

Adipocytokines: The pied pipers

Hardik Gandhi, Aman Upaganlawar, Balaraman R

Department of Pharmacy, Faculty of Technology and Engineering, The M. S. University of Baroda, Vadodara – 390 001, Gujarat, India

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.^[1,2] 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).^[3-5] 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.^[6] These molecules have endocrine, paracrine, autocrine or juxtacrine

Address for correspondence:

Dr. Hardik Gandhi, Pharmacy Department., Faculty of Technology & Engineering, Kalabhavan, Dandia Bazaar, Vadodara-390001, Gujarat, India. Email: gandhihardikp@gmail.com

DOI:10.4103/0976-500X.64530

modes of action.^[7] Besides, they have been recently recognized as mediators of several inflammatory processes.^[8] Their proinflammatory properties are responsible for elevated risks to several morbid conditions.^[9] Organs of metabolic importance like, brain, liver, skeletal system, etc. are targets that receive signals from adipocytokines.^[10] Lipid metabolism, insulin sensitivity (adiponectin, resistin), homeostasis (PAI-1), blood pressure regulation (angiotensinogen) and angiogenesis are a few physiologic processes implicated with adipocytokines.^[11,12] It is also true that certain pathologic conditions also control the level of adipocytokines.^[13] Altered production and secretion of several adipocytokines may be concerned with the pathogenesis of metabolic syndrome, as is suggested by some studies.^[14,15] Within the central nervous system, adipocytokines are found to communicate with the blood brain barrier. They may thus be effecting a few neuroendocrine functions as well.^[16] The mass of adipose tissue and its energy status is also regulated by the adipocytokines.^[17] Since several adipocytokines are involved in the partial regulation of a battery of physiologic processes, they may also provide a connection toward the pathology involving the same physiologic processes [Figure 1]. They may thus provide molecular links between the development of obesity, insulin resistance, metabolic syndrome, cardiovascular diseases, type 2 diabetes mellitus, and so on. They may also be used as biomarkers in the diagnosis of pertinent diseases.^[18]

Understanding the effects of adipocytokines in totality remains incomplete^[10] and imperceptible when quite a lot of them remain to be discovered. However, due to such a herculean involvement in daily metabolic processes, there lays a vast ocean of latent resources to be explored as adipokine-manuevered treatments. The current review thus converges upon the role and therapeutic potential of variety of adipocytokines. Favorably, the role of adipocytokines, with a special mention to adiponectin and resistin, will be dealt with, along with that of RBP-4, leptin and visfatin.

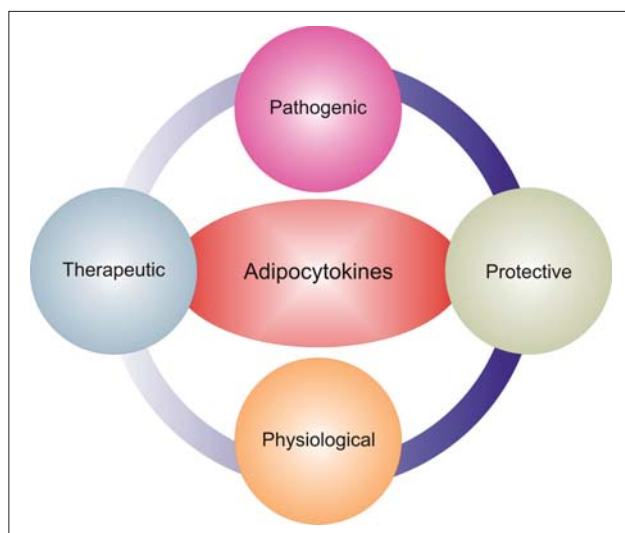


Figure 1: The roles of adipocytokines

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 mechanismsadiponectin binding, dampens 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^[33] 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:

- Its insulin sensitizing effect which in turn regulates glucose metabolism through stimulation of AMP activated protein kinase (AMPK), a stress kinase^[45]
- Enhanced oxidation of muscle fat and glucose transport mediated through AMPK activation and acetyl-CoA carboxylase inhibition^[46]
- Inhibition of hepatic gluconeogenesis through decrease in the expression of phosphoenolpyruvate carboxylase and glucose-6-phosphatase^[43,45]
- Increased fatty acid combustion and energy consumption, partly through peroxisome proliferator activated receptor α (PPAR α) 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]

Statnick *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 PPAR α 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.^[37] 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

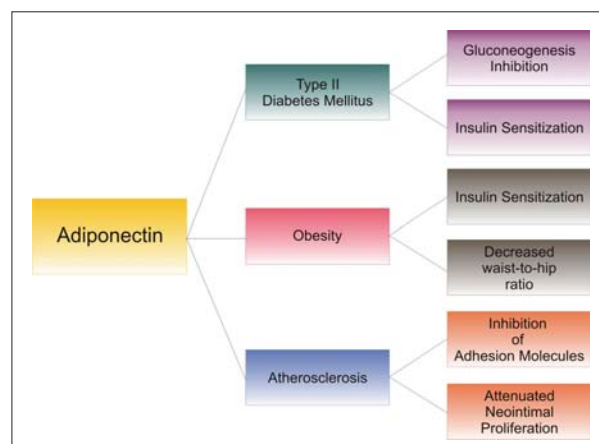


Figure 2: Protective effects of adiponectin

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.^[52] They are highly involved in leukocyte trafficking in the mesenteric tissue.^[9] Adiponectin has been found to activate cAMP-dependent protein kinase A, thus inhibiting endothelial nuclear factor κ B (NF- κ B) signaling. This is one mechanism found to be responsible for attenuated expression of cell adhesion molecules.^[65] Toll-like receptor-mediated NF- κ B 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.)^[59] 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 atherosclerosis through several mechanisms, the prime ones being antiinflammatory in nature.

