Adipocytokines: The pied pipers

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ABSTRACT
Even though there have been major advances in therapy, atherosclerosis and coronary artery disease retain their lead as one of the major causes of morbidity and mortality in the first decade of 21st century. To add to the woes, we have diabetes, obesity and insulin resistance as the other causes. The adipose tissue secretes several bioactive mediators that influence inflammation, insulin resistance, diabetes, atherosclerosis and several other pathologic states besides the regulation of body weight. These mediators are mostly proteins and are termed “adipocytokines”. Adiponectin, resistin, visfatin, retinol binding protein-4 (RBP-4) and leptin are a few such proteins. Adiponectin is a multimeric protein, acting via its identified receptors, AdipoR1 and AdipoR2. It is a potential biomarker for metabolic syndrome and has several antiinflammatory actions. Adiponectin increases insulin sensitivity and ameliorates obesity. Resistin, another protein secreted by the adipose tissue, derived its name due to its involvement in the development of insulin resistance. It plays a role in the pathophysiology of several conditions because of its robust proinflammatory activity mediated through the activation of extracellular signal regulated kinases 1 and 2 (ERK 1/2). In 2007, resistin was reported to have protective effect in ischemia-reperfusion injury and myocyte-apoptosis in the setting of myocardial infarction (MI). RBP-4 is involved in the developmental pathology of type 2 diabetes mellitus and obesity. Visfatin has been described as an inflammatory cytokine. Increased expression of visfatin mRNA has been observed in inflammatory conditions like atherosclerosis and inflammatory bowel disease. Leptin mainly regulates the food intake and energy homeostasis. Leptin resistance has been associated with development of obesity and insulin resistance. Few drugs (thiazolidinediones, rimonabant, statins, etc.) and some lifestyle modifications have been found to improve the levels of adipocytokines. Their role in therapy has a lot in store to be explored upon.

Key words: Adipokine, adiponectin, leptin, resistin, retinol binding protein-4, visfatin

INTRODUCTION
The adipose tissue is no longer considered as a sluggish piece of fat. The white adipose tissue (WAT) is found to be involved not only in energy storage but also in various physiologic processes. Several proteins produced by the adipose tissue have been implicated in a multitude of pathologic conditions. These proteins are justifiably termed preferably as “adipocytokines”.

The various cell signaling proteins secreted by the mature adipocytes include adiponectin, tumor necrosis factor-α (TNF-α), resistin, retinol binding protein-4 (RBP-4), visfatin, plasminogen activator inhibitor 1 (PAI-1), leptin, omentin, interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1). Under basal conditions, only a restricted number of adipocytokines are released into the systemic circulation, of which, not many fall in the existing detection limits. They may be released as enzymes, hormones, growth factors, etc. These adipocytokines integrate a myriad of metabolic outcomes, hence the adipose is no less than an endocrine organ. These molecules have endocrine, paracrine, autocrine or juxtacrine

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Adiponectin
Adiponectin, discovered in 1996,[19] is a 244 amino acid long, 30 kDa polypeptide, termed as Acrp30 or AdipoQ (also apM1 and GBP-28). It is structurally similar to complement 1q with a C-terminal globular domain and an N-terminal collagen domain.[20] Forming characteristic multimers is a characteristic feature of this protein.[21] It has several oligomeric forms which are abundantly found in plasma.[22,23] Two adiponectin receptors, AdipoR1 (skeletal muscle and heart) and AdipoR2 (liver), have been identified, both of which belong to a new family of seven transmembrane receptors distinct from G-protein coupled receptors.[24,25] T-cadherin (T-cad) is a perceptibly different extracellular. The proposed mechanisms adiponectin binding, damps AdipoR1/R2 signaling.[26] AdipoR1 and AdipoR2 rapidly activate extracellular signal regulated kinases 1 and 2 (ERK1/2) through Ras-activation which is Src-dependent.[27] Adiponectin has been found to play a major role in regulating the metabolic effects within the body. Adiponectin itself has a lot of metabolic consequences like improving the blood glucose level and oxidation of muscle fat.[19,28] Functionally, it is mainly involved in glucose regulation and fatty acid catabolism. It decreases gluconeogenesis, increases glucose uptake, stimulates β-oxidation and triglyceride clearance.[29,30] Expression of AdipoQ is found to be encrypted through APM1 gene,[29] which, in the visceral adipose tissue, is negatively controlled by glucocorticoids and TNF-α and positively by insulin and insulin derived growth factor-1 (IGF-1).[31] Plasma concentrations of the protein show sexual dimorphism with two to threefold higher levels in females than in males. The oligomeric forms also show similar dimorphism.[25] Serum levels of adiponectin are found to be in agreement with insulin sensitivity and the reduced levels of which are associated with the etiopathology of type 2 diabetes mellitus and obesity.[32] Adiponectin has been termed as a “potential biomarker” for metabolic syndrome.[33] It has been proved to increase insulin sensitivity.[34] Adiponectin reveals a deck of antiinflammatory properties. On the contrary, proinflammatory cytokines are found to decrease expression of adiponectin in the adipose tissue.[34,35] There are also a few conditions (like the Laron syndrome) which are associated with increased levels of adiponectin.[36]

