

# Possible role of adipokines in systemic lupus erythematosus and rheumatoid arthritis

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## ABSTRACT

In recent years, mediators synthesized in the adipose tissue, the so-called adipokines, have been described. They have a hormonal action, regulating appetite and glucose metabolism, but also act as cytokines with effects on the immune system, including effects on autoimmunity. The most important adipokines are leptin, adiponectin, resistin and visfatin, and some of them have been assessed in autoimmune rheumatic diseases, especially systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Studies have shown high levels of leptin and adiponectin in SLE, but correlation with disease activity is questionable. In RA, studies have also reported increased levels of leptin and adiponectin, and correlation with disease activity and joint erosion, but the results are conflicting. This review describes the role of leptin and adiponectin on the immune system, as well as on SLE and RA.

**Keywords:** adipokines, leptin, adiponectin, systemic lupus erythematosus, rheumatoid arthritis.

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## INTRODUCTION

The immune system requires a proper energy balance for its physiological functions. In past years, an important connection has been evidenced between that system and metabolism,<sup>1</sup> with the identification of obesity as a predisposing factor for the development of several disorders, such as atherosclerosis, *diabetes mellitus* and some immune-mediated diseases.

The adipose tissue is not inert, and has been considered an organ with immune and neuroendocrine functions. That tissue produces several mediators, such as tumor necrosis factor alpha (TNF- $\alpha$ ), interleukin 6 (IL-6), interleukin 1 (IL-1), chemokine ligand 2 (CCL2), plasminogen activator inhibitor type 1, and complement components, all participating in the innate immune response as pro-inflammatory mediators.<sup>1</sup>

Although macrophages in the adipose tissue are the major source of TNF, adipocytes contribute with almost one third of the IL-6 concentration in the circulation of obese patients. In addition, CCL2, produced by adipocytes, is an important factor

for macrophage infiltration in that tissue. The presence of active macrophages, along with adipocytes and other immune tissue cells, can perpetuate a vicious circle, recruiting more macrophages and producing more pro-inflammatory cytokines.<sup>1</sup> All such cytokines are also implicated in autoimmune diseases.

The interrelation between adipose tissue and immune system is increasingly evident. The NLRP3 inflammasome, present in innate immune cells, has recently been shown to detect signals of danger associated with obesity, leading to the activation of caspase-1 and the production of interleukin 1b and interleukin 18, contributing to obesity-induced chronic inflammation.<sup>2</sup>

Currently, white adipose tissue is considered the largest endocrine organ, secreting a variety of mediators called adipokines (adipocytokines). The most important are leptin, adiponectin, visfatin, and resistin, which act like hormones in glucose homeostasis and appetite regulation, and like cytokines, promoting the connection of obesity and insulin resistance with the immune system and inflammatory process.<sup>1,3,4</sup> Some adipokines, such as

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leptin, act similarly to inflammatory cytokines, such as TNF- $\alpha$ , IL-6 and IL-1.<sup>5</sup> Others, such as adiponectin, have antidiabetic, antiatherogenic and anti-inflammatory effects.<sup>1,4,6</sup>

After understanding the nature and mechanism of action of adipokines, it is clear that the adipose tissue is not only an endocrine organ, but also an immune organ. Leptin and adiponectin are the adipokines most abundantly produced in adipocytes, studied in autoimmune rheumatic diseases, such as rheumatoid arthritis (RA),<sup>7,8</sup> Behçet's disease<sup>9</sup> and systemic lupus erythematosus (SLE).<sup>10</sup>

Thus, knowledge on the participation of those mediators in the pathogenic mechanisms of autoimmune rheumatic diseases might contribute to better understand that group of diseases.

It is worth reviewing the action of leptin and adiponectin in the immune system and their possible roles in SLE and RA.

