ADIPOKINES AND ITS THERAPEUTIC INTERVENTIONS

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ABSTRACT

Adipocytes or lipocytes are fat storing cells but now it is recognized to be an active participant in energy homeostasis and physiological functions. Recently, endocrine and secretory effects have been discovered in fat tissues. Adipokines (“adipo” – fat, “kinos” – movements) are bioactive molecule secreted by adipocytes. More than 600 bioactive molecules (leptin, adiponectin, resistin and visfatin, cytokines and chemokines such as TNF - alpha, interleukin-6 and monocyte chemoattractant protein-1 etc.) are secreted by lipocytes. This review describes about the current status of Leptin, adiponectin, resistin, visfatin, apelin, cytokines and chemokines such as tumor necrosis factor-alpha, interleukin-6 etc. Adipokines may represent link between obesity and hypertension, endothelial function, hemostasis and immune cell infiltration in adipose tissue. Overall, the current report suggests that adipokines plays an inevitable role in human body. Obesity and obesity-related disorders play an important role in clinical medicine. Adipose tissue, with its soluble mediators called adipocytokines, has emerged as a major endocrine organ. They play major roles in key aspects of metabolism, such as insulin resistance, fatty acid oxidation, inflammation and immunity. It has been recognized for many decades that obesity is accompanied by an increase in cancer and potentially some immune-mediated diseases. Understanding this new exciting world of adipocytokines will be of importance in the development of novel therapies for obesity-associated diseases. Several studies have investigated plasma levels of adiponectin in patients with nonalcoholic fatty liver disease, to establish correlations with the underlying state of insulin resistance and with the type and severity of hepatic damage. Hepatitis C is another
disease where adipokines may represent a link between viral infection, steatosis, and metabolic disturbances. This review describes how adipokines regulate inflammation in these diseases and their therapeutic implications.

KEYWORDS: Adipokines, leptin, apelin, adiponectin, visfatin, vaspin.

INTRODUCTION
The main purpose of adipocytes in human body is to store energy in the form of fat. The regulation of lipid and its storage within the human body is regulated by hormones. Adipocytes are of two types, white fat cells and brown fat cells. White fat cell store energy while brown fat cell has thermogenic properties. If the body senses that a large amount of glucose is present in the blood stream, a hormone called insulin stimulates fat cells to collect fatty acids from the blood stream and store them as lipids. In contrast, if the body is running low on glucose, hormones can cause the fat cells to release their contents for use as energy. Adipose tissue is now widely recognized as "an organ" able to synthesize and secrete hundred factors collectively called adipokines. Adipokines play important role in regulation of appetite, fat distribution, insulin sensitivity, insulin secretion, energy expenditure, inflammation, blood pressure, hemostasis and endothelial functions.

ADIPOKINES
Adipokines are involved in the regulation of appetite and satiety, energy expenditure, activity, endothelial function, hemostasis, blood pressure, insulin sensitivity, energy metabolism in insulin sensitive tissues, adipogenesis, fat distribution and insulin secretion in pancreatic β-cells. First adipokine to be discovered to be leptin.[1]

1 LEPTIN
Leptin exclusively secreted by lipocytes, is actually a non-glycosylated peptide belonging to cytokine class I superfamily.[2]

Leptin – The Satiety Hormone
Leptin plays a very crucial role in regulation of appetite and body weight. Leptin decreases orexigenic and increases anorexigenic peptide synthesis in the hypothalamus. Leptin acts on its specific leptin receptors to reduce the consumption of food. Therefore, the obesity is associated with increased leptin concentration leads to the development of insulin resistance and metabolic syndrome.[1,2]
Cardiovascular System and Leptin
Leptin promotes platelet aggregation, arterial thrombosis, promote angiogenesis, impair arterial distensibility and induce proliferation and migration of vascular smooth muscle cells. So, high levels of circulating leptin may induce cardiovascular risk.[1]

Immune System and Inflammatory Responses of Leptin
Adipocytes also has significant role in regulation of immune system through adipokines. Leptin modifies T-cell balance, induces T-cell activation and changes the pattern of T-cell cytokine production by driving T-cell differentiation, accounting for its pro-inflammatory role. Leptin mRNAs and circulating levels of leptin are increased by a no. of inflammatory stimuli, including IL-1, IL-6 and lipopolysaccharides. Leptin level was found to be elevated during auto immune disorder like rheumatoid arthritis. During fasting, level of leptin decreases due to hypo reactivity of CD 4+lymphocytes and increased interleukin-4.

