

Review Article

Adipokines: mediators of immunity and inflammation

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ABSTRACT

White adipose tissue has emerged as a highly dynamic organ that releases a plethora of immune and inflammatory mediators that are involved in obesity, metabolic syndrome and immune mediated diseases. Adipokines have complex role in various physiological and pathological processes by exerting potent modulatory actions on target tissues. In this Review, In this review, we explore the effects of different adipokines, focusing primarily on leptin, adiponectin, visfatin and resistin in causing immune-mediated and/or inflammatory diseases.

Keywords: Adipokines, Immunity, Immune-mediated diseases, Pro-inflammatory

INTRODUCTION

Adipose tissue was recognized as long term energy storage organ but now it is being acknowledged as a complex and highly dynamic organ responsible to maintaining systemic metabolism, endocrine and immune functions. All the functions are mediated by plethora of factors released from adipocytes.¹The main physiological and biochemical characters of adipose tissue subtypes have been described in table 1.² White adipose tissue release/produce factors called adipokines, which have autocrine, endocrine or paracrine function on physiological or pathophysiological processes.³ In this review, we explore the effects of different adipokines in causing immune-mediated and/or inflammatory diseases.

Leptin

Adipocyte derived protein, derived through a Greek work "leptos" meaning "thin", discovered in 1995. There are many role of leptin in human physiology in regulation of energy homeostasis, neuroendocrine function, and metabolism, mainly in states of energy deficiency and not

energy excess (that is, obesity).⁴ Secreted mainly from white adipose tissue and levels are related directly to adiposity and higher levels being in women. Leptin secretion has pulsatile fashion, levels more in evening and early morning hours.⁵ Leptin mediate its effect through leptin receptors, present in brain and peripheral tissues. These receptors are long, short and soluble isoform, further having subtypes Ob-Rb for long isoform, Ob-Ra, c, d, f for short isoform, Ob-Re for soluble isoform. Leptin binds to long isoform of leptin receptors, causing homodimerization of receptors, this activates JAKs and subsequent phosphorylation of leptin receptor. This phosphorylation helps in association with STAT3 and phosphorylated STAT3 dissociate from receptor, translocating into nucleus causing gene expression.⁶

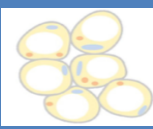
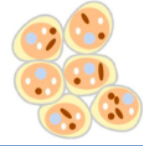
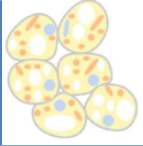
Adiponectin

Lodish and colleagues first described Adiponectin as a protein similar to complement factor C1q and named it Acrp30 (adipocyte complement-related protein of 30 kDa). Adiponectin is very unique in structure with a collagen-like domain at the N-terminus, and a globular

domain at the C-terminus having structural homology to proteins such as collagens VIII and X and complement factor C1q.⁷ This is adipocyte derived protein released mainly from adipose tissue and has role in energy homeostasis and regulation of adiposity. The amount of adiponectin in circulation is inversely correlated with adiposity and conditions associated with insulin

resistance including cardiovascular diseases, hypertension, and metabolic syndrome.⁸ Adiponectin mediate its action through AdipoR1, AdipoR2, T-cadherin. Adiponectin mediate its action via AMPK/PPAR- α signalling, which key mediator in anti-inflammatory pathway.⁹

Table 1: Overview of types of adipose tissue.

			
	White adipose tissue	Brown adipose tissue	Beige adipose tissue
Location in body	Subcutaneous Intra-abdominal Epicardial Gonadal	Paravertebral Supraclavicular Interscapular	Has functions similar to brown adipose tissue but dispersed in white adipose tissue depots
Morphology	Spherical with single lipid droplets and few mitochondria	Elliptical with large number of small sized lipid droplets and large number of mitochondria	Spherical with small lipid droplets. Mitochondria appear after stimulation (cold exposure or sympathetic stimulation)
Functions	Energy storage Endocrine functions	Energy expenditure Thermogenesis	Thermogenesis