RESISTIN

Resistin was identified as an adipocytokine 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 depreciated by insulin, somatotropin, fasting, estrogen, epinephrine, PPAR γ , 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. CD40 ligand mediated endothelial cell activation is heightened by elevated levels of resistin. Also, the expression of tumor necrosis associated factor-3 (TRAF-3), a potent inhibitor of CD40 mediated endothelial cell activation, is inhibited by resistin *in vitro*. Besides, the expressions of VCAM-1 and MCP-1, instrumental in the development of the atherosclerotic lesion, are also increased by resistin. The proinflammatory effects of resistin on smooth muscle cells are found to play a role in the occurrence of restenosis of coronary arteries in diabetic patients.^[9,87] The robust expression of resistin in the monocytes confirms its proinflammatory role.^[88,89]

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.^[78] 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

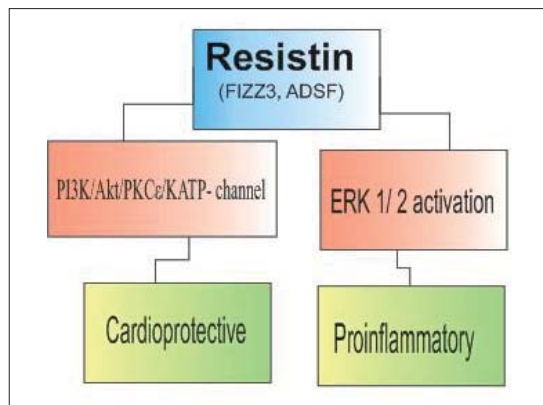


Figure 3: Mechanisms of resistin

from animal studies and need to be extrapolated to human populace.

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.^[90,91] The liver damaging actions of resistin can be attributed to elevated expression of PAI-1 and enhanced activation of ERK 1/2.^[92] These ultimately contribute to the increased activity of proinflammatory genes,^[90] 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.^[93] 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.^[93,94] It is preferentially expressed in the visceral adipose tissue.^[95] Elevated levels of the protein are seen in insulin resistance, type 2 diabetes mellitus, dyslipidemia and similar metabolic abnormalities.^[96,97] RBP-4 is also concerned with hypertension.^[98] Adipose-*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 *ob/ob* mice show a 2.8-fold and 13-fold rise in basal serum RBP-4 levels, respectively.^[96] Rosiglitazone, a thiazolidinedione, completely reverses insulin resistance and glucose intolerance in adipose-*Glut4*^{-/-} mice.^[99] The *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.^[96] Mohapatra *et al.* (2009) have reported a positive correlation between upregulation of RBP-4 expression and low density lipoprotein (LDL)-cholesterol.^[100] 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.^[97,101-103] 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.^[104,105] It was later found to possess NAD (Nicotinamide Adenine Dinucleotide) biosynthetic activity, which is essential for B-cell function.^[106] Visfatin, with its insulinomimetic actions, was identified to be predominantly expressed in the visceral adipose tissue.^[107] Plasma visfatin was positively associated with BMI in one study,^[108] but not in others.^[109,110] Variable results were obtained regarding the relationship between visfatin and diabetes or insulin resistance.^[109-112] Mohapatra *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.^[113] An increase in the expression of visfatin mRNA has been observed in inflammatory conditions like atherosclerosis and inflammatory bowel disease.^[114,115] Besides, it has also been implicated in rheumatoid arthritis, where it is known to activate NF- κ B and other germane cytokines.^[116] 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.^[117-120] It is a 16-kDa protein, identified in 1994 and is found to contain 167 amino acids.^[121] Adipose tissue is the chief secretory tissue of leptin secretion. Leptin mainly regulates food intake and energy homeostasis.^[122-124] 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.^[125] Leptin plays diverse roles in the regulation of cellular metabolism. It reverses hyperglycemia in *ob/ob* mice before a correction in body weight.^[120] 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.^[127,128] The proliferation and migration of vascular endothelial cells (VEC)^[129] and vascular smooth muscular cells (VSMC)^[130] 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.^[127,128] When increased levels of leptin are observed without significant end-organ response, it can be termed as “leptin resistance”.^[131] 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.^[131,132] Concisely, leptin is the major “adipostat” interplaying with several other metabolic processes^[10] and it has preponderance over other adipocytokines in the pathogenesis of cardiovascular disease.

THERAPEUTIC INTERVENTIONS

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.^[9] 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.^[9] Many of these drugs, like rosiglitazone in particular, reduce the proatherogenicity of the adipocytokines.^[133] 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.^[113] 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.^[9] 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.^[134] 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).^[81] This may lead to steatosis and hyperlipidemia in ob/ob mice, which was ameliorated by insulin-sensitizing drugs.^[126] 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.^[41]

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.^[135] Mediterranean diet, soy protein and increased physical activity have been reported to increase adiponectin levels.^[135,136] These results are consistent with studies carried out in wistar rats by Nagasawa *et al*, 2003,^[136] but not with those carried out in obese KK-A mice.^[137] Human studies show a positive result between PPAR γ agonist treatment and improving adiponectin levels.^[138] This may be one of the reasons for the effectiveness of thiazolidinediones, which are potent agonists of PPAR γ . Pioglitazone improves lesions of nonalcoholic steatohepatitis and also increases adiponectin levels, suggesting a possible adiponectin effect.^[139] 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.^[43] 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.^[140] Upon receipt of positive results, obesity pharmacotherapy may witness new dimensions.