Adiponectin, type 2 diabetes mellitus and insulin sensitization
Adiponectin, as stated above, is associated with the etiopathology of type 2 diabetes mellitus[31] and its levels are found to be decreased in the serum in patients with type 2 diabetes mellitus.[37,38] Monkeys with decreased plasma levels of adiponectin (before the onset of diabetes) later developed type 2 diabetes mellitus and the data were in close correlation with those from humans.[37-40] On the contrary, high levels of
Adiponectin were identified to possibly thwart the development of type 2 diabetes.[40] Adiponectin was found to backslide the developed insulin resistance in mouse models of lipodystrophy and obesity.[41] Adiponectin has been shown to protect mice of respective specific strains from diabetes and atherosclerosis.[42] Studies in the past decade have found analogy between low levels of adiponectin and insulin resistance. Also, adiponectin has been reported to sensitize the body tissues toward actions of insulin. This insulin sensitizing activity of adiponectin was initially identified by Yamauchi et al, Berg et al, and Fruebis et al, independently in 2001 and was later supported by other groups.[30,43,44]

The proposed mechanisms of action for adiponectin include:

a. Its insulin sensitizing effect which in turn regulates glucose metabolism through stimulation of AMP activated protein kinase (AMPK), a stress kinase[45]
b. Enhanced oxidation of muscle fat and glucose transport mediated through AMPK activation and acetyl-CoA carboxylase inhibition[46]
c. Inhibition of hepatic gluconeogenesis through decrease in the expression of phosphoenolpyruvate carboxylase and glucose-6-phosphatase[43,45]
d. Increased fatty acid combustion and energy consumption, partly through peroxisome proliferator activated receptor α (PPARα) activation, leading to decreased triglyceride content in skeletal muscles and liver.[42]

The high molecular weight oligomer of adiponectin is the chief form responsible behind the insulin sensitizing action of adiponectin.[47] Thiazolidinediones have been reported to upregulate the expression of adiponectin.[48] Predominantly, the high molecular weight oligomers (dodecamer or tridecamer) are increased in the circulation by the thiazolidinediones.[49]

Statnicks et al, 2000, have shown that serum adiponectin levels are decreased in patients with type 2 diabetes.[32] Type 2 diabetes is associated with insulin resistance, which is ameliorated, in part, by the high circulating levels of endogenous adiponectin, especially the high molecular weight counterpart. The key players in this proceeding of adiponectin are AMPK activation and PPARα activation and their resulting metabolic effects. The adiponectin function is carried out through its binding with the AdipoR1/R2 receptors[24] and the signal transduction mechanisms that follow suit. Adiponectin oligomers (when purified) may thus develop to be a promising candidate in the therapy of type 2 diabetes.

