The Complex Role of Leptin in SLE: Is Leptin A Key Link Between Metabolic Syndrome, Accelerated Atherosclerosis and Autoimmunity?

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Abstract

Adipokines discovery opened a new research field that investigates the interface and the relationship between immune response, nutrition, and metabolism. Leptin is the first adipokine discovered and exerts a wide spectrum of biologic function such as control of food intake and energy expenditure, modulation of insulin sensitivity, regulation of neuro-endocrine system and activation of immunity. Leptin involvement is described in many autoimmune diseases. In SLE, leptin seems playing a complex role, linking metabolic syndrome, atherosclerosis, and autoimmune disease activity.

Keywords: Leptin; SLE; Metabolic syndrome; Atherosclerosis

Leptin in SLE

In recent years the concept of the adipose tissue has dramatically changed. The adipose tissue is no longer considered an inert site of energy storage and temperature control, but an endocrine organ, capable of secreting a wide range of mediators, called adipokines [1]. Adipokines are involved in metabolism, appetite and energy balance, insulin sensitivity, endocrine and reproductive function, bone metabolism, atherogenesis and immunity [1,2]. Adipokines discovery opened a new research field that investigates the interface and the relationship between immune response, nutrition, and metabolism. Crescent evidences demonstrated the presence of an inflammatory background in many apparent non-immunologic diseases such as type 2 diabetes, obesity and atherosclerosis. It has been widely demonstrated that inflammatory mediators as tumor necrosis factor alpha (TNFalpha), C-reactive protein (CRP) or interleukin-6 (IL-6) are capable to modulate insulin sensitivity leading to insulin resistance. A pro-inflammatory status, with increased levels of circulating inflammatory cytokines and reduction of T regulatory cells, has been described in metabolic syndrome and obesity [1-3]. Instead, atherosclerosis is now considered an immune-mediated disease in which inflammation is involved in all disease stages, from endothelial dysfunction to plaque formation and progression and finally to plaque rupture. In all these conditions adipokines are involved linking adipose tissues to inflammation [1-3].

Research on adipokines began in the late 90’s with the discovery of leptin and its receptor. Leptin gene (ob, derived from obese) was cloned by Friedman et al in 1994 studying ob/ob mice, a murine model characterized by morbid obesity, insulin resistance and infertility. Ob gene was found to encode a 16 kD protein, named leptin, from the Greek word “leptos” that means thin. Leptin is a 167-amino acid peptide with a four-helix bundle motif similar to helicoidal cytokines as IL-12. Leptin is produced predominantly in the subcutaneous white adipose tissue but is also expressed in a variety of other tissues, including placenta, ovaries, mammary glands, gastric mucosa, pituitary glands, bone marrow, and lymphoid tissues. Leptin is secreted in a pulsatile manner displaying a circadian rhythm with highest levels at midnight [4,5]. Leptin circulating levels are proportional to fat deposits. Factors increasing leptin levels are excess energy stored and overfeeding, estrogen and insulin. Conversely, low energy states with decreased fat stores and fasting, adrenergic agonists, thyroid hormones and testosterone decrease leptin levels. Leptin binds to leptin receptors (ObRs) located throughout the central nervous system and peripheral tissues, with six receptor isoforms (ObRα, ObRb, ObRc, ObRd, ObRe and ObRf) generated by alternative splicing of db gene. LepRb is the long receptor isoform and is responsible for the main effects of leptin on energy homeostasis and neuroendocrine functions. LepRb displays high affinity with class I cytokine receptors [4,5].

Leptin: Metabolic Functions

Leptin is transported across the blood-brain barrier, probably through short LepR isoforms. Leptin binds LepRb on the arcuate nucleus (ACR) neurons, activating a complex neural circuit involved in food intake control. In particular leptin activates anorexigenic neurons that synthesize pro-opiomelanocortin (POMC) and cocaine- and amphetamine-regulated transcript (CART), and inhibiting orexigenic neurons that synthesize agouti-related peptide (AgRP) and neuropeptide Y (NPY). Circulating leptin levels fall during fasting, leading to increased expression of orexigenic neuropeptides and decreased expression of anorexigenic neuropeptides. In addition, the decline of leptin modulates mesolimbic dopaminergic system in ventral tegmental area (VTA) and hindbrain circuits to increase food intake. Moreover, leptin levels reduction inhibits sympathetic nervous system, resulting in decrease energy expenditure [6]. Leptin displays important neuroendocrine functions, modulating hypothalamic-pituitary-gonadal axis, hypothalamic-pituitary-thyroid axis and hypothalamic-pituitary-adrenal axis. In condition of energy deficiency, leptin reduces production of reproductive hormones, down-regulates thyroid hormones and increases glucocorticoids levels [7].