## LEPTIN AND THE IMMUNE SYSTEM

Leptin (from the Greek word *leptos* = thin) was the first adipokine identified. It is a protein (16kDa) with 167 amino acids, codified by the obese (*ob*) gene located on chromosome 7q31.3,<sup>11</sup> with tridimensional structure similar to that of the IL-6 family cytokine. It acts on OB-R receptors,<sup>12,13</sup> which are members of the class 1 cytokine receptor superfamily, codified by the diabetes gene, expressed in different tissues, such as the central nervous (CNS) and the cardiovascular systems, and in immune system cells, such as monocytes, natural killer cells (NK),<sup>14</sup> and the T lymphocytes CD4<sup>+</sup> and CD8<sup>+</sup>. Leptin serum concentration is measured in ng/mL, and its levels correlate with body mass.

Leptin acts on appetite control within the gut-brain axis, promoting satiety due to its action on receptors in the hypothalamus.<sup>15</sup> Mice with mutation in the *ob* gene (*ob/ob* mouse)<sup>16</sup> or deficiency of the leptin receptor (*db/db* mouse) develop severe obesity due to lack of that signaling. Other secondary abnormalities have also been reported in reproduction,<sup>17</sup> hematopoiesis,<sup>18</sup> angiogenesis,<sup>19</sup> insulin secretion,<sup>20</sup> bone metabolism,<sup>21</sup> lipid and glucose metabolisms,<sup>20</sup> and adaptive and innate immune system.<sup>5,22,23</sup> Leptin, thus, is a pleiomorphic molecule with several biological actions.

That cytokine has pro-inflammatory activity, acting like an acute-phase protein<sup>5</sup> similarly to IL-1 and TNF- $\alpha$ . In monocytes and macrophages, it increases phagocytosis and the production of pro-inflammatory cytokines, such as TNF- $\alpha$ , IL-6, and interleukin 12 (IL-12),<sup>24</sup> and stimulates the proliferation and activation of monocytes. In neutrophils, it increases the expression of CD11b, chemotaxis and oxidative explosion,<sup>25</sup> and is involved in the development, differentiation, proliferation, activation and cytotoxicity of NK cells.<sup>26</sup>

Leptin increase during acute infection suggests it plays a role in the innate immune response.<sup>5,27</sup> Its human congenital deficiency is rare and is associated with a higher incidence of death due to infections during adolescence.<sup>28</sup> It is also associated with a reduction in circulating T lymphocyte CD4<sup>+</sup> and its cytokines.<sup>29</sup> Such alterations can be reversed with the administration of recombinant leptin, leading to the conclusion that it has a protective effect against infection. However, obese individuals have a higher incidence of infections, despite their increased leptin levels, which could indicate a state of resistance in such individuals.

The presence of OB-R receptors in T and B lymphocytes indicates that leptin might play a role in the activation of the adaptive immune system.<sup>23</sup> Its major action seems to occur in the regulation of T lymphocyte CD4<sup>+</sup>,<sup>22,29</sup> promoting the differentiation of T helper 1 lymphocytes (Th1). In lymphocyte cultures, leptin induces the proliferation of T lymphocytes CD4<sup>+</sup>CD45RA<sup>+</sup> and inhibits the proliferation of T lymphocytes CD4<sup>+</sup>CD45RO<sup>+</sup> (memory cells). Leptin increases the production of cytokines Th1, such as interleukin 2 (IL-2) and interferon gamma (IFN- $\gamma$ ), and suppresses the production of cytokines of T helper 2 lymphocytes (Th2), such as interleukin 4 (IL-4).<sup>30</sup> Leptin protects lymphocytes T against corticosteroid-induced apoptosis<sup>31</sup> and increases the expression of adhesion molecules, such as intercellular adhesion molecule 1 (ICAM1) and very late antigen 2 (VLA2), which might contribute to the activation and migration of immune cells to the inflammation site.<sup>5</sup>

In humans, the increase in leptin is associated with several chronic inflammatory conditions, such as non-alcoholic hepatitis,<sup>32</sup> chronic pulmonary inflammation,<sup>33,34</sup> intestinal inflammatory disease,<sup>35</sup> nephritis,<sup>36</sup> Behçet's disease,<sup>9,37</sup> Graves' disease,<sup>38</sup> type 1 *diabetes mellitus*,<sup>39</sup> RA,<sup>7,8,40</sup> and SLE.<sup>10,41</sup>