**Obesity and insulin resistance**

Adiponectin provides the required link between obesity and insulin resistance along with the involvement of other adipocytokines like leptin, visfatin, etc.[50] The induction of the insulin-resistant condition is closely associated with weight gain.[51] It has been shown that mice lacking adiponectin expression have reduced insulin sensitivity or are more likely to suffer from insulin resistance.[52-54] Favorably, adiponectin overexpression in ob/ob mice casts a dramatic improvement in the metabolic derangements.[55] Adiponectin levels are explicitly correlated with fat cell size and are found to be negatively related to basal metabolic index (BMI).[56] Without taking the body fat percentage into account, a low waist-to-hip ratio is associated with superior levels of adiponectin in the plasma.[57] Adiponectin levels are significantly lower in obese subjects.[33] This discovery is found to be consistent in animal studies as well. Plasma adiponectin concentrations and expression of adiponectin within the tissues are reduced in animal models of obesity like high-fat diet fed mice, leptin deficient ob/ob mice and leptin resistant db/db mice.[30]

Prospective studies in Pima Indian (Arizonian ethnicity having the highest prevalence of obesity associated with insulin resistance and type 2 diabetes) children[58] have revealed a decisive role of adiponectin deficiency in obesity and insulin resistance.[59] Insulin sensitivity, which is reduced in obese individuals, is improved by the actions of adiponectin. Adiponectin, all in all, plays an important role toward amelioration of obesity and insulin resistance [Figure 2].

**Adiponectin in relation to inflammation and atherosclerosis**

Inflammation is considered to be a sine qua non in the induction of atherosclerosis.[60] Evidence is building to prove the involvement of several adipocytokines in the development of endothelial dysfunction, which is an early event in the atherosclerotic disease.[61] TNF-α and other cytokines, as well as high levels of glucose[25,62] are found to be associated with triggering of inflammatory cascades. These cascades initiate leukocyte interactions, thereby stimulating the adhesion molecules (intracellular cell adhesion molecule [ICAM], vascular cell adhesion molecule [VCAM], etc.). All these effects consequently lead to a few of the early complications leading to atherosclerosis.[52] TNF-α induced expression of cell adhesion molecules was found to be inhibited by the binding
of adiponectin to aortic endothelial cells. Downregulation of cell adhesion molecules in the endothelium was one of the earliest vasoprotective actions reported for adiponectin toward modulation of vascular inflammation.[63-65] Adiponectin deficient mice show a considerable increase in the expression of cell adhesion molecules in the endothelium. These include, VCAM 1 and E-selectin.[92] They are highly involved in leukocyte trafficking in the mesenteric tissue.[99] Adiponectin has been found to activate cAMP-dependent protein kinase A, thus inhibiting endothelial nuclear factor κB (NF-κB) signaling. This is one mechanism found to be responsible for attenuated expression of cell adhesion molecules.[65] Toll-like receptor-mediated NF-κB signaling in macrophages is also inhibited by adiponectin.[66] Adiponectin inhibits vascular smooth muscle migration and proliferation.[67,68] This action is effected on binding of adiponectin to platelet derived growth factor-BB (PDGF-BB) and thus inhibiting p42/44 ERK phosphorylation in PDGF-BB stimulated smooth muscle cells.[69] The conversion of macrophages to lipid-laden foam cells is suppressed to a large extent by adiponectin.[70] Adiponectin deficient mice have been reported to show a twofold increase in neointimal proliferation.[52] By suppressing the expression of class A scavenger receptor (SR-A), adiponectin reduces intracellular cholesteryl ester content of the macrophages. This is the chief action responsible holding the macrophage to foam cell transformation.[70] The ameliorative effects of adiponectin upon growth factors (PDGF, epidermal growth factor [EGF], heparin binding epidermal growth factor [HB-EGF]) and cell-adhesion molecules (VCAM 1, ICAM, etc.),[99] by retarding the progression of the atherosclerotic lesion, may be, in part, through direct stimulation of nitric oxide (NO) production.[71,72] This mechanism involves the phosphatidylinositol-3-kinase (PI3K) pathway involving phosphorylation of endothelial nitric oxide synthase (eNOS).[73] Adiponectin stimulates the production of interleukin-10, which is an antiinflammatory cytokine.[74] Adiponectin may also inhibit the production of inducible nitric oxide synthase (iNOS), which is released under some pathologic conditions.[75] Precisely, adiponectin confers salvaging actions against the progression of atherosclerotic lesions through several mechanisms, the prime ones being antiinflammatory in nature.