The role of leptin will not confine to the above matters. It also causes cartilage damage by synthesizing metalloproteinases like MMP’s-MMP9 &MMP13. Small interfering RNA against leptin directly deactivates MMP13.[2]

2. ADIPONECTIN
Adiponectin is the most important, promising gene product of adipose tissue consisting of 244 amino acid polypeptide chain, exclusively synthesized by white adipose cells. This hormone is the most abundant adipokine present in the bloodstream compared to other adipokines.[2]

Adiponectin and Atherosclerosis
Adiponectin might regulate many steps in the atherogenic process, such as antiapoptotic actions on endothelial cells and angiogenic effects on the vasculature. Anti-atherosclerotic effects of adiponectin were exerted through multiple actions on almost each vascular cell type, such as cardiomyocyte endothelial cell and endothelial progenitor cell. Particularly, adiponectin inhibits neointimal formation by suppressing proliferation and migration of vascular smooth muscle cells, blocks inflammation and foam cell formation from macrophages and stimulates the production of the anti-inflammatory cytokine IL-10 and of interleukin 1 receptor antagonist (IL1Ra) by macrophages. Adiponectin also was able to inhibit the production of reactive oxygen species (ROS) in cultured endothelial cells. In addition to its effects on the vasculature, several studies in vitro and in vivo demonstrated that
adiponectin acts directly on cardiomyocytes to protect the heart from ischemic injury, hypertrophy, cardiomyopathy and systolic dysfunction. In particular, the cardioprotective effects of adiponectin are attributed to its ability in suppressing apoptosis, oxidative/nitrative stress, and inflammation in cardiomyocytes. Also, high plasma adiponectin levels are associated with a lower risk of myocardial infarction in men, a reduced coronary heart disease risk in patients with diabetes mellitus, and a lower risk of acute coronary syndrome.\[2\]

**Adiponectin: Role in Metabolic Syndrome**
Adiponectin promotes fatty acid oxidation while reduces the synthesis of glucose. Adiponectin can affect hepatic glucose and decrease mRNA for gluconeogenesis enzyme, indicating that it may be a useful target in metabolic disease. Level of adiponectin was found to be reduced in diabetics compared to non-diabetics. Weight reduction significantly increased circulating levels. The recent studies demonstrate that the adiponectin in combination with leptin has been shown to completely reverse insulin resistance in mice.

**Adiponectin and Obesity**
Obesity driven imbalance develops from the secretion of pro and anti-inflammatory adipokines, thus obesity is a chronic inflammatory condition. Most important feature of adiponectin is its lower expression in adipose tissue and lower concentration in plasma of obese, overweight and diabetic patients. Weight loss leads to increased levels of adiponectin in plasma.

Further elucidation of mechanism of action of adiponectin, particularly the identification of inhibitors of adiponectin expression in obesity has potential to create novel and powerful target for developing intervention strategies for obesity related diseases.\[4\]

**Role in Inflammation**
Adiponectin suppress vascular inflammation by facilitating uptake of apoptotic cell debris by macrophages, Interferes with macrophage function, Induces production of anti-inflammatory factors (IL-10, IL-IRA) but pro-inflammatory in skeletal joints.

**Adiponectin: Role in Suppression of Growth and Proliferation**
In vitro, adiponectin suppresses vascular SMC proliferation and migration. Directly affects signaling pathways important for cell proliferation and growth. Bind to growth factors and modulate their activity by controlling their bioavailability at receptor level.
Mechanism
Adiponectin acts via AdipoR1-found in skeletal muscles, AdipoR2-found in liver.
Adiponectin signal causes the activation of protein kinase AMPK, PPAR. [2]

Metabolic Effect of Adiponectin
Adiponectin affects
1. Glucose flux causes decreased gluconeogenesis and increased glucose uptake.
2. Lipid catabolism-β-oxidation, triglyceride clearance.
3. Protection from endothelial dysfunction, insulin sensitivity, weight loss, control of energy metabolism, upregulation of uncoupling proteins.

Hypo adiponectinemia
A low level of adiponectin is an independent risk factor for developing and Metabolic syndrome and Diabetes mellitus.

3. Resistin
Resistin is a cysteine rich polypeptide, directly involved in pathogenesis of atherosclerosis. Resistin concentration are elevated in patients with type-II diabetes and are associated with obesity and insulin resistance. [2]

4. Visfatin
Visfatin, also called PBEF (pre-B-cell colony-enhancing factor), and Nampt (nicotinamide phosphoribosyltransferase), is a protein of approximately 471 amino acids and 52 kDa. It is a hormone that originally was discovered in liver, bone marrow, and muscle, but it is also secreted by visceral fat. It has been reported that visfatin is increased in obesity. Moreover, leucocytes from obese patients produce higher amounts of visfatin compared with lean subjects, and specifically, granulocytes and monocytes are the major producing cells.