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; AMPK – AMP activated protein kinase; PDGF – platelet derived growth factor; EGF – epidermal growth factor; HB-EGF – heparin binding epidermal growth factor; eNOS – endothelial nitric oxide synthase; iNOS – inducible nitric oxide synthase; MCP-1 – monocyte chemoattractant protein-1; IRS – insulin receptor substrate; MAPK – mitogen activated protein kinase; JAK – Janus activated kinase; STAT – signal transducers and activators of transcription; VEC – vascular endothelial cells; VSMC – vascular smooth muscular cells; SREBP – sterol regulatory element binding protein; HMGCoAR – hydroxymethyl glutaryl CoA receptor; DGAT

– diacylglycerol acyltransferase; WAT – white adipose tissue

REFERENCES

- Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003;112:1796-808.
- Fantuzzi G. Adipose tissue, adipocytokines and inflammation. *J Allergy Clin Immunol* 2005;115:911-9.
- MacDougald OA, Burant CF. The rapidly expanding family of adipokines. *Cell Metab* 2007;6:159-61.
- Antuna-Puente B, Fève B, Fellahi S, Bastard JP. Obesity, inflammation and insulin resistance: Which role for adipokines. *Thérapie* 2007;62:285-92.
- Calabro P, Yeh ET. Obesity, inflammation and vascular disease: The role of the adipose tissue as an endocrine organ. *Subcell Biochem* 2007;42:63-91.
- Ahima R, Flier JS. Adipose tissue as an endocrine organ. *Trends Endocrinol Metab* 2000;11:327-32.
- Mohammed-Ali V, Pinkney JH, Coppack SW. Adipose tissue as an endocrine and paracrine organ. *Int J Obes Relat Metab Disord* 1998;22:1145-58.
- Trayhurn P, Wood IS. Signalling role of adipose tissue: Adipokines and inflammation in obesity. *Biochem Soc Transac* 2005;33:1078-81.
- Lau DC, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: Molecular links between obesity and atherosclerosis. *Am J Physiol Heart Circ Physiol* 2005;288:H2031-41.
- Rabe K, Lehrke M, Parhofer KG, Broedl UC. Adipokines and insulin resistance. *Mol Med* 2008;14:741-51.
- Trayhurn P, Beattie JH. Physiological role of adipose tissue: White adipose tissue as an endocrine and secretory organ. *Proc Nutr Soc* 2001;60:329-39.
- Rajala MW, Scherer PE. Minireview: The adipocyte--at the crossroads of energy homeostasis, inflammation, and atherosclerosis. *Endocrinology* 2003;144:3765-73.
- Pini M, Gove ME, Senello JA, van Baal JW, Chan L, Fantuzzi G. Role and regulation of adipokines during zymosan-induced peritoneal inflammation in mice. *Endocrinology* 2008;149:4080-5.
- Hallikainen M, Kolehmainen M, Schwab U, Laaksonen DE, Niskanen L, Rauramaa R, *et al.* Serum adipokines are associated with cholesterol metabolism in the metabolic syndrome. *Clin Chim Acta* 2007;383:126-32.
- Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with the determinants of metabolic syndrome. *Eur J Endocrinol* 2007;156:279-84.
- Pan W, Kastin AJ. Adipokines and the blood-brain barrier. *Peptides* 2007;28:1317-30.
- Mora S, Pessin JE. An adipocentric view of signaling and intracellular trafficking. *Diabetes Metab Res Rev* 2002;18:345-56.
- Inadera H. The usefulness of circulating adipokine levels for the assessment of obesity-related health problems. *Int J Med Sci* 2008;5:248-62.
- Maeda K, Okubo K, Shimomura I, Funahashi T, Matsuzawa Y, Matsubara K. cDNA cloning and expression of a novel adipose specific collagen-like factor, apM1 (Adipose Most abundant Gene transcript 1). *Biochem Biophys Res Commun* 1996;221:286-9.
- Shapiro L, Scherer PE. The crystal structure of a complement-1q family protein suggests an evolutionary link to tumor necrosis factor. *Curr Biol* 1998;8:335-8.
- Crouch E, Persson A, Chang D, Heuser J. Molecular structure of pulmonary surfactant protein D (SP-D). *J Biol Chem* 1994;269:17311-9.
- Goldstein BJ, Scalia R. Adiponectin: A novel adipokine linking adipocytes and vascular function. *J Clin Endocrinol Metab* 2004;89:2563-8.
- Scherer PE. Adipose tissue: From lipid storage compartment to endocrine organ. *Diabetes* 2006;55:1537-45.
- Yamauchi T, Kamon J, Ito Y, Tsuchida A, Yokomizo T, Kita S, *et al.* Cloning of adiponectin receptors that mediate antidiabetic metabolic effects. *Nature* 2003;423:762-9.
- Goldstein BJ, Scalia RG, Ma XL. Protective vascular and myocardial effects of adiponectin. *Nat Clin Pract Cardiovasc Med* 2009;6:27-35.
- Hug C, Wang J, Ahmad NS, Bogan JS, Tsao TS, Lodish HF. T-cadherin is a receptor for hexameric and high-molecular-weight forms of Acrp30/adiponectin. *Proc Natl Acad Sci U S A* 2004;101:10308-13.