Mice with leptin deficiency have a severe thymus atrophy, suggesting the importance of leptin in thymopoiesis and adaptive immune response.<sup>16,22,42</sup> The exogenous administration of leptin prevents immunosuppression<sup>22</sup> and thymus atrophy, and increases thymic cellularity.<sup>42</sup> Those mice are also resistant to autoimmune diseases, such as experimental autoimmune encephalomyelitis,<sup>43-45</sup> type 1 *diabetes mellitus*,<sup>46</sup> experimental colitis,<sup>47</sup> antigen-induced arthritis,<sup>48</sup> and experimental glomerulonephritis.<sup>49</sup> The administration of leptin establishes susceptibility to autoimmunity.

Another indication of the leptin involvement in autoimmunity is its two-to three-times more elevated serum concentration in women than in men.<sup>50,51</sup> In addition, leptin potentiates experimental encephalomyelitis in female mice.<sup>45</sup> Leptin is one of the hormones favoring the greater predisposition of women to autoimmune diseases.

## ADIPONECTIN AND THE IMMUNE SYSTEM

Adiponectin is a globular monomeric protein with 244 amino acids that form a trimer (30 kDa), which polymerizes and form a large complex polymer that ranges from 180 kDa to 400–600 kDa.<sup>1,6,52</sup> Its structure is similar to that of collagens VIII and X and the complement component C1q. It is mainly synthesized by adipocytes, but is also produced in skeletal muscles, cardiac myocytes, and endothelial cells.<sup>1</sup> The human adiponectin gene is located on chromosome 3q27. Adiponectin has three receptors: AdipoR1, AdipoR2<sup>53</sup> and T-cadherin,<sup>54</sup> of which, the first is expressed more abundantly in skeletal muscle; the second in the liver; and the third in the heart and arteries. In the serum, adiponectin can be found as polymers or proteolytic fragments.<sup>6</sup> Its human serum concentration ranges from 5–10 mg/mL.<sup>4</sup>

Serum adiponectin is reduced in the following cases: visceral obesity; insulin resistance; non-alcoholic liver steatosis; and type 2 *diabetes mellitus*.<sup>55</sup> Obese animals treated with adiponectin show a decrease in hyperglycemia and lipemia, and improve their sensitivity to insulin.<sup>56</sup> Thus, protection against insulin resistance and an antidiabetic effect are attributed to adiponectin.

While leptin has a pro-inflammatory activity, adiponectin seems to have an anti-inflammatory activity,<sup>4,6</sup> acting on endothelial cells by inhibiting the expression of TNF-induced adhesion molecules.<sup>57</sup>

In the innate immune system, adiponectin suppresses the increase in the cytotoxic activity of NK cells by IL-2 and also the production of IFN- $\gamma$ .<sup>58</sup> It exerts its anti-inflammatory effect by reducing the production and activity of TNF- $\alpha$  and IL-6, and

also by inducing the production of anti-inflammatory mediators, such as interleukin 10 (IL-10) and interleukin 1 receptor antagonist (IL-1 RA).<sup>59</sup> In addition, adiponectin inhibits the proliferation and phagocytic activity of monocytes, and reduces the phagocytic capacity of macrophages.<sup>59</sup> However, adiponectin promotes phagocytosis of apoptotic cells by macrophages, whose accumulation can trigger inflammation or immune system dysfunction.<sup>60</sup>

Although adiponectin acts contrary to leptin, inhibiting the activation and proliferation of T lymphocytes and B lymphopoi-esis,<sup>61</sup> its effect on the production of cytokines seems to depend on its isoform,<sup>62</sup> target cell type and activation, and presence of pro-inflammatory cytokines that can modify its expression.<sup>1</sup>

## ADIPOKINES AND AUTOIMMUNE RHEUMATIC DISEASES

In past years, efforts have been made to clarify the role of adipokines, mainly leptin and adiponectin, in autoimmune diseases, especially in rheumatic diseases, such as RA<sup>63–67</sup> and SLE.<sup>68</sup>

### Adipokines and systemic lupus erythematosus

Adipokines are increased in SLE,<sup>10,68–71</sup> but most studies have failed to show their correlation with disease activity (Table 1).