In physiological conditions leptin is a crucial modulator of insulin sensitivity, not only acting on central control of food intake and energy expenditure, but also exerting a direct effect on peripheral tissues. In liver, leptin inhibits gluconeogenesis and fatty acid production. Leptin...
stimulates skeletal muscles to uptake glucose and to fatty acid oxidation. Moreover, the adipokine reduces insulin production by pancreas beta-cells [6,7].

In contrast to physiological condition, in obesity, diabetes mellitus and metabolic syndrome, leptin is unable to reduce appetite and increase energy expenditure. These diseases are associated with hyperleptinemia, but central nervous system and peripheral tissues are resistant or tolerant to the effects of leptin, leading to a leptin-resistance condition. Moreover, as a consequence of peripheral resistance, leptin fails to modulate insulin sensitivity.

The hyperleptinemia condition plays a role in atherogenesis, promoting oxidative stress, production of inflammatory mediators, expression of adhesion molecules by vascular endothelium and monocytes recruitment, interfering with vasodilation, stimulating vascular hypertrophy and proliferation of foam cells. These events lead to endothelial dysfunction and plaque formation [8].

Leptin: Role in Immunity and Autoimmunity

Leptin plays important immunological function, both on innate and acquire immune system. The immunological role of leptin is related to its molecular structure with high affinity with long-chain helical cytokine family such as IL-2 or IL-12. Leptin promotes chemotaxis and inflammatory macrophages, leptin leads to cell activation, production of pro-inflammatory cytokines (TNFalpha, IL-6), induction of phagocytosis and expression of type 2 cyclo-oxygenase (COX2). Leptin is involved in lymphocytes functions. The adipokine induces activation and proliferation of naïve T cells, by production of IL-2. Moreover, leptin promotes T helper 1 (Th1) immune responses and inhibits function and proliferation of T regulatory cells [9-11] (Figure 1).

Experiments on murine models of systemic autoimmunity, such as collagen-induced arthritis and autoimmune encephalomyelitis, clearly demonstrate the importance of leptin in autoimmunity pathogenesis. Recent scientific data confirm the leptin involvement in many human diseases as rheumatoid arthritis, psoriatic arthritis and anklyosing spondylitis, systemic sclerosis [9-12].

Leptin: Involvement in SLE

A number of studies explored the role of leptin in SLE, with contrasting results. A recent meta-analysis did not show significant differences in circulating leptin levels among SLE and healthy subjects, although leptin were higher than controls in a subgroup of SLE with age over 40 years and BMI below 25 kg/m². The conflicting results of serum/plasma leptin expression in SLE underline the wide heterogeneity of the populations enrolled in the different studies. However, most of these studies found leptin hyperexpression in SLE patients (Table 1).

We published several studies of leptin in SLE. In our SLE population we reported an increased prevalence of metabolic parameters (fasting insulin, HOMA-IR, body mass index, waist circumference) and cardiovascular risk factor (total and LDL cholesterol, homocysteine, CRP).

The differences in these parameters between SLE and healthy controls were particularly evident considering only fertile age women. Moreover we found an augmented prevalence of metabolic syndrome in SLE, particularly in women of childbearing age.

In the same study, leptin was hyper-expressed in sera of SLE patients, especially in fertile age. In accordance with literature data, in our study leptin correlated with metabolic parameters such as BMI and insulin levels but also with Italian cardiovascular risk score.

Interestingly, in a multivariate analysis, determinant of leptin levels were insulin levels, triglycerides, BMI, but also median daily prednisone dosage and SLE disease activity index SLEDAI-2K. We confirmed these results in another study, in which we also demonstrated a relation of leptin with carotid vascular stiffness parameters, ultrasonographic markers of subclinical atherosclerosis.

Our results suggest that leptin plays a complex role in SLE, linking metabolic syndrome, accelerated atherosclerosis and disease activity. On this basis it is possible to hypothesize that leptin directly contributes to lupus pathogenesis [13-15].

Several studies suggest a direct involvement of leptin in lupus autoimmune phenomena. We summarized these evidences in Table 1.

