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Association of adipokines with insulin resistance and metabolic syndrome including obesity and diabetes

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Abstract: Adipose tissue (AT) acts as a highly active endocrine organ, which secretes a wide range of adipokine hormones. In the past few years, several adipokines (leptin, adiponectin, resistin *etc*.) have been discovered showing metabolic consequences in relation to insulin resistance (IR), obesity and diabetes. These adipokines are considered to be an important component playing an important role in the regulation of energy metabolism. They have been shown to be involved in the pathogenesis of metabolic syndrome (MetS) and cardiac diseases. The current article provides a holistic summary of recent knowledge on adipokines and emphasizes their importance in association with IR, obesity, diabetes and MetS. Adipokines such as leptin, adiponectin, resistin and tumor necrosis factor-alpha (TNF-α) have been involved in the regulation of an array of metabolic functions and disease associated with it, *e.g*. appetite and energy balance of the body, suppression of atherosclerosis and liver fibrosis, obesity with type 2 diabetes (T2D) and IR. An important adipokine, Interleukin-6 (IL-6), also correlates positively with human obesity and IR and also the elevated level of IL-6 predicts development of T2D. All of these hormones have important correlation with energy homeostasis, glucose and lipid metabolism, cardiovascular function and immunity. All the possible connections have extended the biological emphasis of AT secreted adipokines as an investigator in the development of MetS, and are now no longer considered as only an energy storage site.

***Keywords*:** adipose tissue, lipid, glucose, appetite, homeostasis

Introduction

Metabolic syndrome (MetS) is a constellation of interconnected physiological and biochemical abnormalities characterized by high fasting glucose, abnormal cholesterol and triglyceride levels, hypertension, central obesity and many more (*1*). MetS is a widely distributed disorder present in 20-25% of the world's adult population. Many factors such as genetic, environmental, metabolic and others contribute to the development of MetS (*2*). Kim *et al.* demonstrated the role and associated mechanisms of adipokines in the development of MetS (*3*), but mechanisms remain controversial and require further research to open unexplored metabolic pathways. One of the most accepted classifications for defining MetS is the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation and Treatment of High Blood Cholesterol in Adults (Table 1) (*4*). Obesity is a well-recognized risk factor for the development of insulin resistance (IR) and MetS. An increase in total body fatness and preferential upper body accumulation of fat tissue is independently related to IR. Obesity with a greater proportion of upper body fat tissue tends to be more insulin resistant, hyperinsulinemic, glucose intolerant and dyslipidemic than obesity with a greater proportion of lower body fat. So, the distribution of body fat tissue is an important correlate of MetS.

Due to the dramatic rise in obesity and associated metabolic abnormalities worldwide, research pertaining to, adipose tissue (AT) has gained tremendous scientific interest for several years. Previous research demonstrated that AT acts in an autocrine, paracrine or endocrine reservoir to control various metabolic functions and may contribute to the development of obesity mediated MetS. AT secretes various proteins or factors with diverse functions termed as bioactive mediators or "adipokines" (previously designated as "adipocytokines") modulating hemostasis, blood pressure, lipid and glucose metabolism, inflammation, and atherosclerosis (Table 2). In 2004, Trayhurn and Wood proposed an integrative term, "adipokinome", which, together with the lipid moieties released and adipokines constitute the "secretome" of fat cells (*5*). These adipokines secreted from adipocytes are defined as insulin antagonists (TNF-α, IL-6 and Resistin) and insulin sensitizers (Leptin and Adiponectin) (Figure 1) (*6*). These adipokines may act locally or distally to alter insulin sensitivity in insulin-targeted organs such