In 2002, Garcia-Gonzalez et al.,<sup>10</sup> assessing 41 women with SLE, found increased leptin levels as compared with those of controls, although with no correlation with disease activity, age or disease duration.

**Table 1**  
Measurement of adipokines in systemic lupus erythematosus

Author and year	Type of study	Patients	Controls	*Leptin concentration	*Adiponectin concentration	Disease activity	Observations
Garcia-Gonzalez et al., 2002 <sup>10</sup>	Cross-sectional	41	23	Increased (serum)	Not performed	No correlation	
Sada et al., 2006 <sup>69</sup>	Cross-sectional	37	80	Increased (serum)	Increased (serum)	Not assessed	
Al et al., 2009 <sup>71</sup>	Cohort	105	77	Increased (serum)	No difference	No correlation	
Wisłowska et al., 2008 <sup>41</sup>	Cross-sectional	30	30	No difference (serum)	Not performed	No correlation	Serum leptin levels were lower in patients with arthritis and CNS involvement
Rovin et al., 2005 <sup>70</sup>	Cohort	47 (active) 33 (inactive)	28	Not performed	Increased (serum and urine)	Correlation with renal activity	Urinary adiponectin level can be a renal marker
Chung et al., 2009 <sup>68</sup>	Cross-sectional	109	78	Increased (serum)	Increased (serum)	No correlation	Serum leptin levels correlated with insulin resistance

\*Leptin or adiponectin as compared with controls. CNS: central nervous system.

Sada et al.<sup>69</sup> have shown a higher concentration of leptin and adiponectin in patients with SLE. Adiponectin was significantly elevated in patients with SLE with no insulin resistance, suggesting a role for that adipokine in insulin resistance.

Al et al.,<sup>71</sup> assessing children with SLE, have reported a higher concentration of leptin (34%) as compared with controls, but no difference in adiponectin concentration. They have assessed 105 patients with SLE (21 males and 84 females; mean age of 14.98 years), who were compared with healthy children. Similarly to the studies with adults, no correlation of leptin was observed with disease activity indices. Those authors have suggested that adipokines are not markers of activity.

Wisłowska et al.,<sup>41</sup> assessing 30 patients with SLE and 30 controls, have shown no difference in leptin serum levels between patients with SLE and the control group. However, leptin levels were lower in patients with arthritis and CNS involvement than in patients without such manifestations. Those authors have suggested that active chronic inflammation might reduce leptin concentration.

Rovin et al.<sup>70</sup> have reported an increase in adiponectin plasma levels in patients with SLE and renal involvement as compared with those in patients without renal involvement and in healthy controls. The adiponectin urinary level significantly increases in the presence of renal activity, suggesting that urinary adiponectin might be a marker of renal activity.

Chung et al.<sup>68</sup> have assessed the concentrations of resistin, visfatin, leptin and adiponectin in 109 patients with SLE and their correlations with coronary atherosclerosis, insulin resistance and inflammation. Patients with SLE showed higher concentrations of adiponectin, leptin and visfatin than those of the control group, but no adipokine correlated with coronary atherosclerosis. Low adiponectin and high leptin concentrations have been associated with insulin resistance, body mass index (BMI), and C-reactive protein (CRP). Those authors have suggested that adipokines promote the connection between insulin resistance and inflammation.

### Adipokines and RA

Regarding RA, studies have reported conflicting results concerning the role of adipokines.<sup>72</sup>

### Leptin and RA

Several studies have reported higher leptin levels in patients with RA than in controls,<sup>40,63–65,73,74</sup> and some have demonstrated their correlation with disease activity<sup>40,63,64,73</sup> (Table 2).