- Lee MH, Klein RL, El-Shewy HM, Luttrell DK, Luttrell LM. The adiponectin receptors AdipoR1 and AdipoR2 activate ERK1/2 through a Src/Ras-dependent pathway and stimulate cell growth. *Biochemistry* 2008;47:11682-92.
- Scherer PE, William S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. *J Biol Chem* 1995;270:26746-9.
- Vasseur F, Leprêtre F, Lacquemant C, Froguel P. The genetics of adiponectin. *Curr Diab Rep* 2003;3:151-8.
- Yamauchi T, Kamon J, Waki H, Terauchi Y, Kubota N, Hara K, *et al.* The fat-derived hormone adiponectin reverses insulin resistance associated with both lipodystrophy and obesity. *Nat Med* 2001;7:941-6.
- Wajchenberg BL. Subcutaneous and visceral adipose tissue: Their relation to metabolic syndrome. *Endocr Rev* 2000;21:697-738.
- Statnick MA, Beavers LS, Conner LJ, Corominola H, Johnson D, Hammond CD. Decreased expression of apM1 in omental and subcutaneous adipose tissue of humans with type 2 diabetes. *Int J Exp Diabetes Res* 2000;1:81-8.
- Hug C, Lodish HF. The role of the adipocyte hormone adiponectin in cardiovascular diseases. *Curr Opin Pharmacol* 2005;5:129-34.
- Tataranni PA, Ortega E. A burning question: Does and adipokine-induced activation of the immune system mediate the effect of overnutrition on type 2 diabetes? *Diabetes* 2005;54:917-27.
- Ouchi N, Kihara S, Funahashi T, Matsuzawa Y, Walsh K. Obesity, adiponectin and vascular inflammatory disease. *Curr Opin Lipidol* 2003;14:561-6.
- Kanety H, Hemi R, Ginsberg S, Pariente C, Yissachar E, Barhod E, *et al.* Total and high molecular weight adiponectin are elevated in patients with Laron syndrome despite marked obesity. *Eur J Endocrinol* 2009;161:837-44.
- Arita Y, Kihara S, Ouchi N, Takahashi M, Maeda K, Miyagawa J, *et al.* Paradoxical decrease of an adipose-specific protein, adiponectin, in obesity. *Biochem Biophys Res Commun* 1999;257:79-83.
- Hotta K, Funahashi T, Arita Y, Takahashi M, Matsuda M, Okamoto Y, *et al.* Plasma concentrations of a novel, adipose-specific protein, adiponectin, in type 2 diabetic patients. *Arterioscler Thromb Vasc Biol* 2000;20:1595-9.
- Hotta K, Funahashi T, Bodkin NL, Ortmeier HK, Arita Y, Takahashi M, *et al.* Circulating concentrations of the adipocyte protein adiponectin are decreased in parallel with reduced insulin sensitivity during the progression to type 2 diabetes in rhesus monkeys. *Diabetes* 2001;50:1126-33.
- Lindsay RS, Funahashi T, Hanson RL, Matsuzawa Y, Tanaka S, Tataranni PA, *et al.* Adiponectin and development of type 2 diabetes in Pima Indian population. *Lancet* 2002;360:57-8.
- Kadowaki T, Yamauchi T, Kubota N, Hara K, Ueki K, Tobe K. Adiponectin and adiponectin receptors in insulin resistance, diabetes and the metabolic syndrome. *J Clin Invest* 2006;116:1784-92.
- Yamauchi T, Kamon J, Waki H, Imai Y, Shimozawa N, Hioki K, *et al.* Globular adiponectin protected ob/ob mice from diabetes and ApoE-deficient mice from atherosclerosis. *J Biol Chem* 2003;278:2461-8.
- Berg AH, Combs TP, Du X, Brownlee M, Scherer PE. The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 2001;7:947-53.
- Fruebis J, Tsao TS, Javorschi S, Ebbets-Reed D, Erickson MR, Yen FT, *et al.* Proteolytic cleavage product of 30-kDa adipocyte complement-related protein increases fatty acid oxidation in muscle and causes weight loss in mice. *Proc Natl Acad Sci* 2001;98:2005-10.
- Yamauchi T, Kamon J, Minokoshi Y, Ito Y, Waki H, Uchida S, *et al.* Adiponectin stimulates glucose utilization and fatty-acid oxidation by activating AMP-activated protein kinase. *Nat Med* 2002;8:1288-95.
- Tomas E, Tsao TS, Saha AK, Murray HE, Zhang Cc C, Itani SI, *et al.* Enhanced muscle fat oxidation and glucose transport by ACRP30 globular domain: Acetyl-CoA carboxylase inhibition and AMP-activated protein kinase activation. *Proc Natl Acad Sci* 2002;99:16309-13.
- Lara-Castro C, Luo N, Wallace P, Klein RL, Garvey WT. Adiponectin multimeric complexes and the metabolic syndrome trait cluster. *Diabetes* 2006;55:249-59.
- Combs TP, Wagner JA, Berger J, Doebber T, Wang WJ, Zhang BB, *et al.* Induction of adipocyte complement-related protein of 30 kilodaltons by PPARgamma agonists: A potential mechanism of insulin sensitization. *Endocrinology* 2002;143:998-1007.
- Pajvani UB, Hawkins M, Combs TP, Rajala MW, Doebber T, Berger JP, *et al.* Complex distribution, not absolute amount of adiponectin, correlates with thiazolidinedione-mediated improvement in insulin sensitivity. *J Biol Chem* 2004;279:12152-62.