Table 1. Criteria for clinical diagnostic of the MetS

No.	Obesity	Obesity		Dyslipidemia		Blood pressure	Glucose	Insulin resistance	Others
	Diagnosis	Male	Female	Male	Female				
1.	NCEP-ATP III (≥ 3 of any criteria), 2001	Abdominal obesity WC ≥ 102 cm or 40 inches	Abdominal obesity WC > 88 cm or 36 inches	TG ≥ 150 mg/dl HDL-C < 40 mg/dl or on therapy	TG ≥ 150mg/dl HDL-C < 50 mg/dl or on therapy	≥ 130/85 mmHg or on therapy	Fasting Glucose > 110 mg/dl (≥ 6.1 mmol/L)	—	—
2.	WHO (5th or 6th + ≥ 2 of any criteria), 1999	WHR > 0.90 and/or BMI > 30 Kg/m^2	WHR > 0.85 and/or BMI > 30 Kg/m^2	TG ≥ 150 mg/dl (≥ 1.7 mmol/L) HDL-C < 35 mg/dl (≤ 0.9 mmol/L)	TG ≥ 150mg/dl (≥ 1.7 mmol/L) HDL-C < 39 mg/dl ≤ 1.0 mmol/L)	≥ 140/90 mmHg	T2DM, IFG, IGT	IR measured under hyperinsulinaemic-euglycemic conditions	Urinary albumin excretion rate ≥ 20 µg/min or albumin: creatinine ratio ≥ 30 mg/g min
3.	EGIR (5th + ≥ 2 of any criteria), 1999	WC ≥ 94 cm	WC ≥ 80 cm	TG ≥ 177mg/dl (≥ 2.0 mmol/L) HDL-C < 39 mg/dl (< 1.0 mmol/L)		≥ 140/90 mmHg or on medication	Fasting Glucose >110 mg/dl (≥ 6.1 mmol/L)	IR	—
4.	AHA/ NHLBI or Updated NCEP criteria, 2005	WC ≥ 102 cm (Asian ≥ 90) or 40 inches	WC > 88 cm (Asian ≥ 80) or 36 inches	TG ≥ 150mg/dl (≥ 1.7 mmol/L) HDL-C < 40 mg/dl (1.0 mmol/L) or on therapy	TG ≥ 150mg/dl (≥ 1.7 mmol/L) HDL-C < 50 mg/dl (1.0 mmol/L) or on therapy	≥ 130/85 mmHg or on medication	Fasting Glucose > 100 mg/dl (5.6 mmol /L)	—	—
5.	IDF (1st + ≥ 2 of any other criteria), 2005	Waist circumference ethnic specific (≥ 90 cm for men and ≥ 80 cm for women) for Asian Indian subjects *If BMI is > 30 Kg/m^2, central obesity can be assumed and WC does not need to be measured		TG ≥ 150 mg/dl (≥ 1.7 mmol/L) HDL-C < 40 mg/dl (1.03 mmol/L) or on therapy	TG ≥ 150 mg/dl (≥ 1.7 mmol/L) HDL-C < 50 mg/dl (1.3 mmol/L) or on therapy	≥ 130/85 mmHg or on therapy	Fasting Glucose > 100 mg/dl (5.6 mmol /L) or DM	—	—

Mets, metabolic syndrome; NCEP ATPIII, National Cholesterol Education Program-Adult Treatment panel III; WHO, World Health Organization; EGIR, European Group of Insulin Resistance; AHA/NHLBI, American Heart Association/Normal Heart, Lung, and Blood Institute; IDF, International Diabetes Federation; WC, waist circumference; WHR, waist to hip ratio; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; TC, total cholesterol; HDL, high density lipoprotein; TG, triglyceride; LDL, low density lipoprotein; VLDL, very low density lipoprotein; FPG, fasting plasma glucose; FPI, fasting plasma insulin; HOMA-IR, homeostatic model assessment-insulin resistance; DM, diabetes mellitus.

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as muscle and liver or may act through neuro-endocrine, autonomic or immune pathways. This disequilibrium between pro and anti-inflammatory adipokines induces low-grade inflammation, associated mainly with adiposity and IR. In this regard, it is known that increased adiposity is a major determinant of IR and that altered adipokine regulation is the underlying reason.

Several of these adipokines are interdependent, and the crosstalk among themselves may play an important role in the pathophysiology and management of MetS (*7*). In this review article, our focus is on major adipokines, the interplay between adipokines, and tries to ascertain their role in MetS with the current state of information available and how they may influence insulin sensitivity.

Table 2. Candidate biomarkers associated with MetS

Association	Candidates biomarkers
Genes causing monogenic obesity	Leptin
	Leptin receptor
	Melanocortin receptor
Genes regulating FFA metabolism	Adiponectin
	Fatty acid binding protein-2
	Lipases
	Uncoupling proteins
Genes affecting insulin sensitivity	Resistin
	Peroxisome proliferators
	Insulin receptor substrates
	Skeletal muscle glycogen synthase 1
Genes affecting lipid metabolism	CD36
	Apolipoprotein E
	Upstream transcription factor 1
Genes related to inflammation	IL-6
	TNF-α
	C-reactive protein

MetS, metabolic syndrome; FFA, free fatty acid; CD36, cluster of differentiation; IL-6, interleukin-6; TNF-α, tumor necrosis factor-α.

Adipokines, IR and central obesity

There is a close relationship between IR, central/visceral adiposity and adipokines (Figure 2). IR is associated with an overabundance of metabolic risk factors such as abnormal elevated cholesterol or lipids, high blood pressure, body functional inabilities, low level of inflammation, dysregulated adipokine production and many of these can either alone or jointly speedup the atherogenic process and malfunctioning of glucose metabolism. IR should be conceptualized in a very broad manner that takes into account the interplay between nutrition, insulin and adipokines in various tissues of metabolic importance. IR correlates with the degree of obesity (visceral obesity) and is a strong predictor of the development of T2D.