**RESISTIN**

Resistin was identified as an adipokine in 2001.[76] Resistin is expressed in the WAT, with a higher preference seen in the WAT of abdominal region and female gonadal adipose tissue.[77] Placenta, pituitary, pancreatic islets, brown adipose tissue, etc. also show a significant expression of resistin.[78] Resistin is a cysteine-rich, 114 amino acid long, polypeptide.[76] Resistin, also termed as FIZZ3 and “adipocyte-derived secretory factor” (ADSF), has been linked with many facets of the metabolic syndrome,[79,80] principally, obesity, insulin resistance and hyperlipidemia.[81] In murine models of genetic and diet-induced obesity, resistin levels are found to be synchronously increased. Nullification of resistin through specific antibodies improves insulin sensitivity and also lowers glucose levels in blood. The effect of resistin upon insulin resistance is mediated through increased expression of suppressor of cytokine signaling-3 (SOCS-3), which is a known inhibitor of insulin signaling. Mice injected with resistin showed insulin resistance. Resistin was thus found to attend endocrine functions that led to insulin resistance.[76] Increased expression of resistin was found to be associated with dyslipidemia and non-alcoholic fatty liver disease (NAFLD) in a few medical ranks. In patients with NAFLD, serum resistin levels were higher than those in control lean and obese patients. The presence of metabolic syndrome with elevated levels of plasma resistin is associated with increased cardiovascular risk.[82,83] Within the tissues, the levels of resistin are deprecated by insulin, somatotropin, fasting, estrogen, epinephrine, PPARγ, insulin-like growth factor 1 (IGF-1), etc. Its levels are amplified by hyperglycemia, aging, neuropeptide Y, growth hormone, etc.[84] Clinically, resistin was found to be downregulated by the antidiabetic rosiglitazone and congeners troglitazone, darglitazone, etc.[85,86] Resistin is anticipated in the development of endothelial dysfunction in subjects suffering from insulin resistance.

**Resistin in myocardial infarction: Any therapeutic benefit?**

In a study by Gao et al, 2007, it was found that resistin offered protective effects against MI. Resistin was shown to protect against ischemia-reperfusion injury at a dose of 10 nM.[76] It was found that pretreatment with resistin for 30 minutes before 60 minutes of left anterior descending (LAD) coronary artery ligation, followed by 4 hours of reperfusion reduced the infarct size. This suggested a late preconditioning of resistin. This means that resistin plays its protective role before the development of infarction. Programmed cell death associated with ischemia-reperfusion in MI is also attenuated by resistin [Figure 3]. These cardioprotective effects occur by a PI3K/Akt (Protein Kinase B)/PKC (Protein Kinase C)/KATP-channel-dependent pathway. Activation of PI3K leads to PKC which causes mitoKATP channel opening. This along with Akt phosphorylation was found to be responsible for the cardioprotective effect.[78] All these data have been gathered
Involvement in pathophysiology

Apart from its role in the development of metabolic syndrome, resistin is also accused of having a role in the evolution of liver damage and acute coronary syndromes. Contrary to the above findings, resistin is strongly implicated in the pathogenesis of acute MI and atherosclerosis. The liver damaging actions of resistin can be attributed to elevated expression of PAI-1 and enhanced activation of ERK 1/2. These ultimately contribute to the increased activity of proinflammatory genes, consequently leading to more damage. Kim et al, report that resistin is also involved in altering cardiac contractility and promoting cardiac hypertrophy, possibly via the insulin receptor substrate-1 (IRS-1)/mitogen activated protein kinase (MAPK) pathway. It can be thus concluded that resistin affects the pathophysiology of several critical illnesses through its proinflammatory activities.