Visfatin

Visfatin identified in 2004 is predominantly produced and secreted in visceral fat. It is identical to pre-B cell colony-enhancing factor (PBEF) and also recognized as the formerly described Nicotinamide phosphoribosyltransferase (Nampt), the limiting enzyme in nicotinamide adenine dinucleotide (NAD) biosynthesis. It inhibit expression of miR-199a-5p expression via ERK, P38, JNK signalling pathway and induce production of IL-6 and TNF- α .¹⁰

Resistin

Described in 2001 and named for its ability to resist insulin action. Resistin may modulate molecular pathways involved in metabolic, inflammatory and autoimmune diseases, in addition to its cardiovascular targets.¹¹ There has been only one published report where the authors show that resistin competes with lipopolysaccharide for binding to TLR4 receptor in human myeloid and epithelial cells and TLR activation initiates a cascade of intracellular events leading to alterations in transcription and signalling pathways, including NF κ B signalling.¹²

Effect of adipokines on immunity

Adipokines affects both innate and acquired immunity (Figure 1).¹³ In innate immunity, leptin increase

proliferation of monocytes, enhances macrophages phagocytosis activity, increases chemotaxis and release of oxygen radicals.

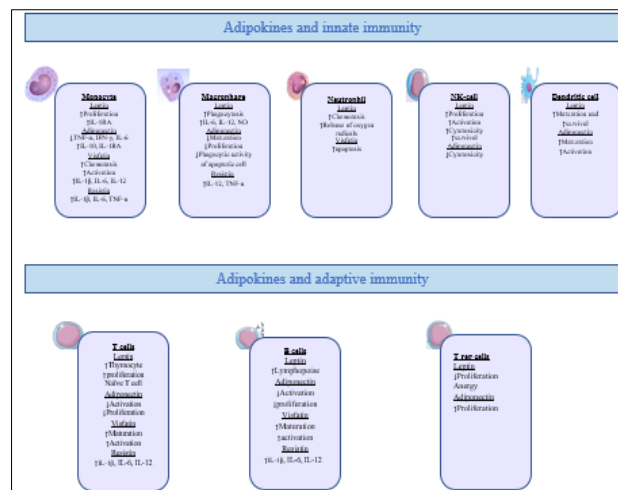


Figure 1: Effect of adipokines on immune system.

It enhance proliferation, differentiation, activation and cytotoxicity of NK cells. Leptin is also an important regulator of the acquired response. Indeed, leptin-deficient mice have defective cellular immunity and exhibit thymic and lymphoid atrophy. Furthermore, it inhibits the proliferation of T-regulatory cells. Adiponectin promotes phagocytosis of apoptotic cells by

macrophages, whose accumulation can trigger inflammation or immune system dysfunction. It reduces the secretion and activity of TNF- α and IL-6, and induces production of anti-inflammatory mediators, such as IL-10 and IL-1 receptor antagonist in monocytes, macrophages, and dendritic cells. Adiponectin also increases the number of T regulatory cells. Conversely, it promotes the maturation and activation of dendritic cells. Interestingly, both TNF α and IL-6 are potent inhibitors of adiponectin secretion, which suggests the existence of a negative feedback between adiponectin and pro-inflammatory cytokines.

Further anti-inflammatory effects of adiponectin involve suppression of IL-2-induced NK cell cytotoxic activity. In acquired immunity, it inhibits the activation and proliferation of T lymphocytes and B-cell lymphopoiesis. Visfatin acts as a chemotactic factor on monocytes and lymphocytes. It strongly affects the development of both T- and B-lymphocytes.¹³

DISCUSSION

Role of adipokines in rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disease affecting typically synovial joints and leading to progressive articular damage, disability, and reduced quality of life. Despite better recent therapeutic strategies improving long-term outcomes, RA is associated with a high rate of comorbidities, infections, malignancies, and cardiovascular disease.¹⁴ Adipocytokines modulate the function of different tissues and cells, and in addition to energy homeostasis and metabolism, amplify inflammation, immune response, and tissue damage. Adipocytokines may contribute to the proinflammatory state in RA patients (Figure 2) and development of bone damage.^{15,16}