It is supposed that visfatin has insulin mimetic properties; however, the role of this adipokine in glucose metabolism is still unclear]. Visfatin is upregulated in models of acute injury and sepsis and its synthesis is regulated by other factors such as glucocorticoids, IL-6, and growth hormone (GH). Moreover, visfatin has been shown to induce chemotaxis and the production of IL-1, TNF-α, and IL-6 in lymphocytes. [2]
5. APELIN
Apelin, the adipokine is a bioactive peptide of endogenous ligand of G-protein coupled receptor which is a potent vasodilator. The apelin is involved in body fluid homeostasis due to its potent diuretic effect through inhibition of arginine vasopressin and it also modulate pituitary hormone release, food and water intake, Furthermore, apelin secretion appeared linked to insulin secretion, regulate insulin sensitivity and stress.[2]

Therapeutic Activity of Apelin
Apelin plays a role in regulation of glucose homeostasis and contribute to a link between increased adipose tissue mass and obesity related metabolic diseases. High serum concentration in patients with obesity, insulin resistance & liver cirrhosis. Treatment of rats with apelin receptor antagonist showed hepatic fibrosis & loss of ascites suggesting apelin as a novel therapeutic target in liver diseases.[2]

6. EOTAXIN
Eotaxin, the chemokine produced by adipose tissue which binds with high affinity and specificity to chemokine receptor and plays an important role in pathogenesis of allergic diseases.

Eotaxin and cytokines directly influence airway hyper-responsiveness leads to asthma in obese individuals

ADIPOKINES: THE THERAPEUTIC TOOL
Leptin as therapy for lipodystrophy and leptin deficiency
Exogenous leptin can insulin resistance, glucose and lipid metabolism when endogenous lipid levels are as in patients with lipodystrophy. In women with hypothalamic amenorrhea, recombinant leptin therapy improved reproductive, thyroid & growth hormone axes & serve as markers of bone formation.

Dpp-4: The Target of Adipokines
DPP-4 is a 766-amino acid membrane associated serine protease enzyme detected in numerous tissues.[1] DPP-4 may be involved in linking adipose tissue to impaired glucose homeostasis. Inhibition of DPP-4 is now a well-established therapeutic principle to lower hyperglycemic in patients with type II diabetes.[1] DPP-4 rapidly degrades glucose dependent insulinotropic polypeptide(GIP) and glucose like peptide 1(GLP-1).[1]
**Il 1 Beta – Target of Adipokines**

IL-1β is a pro-inflammatory cytokine.[1] Role in inflammatory pancreatic β cell destruction leading to type-I diabetes. IL-1β inhibits the function and promotes apoptosis of β cells. Blockage of IL-1 with a recombinant human IL-1 receptor antagonist improve glycemic and β-cell function.[1]

**Vaspin**

Treatment of different mouse models with recombinant vaspin leads to sustained glucose lowering and reduction of food intake.[1]

**ADIPOKINES: BIOMARKERS**

Biomarker for fat mass, fat distribution, adipose tissue function, liver fat content, insulin sensitivity, inflammation associated with metabolic diseases. Leptin frequently reflect weight changes & predict how successful is weight loss strategy selected.[1]

**Fat Distribution**

Circulating biomarkers for abdominal visceral accumulation include adiponectin, RBP4, vaspin, chemerin, progranulin, omentin. Adiponectin decreases with increased visceral fat mass. RBP4, vaspin, chemerin, omentin increased with increase in fat mass. VISFATIN is the marker for visceral body mass. Increased Vaspin levels are associated with obesity, impaired insulin sensitivity and fitness level. Increased RBP4 serum concentration link obesity to insulin resistance and it associated metabolic diseases. Chemerin- decreases when insulin sensitivity is increased. Progranulin serum concentration associated with visceral obesity.[1]

**Inflammation and Dysfunction of Adipose Tissue**

Adipose tissue dysfunction causes Insulin resistance & CV diseases. TNF soluble antibody- Improves insulin sensitivity There is a link between pro-inflammatory cytokines & development of insulin resistance associated with obesity progression.[1]

**CONCLUSION**

Adipokines stand at the interface between metabolism and immunity in modulating inflammation, immune, metabolic and autoimmune reactivity. The identification of adipokine related mechanisms will be a prerequisite for translation into novel pharmacological treatment approaches of obesity, insulin resistance and type II diabetes.
The molecular effects of adipokines are a challenging area of research and their in-depth understanding will undoubtedly lead to the discovery of effective therapeutic interventions.

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