In 1988, it was hypothesized that IR is a contributory central component of MetS or syndrome X. Insulin action impaired in AT causes increased lipolysis and release of free fatty acid (FFA). The increased flux of FFA not only impairs insulin secretion by pancreatic islet β-cells, but also induces IR by interfering with glucose transport and insulin-mediated glucose uptake in muscle and liver. Adipokines appear to play a central role and plasma levels may serve as candidate biomarkers for mediating both the MetS of IR and the endothelial dysfunction in obesity. Adipokine levels appear to correlate closely with adiposity, with increasing levels in subjects with higher body mass index (BMI) values. Many of the pro-inflammatory adipokines exert multiple actions in a variety of cellular processes leading to a complex array of abnormalities and are characteristic

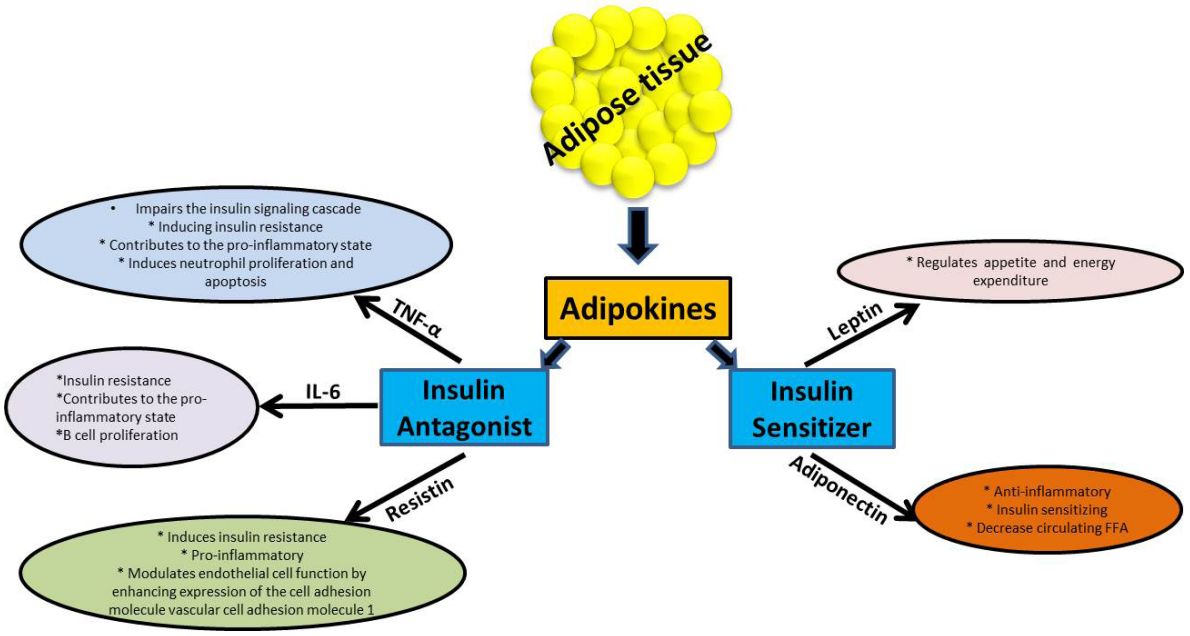

Figure 1. Bioactive proteins secreted by adipose tissue that causes IR. IL-6, interleukin-6; TNF-α, tumor necrosis factor-α. IR, insulin resistance.

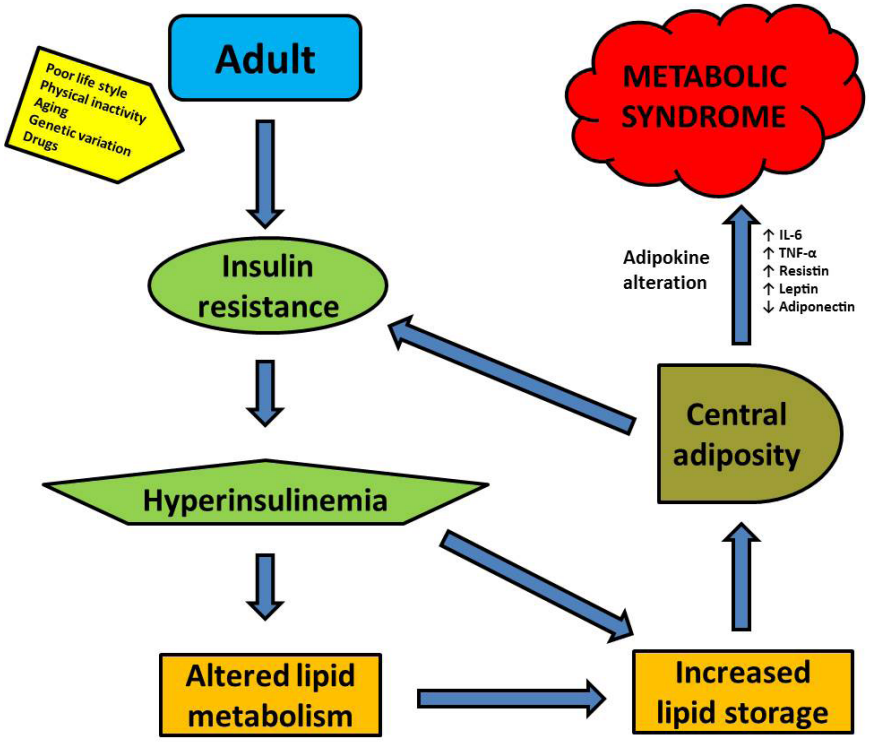

Figure 2. Pathophysiological mechanism of MetS. IL-6, interleukin-6; TNF-α, tumor necrosis factor-α. MetS, metabolic syndrome.

of MetS whereas anti-inflammatory adipokines work differently. The principal effects and the association of AT derived adipokines with IR, obesity and MetS are discussed in this article.