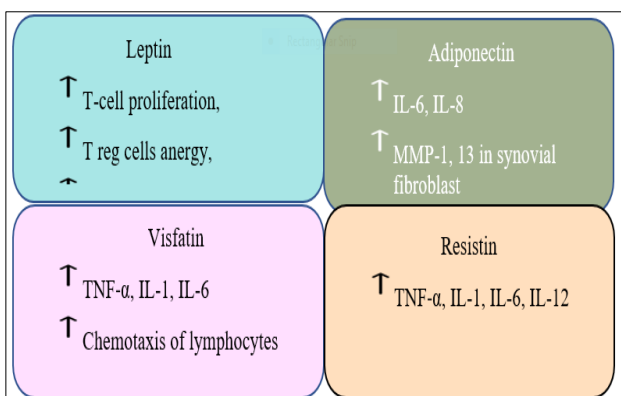


Figure 2: Overview of role of adipokines in pathogenesis of rheumatoid arthritis.

Leptin showed a significant effect on increasing the expression of Th1 cytokines. Targońska-Stepniak et al assessed leptin levels in patients with RA and found positive correlation between leptin levels and Disease

Activity Score (DAS)-28.¹⁷ In study by Yoshino et al leptin levels significantly higher in RA patients compared to controls, and it correlated with C-Reactive Protein (CRP) levels, suggesting that leptin can act as a proinflammatory.¹⁸ Some studies do not corroborate with these associations. Allam e Radwan and Abdalla et al showed that patients of RA had higher serum leptin level when compared to control, but there was no correlation between serum leptin levels and disease activity.^{19,20}

Adiponectin is an anti-inflammatory adipokine. Paradoxically, in the pathogenesis of rheumatoid arthritis adiponectin seems to have proinflammatory effects in the joints, because its ability to stimulate the secretion of inflammatory mediators Alkady et al showed that adiponectin levels correlated with disease activity and may be involved in the progression of RA.^{21,22} Study by Yosino et al did not show positive correlation between levels of serum adiponectin and CRP.¹⁸ Klein-Wieringa et al showed an association of adiponectin in radiographic progression of RA.²³

Alkady et al showed that visfatin levels correlated with disease activity and may be involved in the progression of RA.²² Khalifa et al suggested that visfatin has a role in the pathogenesis of RA, and it may be considered as a marker of the disease and the radiographic bone lesion score.²⁴ Due to its inflammatory effect, role of resistin in the pathogenesis of RA has been studied. Yoshino et al compared serum resistin levels from RA patients and healthy control subjects.¹⁸

The authors found that the level of resistin in serum did not differ between patients and controls, but observed that serum resistin were positively associated with CRP levels in RA patients, suggesting a pro inflammatory action of this cytokine. Bustos Rivera-Bahena et al demonstrated that resistin levels correlated positively with clinical manifestations of disease activity in patients with RA, albeit of patient body mass index.²⁵ There are various studies conducted to show association between different adipokines with disease activity in RA (Table 2).

Role of adipokines in Osteoarthritis

Excess body weight leads to cartilage degeneration by increasing the mechanical forces across weight-bearing joints. There are various studies showing relation between obesity and OA in non-weight bearing joints like hands. There are additional factors contributing to high prevalence of OA amongst obese, so adipokines are studied as potential factors predisposing to increasing prevalence of OA (table 3), either by increasing body weight or various other pathogenic factors.^{26,27} Filkova M et al demonstrated that increased serum levels of adiponectin in female patients with erosive compared with non- erosive osteoarthritis of the hands, suggesting that adiponectin may play a role in the pathophysiology of the erosive subtype of osteoarthritis.²⁸

Table 2: Studies on association of adipokines and rheumatoid arthritis.