50. Tilg H, Moschen AR. Adipocytokines: Mediators linking adipose tissue, inflammation and immunity. *Nat Rev Immunol* 2006;6:772-83.
51. Muoio DM, Newgard CB. Metabolism: A is for adipokine. *Nature* 2005;436:337-8.
52. Kubota N, Terauchi Y, Yamauchi T, Kubota T, Moroi M, Matsui J, *et al.* Disruption of adiponectin causes insulin resistance and neointimal formation. *J Biol Chem* 2002;277:25863-6.
53. Maeda N, Shimomura I, Kishida K, Nishizawa H, Matsuda M, Nagaretani H, *et al.* Diet-induced insulin resistance in mice lacking adiponectin/ACRP30. *Nat Med* 2002;8:731-7.
54. Nawrocki AR, Rajala MW, Tomas E, Pajvani UB, Saha AK, Trumbauer ME, *et al.* Mice lacking adiponectin show decreased hepatic insulin sensitivity and reduced responsiveness to peroxisome proliferator-activated receptor gamma agonists. *J Biol Chem* 2006;281:2654-60.
55. Kim JY, van de Wall E, Laplante M, Azzara A, Trujillo ME, Hofmann SM, *et al.* Obesity-associated improvements in metabolic profile through expansion of adipose tissue. *J Clin Invest* 2007;117:2621-37.
56. Johnson JA, Ynada Y, Flancbaum L, Albu J. Cytokine release in deep subcutaneous, abdominal and visceral tissue depots. *Diabetes* 2001;50:A88.
57. Staiger H, Tschritter O, Machann J, Thamer C, Fritsche A, Maerker E, *et al.* Relationship of serum adiponectin and leptin concentrations with body fat distribution in humans. *Obes Res* 2003;11:368-72.
58. Lillioja S, Nyomba BL, Saad MF, Ferraro R, Castillo C, Bennett PH, *et al.* Exaggerated early insulin release and insulin resistance in a diabetes-prone population: A metabolic comparison of Pima Indians and Caucasians. *J Clin Endocrinol Metab* 1991;73:866-76.
59. Shimada K, Miyazaki T, Daida H. Adiponectin and atherosclerotic disease. *Clin Chim Acta* 2004;344:1-12.
60. Ross R. Atherosclerosis-- an inflammatory disease. *N Engl J Med* 1999;340:115-26.
61. Goldstein BJ, Scalia R. Adipokines and vascular disease in diabetes. *Curr Diab Rep* 2007;7:25-33.
62. Zhu W, Cheng KK, Vanhoutte PM, Lam KS, Xu A. Vascular effects of adiponectin: Molecular mechanisms and potential therapeutic interventions. *Clin Sci* 2008;114:361-74.
63. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, *et al.* Novel modulator for endothelial adhesion molecules: Adipocyte-derived plasma protein adiponectin. *Circulation* 1999;100:2473-6.
64. Ouchi N, Kihara S, Arita Y, Okamoto Y, Maeda K, Kuriyama H, *et al.* Adiponectin, an adipocyte-derived plasma protein, inhibits endothelial NF- κ B signaling through a cAMP-dependent pathway. *Circulation* 2000;102:1296-301.
65. Ouedraogo R, Gong Y, Berzins B, Wu X, Mahadev K, Hough K, *et al.* Adiponectin deficiency increases leukocyte-endothelium interactions via upregulation of endothelial cell adhesion molecules *in vivo*. *J Clin Invest* 2007;117:1718-26.
66. Yamaguchi N, Arueta JG, Mashuiro Y, Kagishita M, Nonaka K, Saito T, *et al.* Adiponectin inhibits Toll-like receptor family-induced signaling. *FEBS Lett* 2005;579:6821-6.
67. Okamoto Y, Kihara S, Ouchi N, Nishida M, Arita Y, Kumada M, *et al.* Adiponectin reduces atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2002;106:2767-70.
68. O'Rourke L, Gronning LM, Yeaman SJ, Shepherd PR. Glucose-dependent regulation of cholesterol ester metabolism in macrophages by insulin and leptin. *J Biol Chem* 2002;277:42557-62.
69. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, *et al.* Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB-binding protein and regulates growth factor-induced common postreceptor signal in vascular smooth muscle cell. *Circulation* 2002;105:2893-8.
70. Ouchi N, Kihara S, Arita Y, Nishida M, Matsuyama A, Okamoto Y, *et al.* Adipocyte-derived plasma protein, adiponectin, suppresses lipid accumulation and class A scavenger receptor expression in human monocyte-derived macrophages. *Circulation* 2001;103:1057-63.
71. Matsuda M, Shimomura I, Sata M, Arita Y, Nishida M, Maeda N, *et al.* Role of adiponectin in preventing vascular stenosis: The missing link of adipo-vascular axis. *J Biol Chem* 2002;277:37487-91.
72. Comuzzie AG, Funahashi T, Sonnenberg G, Martin LJ, Jacob HJ, Black AE, *et al.* The genetic basis of plasma variation in adiponectin, a global endophenotype for obesity and the metabolic syndrome. *J Clin Endocrinol Metab* 2001;86:4321-5.