Adipokines and their genetic interactions with IR, obesity and MetS

Leptin

Leptin, 16kDa protein, is an adipokine secreted by AT in proportion to its mass, regulate energy homeostasis, facilitate glucose utilization, and improve insulin sensitivity. Leptin, discovered in 1994, exerts its effects through binding to the leptin receptor (Ob-R), a member of the cytokine family of trans-membrane receptors. Ob/Rb receptor has been identified as the best out of six forms of leptin receptor. The leptin receptor is in the hypothalamus increases energy expenditure and reduce appetite. The receptor is also found in kidney, liver, pancreas, smooth muscle and endometrium of heart. Patients with a complete deficiency in leptin, as a result of a mutation in the leptin gene, have been found to possess beneficial effects on energy intake, fat mass, hyperinsulinemia, and hyperlipidemia (*8*). However, in humans, leptin levels correlate with body fat, MetS or adiposity, suggesting that most obese individuals become insensitive to endogenous leptin and exogenous leptin administration is unlikely to have a major effect (*9*).

A study in normal adolescents with variable BMI found increased leptin concentration to be associated with impaired vascular function, independent of the metabolic and inflammatory disturbances associated with obesity (*10*). Leptin makes an action on adipocyte cells in a paracrine fashion. Leptin expression and secretion by adipocyte cells can be induced by IL-6 and inhibited by TNF-α. In turn, leptin, suppresses the expression of resistin and increases adiponectin expression in leptin deficient ob/ob mice (*11,12*). It is expected that, in the absence of AT, leptin levels are very low in generalized lipodystrophy, and nonetheless the subjects are often insulin resistant.

The concept of leptin resistance or an alternate concept, "hypothalamic leptin insufficiency", has been challenged and is still unclear (*12*). The development of leptin resistance may involve several mechanisms including mutation in the gene, permeability of blood brain barrier, and self-regulation. One of the possible mechanisms may be the induction of leptin on suppressor of cytokine signaling-3, which interrupts the intracellular pathway of leptin (*13*). Second, it may be the diminished transport of leptin across the blood-brain barrier (BBB), which inhibits leptin signaling (*14*). Leptin signaling preserved the β-cells from the adverse effects of excessive nutrition when the fat increases and lipid accumulates in the body. Thus, improving β-cells function (*15*). Although, leptin receptor-mediated JAK-STAT and leptin-stimulated PI3-kinase signaling, appears to be essential in glucose metabolism for the regulation of food intake and body weight regulation, respectively

(*16*). Leptin hinders de novo lipogenesis (DNL) and stimulates the oxidation of FFA in liver cells. This induces lipotoxicosis and lipoapoptosis due to reduction of hepatic liver content (*17*). Leptin also reduces hepatic glucose release by inhibiting glycogenolysis although its molecular mechanism effecting gluconeogenesis still remains to be elucidated. Suppression of hepatic glucogenesis helps in creating an insulin-sensitizing milieu and reduces glucotoxicity (*18*).

The obese (ob) gene of leptin (LEP) is an adipocyte specific gene, which plays a central role in energy metabolism and co-modulation of body weight. The discovery of a mutation in the leptin ob-gene results in the complete absence of leptin in the ob/ob mouse. The human homologue of the leptin gene is located on chromosome 7q31.3. There are several other studies indicating the involvement of leptin gene and its receptor variations with MetS, IR, and obesity (*19-21*). Common SNP in the promoter region (G-2548A) of the LEP gene has been associated with variations in plasma leptin and body mass index (BMI) in obese individuals (*22,23*). Leptin 2548 G/A and Gln223Arg leptin receptor gene polymorphism were studied broadly because 2548 G/A gene associated with the secretion and production of leptin while Gln223Arg associated with impaired signaling capacity of the leptin receptor (*24,25*). A functional study explains that Leptin G-2548A polymorphism influenced leptin mRNA expression at the transcriptional level and therefore also adipose secretion levels of the hormone (*24*). However, supporting evidence for an association of G2548A and Gln223Arg polymorphism with leptin concentrations and MetS conflict with other studies (*26,27*). A separate discovery showed Leptin C/A polymorphism, at locus 2549 in the promoter region and is related to serum leptin level in western populations (*22*). A study of Le Stunff and his researchers has shown that girls of comparable adiposity have different circulating leptin levels, depending on their genotype at the promoter region of the leptin gene (*23*). Girls with Leptin 2549 C/A genotype have 25% lower mean leptin levels than girls with other genotypes. The study of the association between IR by Homeostatic Model Assessment (HOMA) and leptin genotype indicated that people carrying C-allele have more severe IR (*23*). Leptin gene at position 2549 carrying AA genotype was also strongly associated with cardio MetS (*28*).