In 2003, Bokarewa et al.<sup>40</sup> assessed leptin levels in the serum and synovial fluid of 76 patients with RA, and correlated them with disease duration and activity, and radiological changes. They reported a significant increase in leptin serum

**Table 2**  
Measurement of leptin in rheumatoid arthritis

Author and year	Type of study	Patients	Controls	*Leptin concentration	Disease activity	Observation
Bokarewa et al., 2003 <sup>40</sup>	Cross-sectional	76	34	Increased (serum and synovial fluid)	Correlation	Lower concentration in synovial fluid was associated with non-erosive disease
Otero et al., 2006 <sup>73</sup>	Cross-sectional	31	18	Increased (serum)	Correlation	
Lee et al., 2007 <sup>63</sup>	Cross-sectional	50	No	Increased (serum)	Correlation	
Targonska-Stepniak et al., 2008 <sup>64</sup>	Cross-sectional	37	No	Increased (serum)	Correlation	Correlation with erosive RA and long duration
Salazar-Páramo et al., 2001 <sup>75</sup>	Cross-sectional	30	30	Increased (serum)	No correlation	
Gunaydin et al., 2006 <sup>74</sup>	Cross-sectional	50	34	Increased (serum)	No correlation	
Seven et al., 2009 <sup>65</sup>	Cross-sectional	20	25	Increased (serum and synovial)	No correlation	
Anders et al., 1999 <sup>8</sup>	Cross-sectional	58	16	No difference (serum)	No correlation	
Popa et al., 2005 <sup>78</sup>	Cross-sectional	31	18	No difference (serum)	Inverse correlation	Anti-TNF- $\alpha$ did not change leptin levels
Hizmetli et al., 2007 <sup>77</sup>	Cross-sectional	41	25	No difference (serum)	No correlation	
Wisłowska et al., 2007 <sup>76</sup>	Cross-sectional	30	30	No difference (serum)	No correlation	

\*Leptin measurement as compared with controls. RA: rheumatoid arthritis.

levels of patients as compared with those of healthy controls, and those levels were higher than synovial fluid levels. No correlation with disease duration was observed, and lower leptin synovial fluid levels were associated with non-erosive disease. Those authors have suggested that the lower synovial fluid levels are due to local consumption, and can provide a protective effect against joint damage.

Otero et al.<sup>73</sup> have also reported higher plasma levels of leptin, adiponectin and visfatin in patients with RA than in controls, suggesting a modulator role of inflammation in those patients.

Lee et al.<sup>63</sup> have assessed whether leptin levels were elevated in patients with active RA and whether such levels correlated with disease activity. Those authors reported a significant increase in leptin levels in patients with highly active disease, and positive correlation between leptin, DAS28, and CRP. In patients with highly active disease, who were followed up and showed a reduction in DAS28, a significant reduction in leptin level was observed. Those authors have concluded that leptin levels correlate with disease activity.

Targonska-Stepniak et al.,<sup>64</sup> assessing 37 patients with RA, have reported a significant increase in the leptin concentration in erosive disease and in patients with long-term disease. Leptin levels correlated positively with DAS28 level, erythrocyte sedimentation rate (ESR), and the number of painful joints, suggesting that leptin is associated with disease activity and the risk of progressive joint destruction.

In other studies,<sup>65,74,75</sup> although leptin levels were more elevated in patients with RA as compared with those of controls, neither clinical nor laboratory correlation with disease activity was observed.

In 2001, Salazar-Paramo et al.<sup>75</sup> reported that the mean leptin level was twice greater in patients with RA than in controls, and that no association was observed between the number of swollen joints, duration of morning stiffness and ESR. Comparing leptin levels of patients with active disease with those of patients in remission, no significant difference was observed.

Gunaydin et al.<sup>74</sup> have assessed leptin serum levels in patients with RA and correlated them with clinical and laboratory parameters of disease activity. Although leptin serum levels were higher in patients with RA, no correlation was observed between leptin levels and disease duration, number of painful and swollen joints, DAS28, CRP, ESR, TNF- $\alpha$ , and use of corticoid and methotrexate (MTX). No significant difference was observed between leptin levels in patients with high or low disease activity. Leptin levels were significantly higher in patients with RA than in controls,

but neither clinical nor laboratory correlation with disease activity was observed.