**RETINOL BINDING PROTEIN-4, VISFATIN AND LEPTIN**

**Retinol binding protein-4**

RBP-4 was established as an adipocytokine in the 1990s. Elevated levels of the protein are seen in insulin resistance, type 2 diabetes mellitus, dyslipidemia and similar metabolic abnormalities. RBP-4 is also concerned with hypertension. Adipose-\textit{Glut4}^{-/-} mice show elevated expressions of RBP-4, as verified in the serum. Several insulin resistant states in mice are also consistent with an elevation of serum RBP-4 levels. These findings are reconcilable with those in humans. Also the reduction in serum RBP-4 levels improves insulin action. Mice on high fat diet and \textit{ob/ob} mice show a 2.8-fold and 13-fold rise in basal serum RBP-4 levels, respectively. Rosiglitazone, a thiazolidinedione, completely reverses insulin resistance and glucose intolerance in adipose-\textit{Glut4}^{-/-} mice. The \textit{Rbp4} mRNA levels in adipose tissue were reduced on treatment with rosiglitazone. This suggests a possible role for RBP-4 in the pathophysiology of diabetes mellitus. Mohaptra et al. (2009) have reported a positive correlation between upregulation of RBP-4 expression and low density lipoprotein (LDL)-cholesterol. This shows the potential involvement of RBP-4 in the pathogenesis of obesity. Interventions that may improve insulin sensitivity like exercise, lifestyle modifications and gastric banding surgery were shown to reduce serum RBP-4 levels in humans. However, further studies will be required to delineate the exact role of RBP-4 in the pathophysiology of metabolic syndrome.

**Visfatin**

Visfatin, initially termed as pre-B cell colony-enhancing factor (PBEF), was earlier supposed to have multiple biological actions. It was later found to possess NAD (Nicotinamide Adenine Dinucleotide) biosynthetic activity, which is essential for B-cell function. Visfatin, with its insulinomimetic actions, was identified to be predominantly expressed in the visceral adipose tissue. Plasma visfatin was positively associated with BMI in one study, but not in others. Variable results were obtained regarding the relationship between visfatin and diabetes or insulin resistance. Mohaptra et al. (2009) have shown that rimonabant (cannabinoid receptor antagonist), an antiobesity drug, significantly reduced visfatin mRNA expression. This shows that visfatin might be involved in the development of obesity. Visfatin has also been described as an inflammatory adipocytokine by several authors. An increase in the expression of visfatin mRNA has been observed in inflammatory conditions like atherosclerosis and inflammatory bowel disease. Besides, it has also been implicated in rheumatoid arthritis, where it is known to activate NF-κB and other germane cytokines. Yet, several possibilities remain to be explored, since the data found till date have several inconsistencies.

**Leptin**

Leptin was the first of the adipocytokines discovered to have a role in the modulation of adiposity. It is a 16-kDa protein, identified in 1994 and is found to contain 167 amino acids. Adipose tissue is the chief secretory tissue of leptin secretion. Leptin mainly regulates food intake and energy homeostasis. It acts through a unique mechanism. Leptin receptor activation leads to repression of orexigenic pathways, involving neuropeptide-Y (NPY) and agouti-related peptide (AgRP). Simultaneously, it leads to activation of anorexigenic pathways, entailing pro-opiomelanocortin (POMC) and cocaine and amphetamine regulated transcript (CART). All these actions are mediated through the Janus activated kinase (JAK)/signal transducers and activators of transcription (STAT) pathway. Leptin plays diverse roles in the regulation of cellular metabolism. It reverses hyperglycemia in \textit{ob/ob} mice before a correction in body weight. It improves glucose
homeostasis in lipodystrophic mice, which is consistent with the clinical data. It even improves insulin sensitivity,[126] which may be the resultant of improved glucose homeostasis and its role in ameliorating obesity. Such a study in mice needs further evaluation and refinement so that it can be extrapolated to humans as well. Leptin has potential prooxidant and proinflammatory roles and hence it has also been linked to the development of cardiovascular disease, especially atherosclerosis. It promotes ET-1 (Endothelin 1) upregulation and reactive oxygen species (ROS) accumulation. The proliferation and migration of vascular endothelial cells (VEC) and vascular smooth muscular cells (VSMC) is also enhanced by leptin. It thus leads to endothelial dysfunction. Through a leptin receptor dependent pathway, it also stimulates platelet aggregation, thereby increasing the risk of CAD. When increased levels of leptin are observed without significant end-organ response, it can be termed as “leptin resistance”. Studies with obese rodents have suggested an impairment of leptin transport across the BBB (Blood Brain Barrier), reduction in JAK/STAT signaling and SOCS-3 induction in the development of resistance. The C-terminal globular domain of adiponectin is pharmacologically active. Injection of recombinant adiponectin can reduce glucose levels, without having an effect upon the insulin levels. Leptin may also be clinically applicable in near future, for the treatment of obesity. Co-administration of leptin with amylin restores hypothalamic sensitivity to leptin, thereby ameliorating leptin resistance. However, the confirmation of this datum is pending in humans. Upon receipt of positive results, obesity pharmacotherapy may witness new dimensions.