In summary, leptin serves as a major "adipostat" by repressing food intake and promoting energy expenditure, suggesting that leptin acts as a signal that contributes to regulation of total-body sensitivity to insulin.

Adiponectin

Adiponectin is the most abundant AT derived adipocytokine comprised of a 247-amino acid protein with an increasingly important role in energy homeostasis and insulin sensitivity. It was first isolated during adipocyte differentiation of 3T3-L1 preadipocytes following large-scale sequencing of the human adipose cDNA library. In AT, human adiponectin was cloned after mouse cloning. However, human adiponectin shared over 80% similarity with the mouse amino acids (AA). It is the only adipokine that is known to be downregulated in obesity. In addition to the association with whole-body fat mass, adiponectin levels differ with the distribution of body fat. Adiponectin is present at high concentrations in the circulation of mice and healthy humans. A study on obese mice lacking adiponectin show reduced responsiveness to peroxisome proliferator-activated receptor-gamma (PPARγ) agonists and decreased hepatic insulin sensitivity (*29*).

In human studies, plasma adiponectin levels are negatively correlated with adiposity, waist-to-hip ratio (WHR) and IR, dyslipidemia and MetS, whereas levels are positively correlated with markers of insulin sensitivity (*30-32*). Evidence suggested that adiponectin is an important contributor to IR and MetS but the actual physiological role of adiponectin is still unclear. Due to insulin-sensitizing effect of adiponectin, it may alter glucose metabolism by fat tissue through increasing pancreatic insulin stimulated glucose uptake (*33*). Adiponectin gene expression in human visceral AT is negatively regulated by TNF-α and positively by insulin (*34*). Visceral fat was reported to be inversely associated with plasma adiponectin levels in healthy women (*35*). In case-control studies, low plasma adiponectin was an independent risk factor for development of T2D but not for obesity (*36,37*). Variations in serum adiponectin concentration have been proposed to have a strong heritable component in both predominantly Pima Indian and Northern European populations (*36,38*). Another study showed the changes in serum adiponectin level in postmenopausal women with MetS (*39*). Alternatively, adiponectin secretion may be regulated by insulin and therefore, circulating levels may be a marker of IR and a causal factor as well (*40*). Evidence suggests that there is a close association between IR and low adiponectin level (*41*).

Reproducible results of human genetic studies of diverse ethnic origin may provide evidence for its causative role in pathogenesis of the MetS and further insight into the genetic constitutions of MetS. Adiponectin is encoded by ADIPOQ (also known as APM1), located on chromosome 3q27, spans 17kb and contains 3 exons and 2 introns. Human adiponectin gene polymorphism is commonly found at the promoter region, exon and intron 2, and nonsynonymous mutations, which are rare at exon 3 region were repeatedly shown in different ethnic populations associated with the phenotypes related to body weight, glucose metabolism, insulin sensitivity, T2D and MetS (*42,43*).

Notably, additional support for the important role of adiponectin in IR comes from genetic studies

that have mapped a susceptibility locus for T2D and MetS in which the gene is located (*44*). Adiponectin gene transcription and secretion were decreased by pro-inflammatory markers, TNF-α and IL-6 (*45*). Adiponectin SNPs have been associated variably with increased BMI, IR-related traits and T2D (*43*). The adiponectin gene has been found to be consistently and significantly associated with plasma adiponectin in genetic association studies (*46*). The two most common reported variants of the adiponectin gene in different populations, a silent T/G substitution at position 45 in exon 2 and a G/T substitution at position 276 in intron 2, were closely associated with type II diabetes in Chinese and Japanese, visceral obesity in Swedish and Taiwanese populations and several components of MetS in Chinese and Caucasians, and IR syndrome in North Indian populations (*47-53*). However, the findings are still conflicting. Furthermore, +45T/G polymorphism was associated with circulating adiponectin level that added a much greater contribution to MetS. Adiponectin levels might also influence cardiac stroke, which is considered a cardiovascular event of MetS (*54,55*). An association between the +276G/T genotype and adiponectin levels has been observed in obese Japanese, and Spanish populations (*48,56*). However, in a systematic meta-analysis of all published data on adiponectin SNPs, only the +276G/T variant was a strong determinant of IR with minor allele homozygotes having a lower IR index (based on HOMA) than carriers of other genotypes. These human genetic studies on adiponectin and MetS strongly suggest that adiponectin is one of the causative factors in its pathogenesis and provide significant insights into the genetic makeup of MetS.