In 2009, Seven et al.<sup>65</sup> have reported significantly higher leptin levels in the serum and synovial fluid of patients with RA as compared with those of controls, and in patients with moderate disease activity as compared with those with low disease activity. Serum levels of leptin depended neither on age nor on inflammation markers. Those authors suggested that leptin levels could not be used to assess disease activity.

Despite such findings, some studies<sup>8,76,77</sup> have shown that the leptin concentration of patients with RA is similar to that of healthy controls.

In 1999, Anders et al.,<sup>8</sup> assessing the serum levels of leptin in 58 patients with RA and 16 controls, reported no significant difference. Leptin correlated with the percentage of body fat, but not with disease activity.

Popa et al.<sup>78</sup> have tried to correlate leptin with inflammation, and have assessed whether anti-TNF- $\alpha$  modulated its concentration. Those authors have found no difference in leptin concentration between patients with RA and controls, but an inverse correlation with inflammation. After two weeks of treatment with anti-TNF- $\alpha$ , no change in leptin concentration was observed. Those authors have suggested that chronic inflammation can reduce leptin levels.

Hizmetli et al.<sup>77</sup> have reported no significant difference in leptin level between patients with RA and healthy controls. Neither serum nor synovial fluid levels correlated with disease duration, ESR, CRP, rheumatoid factor, and articular erosions. Those authors have concluded that leptin does not correlate with disease activity.

Wislowska et al.<sup>76</sup> have found no significant difference in leptin serum levels between patients with RA and controls with osteoarthritis.

### Adiponectin and RA

The increase in adiponectin levels observed in patients with RA<sup>79-81</sup> has suggested the existence of a pro-inflammatory, rather than anti-inflammatory, activity (Table 3).

Senolt et al.<sup>79</sup> have reported significantly higher serum levels of adiponectin in patients with RA than in healthy controls, comparable with the levels in patients with osteoarthritis. However, the concentration in the synovial fluid of patients with RA was higher than that of those with osteoarthritis. Those authors have concluded that the increase in adiponectin in the synovial fluid of patients with RA can counteract the local inflammatory process.

**Table 3**  
Measurement of adiponectin in rheumatoid arthritis

Author and year	Type of study	Patients	Controls	* Adiponectin concentration	Disease activity	Observations
Senolt et al., 2006 <sup>79</sup>	Cross-sectional	20	21 (OA) 23 (healthy)	Increased (serum and SF)	No correlation	In RA, a negative correlation with leukocyte count was observed in the SF
Laurberg et al., 2009 <sup>80</sup>	Cohort	114	35 (OA) 45 (healthy)	Increased (serum)	No correlation	Greater increase in patients treated with MTX
Ebina et al., 2009 <sup>81</sup>	Cohort	37 (mild RA) 53 (severe RA)	42	Increased (serum)	No correlation	Correlation with intensity
Targonska-Stepniak et al., 2010 <sup>82</sup>	Cross-sectional	80	No	Not assessed	Negative correlation	Correlation with long-term disease
Nagashima et al., 2008 <sup>83</sup>	Cohort	46 (IFX) 28 (ETN) 37 (without anti-TNF- $\alpha$ )	19	No difference (serum)	Not shown	Increased serum levels after treatment with anti-TNF- $\alpha$
Komai et al., 2007 <sup>84</sup>	Cohort	15 (IFX)	No	Not assessed	Negative correlation	Increased serum levels after treatment with anti-TNF- $\alpha$
Nashida et al., 2008 <sup>85</sup>	Cohort	97 (IFX)	No	Not assessed	No correlation	Increased serum levels after treatment with anti-TNF- $\alpha$
Härle et al., 2006 <sup>86</sup>	Cohort	32 (ADA)	No	Not assessed	No correlation	No change in serum levels after treatment with anti-TNF- $\alpha$

\*Adiponectin measurement as compared with controls. OA: osteoarthritis; SF: synovial fluid; RA: rheumatoid arthritis; MTX: methotrexate; IFX: infliximab; ADA: adalimumab; ETN: etanercept.

