

Potential Influence of Adiponectin on
Systemic Lupus Erythematosus and
Rheumatoid Arthritis TherapyRenan Grecco Costa¹, Ligia Grecco Costa Dall'Aqua¹, Andrea Name Colado Simao² and Isaias Dichi^{3*}¹Department of Experimental Pathology, University of Londrina, Brazil²Department of Pathology, University of Londrina, Brazil³Department of Internal Medicine, University of Londrina, Brazil

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Editorial

There is growing efforts in developing pharmacological and non-pharmacological therapies directed to decrease both the inflammatory status and the metabolic complications associated to Systemic Lupus Erythematosus (SLE) and Rheumatoid Arthritis (RA). Nevertheless, these aims provoke a continuum challenge due to the pathophysiological complexity of these rheumatic diseases. SLE consists in the development of auto antibodies, which can affect several systems, such as mucocutaneous, musculoskeletal, renal and central nervous system [1], whereas the main AR features are pain, swelling and morning stiffness in distal joints [2].

Whereas the impact of infections and active disease on mortality has diminished dramatically over the years due to intensive treatment, Cardiovascular Disease (CVD) has emerged as the leading cause of death in these patients [3]. The incidence of myocardial infarction is 5 times as high in patients with lupus as in the general population, and in young women the age-specific incidence is increased by a factor of as much as 50 [4]. Similarly, patients with RA present higher cardiovascular risk, as shown by one to one and a half fold coronary diseases; two fold congestive heart disease and two to three fold thromboembolism [5].

Adiposity and insulin resistance are the main pathophysiological mechanisms underlying Metabolic syndrome (Mets). Obesity is considered one of the most important determinants of the low-grade chronic inflammation present in MetS, however, there are normal-weight individuals with MetS. Furthermore, in some classical inflammatory diseases, such as SLE and RA, insulin resistance rather than obesity [6] better explain the higher prevalence of MetS. Therefore, in addition to the continuous efforts to expand the knowledge on the beneficial effects of anti-inflammatory therapy, the development of new drugs to overcome insulin resistance is needed.

Adiponectin is one of the most frequent types of adipocytokines, with a physiologic range concentration between 5 and 30 µg/ml. It is secreted by adipocytes in three main forms: trimer, hexamer and high molecular weight multimer comprising at least 18 monomers [7]. Differently from other adipocytokines, its concentration is inversely associated with adiposity, adipocyte size and insulin sensitivity [8]. Adiponectin has been investigated due to its antidiabetic [9], antiatherogenic, and anti-inflammatory [11] effects.

Adiponectin protective capacity is mainly related to endothelial nitric oxide synthase induction [12,13] and reactive oxidative species inhibition [14] and thus is becoming a potential target to several inflammatory conditions, including autoimmune diseases and the low-grade chronic inflammation verified in Mets patients.

Tumor Necrosis Factor alpha (TNF-α) has an important pro inflammatory rule in autoimmune diseases and its signalization pathway, Nuclear Factor κB (NF-κB), may induce molecules which recruit leukocytes and generates tissue injury. Adiponectin may suppress this pathway through a cAMP dependent pathway in aortic endothelial cells [15].

The immunomodulator role of Adiponectin is Reinforced by the Presence of Receptors (ADIPOR1 e ADIPOR2) at the extracellular surface in mononuclear cells. Pang & Narendran [16] verified a higher expression in monocytes (93%), followed by B lymphocytes (47%), natural killer (21%) and T lymphocytes (1%). Adiponectin induces T cells apoptosis which suggest a role of adiponectin as a T lymphocytes negative regulator [17]. Dendritic cells co-cultured *in vitro* (treated with adiponectin) with allogenic T cells reduced lymphocytes proliferation, IL-2 production, and increased T CD4⁺CD25⁺FoxP3⁺ cells. Adiponectin also induces the secretion of anti-inflammatory mediators such as IL-10 e IL-1RA by monocytes, macrophages, and dendritic

cells; its anti-inflammatory activity enhances with IFN- γ inhibition by macrophages [11].

The negative adiponectin regulation can occur by the influence of pro inflammatory cytokines. Adiponectin expression and secretion in adipocytes 3T3-L1 is decreased in a dose-dependent way as TNF- α (0,1 ng/ml) is able to reduce adiponectin gene promoter activity in 80% [19]. In addition, 3T3-L1 cells treated with IL-6 showed a reduction in adiponectin secretion [20].

Rizo et al. [21] showed that Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) score was directly associated with Macrophage Inhibitor Factor (MIF) and adiponectin concentrations. They also verified an inverse correlation between adiponectin and serum glucose and body mass index, whereas there was a positive correlation with prednisone doses.

In a murine lupus model, a Peroxisome Proliferator-Activated Receptor gamma (PPAR γ) agonist (rosiglitazone) used as an antidiabetic drug, diminished autoantibodies production, renal disease and atherosclerosis. These actions were dependent on adiponectin induction, as deficient adiponectin animals did not show the aforementioned beneficial effects [22]. Recently, our group showed that n-3 fatty fish oil fatty acids (3g/d) decreased SLEDAI score, triacylglycerols and leptin concentrations, whereas there was an increase in adiponectin levels [23]. Fish oil also acts as a PPAR γ agonist leading to the enhancement of adiponectin concentrations.

Some studies assessed adiponectin levels in patients with RA who received anti-TNF- α therapy. The associated administration of infliximab and etanercept increased adiponectin in women, but not in men [24], whereas other study showed a positive correlation between adiponectin and endothelial dependent vasodilation with infliximab [25]. Additionally, long-term infliximab treatment augmented adiponectin and HDLc levels and decreased C-reactive protein [26].

More studies are warranted to expand our knowledge on the physiopathological mechanisms involved in adiponectin regulation in autoimmune diseases. Moreover, pharmacological and non-pharmacological approaches are needed to determine the association of increasing adiponectin concentrations and the beneficial effects on features related to SLE and RA.

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