Figure 1: Adipocytes and immune cells are functionally linked by a molecular cross-talk, in which leptin and other adipokines and cytokines are produced. Leptin receptor is widely expressed on immune cells. Leptin modulates function of both innate and adaptive immunity. IL: Interleukin; TNF: Tumour Necrosis Factor; CD: Cluster of Differentiation; mTOR: Mammalian Target of Rapamycin; Ig: Immunoglobulin; NO: Nitric Oxide; LT: Leukotriene; INF: Interferon.
Leptin Levels in human SLE. ↑ After adjusting by metabolic variables, the serum leptin levels remained higher in SLE than in controls. [16]

↑ Plasma leptin, TNF-α, adiponectin levels were higher in SLE patients than controls [17]

= Leptin correlation with BMI, age, SLE disease duration [18]

↓ Patients with SLE have increased concentrations of adiponectin, leptin and visfatin. [19]

↑ Leptin levels were lower and adiponectin, ghrelin and visfatin levels were higher in the patients. [20]

↑ Independent determinants of leptin were insulin levels, triglycerides, body mass index, corticosteroid dosage, and SLE Disease Activity Index [13]

↑ The leptin levels of SLE patients were higher than those of normal healthy controls, while the ghrelin levels of the SLE were lower. [21]

↑ High leptin levels greatly increase the risk of subclinical atherosclerosis in SLE, and are also associated with an increase in inflammatory biomarkers of atherosclerosis such as pHDL, Lp(a) and OxPL/apoB100. [22]

↑ positive correlation of leptin with stiffness parameters. [14]

↑ The expression of adiponectin and resistin was increased in both sera and urine from LN patients, while leptin was increased in LN patient sera, compared to matched controls [23]

↑ Leptin role in autoimmune processes. In vitro studies and lupus-prone mice models. In the lupus-prone mice BWF1, addition of leptin increased pro-inflammatory high-density lipoprotein scores and atherosclerosis, and accelerated proteinuria. [24]

↑ Fasting-induced hypoleptinemia in (NZB x NZW)F(1) lupus-prone mice induced an expansion of functional regulatory T cells that was reversed by leptin replacement. [25]

↑ Leptin promotes the survival and proliferation of autoreactive T-cells in mice with an autoreactive T-cell repertoire, including (NZB x NZW)F1 lupus-prone mice [26]

↑ Leptin promoted Th17 responses in normal human CD4(+) T cells and in mice, both in vitro and in vivo, by inducing RORgammat transcription. Leptin also increased Th17 responses in (NZB x NZW)F1 lupus-prone mice, [27]

↑ leptin promoted phagocytosis of apoptotic cells by macrophages by modulating cAMP levels in macrophages in (NZB x NZW)F1 lupus mice [28]

↑ Leptin-deficient MRL/Mp-Fas/lpr) mice showed low lpr cells, low titer of anti-dsDNA, reduction of kidney damage, increased spleen Tregs. Leptin suppressed regulatory T cells and enhanced Th17 cells in vitro. [29]

↑ Leptin and Neutrophil-Activating Peptide 2 act synergistically to promote mesenchymal stem cells senescence through enhancement of the PI3K/Akt signaling pathway in SLE patients. [30]

Table 1: In the table we summarized studies concerning circulating leptin levels in human SLE. In the second part of the table we reported the evidences of leptin involvement in autoimmune processes.

In conclusion, leptin is widely involved in SLE, not only in promotion of metabolic syndrome and accelerated atherosclerosis, but also in systemic inflammation and autoimmune processes. These evidences offer relevant possibilities for leptin targeting as future lupus therapy.