Author	Study design	Subgroup	Results
Targońska-Stepniak et al. ¹⁷	Cross-sectional study evaluating correlation between disease activity and serum adipokine levels.	80 RA patients	Positive correlation between serum leptin and DAS28.
Yoshino et al. ¹⁸	Case-control study evaluating correlation between inflammation markers and serum adipokine levels.	141 RA patients 146 healthy controls	Positive correlation between serum leptin and CRP but no correlation between serum adiponectin and CRP.
Allam e Radwan ¹⁹	Case-control study evaluating correlation between serum leptin levels and disease activity.	37 RA patients 34 controls without RA	No correlation between leptin levels and disease activity.
Abdalla et al. ²⁰	Case-control study evaluating correlation between serum leptin levels and clinical manifestations of disease activity.	60 RA patients 30 healthy controls	No correlation between leptin levels and clinical and laboratory markers of disease activity.
Alkady et al. ²²	Case-control study evaluating correlation between serum and synovial liquid adipokines and disease activity.	70 RA patients 30 controls	Positive correlation between serum and synovial adiponectin & visfatin levels and disease activity.
Klein-Wieringa et al. ²³	Cohort study evaluating baseline adipokine levels to predict radiographic progression of RA over a period of 4 years.	253 RA patients	Positive correlation between serum levels of adiponectin and radiographic progression of RA.
Khalifa et al. ²⁴	Case-control study evaluating correlation between serum visfatin and inflammation markers.	60 RA patients 20 controls	Positive correlation between visfatin levels and IL-6, CRP, ERS, TNF- α and DAS-28 in RA.
Bustos Rivera-Bahena et al. ²⁵	Cross-sectional study evaluating correlation between adipokines levels and disease activity.	121 RA patients	Positive correlation between resistin levels and disease activity.

Table 3: Overview of role of adipokines in pathogenesis of osteoarthritis.

Adipokine	Protease	Cytokine	Inflammation	Cartilage	Bone
Leptin	↑MMP-1,3,9,13 ↑ADAMTS-4,5	↑IL-1 β ,6,8 ↑TNF- α	↑COX-2 ↑PGE2 ↑NOS	↑Chondrocyte proliferation ↑Proteoglycan synthesis ↑Collagen synthesis	↑Osteoblast proliferation ↑ALP ↑Osteocalcin
Adiponectin	↑MMP-1,3,9,13 ↑TIMP-1,2	↑IL-6,8 ↑MCP-1	↑COX-2 ↑PGE2 ↑VEGF	↑Chondrocyte proliferation ↑Proteoglycan synthesis ↑Collagen synthesis Matrix mineralisation	Osteoblast Proliferation Osteoclast differentiation ↑RANKL ↓OPG
Visfatin	↑MMP-3,13 ↑ADAMTS-4,5	↑IL-1,6 ↑TNF- α	↑NO ↑PGE2	↓Proteoglycan synthesis ↓Collagen synthesis	↑Osteoblast Proliferation ↓Osteoclast differentiation
Resistin	↑MMP-1,13 ↑ADAMTS-4,5	↑IL-6 ↑TNF- α	↑PGE2	↓Proteoglycan synthesis ↓Collagen synthesis	↑Osteoblast Proliferation ↓Osteoclast differentiation

Role of adipokines in systemic sclerosis

Systemic sclerosis (SSc) is an autoimmune connective tissue disease, characterized by a chronic course, significantly affecting quality of life. The hallmarks of SSc are progressive skin thickening and visceral fibrosis associated with atrophy of subcutaneous tissue, vascular involvement as well as immune dysregulation.²⁹ Adiponectin may increase IL-10 and IL-1 receptor antagonist release in monocytes. It causes polarization of CD4+ lymphocytes into Th1 and preventing from Th2 subtype dominance. It was observed that adiponectin

levels decrease in the early stage of SSc, resulting in a prevalence of Th2 lymphocytes and thus have profibrotic action in this stage. In the later phase, adiponectin levels were raised, suggesting Th1 cells and their antifibrotic effect domination.³⁰

Leptin polarizes Th lymphocytes into Th1 and suppress Th2 phenotype, thereby increasing production of pro-inflammatory cytokines. In keratinocytes, leptin increases production of IL-6, IL-8 and TNF- α as well as expression of genes related to wound healing such as metalloproteinase-1 (MMP-1).³¹ Furthermore, leptin

enhances subtype M1 macrophage growth and differentiation. Leptin activates endothelial cells and acts as a chemokine, causing attraction of macrophages into adipose tissue, hence it is involved in creating a local inflammatory niche in patients with SSc.³²