73. Chen H, Montagnani M, Funahashi T, Shimomura I, Quon MJ. Adiponectin stimulates production of nitric oxide in vascular endothelial cells. *J Biol Chem* 2003;278:45021-6.
74. Kumada M, Kihara S, Ouchi N, Kobayashi H, Okamoto Y, Ohashi K, *et al.* Adiponectin specifically increased tissue inhibitor of metalloproteinase-1 through interleukin-10 expression in human macrophages. *Circulation* 2004;109:2046-9.
75. Li R, Wang WQ, Zhang H, Yang X, Fan Q, Christopher TA, *et al.* Adiponectin improves endothelial function in hyperlipidemic rats by reducing oxidative/nitrate stress and differential regulation of eNOS/iNOS activity. *Am J Physiol Endocrinol Metab* 2007;293:E1703-8.
76. Stepan CM, Bailey ST, Bhat S, Brown EJ, Banerjee RR, Wright CM, *et al.* The hormone resistin links obesity to diabetes. *Nature* 2001;409:307-12.
77. Oliver P, Pico C, Serra F, Palou A. Resistin expression in different adipose tissue depots during rat development. *Mol Cell Biochem* 2003;252:397-400.
78. Gao J, Chang Chua C, Chen Z, Wang H, Xu X, C Hamdy R, *et al.* Resistin, an adipocytokine, offers protection against acute myocardial infarction. *J Mol Cell Cardiol* 2007;43:601-9.
79. Holcomb IN, Kabakoff RC, Chan B, Baker TW, Gurney A, Henzel W, *et al.* FIZZ1, a novel cysteine-rich secreted protein associated with pulmonary inflammation, defines a new gene family. *EMBO J* 2000;19:4046-55.
80. Kim KH, Lee K, Moon YS, Sul HS. A cysteine-rich adipose tissue-specific secretory factor inhibits adipocyte differentiation. *J Biol Chem* 2001;276:11252-6.
81. Singhal NS, Patel RT, Qi Y, Lee YS, Ahima RS. Loss of resistin ameliorates hyperlipidemia and hepatic steatosis in leptin-deficient mice. *Am J Physiol Endocrinol Metab* 2008;295:E331-8.
82. Norata GD, Ongari M, Garlaschelli K, Raselli S, Grigore L, Catapano AL. Plasma resistin levels correlate with determinants of the metabolic syndrome. *Eur J Endocrinol* 2007;156:279-84.
83. Pagano C, Soardo G, Pilon C, Milocco C, Basan L, Milan G, *et al.* Increased serum resistin in nonalcoholic fatty liver disease is related to liver disease severity and not to insulin resistance. *J Clin Endocrinol Metab* 2006;91:1081-6.
84. Adeghate E. An update on the biology and physiology of resistin. *Cell Mol Life Sci* 2004;61:2485-96.
85. Haugen F, Jorgensen A, Drevon CA, Trayhurn P. Inhibition by insulin of resistin gene expression in 3T3-L1 adipocytes. *FEBS Lett* 2001;507:105-8.
86. Shojima N, Sakoda H, Ogihara T, Fujishiro M, Katagiri H, Anai M, *et al.* Humoral regulation of resistin expression in 3T3-L1 and mouse adipose cells. *Diabetes* 2002;51:1737-44.
87. Calabro P, Samudio I, Willerson JT, Yeh ET. Resistin promotes smooth muscle cell proliferation through activation of extracellular signal-regulated kinase 1/2 and phosphatidylinositol 3-kinase pathways. *Circulation* 2004;110:3335-40.
88. Kaser S, Kaser A, Sandhofer A, Ebenbichler CF, Tilg H and Patsch JR. Resistin messenger-RNA expression is increased by proinflammatory cytokines *in vitro*. *Biochem Biophys Res Commun* 2003;309:286-90.
89. McTernan PG, Kusminski CM, Kumar S. Resistin. *Curr Opin Lipidol* 2006;17:170-5.
90. Beier JJ, Guo L, von Montfort C, Kiaser JP, Joshi-Barve S, Arteel GE. New role of resistin in lipopolysaccharide-induced liver damage in mice. *J Pharmacol Exp Ther* 2008;325:801-8.
91. Qiao Xz, Yang Ym, Xu Zr, Yang LA. Relationship between resistin level in serum and acute coronary syndrome or stable angina pectoris. *J Zhejiang Univ Sci B* 2007;8:875-80.
92. Hamaguchi E, Takamura T, Shimizu A, Nagai Y. Tumor necrosis factor- α and troglitazone regulate plasminogen activator inhibitor type 1 production through extracellular signal-regulated kinase- and nuclear factor- κ B-dependent pathways in cultured human umbilical vein endothelial cells. *J Pharmacol Exp Ther* 2003;307:987-94.
93. Kim M, Oh JK, Sakata S, Liang L, Park W, Hajjar RJ, *et al.* Role of resistin in cardiac contractility and hypertrophy. *J Mol Cell Cardiol* 2008;45:270-80.
94. Montague CT, Prins JB, Sanders L, Zhang J, Sewter CP, Digby J, *et al.* Depot-related gene expression in human subcutaneous and omental adipocytes. *Diabetes* 1998;47:1384-91.
95. Tsutsumi C, Okuno M, Tannous L, Piantadosi R, Allan M, Goodman DS, *et al.* Retinoids and retinoid-binding protein expression in rat adipocytes. *J Biol Chem* 1992;267:1805-10.