In obese patients, who underwent gastric partition surgery, an increase in the levels of adiponectin, a protective adipokine, was observed. This was accompanied by a reduction in BMI as well. Mediterranean diet, soy protein and increased physical activity have been reported to increase adiponectin levels. These results are consistent with studies carried out in wistar rats by Nagasawa et al., 2003, but not with those carried out in obese KK-A mice. Human studies show a positive result between PPARγ agonist treatment and improving adiponectin levels. This may be one of the reasons for the effectiveness of thiazolidinediones, which are potent agonists of PPARγ. Pioglitazone improves lesions of nonalcoholic steatohepatitis and also increases adiponectin levels, suggesting a possible adiponectin effect. The C-terminal globular domain of adiponectin is pharmacologically active. Injection of recombinant adiponectin can reduce glucose levels, without having an effect upon the insulin levels. Leptin may also be clinically applicable in near future, for the treatment of obesity. Co-administration of leptin with amylin restores hypothalamic sensitivity to leptin, thereby ameliorating leptin resistance. However, the confirmation of this datum is pending in humans.

There still remains a vast number of possibilities to be explored for amelioration of pathophysiologic states generated through adipocytokines. Evolving methodologies, in the near future, will have to focus keenly upon the forerunners of pathologic states of the adipocytokines.

**ABBREVIATIONS**

ICAM – intracellular cell adhesion molecule; VCAM – vascular cell adhesion molecule; RBP-4, PAI-1, etc). Lifestyle modification is the only currently employed therapy to reduce the effect of pathogenic adipocytokines (resistin, TNF-α, RBP-4, PAI-1, etc). Lifestyle modifications like weight loss and regular exercise have attenuated the circulating levels of pathogenic adipocytokines. However, there are also a few drugs that can decrease the levels of inflammatory adipocytokines. These include thiazolidinediones, angiotensin receptor blockers (ARBs), ACE (Angiotensin Converting Enzyme) inhibitors, statins, etc. Many of these drugs, like rosiglitazone in particular, reduce the proatherogenicity of the adipocytokines. Rimonabant, a CB1 receptor antagonist, reduces visfatin mRNA expression, which might alleviate the inflammatory effects of visfatin. Rimonabant has insulin sensitizing effects in ob/ob mice. These may involve a decrease in the expression of RBP-4 and TNF-α and a simultaneous increase in adiponectin levels. Thiazolidinediones like pioglitazone and rosiglitazone reduce the expression of TNF-α in adipocytes and TNF-α induced expression of cell adhesion molecules (VCAM-1 and ICAM-1) in endothelial cells. Subtherapeutic doses of pioglitazone produced antiinflammatory effects via suppression of TNF-α and IL-6 in WAT. As suggested by Mohapatra et al., these antiinflammatory effects preceded the insulin-sensitizing effects that were seen at therapeutic doses in db/db mice. Resistin increases lipogenesis through an upregulation of lipogenic genes (sterol regulatory element binding protein [SREBP-1], hydroxy methyl glutaryl CoA receptor [HMGCoAR], diacylglycerol acyltransferase [DGAT2], etc).

This may lead to steatosis and hyperlipidemia in ob/ob mice, which was ameliorated by insulin-sensitizing drugs. This study can be extrapolated to hyperinsulinemic patients suffering from steatosis and/or hyperlipidemia through clinical investigations. Adiponectin too has been proposed to have a role in protection against steatosis in humans.
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