In summary, adiponectin is an adipocyte-derived protein with insulin sensitizing, anti-inflammatory, anti-hyperglycemic, vascular protective and anti-atherogenic properties. Although its physiological and pathophysiological roles have not been fully elucidated. High levels of adiponectin may be an important factor, which activates AMPK and stimulates phosphorylation of acetyl coenzyme A carboxylase (ACC), fatty-acid oxidation, glucose uptake and lactate production in myocytes and reduction of glucose levels *in vivo*. Adiponectin may provide a novel and potential treatment modality for IR, obesity and MetS through therapeutic modulation.

Resistin

Resistin, a 12.5kDa cysteine rich peptide, is derived from AT that has been implicated in the development of IR. Holcom *et al*. first proposed the gene family and its tissue-specific distribution, identifying a protein found in inflammatory zone called FIZZ1 *i.e.* also known as resistin-like molecules (RELM) (*57*). Resistin was first identified in a search for genes that were *i*) induced with adipocyte differentiation but *ii*) down-regulated following exposure to Thiazolidinediones (TZDs). This led to the discovery of a protein named "resistin", known to be resistant to insulin (*58*).

Circulating resistin levels were found to be elevated in both genetic and diet-induced obesity and IR models. Therefore, it also serves as an important link between obesity and IR. A study on mice suggested that resistin selectively impairs the inhibitory action of insulin on hepatic glucose production (*59*). Neutralization of resistin by specific antibodies resulted in decreased blood glucose levels and improved insulin sensitivity, thereby providing a more direct link between fat mass and IR (*58*). By contrast, upregulated circulating resistin levels might contribute to hyperglycemia, IR, T2D, MetS and cardiovascular disease (*60-63*).

Human resistin is a dimeric protein containing 108 amino acids, produced and secreted mainly by peripheral-blood mononuclear cells. Human resistin is only 59% similar to the mouse protein, and this may indicate important differences in the endocrine functions of adipocytes and resistin between rodents and humans. It is also expressed and secreted by mature adipocytes. The secreted protein was found to inhibit 3T3-LI adipogenesis, and it was speculated that resistin was a feedback regulator of adipogenesis. McTernan and coworkers reported a higher mRNA resistin expression in the abdomen than thigh region (*64*). Thus, this study suggested that human resistin could play a significant role in obesity-related IR. Furthermore, at least in part, elevated insulin and TNF-α levels in obesity inhibits resistin expression, which may explain the lower level of resistin found in obese diabetes. However, the role of resistin in obesity-associated IR has become controversial because additional evidence suggested that obesity and IR are associated with decreased resistin expression in AT (*65*).

The resistin gene is located on chromosome 19p13 a short distance from the insulin receptor. It is a small gene that spans less than 2kb and includes four exons and three introns. Screening of the entire resistin gene has eight SNPs variants and a (GAT)n microsatellite identified (*66*). Four SNPs were placed in the 5'-flanking region; two in intron 2, and two in intron 3 in the mouse and two in humans, encode resistin (*67*). These genes are present on chromosome 8 in the mouse and chromosome 19 in humans. Controversial results have been found for SNP studies on genetic variations in the resistin gene. Some case control studies demonstrated genetic variations in the resistin gene to be associated with IR and obesity in humans (*68*). Six SNPs were relatively frequent, with allele frequencies ranging from 0.09 to 0.43. All SNPs were in significant linkage disequilibrium, with only five haplotypes accounting for more than 80% of control chromosomes. Several polymorphisms in the resistin gene have been studied: only few have minor allele frequencies while over 5% are associated with disease risk and a few located in the 5'-flanking

region (G–638A, A–537C, C–420G and G–358A) affect circulating levels of resistin (*69,70*). Studies had reported much more attention to resistin SNP -420C/G, located in the promoter region of the resistin gene, and is the major determinant of plasma resistin concentration and influences resistin expression in humans (*70*). Several research groups identified that the circulating resistin level and specific SNPs are associated with adiposity, MetS, IR and T2D (*71-73*). However, other studies failed to identify changes in resistin levels or SNPs in similar conditions (*74,75*). In addition to SNP 420C/G, it has been reported that other polymorphisms (+299 G/A, rs3219175, rs1423096, rs3745368, and rs1477341) of the resistin gene were strongly associated with circulating resistin levels (*69,76*). Morever, it has been reported that -638G/A (rs34861192) and -358G/A (rs3219175) had the strongest association with circulating resistin levels among the SNPs at the resistin locus (*69,76*).

In summary, resistin may represent a link between inflammation and metabolic signals and circulating resistin was more significantly correlated with central obesity and IR.

TNF-α

TNF-α is a pro-inflammatory cytokine that has been implicated in the pathogenesis of IR. TNF-α is expressed as a 26kDa cell surface trans-membrane protein that undergoes cleavage to produce a 17kDa soluble, biologically active form of TNF-α (*77*). Increased TNF-α production has been observed in AT derived from animal models of obesity and IR as well as in human subjects (*78*).