96. Kloting N, Graham TE, Berndt J, Kralisch S, Kovacs P, Wason CJ, *et al.* Serum retinol-binding protein is more highly expressed in visceral than in subcutaneous adipose tissue and is a marker of intra-abdominal fat mass. *Cell Metab* 2007;6:79-87.
97. Yang Q, Graham TE, Mody N, Preitner F, Peroni OD, Zabolotny JM, *et al.* Serum retinol binding protein 4 contributes to insulin resistance in obesity and type 2 diabetes. *Nature* 2005;436:356-62.
98. Solini A, Santini E, Madec S, Rossi C, Muscelli E. Retinol binding protein-4 in women with untreated essential hypertension. *Am J Hypertens* 2009;22:1001-6.
99. Kotani K, Kim YB, Peroni O, Mundt A, Kahn BB. Rosiglitazone treatment normalizes glucose tolerance in adipose-specific GLUT4 knockout mice but renders muscle-specific GLUT4 knockout more diabetic. *Diabetes* 2001;50:A274.
100. Usui S, Ichimura M, Ikeda S, Okamoto M. Association between serum retinol-binding protein 4 and small dense low-density lipoprotein cholesterol levels in young adult women. *Clin Chim Acta* 2009;399:45-8.
101. Haider DG, Schindler K, Prager G, Bohdjalian A, Luger A, Wolzt M, *et al.* Serum retinol-binding protein 4 is reduced after weight loss in morbidly obese subjects. *J Clin Endocrinol Metab* 2007;92:1168-71.
102. Qi Q, Yu Z, Ye X, Zhao F, Huang P, Hu FB, *et al.* Elevated retinol-binding protein 4 levels are associated with metabolic syndrome in Chinese people. *J Clin Endocrinol Metab* 2007;92:4827-34.
103. Lim S, Choi SH, Jeong IK, Kim JH, Moon MK, Park KS, *et al.* Insulin-sensitizing effects of exercise on adiponectin and retinol-binding protein-4 concentrations in young and middle-aged women. *J Clin Endocrinol Metab* 2008;93:2263-8.
104. Samal B, Sun Y, Stearns G, Xie C, Suggs S, McNiece I. Cloning and characterization of the cDNA encoding a novel human pre-B-cell colony-enhancing factor. *Mol Cell Biol* 1994;14:1431-7.
105. Kitani T, Okuno S, Fujisawa H. Growth phase-dependent changes in the subcellular localization of pre-B-cell colony-enhancing factor. *FEBS Lett* 2003;544:74-8.
106. Revollo JR, Korner A, Mills KF, Satoh A, Wang T, Garten A, *et al.* Namp1/PBEF/Visfatin regulates insulin secretion in β cells as a systemic NAD biosynthetic enzyme. *Cell Metab* 2007;6:363-75.
107. Fukuhara A, Matsuda M, Nishizawa M, Segawa K, Tanaka M, Kishimoto K, *et al.* Visfatin: A protein secreted by visceral fat that mimics the effects of insulin. *Science* 2005;307:426-30.
108. Berndt J, Kloting N, Kralisch S, Kovacs P, Fasshauer M, Schon MR, *et al.* Plasma visfatin concentrations and fat depot-specific mRNA expression in humans. *Diabetes* 2005;54:2911-6.
109. Varma V, Yao-Borengasser A, Rasouli N, Bodles AM, Phanavanh B, Lee MJ, *et al.* Human visfatin expression: Relationship to insulin sensitivity, intramyocellular lipids and inflammation. *J Clin Endocrinol Metab* 2007;92:666-72.
110. Chen MP, Chung FM, Chang DM, Tsai JC, Huang HF, Shin SJ, *et al.* Elevated plasma level of visfatin/pre-B cell colony-enhancing factor in patients with type 2 diabetes mellitus. *J Clin Endocrinol Metab* 2006;91:295-9.
111. Hammarstedt A, Pihlajamäki J, Sopasakis VR, Gogg S, Jansson PA, Laakso M, *et al.* Visfatin is an adipokine, but it is not regulated by thiazolidinediones. *J Clin Endocrinol Metab* 2006;91:1181-4.
112. Haider DG, Schindler K, Schaller G, Prager G, Wolzt M, Ludvik B. Increased plasma visfatin concentrations in morbidly obese subjects are reduced after gastric banding. *J Clin Endocrinol Metab* 2006;91:1578-81.
113. Mohapatra J, Sharma M, Singh S, Pandya G, Chatterjee A, Balaraman R, *et al.* Involvement of adipokines in rimnabant-mediated insulin sensitivity in ob/ob mice. *J Pharm Pharmacol* 2009;61:1493-8.
114. Dahl TB, Yndestad A, Skjelland M, Øie E, Dahl A, Michelsen A, *et al.* Increased expression of visfatin in macrophage of human unstable carotid and coronary atherosclerosis: Possible role in inflammation and plaque destabilization. *Circulation* 2007;115:972-80.
115. Moschen AR, Kaser A, Enrich B, Mosheimer B, Theurl M, Niederegger H, *et al.* Visfatin, an adipocytokine with proinflammatory and immunomodulating properties. *J Immunol* 2007;178:1748-58.