In 2009, Laurberg et al.<sup>80</sup> compared adiponectin levels of patients with initial RA and no use of DMARDs with those of individuals with the following characteristics: chronic RA; osteoarthritis; and healthy. They have also assessed the change in adiponectin levels during treatment with MTX in a subgroup of chronic RA. Adiponectin was significantly greater in healthy individuals as compared with patients with initial RA, chronic RA or osteoarthritis. Patients with chronic RA treated with MTX showed a 13% increase in adiponectin levels.

Ebina et al.<sup>81</sup> have compared the serum levels of adiponectin between patients with severe and mild RA and controls, and have observed a correlation of adiponectin with disease intensity, but no correlation with inflammatory markers (CRP and DAS28), suggesting an association between the number of joints damaged and adiponectin increased levels.

In the study by Targonska-Stepniak et al.,<sup>82</sup> adiponectin levels correlated with long-term disease (> 10 years), showing a positive relation with age increase and disease duration, and a negative relation with disease activity.

Contrary to leptin, whose levels do not change with the use of anti-TNF- $\alpha$ ,<sup>78</sup> some studies have shown the action of that drug on adiponectin levels.<sup>83–85</sup> In the study by Härle et al.,<sup>86</sup> however, that correlation was not evidenced.

Nagashima et al.,<sup>83</sup> assessing adiponectin levels, have reported no significant difference between healthy controls and

patients with RA. However, in the group of women treated with infliximab and etanercept, adiponectin levels were significantly higher.

Komai et al.<sup>84</sup> have reported a significant increase in adiponectin levels on the second and sixth weeks of treatment with infliximab, and suggested TNF- $\alpha$  played a role in the expression of that adipokine.

Nashida et al.<sup>85</sup> have assessed 97 patients with active RA treated with infliximab every eight weeks for 52 weeks, and have reported a significant increase in adiponectin levels and improvement in disease activity and inflammatory markers. Those authors have suggested that adiponectin and TNF- $\alpha$  have opposite effects, and that TNF- $\alpha$  blockade can interfere directly or indirectly with atherosclerosis, via adiponectin, improving the morbidity and cardiovascular mortality of the chronic inflammatory disease.

Härle et al.<sup>86</sup> have assessed the levels of leptin and adiponectin in 32 patients with RA treated with adalimumab for 12 weeks, and they have not found any change during the treatment. In 16 patients previously treated with prednisone, adiponectin levels were significantly lower than those of the patients treated without corticoid, and such difference remained during the whole period studied. Those authors have concluded that, in patients with RA, serum levels of leptin and adiponectin neither relate to inflammation nor decrease after 12 weeks of treatment with anti-TNF- $\alpha$ .

The adiponectin increase observed in patients with RA after treatment with anti-TNF- $\alpha$  suggests it has an anti-inflammatory activity. Thus, the pro- or anti-inflammatory effect of adiponectin in RA still remains uncertain.

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## ADIPOKINES AND JOINT DAMAGE

Some studies<sup>14,87,88</sup> have shown that obesity protects against joint damage in RA. Although its mechanism has not been elucidated, adipokines seems to be involved.

In the study by Giles et al.,<sup>66</sup> adiponectin has shown a strong association with radiological joint damage. The same, however, has been observed with neither resistin nor leptin. Those authors have concluded that adiponectin might represent the connection between a lower fat mass and radiological joint damage, and might also be a new therapeutic strategy for attenuation of the latter.

Rho et al.<sup>67</sup> have assessed the serum concentrations of leptin, resistin, adiponectin and visfatin in 167 patients with

RA and have reported a higher concentration of all those adipokines, as compared with controls. Visfatin showed a positive association with greater radiological joint damage, while leptin showed a negative association. Those authors have suggested that adipokines are increased in patients with RA and might modulate joint damage.

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## FINAL COMMENTS

The discovery of adipokines has shown the important role played by adipose cells in homeostasis, and that their by-products, cytokines and hormones, act on the immune system. However, the results of the studies on those mediators in rheumatic diseases are still controversial. Further comparative studies are required in different phases of diseases, different populations, and with reproducible methods, to better understand the function and importance of those substances in that subgroup of patients.

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