In AT, TNF-α is not secreted in the systemic circulation but acts in an autocrine and paracrine fashion. TNF-α is over expressed in AT of obese individuals. TNF-α is expressed more in visceral than in subcutaneous fat tissue, and more abundantly produced by macrophages than adipocytes (*79*). In humans, expression of TNF-α correlates with BMI, percent body fat and hyperinsulinaemia and weight loss decreased TNF-α levels (*80*). TNF-α significantly increases the expression of IL-6, reduces the expression of resistin and stimulates the secretion of leptin in 3T3-L1 adipocytes (*81-83*). Potential mechanisms by which AT secreted TNF-α increases IR include increased release of FFA by adipocytes and reduction in adiponectin synthesis; the cytokine directly affects insulin sensitivity by inhibiting insulin receptor signaling (*45,84*).

The TNF-α gene is located in the chromosomal region 6p21.1–21.3, next to the major histocompatibility complex (MHC). A SNP at position -308 upstream from the transcription initiation site in the promoter region demonstrated that polymorphism increases transcriptional activation of the TNF-α gene. TNF-α gene transcription is regulated by the promoter region, which consists of an 1,100 base pair stretch of DNA (*85*). A biallelic polymorphism involves the substitution of guanine by adenine at position –308 in the promoter region, produces the less common homozygote TNF-α allele, which has been associated with elevated serum concentrations of TNF-α in certain clinical states (*86,87*).

Although controversial, the majority of the data support a direct role for this biallelic polymorphism in the elevation of TNF-α level observed in homozygotes for the −308 A allele (*88*). Some studies have indicated a key role of the TNF-α gene for the −308 variant in the pathogenesis of various components of MetS and IR (*89,90*). However, many other studies have reported negative results, with no correlation between TNF-α SNP and IR or any other MetS abnormality (*91,92*). A study of Fernandez-Real *et al.* showed that the polymorphism influenced insulin sensitivity *via* an increase in body fat in a group of non-diabetic normotensive Spanish subjects (*93*). While another study by Hamann *et al.* showed no difference between T2D patients and healthy control subjects in the frequency of alleles at –308 (*94*). Walston and coworkers reported that TNF-α polymorphism at –308 polymorphic sites did not relate to any traits of obesity and IR in a group of non-diabetic subjects (*95*).

In summary, TNF-α seems to play an important role in the development of IR in rodents, but the *in vivo* data in humans has not been as conclusive. Additional human studies are needed to understand its role in the pathogenesis of IR in humans.

IL-6

IL-6 is a pleiotropic circulating cytokine with effects ranging from inflammation to host defense to tissue injury and it is one of several pro-inflammatory cytokines that have been associated with MetS as a biological marker. IL-6 is secreted by immune cells, fibroblasts, endothelial cells, skeletal muscle and AT. It circulates as a variably glycosylated 26kDa protein. IL-6 concentrations increase with adiposity, and 15-35% of circulating IL-6 may be released by AT *in vivo*. In AT, IL-6 reduces lipoprotein lipase activity and increases basal lipolysis (*96*).

Studies suggest that IL-6 may stimulate fat lipolysis in human adipocytes thus leading to increase circulating FFA (*97*). Fasting plasma IL-6 concentrations were negatively correlated with the rate of insulin-stimulated glucose disposal in Pima Indians (*98*). Bastard and collogues reported that increased IL-6 values were more strongly correlated with obesity and IR, significant decreases in circulating IL-6 and TNF-α levels responsed to diet-induced weight loss in obese women (*98,99*). Other studies also had similar observations that weight loss results decrease circulating IL-6 levels (*100*). Overall, the association of IL-6 and IR seems complex and IL-6 alone might not be an appropriate marker of IR or MetS. IL-6 may also exert its adverse effects by decreasing adiponectin secretion.

Our study showed increased circulating IL-6 levels in obese and MetS women (*101*). Hyperinsulinemia positively associated with TNF-α and IL-6 gene expression while hyperinsulinemia and glucose intolerance were negatively linked to adiponectin expression in AT (*102,103*). IL-6 also increases the expression of resistin in human peripheral bloods mononuclear cells (*104*). Visceral AT releases two to three times greater IL-6 compared to subcutaneous AT. Although, it seems that the majority of AT-derived IL-6 comes from stromal immune cells and not adipocytes (*105*). Rotter *et al.* reported a reduction in the expression of insulin receptor substrate-1 (IRS-1) and glucose transporter 4 (GLUT4) in adipocytes response to IL-6 treatment (*106*). Due to visceral depots drain into the portal circulation, the metabolic effects of IL-6 in the liver become important. Indeed, there is evidence that suggests IL-6 inhibits insulin receptor signal transduction in hepatocytes that is mediated by induction of SOCS-3 (*107*).