116. Brentano F, Schorr O, Ospelt C, Stanczyk J, Gay RE, Gay S, *et al.* Pre B cell colony enhancing factor/Visfatin a new marker of inflammation in rheumatoid arthritis with proinflammatory and matrix degrading activities. *Arthritis Rheum* 2007;56:2829-39.
117. Friedman JM. Leptin and the regulation of body weight. *Harvey Lect* 1999;95:107-36.
118. Friedman JM. The function of leptin in nutrition, weight, and physiology. *Nutr Rev* 2002;60:S1-14.
119. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, *et al.* Weight-reducing effects of the plasma protein encoded by the obese gene. *Science* 1995;269:543-6.
120. Pellemounter MA, Cullen MJ, Baker MB, Hecht R, Winters D, Boone T, *et al.* Effects of the obese gene product on body weight regulation in ob/ob mice. *Science* 1995;269:540-3.
121. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. *Nature* 1994;372:425-32.
122. Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. *Nature* 1998;395:763-70.
123. Elmquist JK, Elias CF, Saper CB. From lesions to leptin: Hypothalamic control of food intake and body weight. *Neuron* 1999;22:221-32.
124. Bates SH, Myers MG Jr. The role of leptin receptor signaling in feeding and neuroendocrine function. *Trends Endocrinol Metab* 2003;14:447-52.
125. Prodi E, Obici S. Minireview: The brain as a molecular target for diabetic therapy. *Endocrinology* 2006;147:2664-9.
126. Farooqi IS, Matarese G, Lord GM, Keogh JM, Lawrence E, Agwu C, *et al.* Beneficial effects of leptin on obesity, T cell hyporesponsiveness, and neuroendocrine/metabolic dysfunction of human congenital leptin deficiency. *J Clin Invest* 2002;110:1093-103.
127. Cooke JP, Oka RK. Does leptin cause vascular disease? *Circulation* 2002;106:1904-5.
128. Konstantinides S, Schafer K, Koschnick S, Loskutoff DJ. Leptin-dependent platelet aggregation and arterial thrombosis suggests a mechanism for atherothrombotic disease in obesity. *J Clin Invest* 2001;108:1533-40.
129. Artwohl M, Roden M, Holzenbein T, Freudenthaler A, Waldhauser W, Baumgartner-Parzer SM. Modulation by leptin of proliferation and apoptosis in vascular endothelial cells. *Int J Obes Relat Metab Disord* 2002;26:577-80.
130. Park HY, Kwon HM, Lim HJ, Hong BK, Lee JY, Park BE, *et al.* Potential role of leptin in angiogenesis: Leptin induces endothelial cell proliferation and expression of matrix metalloproteinases *in vivo* and *in vitro*. *Exp Mol Med* 2001;33:95-102.
131. Munzberg H, Myers MG Jr. Molecular and anatomical determinants of central leptin resistance. *Nat Neurosci* 2005;8:566-70.
132. El-Haschimi K, Pierroz DD, Hileman SM, Bjørbaek C, Flier JS. Two defects contribute to hypothalamic leptin resistance in mice with diet-induced obesity. *J Clin Invest* 2000;105:1827-32.
133. Verma S, Li SH, Wang CH, Fedak PW, Li RK, Weisel RD, *et al.* Resistin promotes endothelial cell activation: Further evidence of adipokine-endothelial interaction. *Circulation* 2003;108:736-40.
134. Mohapatra J, Sharma M, Singh S, Chatterjee A, Swain P, Balaraman R, *et al.* Subtherapeutic dose of pioglitazone reduce expression of inflammatory adipokines in db/db mice. *Pharmacology* 2009;84:203-10.
135. Yang WS, Lee WJ, Funahashi T, Tanaka S, Matsuzawa Y, Chao CL, *et al.* Weight reduction increases plasma levels of an adipose-derived anti-inflammatory protein, adiponectin. *J Clin Endocrinol Metab* 2001;86:3815-9.
136. Nagasawa A, Fukui K, Kojima M, Kishida K, Maeda N, Nagaretani H, *et al.* Divergent effects of soy protein diet on the expression of adipocytokines. *Biochem Biophys Res Commun* 2003;311:909-14.
137. Nagasawa A, Fukui K, Funahashi T, Maeda N, Shimomura I, Kihara S, *et al.* Effects of soy protein diet on the expression of adipose genes and plasma adiponectin. *Horm Metab Res* 2002;34:635-9.
138. Matsuzawa Y. Adiponectin: Identification, physiology and clinical relevance in metabolic and vascular disease. *Atheroscler Suppl* 2005;6:7-14.
139. Tsochatzis EA, Papatheodoridis GV, Archimandritis AJ. Adipokines in nonalcoholic steatohepatitis: From pathogenesis to implications in diagnosis and therapy. *Mediators Inflamm* 2009;2009:831670.
140. Roth JD, Roland BL, Cole RL, Trevaskis JL, Weyer C, Koda JE, *et al.* Leptin responsiveness restored by amylin agonism in diet-induced obesity: Evidence from nonclinical and clinical studies. *Proc Natl Acad Sci U S A* 2008;105:7257-62.

Source of Support: Nil, Conflict of Interest: None declared