References
1. Exley MA, Hand L, O’Shea D, Lynch L (2014) Interplay between the immune system and adipose tissue in obesity. J Endocrinol 223: 41-8.
2. Bühler M, Mantzoros CS (2015) From leptin to other adipokines in health and disease: facts and expectations at the beginning of the 21st century. Metabolism 64: 131-145.
3. Molica F, Morel S, Kwak BR, Rohner-Jeanrenaud F, Steffens S (2015) Adipokines at the crossroad between obesity and cardiovascular disease. Thromb Haemost 113: 553-566.
4. Park HK, Ahima RS (2015) Physiology of leptin: energy homeostasis, neuroendocrine function and metabolism. Metabolism 64: 24-34.
5. Münzberg H, Morrison C (2015) Structure, production and signaling of leptin. Metabolism: clinical and experimental 64: 13-23.
6. Allison M, Myers M (2014) 20 years of leptin: connecting leptin signaling to biological function. The Journal of endocrinology 223: 25-35.
7. Dalamaga M, Chou SH, Shields K, Papageorgiou P, Polyzos SA, et al. (2013) Leptin at the intersection of neuroendocrinology and metabolism: current evidence and therapeutic perspectives. Cell Metab 18: 29-42.
8. Kömmer AC, Brüning JC (2012) Selective insulin and leptin resistance in metabolic disorders. Cell Metab 8: 144-152.
9. Vadacca M, Margiotta DP, Navarini L, Afeltra A (2011) Leptin in immuno-rheumatological diseases. Cell Mol Immunol 8: 203-212.
10. Procaccini C, Pucino V, Mantzoros CS, Matarese G (2015) Leptin in autoimmune diseases. Metabolism 64: 92-104.
11. Conde J, Scotece M, Abella V, López V, Lazzaro V, et al. (2014) An update on leptin as immunomodulator. Expert Rev Clin Immunol 10: 1165-1170.
12. Abella V, Scotece M, Conde J, López V, Zardi EM, et al. (2013) Adipokines, metabolic syndrome and rheumatic diseases. J Immunol Res 2013: e343746.
13. Garcia-Gonzalez A, Gonzalez-Lopez L, Valera-Gonzalez IC, Cardona-Munoz EG, Salazar-Paramo M, et al. (2002) Serum leptin levels in women with systemic lupus erythematosus. Rheumatol Int 22: 138-141.
14. Sada KE, Yamasaki Y, Maruyama M, Sugiyama H, Yamamura M, et al. (2006) Altered levels of adipokines in association with insulin resistance in patients with systemic lupus erythematosus. J Rheumatol 33: 1545-1552.
15. Wolsowska M, Rok M, Stepien K, Kuklo-Kowalska A (2008) Serum leptin in systemic lupus erythematosus. Rheumatol Int 28: 467-473.
16. Chung CP, Long AG, Solus JF, Rho YH, Oeser A, et al. (2009) Adipokynes in systemic lupus erythematosus: relationship to inflammation, insulin resistance and coronary atherosclerosis. Lupus 18: 799-806.
17. De Sanctis JB, Zabaleta M, Bianco NE, Garmendia JV, Rivas L (2009) Serum adipokine levels in patients with systemic lupus erythematosus. Autoimmunity 42: 272-274.
18. Kim HA, Choi GS, Jeon GY, Yoon JM, Sung JM, et al.(2010) Leptin and ghrelin in Korean systemic lupus erythematosus. Lupus 19: 170-174.
19. McMahon MB, Skaggs J, Sahakian L, Grossman J, FitzGerald J, et al. (2011) High plasma leptin levels confer increased risk of atherosclerosis in women with systemic lupus erythematosus, and are associated with inflammatory oxidised lipids. Ann Rheum Dis 70: 1619-1624.
20. Hutcheson J, Ye Y, Han J, Arriens C, Saxena R, et al. (2015) Resistin as a potential marker of renal disease in lupus nephritis. Clin Exp Immunol 179: 435-443.
21. Hahn BH, Lourenchco EV, McMahon M, Skaggs B, Le E, et al. (2010) Pro-inflammatory high-density lipoproteins and atherosclerosis are induced in lupus-prone mice by a high-fat diet and leptin. Lupus 19: 913-917.
22. Liu Y, Yu Y, Matarese G, La Cava A (2012) Cutting edge: fasting-induced hypo leptinemia expands functional regulatory T cells in systemic lupus erythematosus. J Immunol 188: 2070-2073.
23. Amarilyo G, Ikikuni N, Shi FD, Liu A, Matarese G, La Cava A (2013) Leptin promotes lupus T-cell autoimmunity. Clin Immunol 144: 530-533.
24. Yu Y, Liu Y, Shi FD, Zou H, Matarese G, La Cava A (2013) Cutting edge: Leptin-induced RORgammat expression in CD4+ T cells promotes Th17 responses in systemic lupus erythematosus. J Immunol 190: 3054-3058.
25. Fujita Y, Fuji T, Mimori T, Sato T, Nakamura T, et al. (2014) Deficient leptin signaling ameliorates systemic lupus erythematosus lesions in MRL/Mp-Fas lpr mice. J Immunol 192: 979-984.
26. Chen H, Shi B, Feng X, Kong W, Chen W, et al. (2015) Leptin and Neutrophil-Activating Peptide 2 Promote Mesenchymal Stem Cell Senescence Through Activation of the Phosphatidylinositol 3-Kinase/Akt Pathway in Patients With Systemic Lupus Erythematosus. Arthritis Rheumatol 67: 2383-2393.