The association of IL-6 with MetS is supported by epidemiological and genetic studies. Genetic studies have also demonstrated a strong correlation between IR and IL-6 gene polymorphisms in Native Americans and Caucasians (*108*). Another study, which is in agreement with the study on Caucasian populations, suggests that IL-6 receptor (IL-6R, rs8192284-A/C, Asp358Ala) SNPs may play a role in the pathogenesis of MetS possibly through modulating IL-6 levels (*109*). The −174 G/C variant of IL-6 gene has been shown to influence the transcriptional regulation of IL-6 and human −174 G allele carriers exhibit higher plasma IL-6 levels compared with homozygous C-allele carriers, an effect which is modulated by age and gender both (*110,111*). However, the results have been incompatible in other studies and subjects of different ethnic origins have linked the −174 G/C variant of IL-6 gene to indices of obesity and IR. In Native Americans and Caucasians, the GG genotype was associated with T2D whereas Swedish and French Canadian population showed that the C-allele was associated with indices of obesity (*108,112,113*). In Spanish populations, the G-allele has been related to decreased insulin sensitivity, hyperglycemia and abnormalities in lipids (*114,115*).

Two other functional SNPs in the IL-6 promoter at positions −597 and −572 were also identified (*116,117*). It has also been shown that three SNPs (−174, −572, −597) of the IL-6 promoter do not act independently in the regulation of IL-6 transcription (*118*). Studies showed that an IL-6 SNP within a sequence, bearing partial nucleotide homology with the Sma- and Mad-related protein 4 (Smad4) binding element and the presence of the C-allele may bind Smad 4 more effectively and inhibit IL-6 transcription (*119*). A study of a lipopolysaccharide stimulated IL-6 production result demonstrated that leucocytes from the homozygous carrier of the GGG-haplotype (−597 GG, −572 GG and −174 GG) produced the highest amount of IL-6 (*118*).

In summary, IL-6 plays a crucial role in the regulation of many adipokines, modulation of immune function and the regulation of a variety of cellular functions and IR.

Effect of adipokines on insulin signaling

Do the adipokines affect insulin sensitivity by altering the mechanism of insulin signaling? Insulin binding to insulin receptor activates IRS proteins that subsequently recruit and activate the phosphoinositide 3-kinase (PI3K) pathway. Reduced activation of PI3K by insulin is a predominant feature of IR and has been implicated in the pathogenesis of hypertension in skeletal muscle.

PI3 kinase is able to play a central role in the metabolic and mitogenic actions of insulin. PI3K has also been demonstrated to mediate some of the actions of adiponectin and leptin in various tissues, including vascular endothelium and skeletal muscle (*120,121*). In skeletal muscle, adiponectin stimulates glucose transport by increased GLUT4 translocation, activates insulin signaling, and upregulates molecules involved in fatty acid transport (*122*). Leptin has been demonstrated to impair insulin signaling in adipocytes and modulate insulin action in liver and muscle (*123*). Resistin, a potent inflammatory regulator, may exert an inhibitory effect on nitric oxide production by inhibiting insulin signaling and eNOS phosphorylation in endothelial cells. IL-6 attenuates IRS-1 expression and insulin-stimulated Akt activation in hepatocytes and adipocytes (*106,107,124*). The effects of leptin and IL-6 on insulin signaling in the endothelium remain uncharted. However, TNF-α has been shown to interfere with intracellular insulin signaling pathways in endothelial cells, and therefore represents a candidate mechanism by which it leads to impaired insulin action (*125*). TNF-α has been demonstrated to increase serine phosphorylation of IRS-1 in adipocytes, which reduces its capacity to recruit and activate downstream effectors of insulin (*124,126*).

Future prospective

MetS has reached dramatic proportions affecting adults worldwide. MetS is associated with a plethora of health problems including IR, hypertriglyceridemia, atherosclerosis and T2D. Excess amounts of visceral fat accumulation results in altered release of adipokines, leading to IR. The syndrome epidemic affects children, who are becoming overweight and obese at progressively younger ages. Most of the clinical recommendations for treatment of younger age obesity and associated disorders are based on the combination of several lifestyle interventions, such as eating habits, medication support and regular physical activities. The role of adipokines as biomarkers in physiology and pathophysiology has only been appreciated recently.

Previous studies have shown that targeting circulating

adipokine levels and their receptors expression can decrease IR, improve vascular function, and significantly lower the risk of cardiovascular morbidity and mortality. At least some of the adipokines, such as adiponectin, seems to be important in maintaining metabolic homeostasis, but others may contribute to the development of IR during the time when food is plentiful. The mechanisms by which adipokines promote IR are complex. It appears that intense AT deposition in the omental region, may be exorbitant partially through the secretion of adipokines such as resistin, TNF, and IL-6. In contrast, the presence of AT is vital in the prevention of IR, at least in part, *via* leptin and adiponectin secretion. Some of these adipokines are also recognized in the immune system and may play a role in linking the nutritional system with the immune system. Finally, determining the relative contribution of adipokines to MetS and elucidating the dynamic interactions between adipokines as biomarkers for MetS should be a focus of our research in the future.

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