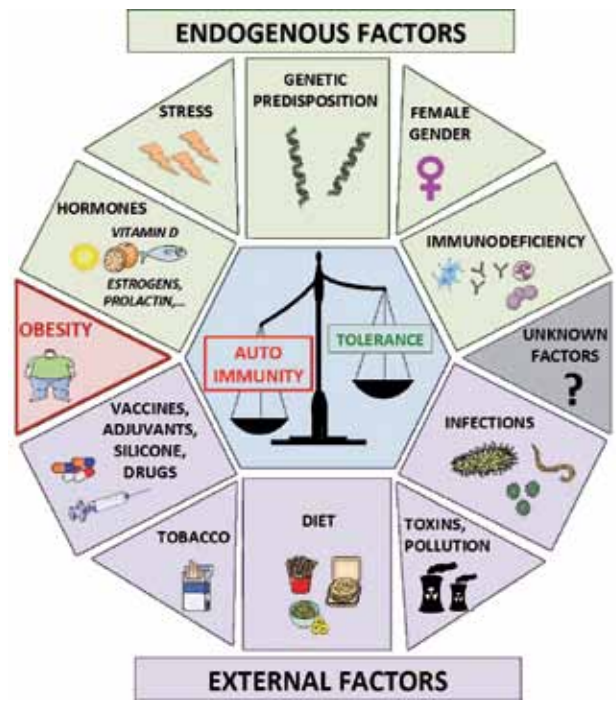
T1D is a juvenile-onset dysregulation of glucose metabolism resulting from autoimmune destruction of insulin-secreting β -cells. The impact of overweightness at different ages of life on the risk of subsequent T1D has been extensively investigated. Therefore, high birth weight, early weight gain in the

first years of life, childhood obesity and adult obesity have been associated with a twofold increased risk of T1D on average [9]. However, it remains a matter of debate whether obesity acts as a real risk factor or just an accelerator shifting the onset of diabetes at an earlier age without changing the lifetime risk. Several mechanisms have been proposed. First, obesity-induced insulin resistance may lead to β -cell overload and apoptosis rendering them immunogenic. Moreover, adipokines have been found to promote an autoimmune response against β -cells as well as metabolic and vascular complications.

• **Obesity and Hashimoto thyroiditis (HT)**

HT is a highly common autoimmune disease responsible for hypothyroidism and characterized by goiter with lymphocytic infiltration and thyroid autoantibodies. It is now recognized that obese subjects often exhibit high levels of thyroid-stimulating hormone (TSH). In most cases it is not related to hypothyroidism or to an autoimmune process, but more likely is an adaptive mechanism of the hypothalamic-pituitary axis partially regulated by leptin to increase energy expenditure. Nevertheless, several studies also demonstrated that obesity may promote the development of thyroid autoimmunity, especially HT-related autoantibodies, and this was correlated with leptin levels as well as Th17 cells, suggesting the involvement of leptin in the pathogenesis of HT [10].

Figure 1. The mosaic of autoimmunity



CONCLUSIONS

The recent increase in incidence of autoimmune diseases is gaining interest. A number of environmental factors have been shown to participate in this phenomenon. Following the discovery of the broad endocrine properties of WAT and particularly its immunomodulatory effects, numerous studies have highlighted the involvement of obesity and its adipokines in the pathogenesis of various autoimmune conditions. Thus, obesity is clearly associated with an increased risk of RA, MS, psoriasis and PsA, and is suggested to promote IBD, T1D and HT. Furthermore, obese patients exhibit a more severe course of RA, SLE, IBD, psoriasis and PsA and reduced therapeutic response in RA, IBD, psoriasis and PsA. Clearly, obesity has emerged as a new piece in the mosaic of autoimmunity [Figure 1].

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