Mechanism of pro-inflammatory action of resistin involves TLR4. Intracellular signals are mediated via NF- κ B and MAPK and causing IL-1, IL-6 and IL-8 secretion. These pro-inflammatory cytokines increase the expression of resistin in human mononuclear cells which triggers a positive feedback loop of self-damaging process, where resistin stimulates pro-inflammatory cytokines secretion and pro-inflammatory cytokines raise resistin's concentration. Vasoactive mechanism of resistin is mediated through enhancing production of ET-1.³³

Visfatin acts as a pro- and anti-inflammatory cytokine, increasing TNF- α , IL-1 β , IL-6 as well as IL-4, IL-10 and IL-1Ra. Visfatin also increase levels of cell adhesion molecules ICAM-1, VCAM-1 and E-selectin in endothelial cells. Also, pro-inflammatory activity of visfatin was abolished when insulin receptor signaling was blocked.³⁴ Concentration of visfatin in the serum is comparable among total SSc patients, diffuse cutaneous SSc, limited cutaneous SSc and healthy individuals. It has been found that an increase of visfatin level in serum is accompanied by regression of skin lesions in late-stage diffuse cutaneous SSc (>6 years duration).³⁵

Role of adipokines in Systemic Lupus Erythematosus

SLE is a chronic inflammatory connective tissue disorder with multiple cellular and serological alterations. Several studies indicated that higher serum leptin levels might contribute to systemic inflammation in SLE patients. Leptin levels are increased in pediatric systemic lupus.³⁶ Serum concentration of adiponectin is elevated in patients with autoimmune inflammatory conditions. The anti- and pro-inflammatory effects of adiponectin may result from the changes in the relative proportion of its various isoforms. It has been confirmed that high molecular weight adiponectin mainly exerts pro-inflammatory effects and serves as a marker for severity of atherosclerosis, suggesting that the ratio of the isoforms may determine adiponectin action.³⁷ The mechanism by which resistin is increased in patients with SLE remains unknown, but postulated explanations include changes in renal function, direct effects of inflammatory mediators on resistin production, alterations in fat distribution, or some combination of these mechanisms.³⁶

Road blocks for the clinical use of selected adipokines

Adipokines may have potential for future pharmacological treatment strategies of obesity and metabolic diseases and immune-mediated disease as these are involved in the regulation of various physiological and pathophysiological functions, also implicated in

disease pathogenesis. There are important road blocks on the way from an adipokine candidate to the clinical use a therapeutic compound. Such road blocks include an incomplete understanding of the mechanism of action, resistance to a specific adipokine, side effects of the adipokine and others (Figure 3).³⁸

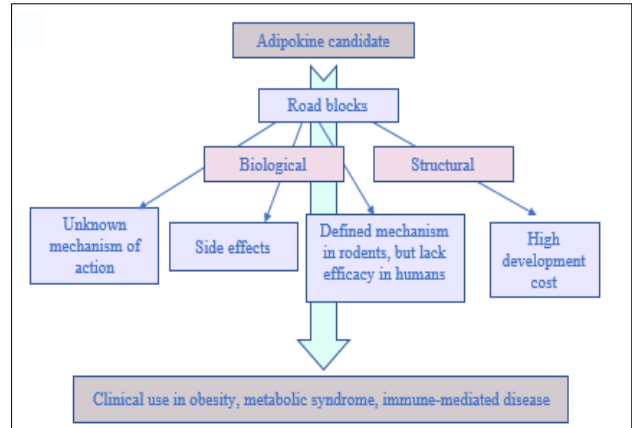


Figure 3: Road blocks for the clinical use of selected adipokines.

CONCLUSION

Adipokines have role in modulation of immune-mediated and inflammatory disease and also immunity influence regulation of adiposity. Also, adipokine network is complex. Given the role of adipokines in pathogenesis of varied autoimmune disease but further evaluation will be necessary for establishing adipokines as biomarkers of autoimmune diseases. Further insights into pathophysiological role of adipokines in the immune system will be crucial for development of novel therapeutic approaches.

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Conflict of interest: None declared

Ethical approval: Not required

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